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CASE REPORT

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Clinical presentation of a patient with cutis laxa with systemic involvement: a case report

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Abstract

Cutis laxa (CL) or elastolysis is a rare inherited or acquired connective tissue disorder in which the skin becomes inelastic and hangs loosely in folds (Mitra *et al.*, 2013). The clinical presentation and the type of inheritance show considerable heterogeneity (Shehzad *et al.*, 2010). We aimed to present the atypical case of a young male patient diagnosed at 36-year-old with CL with systemic involvement. The complex medical history, with a suspected but unconfirmed progeria at nine months, repeated lung and urinary infections, complicated inguinoscrotal hernia, prostatic hypertrophy, bilateral entropion, colorectal diverticula and heart failure, suggested a systemic genetic disease, but the absence of family history made the diagnosis of CL difficult. The skin biopsy and the characteristic features discovered during anatomopathological exam made possible the positive and differential diagnosis, creating the link between the various organ involvement and CL diagnosis. Because of the age of our patient, of normal growth and mental development, and negative family history, we suspected an autosomal dominant form of CL with early onset and severe manifestation. Of course, we cannot exclude a recessive form, due to the heterogeneity of this disease.

Keywords: inherited, cutis laxa, elastase, progeroid syndrome, systemic involvement.

Introduction

Over the last years, the field of hereditary connective tissue disorders has changed consistently. The vast underlying molecular network connecting these disorders opened a vast area of research. Identification and clinical or molecular characterization of new phenotypes within the connective tissue disorder spectrum is often the key to further discover the pathways involved in connective tissue biology and rises up the hypothesis of possible targeted therapies [1]. One of the main representatives of this category is cutis laxa (CL) or elastolysis, a rare inherited or acquired connective tissue disorder in which the skin becomes inelastic and hangs loosely in folds [2]. The clinical presentation and the type of inheritance show considerable heterogeneity [3]. Acquired form is less common and aggressive than the congenital ones, and can involve only the skin [2, 4]. Autosomal dominant, autosomal recessive and X-linked recessive patterns have been noted in inherited forms. The heritable forms of CL predominantly begin at birth, but it may be delayed until adolescence or third decade of life, with extracutaneous manifestations including pulmonary emphysema, umbilical and inguinal hernias, and gastrointestinal and vesicourinary tract diverticula. The acquired forms can be less aggressive, some of them involving only the skin, localized or generalized. An acquired form of the disease occurs in young adults, after arthropod stings or drug administration (D-Penicillamine, Isoniazid) and can be preceded by allergic reaction [4].

Case report

A 36-year-old non-smoking male patient was admitted to the Emergency Unit of "St. Apostle Andrew" Emergency County Hospital of Constanţa, Romania, in April 2013, for aggravating dyspnea, palpitations and collapse. The EKG (electrocardiography) made in emergency conditions showed an atrial flutter with 2:1 block, with hemodynamic impairment. Therefore, the patient was referred to the Department of Cardiology, where he was converted to sinus rhythm using electric shock (50 J, 100 J) and anti-arrhythmic drugs (Amiodarone) (Figure 1).

After two days of hospitalization in Intensive Care Unit, Department of Cardiology, during which the patient was stabilized regarding the cardiac rhythm, he was transferred to the Department of Pneumology, due to the persistent dyspnea associated with fever (38.9^0C), chills, right anterior chest pain, cough, mucopurulent sputum, severe leukocytosis (23×10^3 elements/mm^3) with neutrophilia (20×10^3 elements/mm^3), and a chest X-ray showing a heterogeneous opacity in the lower third of the right hemithorax.

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Evaluating the medical history of our patient, we discovered a complex of diseases: progeria without genetic confirmation at nine months, repeated pulmonary infections including severe bronchopneumonia during childhood, repeated urinary tract infections, prostate adenoma surgically removed and relapsed, right inguinoscrotal hernia complicated with scrotal abscess, bilateral entropion surgically treated and also relapsed, ischemic heart disease complicated with heart failure, but no family history for genetic diseases.

The clinical examination revealed an underweight patient with a BMI (body mass index) 17.2 kg/m^2, with wrinkled, dry, loose skin, micrognathia and bilateral entropion with purulent conjunctiva secretion, bilateral basal crepitations and diminished vesicular murmur, SaO_2 (oxygen saturation) 93% (Figure 2, A and B).

Completing the imagistic, the chest X-rays features were confirmed by the CT (computed tomography) scan, which revealed an inferior right lobe pneumonia, a pulmonary nodule located in inferior left lobe, severe pulmonary emphysema, cylindrical bronchiectasis in the right lung, diffuse fibrosis and right basal pachypleuritis (Figure 3, A and B).

We also performed bronchoscopy, which showed diffuse bronchitis and bronchial division abnormalities: double superior right lobar bronchi and stenosis of superior lingular subsegmental bronchi (Figure 4, A and B). Bronchial aspirates had an inflammatory aspect with a high number of PMN (polymorphonuclear) cells, but without bacterial flora when assessing the patient.

Spirometry highlighted severe ventilatory dysfunction with 78% decrease in FEV (forced expiratory volume), without bronchial reversibility. Having in mind the severe emphysema, a stage IV Gold COPD (chronic obstructive pulmonary disease) in a young non-smoking patient, without exposure to respiratory hazards, but with an important medical history with repeated pulmonary infections including severe bronchopneumonia during childhood, we thought to exclude α1-antitrypsin deficiency as major cause of COPD. The normal serum ranges of α1-antitrypsin helped us to make the difference. Also, normal ranges of immunoglobulins excluded hypogammaglobulinemia as an etiologic factor for repeated lung infections.

Due to the complex medical history, the clinical features and the age of our patient, we suspect a atypical type of progeria, or most probably, a genetic condition associated with a progeroid syndrome, knowing that the survival for patients diagnosed with progeria is usually 13 to15 years, with a maximum of 26 years of age, and our patient was already 36-year-old.

According to literature data, ischemic heart disease can be related to atherosclerosis, which is the most important feature of progeria, being also the main cause of death. Our patient did not present signs of atherosclerosis (cardiac or vascular). For this reason, we performed more accurate investigations. Angiocoronarography did not revealed any sign of atherosclerosis, but few myocardial bridges (D1, D3), duplication of the descending anterior artery and mild aortic insufficiency (Figure 5, A–C). The ultrasound examination of abdominal aorta and abdominal CT scan did not show any atheromatous plaque. Echocardiography revealed dilatation of right cavities, severe pulmonary hypertension, severe tricuspid regurgitation, mild aortic regurgitation, and plastic modification of mitral valves.

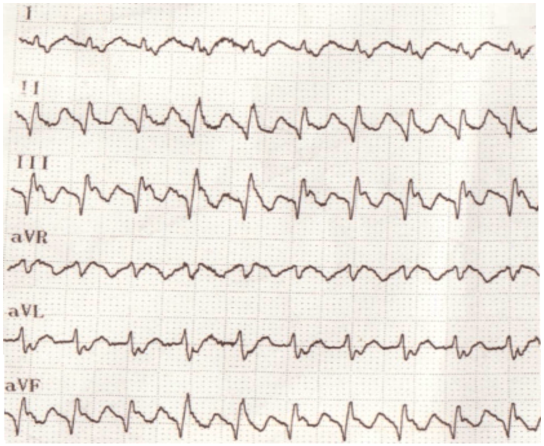

Figure 1 – ***EKG: atrial flutter with 2:1 block.***

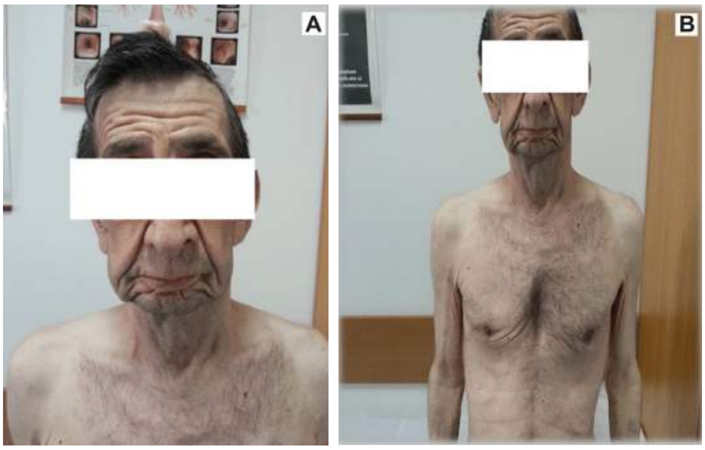

Figure 2 – ***(A and B) Clinical examination: underweight patient, with wrinkled, dry, loose skin, and micrognathia.***

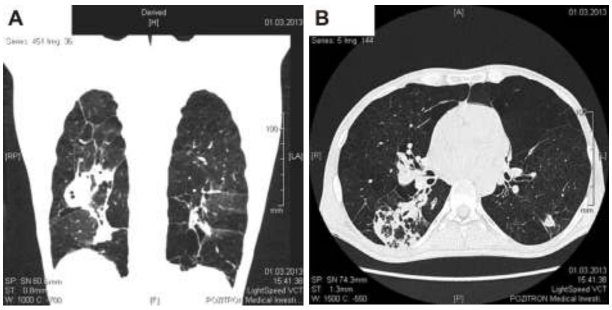

Figure 3 – ***(A and B) Inferior right lobar pneumonia, a pulmonary nodule located in inferior left lobe, severe pulmonary emphysema, bilateral cylindrical bronchiectasis, diffuse fibrosis.***

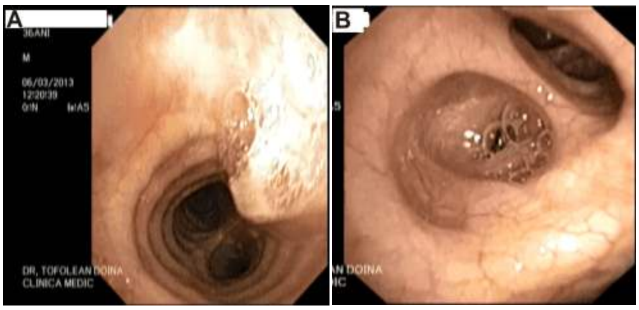

Figure 4 – ***(A and B) Diffuse bronchitis aspect and bronchial division abnormalities: double superior right lobar bronchi and stenosis of superior lingular subsegmental bronchi.***

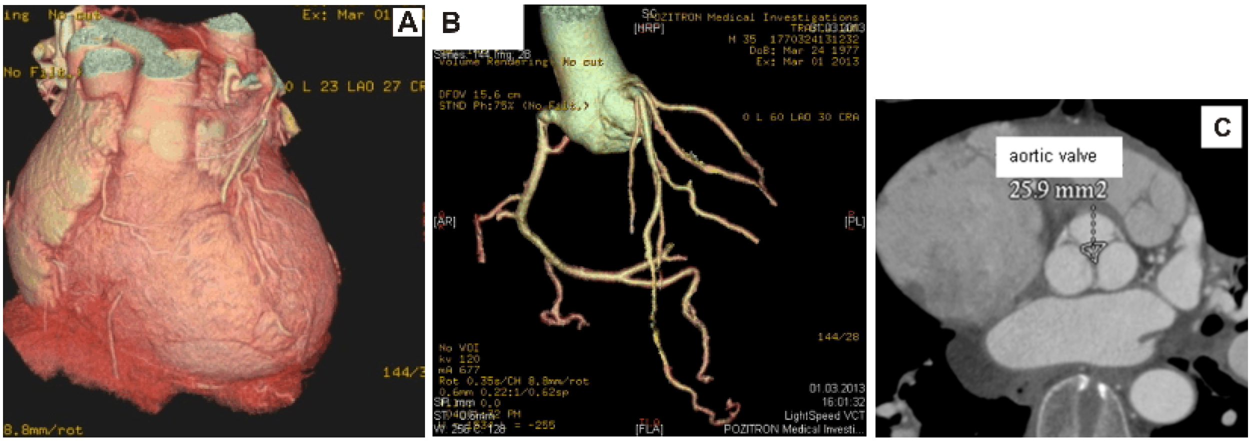

Figure 5 – ***(A–C) Angiocoronarography: myocardial bridges (D1, D3), duplication of the descending anterior artery and mild aortic insufficiency; no signs of atherosclerosis.***

The abdominal CT scan also revealed hepatomegaly with dilatations of intrahepatic bile ducts and supposition of colonic and bladder diverticula (Figure 6, A and B), latter confirmed by UroCT scan (Figure 7) and virtual colonoscopy (Figure 8, A and B).

All the organic manifestations present in our patient: progeroid syndrome, pulmonary emphysema, bronchiectasis, diverticula of digestive and urinary tract, hernias are associated with different types of CL, especially with severe recessive ones. Having in mind the age of our patient, the normal growth and mental development, and the negative family history, we thought of an autosomal dominant type, with early onset and severe manifestation (Figures 9 and 10). Still, we could not exclude a recessive form, due to the heterogeneity of the disease.

According to clinical aspects and all the investigations performed, despite absence of family history, our presumptive diagnosis was cutis laxa, a very rare disease who needs for confirmation the skin biopsy.

Patient informed consent for histopathological exam was obtained. Skin biopsies from the right forearm were than performed, and paraffin-embedded samples sectioned at 5 μm, histological stained with Hematoxylin and Eosin (HE, Merck), and van Gieson (Merck) were referred to microscopic analyze to Department of Pathologic Anatomy, "St. Apostle Andrew" Emergency County Hospital of Constanţa.

Microscopic examination was done with Leica DM750 microscope, camera and image acquisition with Leica ICC 50 HD, software acquisition LAS *ver.* 4.6.0.

The pathologist confirmed the diagnosis of CL, by describing severe reduction of elastic tissue through the dermis and the remaining elastic fibers were disorganized, fragmentized, and shortened; also mentioned no epidermal alteration, and the absence of amyloid (Figures 11–14).

Examination in usual tissue stain illustrates epidermal flattening and thinning, with focal epidermal rete ridges and skin annexes disappearance, dermal thickening due to collagen thickening; this dermal collagen thickening extends into subcutaneous tissue which appears atrophic – scleroderma skin type (Figure 12).

Skin biopsy showed diffuse cutaneous injury of dermal connective tissue, affecting the entire thickness of the dermis, which affects collagen and also elastic tissue (transdermal elastolysis), forming scleroderma-type plaque – histopathology findings that support the clinical diagnosis of congenital cutis laxa.

The typical skin biopsy features and the normal results for some lab tests performed [*e.g.*, α1-antitrypsin, immunological tests: ANA (antinuclear antibody), RF (rheumatoid factor), C3 (complement component 3), CIC (circulating immune complexes), serum immunoglobulins, thyroid hormones, serum level of copper] helped the differential diagnosis.

Figure 6 – ***(A and B) Abdominal CT scan: hepatomegaly with dilatations of intrahepatic bile ducts and supposition of colonic and urinary bladder diverticuli.***

Figure 7 – ***UroCT: urinary bladder diverticuli.***

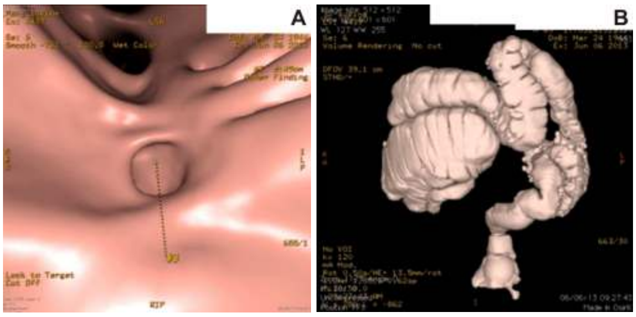

Figure 8 – ***(A and B) Virtual colonoscopy: colonic diverticuli.***

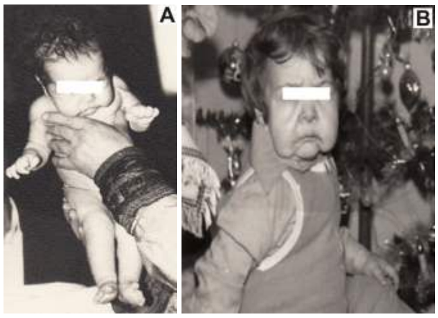

Figure 9 – ***Our patient at the age of six weeks (A), and 2.9 years (B).***

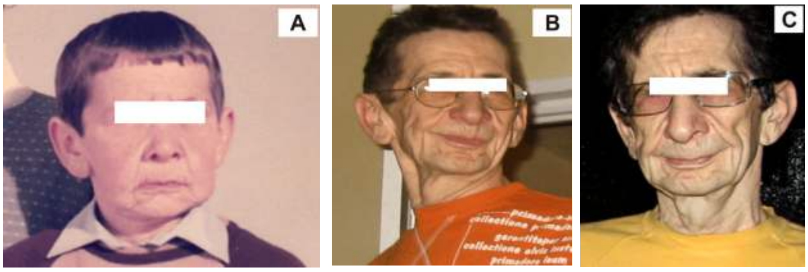

Figure 10 – ***Our patient at the age of nine years (A), 29 years (B), and 32 years (C).***

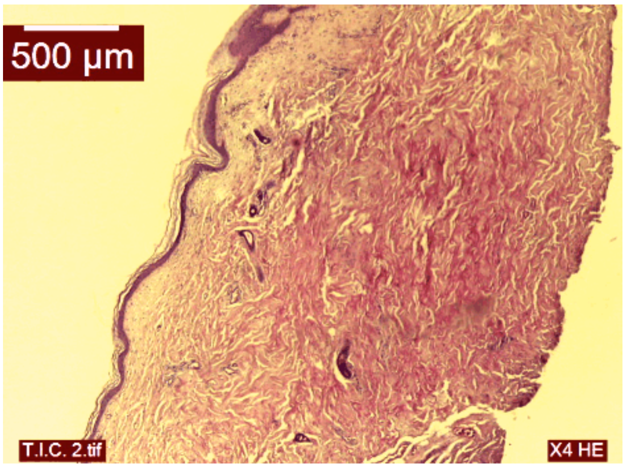

Figure 11 – ***Examination in usual tissue stain illustrates epidermal flattening and thinning , with focal epidermal rete ridges and skin annexes disappearance, dermal thickening due to collagen thickening; this dermal collagen thickening extends into subcutaneous tissue, which appears atrophic – scleroderma skin type. HE staining, ×40.***

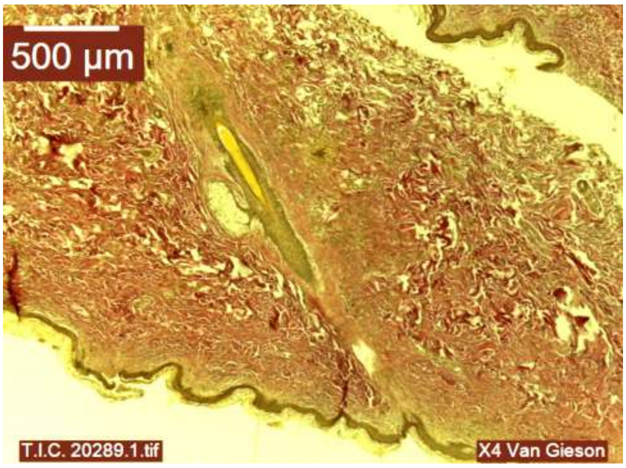

Figure 12 – ***Homogenous thickened collagen fibers; dermal collagen thickening extends into subcutaneous tissue, which appears atrophic – scleroderma skin type. Van Gieson staining, ×40.***

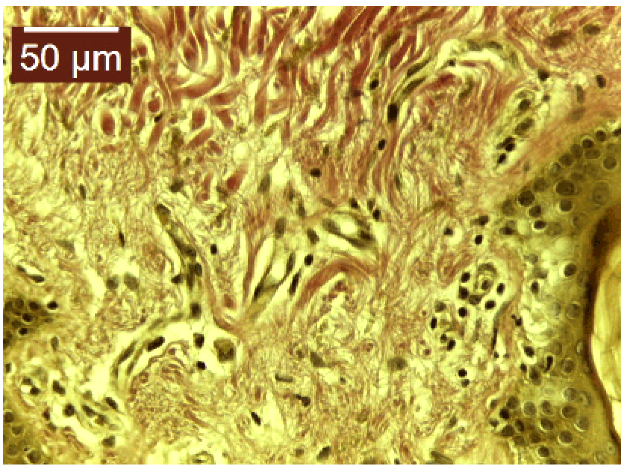

Figure 13 – ***Discrete lympho-monocytic perivascular inflammatory infiltrate. Van Gieson staining, ×200.***

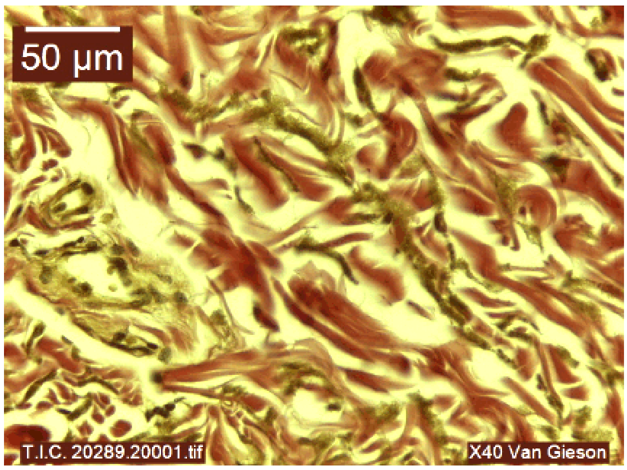

Figure 14 – ***Thickened and shortened collagen fibers; elastic fibers are thin, fragmented, distorted, and low in numbers. Van Gieson staining, ×400.***

Discussion

Cutis laxa (CL), or elastolysis, is a rare, inherited or acquired connective tissue disorder in which the skin becomes inelastic and hangs loosely in folds [2, 3]. Recent molecular studies have provided many new insights into the causes of CL and revealed greater genetic heterogeneity than previously appreciated [5].

In inherited CL, an abnormal synthesis of extracellular matrix proteins occurs due to genetic defects coding for diverse extracellular matrix components. Recently, other different inborn errors of metabolism, such as P5CS, ATP6V0A2-CDG and PYCR1 defects have been found to be associated with CL [6, 7]. Autosomal dominant, autosomal recessive and X-linked recessive patterns have been noted in inherited forms. A serine to proline amino acid substitution in the fibulin 5 (*FBLN5*) gene has been associated with problems in normal elastogenesis, resulting in a recessive form of CL in humans [8–10]. Autosomal recessive CL is a genetically heterogeneous condition [11]. A combined disorder of N- and O-linked glycosylation has been described in children with congenital CL in association with severe central nervous system involvement, brain migration defects, seizures, and hearing loss. The X-linked form is currently classified in the group of copper transport diseases. The precise cause is unknown, but it may be due to abnormal elastin metabolism resulting in markedly reduced dermal elastin content. Autosomal dominant congenital CL (ADCL) is genetically heterogeneous and shows clinical variability. Mutations in the elastin gene (*ELN*) have been described [12].

According to Reed *et al.* [13] hypothesis, trough which due to an unknown cause, the mast cells release mediators of inflammation causing a infiltration of neutrophils and eosinophils around the blood vessels in the papillary dermis and between the collagen fibers in the mid- and reticular dermis. The neutrophils release elastase and elastosis is primarily seen in areas with neutrophilic infiltration around the blood vessels, and between collagen fibers, and then it covers the entire dermis. These features could be localized or generalized, as we found in our patient.

In inherited type, the internal organs are frequently involved. The literature data reported 209 patients at the end of 2012 [14]. Regarding acquired CL, Turner–Stokes *et al.* described pulmonary emphysema as a manifestation of CL in two teenage patients [15], and Reed *et al.* wrote about a 17-year-old boy with CL and emphysema diagnosed after he had presented with an urticarial eruption [13]. Our patient presented multiple internal organs involvement (lung, heart, colon, urinary bladder), and personal history excluded acquired form of CL. Also, skin manifestation were present from birth, which is consistent with an inherited, not an acquired form of CL.

CL with pulmonary emphysema is usually related to recessive, more severe CL, and the manifestation occurs early from few days–weeks of life with severe respiratory distress and death before age of two years. Our patient was diagnosed with pulmonary emphysema at 27-year-old without urticarial eruption, and due to the long evolution of the diseases, we excluded the severe recessive form of CL.

From skin biopsy, no specific histological abnormality was seen on routine HE staining. On Weigert–Van Gieson staining elastic fibers stains, we could see a reduction in the number of elastic fibers throughout the dermis, with remaining fibers shortened, clumped, granular, or fragmented.

In severe cases, no elastic fibers may be present, but only fine, dust-like particles scattered throughout the dermis can be seen. In cases preceded by an inflammatory eruption, such as urticaria or vesicles, the inflammatory infiltrate may be mononuclear (lymphocytes and histiocytes) or mixed, containing neutrophils [16]. When vesicles are present, they are subepidermal, with papillary collections of neutrophils and eosinophils mimicking dermatitis herpetiformis [17]. Electron microscopic examination reveals degenerative changes in the elastic fibers, which are variable from case to case. However, the most significant finding is the presence of electron-dense amorphous or granular aggregates that are irregularly distributed near the elastic fibers.

The skin biopsy confirmed the diagnosis of CL for our patient by describing severe reduction of number, disorganization and fragmentation of elastic fibers, and was negative for amyloid. The positive skin biopsy explains skin and lung involvement, colonic and urinary bladder diverticula, and right inguinoscrotal hernia (19-year-old), all present in our patient.

Genetic tests are not mandatory for positive diagnosis of CL, comparing with progeria in which they must be done for diagnosis (*LMNA* gene mutation) [18].

Differential diagnoses includes all progeroid syndromes and other diseases that affect skin aspect like acrodermatitis chronica atrophicans, anetoderma, atrophoderma of Pasini and Pierini, Costello syndrome, cutaneous T-cell lymphoma, De Barsy syndrome, Ehlers–Danlos syndrome, focal dermal hypoplasia syndrome, geroderma osteodysplasticum hereditaria, Lenz–Majewski hyperostotic dwarfism, lipodystrophy, pseudoxanthoma elasticum, SCARF (skeletal abnormalities, cutis laxa, craniostenosis, ambiguous genitalia, retardation, facial abnormalities) syndrome, Wrinkly skin syndrome and others [19–32].

No treatment exists to prevent disease progression, although Dapsone can be used to control swelling in persons with acquired CL (elastolysis). Penicillamine and Doxycycline are ineffective. Surgical correction of redundant skin folds, prolapses, or hernias may be undertaken. However, surgery often produces only temporary benefit. Botulinum toxin injections are being considered for improving the aged appearance and facial defects seen in persons with CL [2].

The most serious complications, which may be life threatening, are cor pulmonale resulting from severe progressive pulmonary emphysema and respiratory failure.

Conclusions

CL is a rare genetic disease involving the damage of connective tissue, hard to diagnose and accompanied by important morbidity and mortality. The typical skin biopsy features of CL made possible the positive diagnosis of a patient without a family history of genetic diseases, with a complex medical history, admitted in our clinic with severe lung and heart disease and other organ involvement. The skin biopsy proved to be an important link between the various organ dysfunctions and the genetic condition causing the improper elastogenesis and connective tissue disorder.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

First two authors have equal scientific contribution.

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ORIGINAL RESEARCH

Aging and extrapulmonary effects of chronic obstructive pulmonary disease

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Introduction: People with COPD have a decline in functional status, but little is known about the rate of decline and factors that contribute. Of particular concern is the decline in cognitive and functional performance. Decrease in cognitive and functional performance will finally lead to decreased health status, sedentary life style and premature frailty.

Aim: The aim of this study is to compare functional performance and cognitive status in patients with COPD of different ages and to examine the changes in extrapulmonary effects.

Patients and methods: This study included 62 patients with COPD risk class D who were divided into two groups (<70 years, N=30 and >70 years, N=32). Patients first completed the Montreal Cognitive Assessment (MoCA), which is a 30-point test that assesses different cognitive domains, while isometric knee extension (IKE) was measured using a digital handheld dynamometer, and functional exercise level was assessed using the 6-minute walking distance (6MWD) test.

Results: The patients' older age (age higher than 70 years) was associated with a significantly lower body mass index (BMI, 27.50 vs 24.24 kg/m^2; P=0.020), higher vital capacity parameters, forced vital capacity (FVC, 2.74 vs 2.82 L; P=0.799), FVC (%) (73.00 vs 66.50, P=132), forced expiratory volume in the first second (FEV$_1$, 0.93 vs 1.13 L; P=0.001) and FEV$_1$ (%) (28.50 vs 30.50, P=0.605). In addition, patients at older age presented a significantly reduced physical activity capacity, 6MWD (385.93 vs 320.84 m, P<0.001) and IKE (24.75 vs 22.55 kgf, P=0.005), as well as higher values for inflammatory biomarkers, C-reactive protein (8.77 vs 3.34 mg/L, P=0.022). Moreover, patients at older age presented significantly lower score at the cognitive assessment, MoCA (23.50 vs 20.00, P<0.001).

Conclusion: Elderly COPD patients have reduced exercise capacity and muscle strength, deteriorated cognitive function and increased inflammatory markers. Furthermore, inflammation markers were significantly correlated with muscle strength, walking distance and cognitive impairment.

Keywords: aging, inflammation, strength, pulmonary function

Introduction

The rise in life expectancy worldwide has been accompanied by an increased incidence of age-related diseases, representing a high burden on society and health care services. All vital organs lose function with age, the lungs having a progressive decline in pulmonary function after the age of 25 years. A very common pulmonary disease such a COPD shows age-associated features, such as increased cellular senescence and oxidative stress, alteration in the extracellular matrix, etc.[1]

Aging has been defined as "the progressive decline of homeostasis that occurs after the productive phase of life is complete resulting in increased risk of disease or death".[2]

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For a long time, there is growing evidence suggesting that smokers and patients with COPD are prone to early aging, even those who do not smoke are at risk of developing airflow obstruction and reduced elastic recoil that progress with age.[3]

The Global Initiative for chronic Obstructive Lung Disease (GOLD) report defines COPD as a common preventable and treatable disease that is characterized by persistent airflow limitation which is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[4]

The disease is associated in many patients with several systemic manifestations that can result in impaired functional capacity, reduced health-related quality of life, worsening dyspnea, exacerbations, cognitive impairment and mortality. A common factor such as systemic inflammation has been widely reported to be an important link between COPD and other diseases. Important recognized manifestations include the presence of cardiovascular diseases that in large part are due to atherosclerosis, neurocognitive and psychiatric effects which have hypoxia as the central feature and skeletal muscle dysfunction that appears due to inactivity.

These patients have increased risk of neuronal injury, either due to hypoxia or associated comorbidities such as cardiovascular diseases. Studies suggest that up to 77% of patients with COPD hypoxemic or non-hypoxemic have some form of cognitive impairment.[5,6]

People with COPD have a decline in functional status but little is known about the rate of decline and factors that contribute. Of particular concern is the decline in cognitive and functional performance. Decrease in cognitive and functional performance will finally lead to decreased health status, sedentary life style and premature frailty.

Given the abovementioned factors, the purpose of this research was to compare functional performance and cognitive status in patients with COPD of different ages and to examine changes in extrapulmonary effects.

Study design

This research was an observational study that included patients with COPD who came for routine investigations. The study was approved by the ethical committee of the Infectious Diseases and Pneumophtisiology "Dr Victor Babes", Timisoara hospital. All the patients signed an informed consent before entering the study. No invasive interventions were applied, and the medication and treatment were not modified for the purpose of this study. On admission day, blood samples were collected, and all the tests were performed.

Subjects

We included 62 patients with COPD risk class D (former smokers >10 packs-year who met the criteria according to the international guideline)[7] who were divided into two groups (<70 years, N=30 and >70 years, N=32). All the patients were male and diagnosed with COPD for at least 10 years. They were classified according to GOLD guidelines as COPD risk class D. Inclusion criteria: COPD risk class D, no exacerbations in the past 3 months and similar educational level. Exclusion criteria: illiteracy, alcoholism, known cognitive impairment, syncope, severe cardiovascular comorbidities (myocardial infarction, congestive heart failure), medication such as antidepressant drugs and lower-extremity joint replacements.

Patients and methods

Patients first completed the Montreal Cognitive Assessment (MoCA), which is a 30-point test that assesses different cognitive domains such as visual-spatial abilities, executive functions, language, short-term memory, attention, concentration and at the end of the test, orientation. The cutoff score for mild cognitive impairment (MCI) is 26 points. This test is an efficient instrument to use for screening, diagnosis and tracking of MCI. It has become a widely used screening instrument in response to the poor sensitivity of the Mini-Mental State Examination (MMSE) test.[8,9]

Isometric knee extension (IKE) was measured using a digital handheld dynamometer (Chatillon K-FCE-200, USA). Knee extension was tested three times on the dominant foot preferred by the patient with rest period between each test. Only the highest value of the tests was used. Patients were seated upright on the testing chair with the knee bent at 90° with the lower leg hanging down the front of the chair.[10]

Functional exercise level was assessed using the 6-minute walking distance test (6MWD) according to the guidelines of the American Thoracic Society (ATS). The strongest indication for the 6MWD is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. It is also used as a measure of functional status of patients as well as a predictor of morbidity and mortality.[11]

Statistical analysis

Data were presented as mean and standard deviations (SDs) for continuous variables with Gaussian distribution, median and interquartile range (IQR) for continuous variables without Gaussian distribution or percentage (absolute frequency) for categorical variables. Continuous variable distributions were tested for normality using the Shapiro–Wilk test and for equality of variances by using Levene's test.

To assess the significance of the differences between groups, the Student's *t*-test (means, Gaussian populations), Mann–Whitney *U* test (median, non-Gaussian populations) and Pearson chi-square or Fisher's exact test (proportions) were used.

The correlation between studied variables was evaluated using Spearman's rank sum correlation coefficient (non-Gaussian distributed variables), its statistical significance being assessed using the *t*-distribution score test.

Data were analyzed using the SPSS v.17 software (SPSS Inc., Chicago, IL, USA). A *P*-value of 0.05 was considered as the threshold for statistical significance, and a confidence level of 0.95 was considered for estimating intervals.

Results

The study sample included 62 male COPD patients with age ranging from 55 to 80 years, mean 67.82±0.75. The detailed characteristics of the studied sample are presented in Table 1.

The patients' older age (age higher than 70 years) was associated with a significantly lower body mass index (BMI, 27.50 vs 24.24 kg/m^2; P=0.020), higher vital capacity parameters, forced vital capacity (FVC, 2.74 vs 2.82 L; P=0.799), FVC (%) (73.00 vs 66.50, P=132), forced expiratory volume in the first second (FEV_1, 0.93 vs 1.13 L; P=0.001), FEV_1 (%) (28.50 vs 30.50, P=0.605) and FEV_1/FVC (34.00 vs 40.50, P=0.005). In addition, patients at older age presented a significantly reduced physical activity capacity, 6MWD (385.93 vs 320.84 m, $P<0.001$) and IKE (24.75 vs 22.55 kgf, P=0.005), as well as higher values for inflammatory biomarkers, C-reactive protein (CRP), (8.77 vs 3.34 mg/L, P=0.022). Moreover, patients at older age presented significantly lower score at the cognitive assessment, MoCA (23.50 vs 20.00, $P<0.001$) (Table 2).

Table 1 Patients' baseline characteristics

Number of patients	62
Age (years)[a]	67.82±0.75
Education level[b]	12.00 (11.00–12.00)
BMI (kg/m^2)[a]	25.92±0.71
FVC (L)[b]	2.79 (2.45–3.07)
FVC (%)	72.00 (54.00–76.00)
FEV_1 (L)[b]	1.01 (0.87–1.14)
FEV_1 (%)	29.00 (27.00–33.00)
FEV_1/FVC[b]	35.50 (31.00–44.00)
6MWD (m)[b]	360.00 (315.00–400.00)
IKE (kgf)[b]	22.95 (20.60–24.30)
ESR (mm/h)[b]	15.00 (10.00–30.00)
Fibrinogen (g/L)[b]	2.96 (2.44–3.49)
C-reactive protein (mg/L)[b]	4.16 (2.73–18.72)
MoCA[b]	21.50 (20.00–24.00)

Notes: [a]Continuous variables (with Gaussian distribution) are indicated by their mean and standard deviations. [b]Continuous variables (with non-Gaussian distribution) are indicated by their median (interquartile range).

Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IKE, isometric knee extension; MoCA, Montreal Cognitive Assessment; 6MWD, 6-minute walking distance.

We observed that both 6MWD and IKE scores were negatively correlated with the vital capacity parameters, FVC and FEV_1; an observation which points out that the physical activity capacity decreases along with the pulmonary impairment (Table 3). We observed that fibrinogen and CRP very poorly correlated with the vital capacity parameters. Similarly, the cognitive assignment score very poorly correlated with the vital capacity parameters, FVC and FEV_1 (Table 3). However, patients' age significantly reversely correlated with the cognitive capacity (Figure 1).

We applied a hierarchical multiple regression to determine if the addition of physical activity capacity, MoCA score, age and BMI improved the prediction of FEV_1/FVC over and above inflammatory biomarkers alone. Table 4 presents the details of the full regression model.

Presence of linearity by inspecting the partial regression plots and a plot of studentized residuals against the predicted values was observed. At the same time, the residuals were independent, as assessed by a Durbin-Watson statistic of 1.925. In addition, we observed homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There were three studentized deleted residuals greater than ±2 SD.

The full model including inflammatory biomarkers, age and BMI to predict FEV_1/FVC was statistically significant, R^2 =0.467, $F(6, 49)$ =7.161, $P<0.0005$; adjusted R^2 =0.402. The addition of IKE and 6MWD parameters to the prediction led to an unsignificant change in R^2. The addition of age and BMI to the prediction led to a statistically significant increase in R^2 of 0.222, $F(4, 51)$ =3.638, P=0.011. Finally, three of the six variables added significantly to the prediction. Regression coefficients and standard errors are listed in Table 4.

We observed that an increase in CRP and erythrocyte sedimentation rate (ESR) of one SD was significantly associated with a decrease in FEV_1/FVC of 0.108 SD and 0.044 SD, respectively. At the same time, an increase in fibrinogen of one SD was associated with an increase in FEV_1/FVC of 1.536 SD. In addition, we observed that an increase in MoCA score, age and BMI of one SD was associated with an increase in FEV_1/FVC of 0.953 SD, 0.835 SD, and 0.364 SD, respectively (Table 4).

Table 2 Comparison between groups: patients aged <70 years versus patients aged >70 years

Parameter	Group 1 (age <70)	Group 2 (age ≥70)	*P*-value[c]
Number of patients	30	32	
BMI (kg/m^2)	27.50±0.96	24.24±0.96	0.020
FVC (L)[a]	2.74 (2.50–3.07)	2.82 (2.25–3.13)	0.799
FVC (%)[b]	73.00 (59.75–77.25)	66.50 (59.00–74.75)	0.132
FEV_1 (L)[b]	0.93±0.03	1.13±0.05	0.001
FEV_1 (%)[a]	28.50 (25.25–31.50)	30.50 (27.25–33.75)	0.605
FEV_1/FVC[b]	34.00 (26.75–37.00)	40.50 (33.50–46.00)	0.005
6MWD (m)[a]	385.93±9.67	320.84±13.34	<0.001
IKE (kgf)[b]	24.75 (21.87–27.95)	22.55 (20.20–23.40)	0.005
ESR (mm/h)[b]	15.00 (10.00–26.25)	17.50 (10.00–40.00)	0.592
Fibrinogen (g/L)[b]	2.93 (2.35–3.30)	2.95 (2.45–3.50)	0.799
C-reactive protein (mg/L)[b]	8.77 (3.74–28.37)	3.34 (1.30–5.61)	0.022
MoCA[b]	23.50 (22.00–24.25)	20.00 (19.00–21.00)	<0.001

Notes: [a]Continuous variables (with Gaussian distribution) are indicated by their mean and standard deviations. [b]Continuous variables (with non-Gaussian distribution) are indicated by their median (interquartile range). [c]*P*-value was computed using *t*-test for equality of mean values for continuous variables with non-Gaussian distribution and Mann–Whitney *U* test for continuous variables with non-Gaussian distribution.
Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IKE, isometric knee extension; MoCA, Montreal Cognitive Assessment; 6MWD, 6-minute walking distance.

Discussion

Like any other organ, the lung ages with progressive functional impairment and has reduced capacity to environmental stresses and injury. COPD is an age-related condition and accumulating evidence suggests a relationship with a global process of accelerated aging. In this study, we compared two groups of COPD patients with a difference of 10 years between them. We observed significant reductions in functional capacity, lower limb muscle force and cognitive assessment as well as increased inflammatory markers in the older group.

Airflow limitation measured by reduced FEV_1 progresses very slowly over several decades, so that most patients with symptomatic COPD are in late middle age or elderly. The prevalence of COPD is age dependent suggesting an intimate relationship between the pathogenesis of COPD and aging.[12]

Thus, it would seem that older patients with COPD compared to younger would have a reduced FEV_1. Interestingly, we observed that the older patients group had improved FEV_1 and FVC values. Compared to our results, Vestbo et al[13] found in their study that in more than a half of their patients, the rate of decline in FEV_1 over a period of 3 years was not greater than that which has been in people without lung disease. We have to mention that we did not study the same patients so that the decrease in FEV_1 is dependent on other factors such as time from the first diagnosis, treatment, number of exacerbations, etc.

Even though it is commonly assumed that physical activity declines as the disease progresses, there is little information about the natural course of it over time in COPD. The process of decline and aging can be described as a downward

Table 3 Correlation analysis of the relationships between the vital capacity and physical activity capacity, inflammatory biomarkers and cognitive function

Explanatory variables	FVC (L)		FEV_1 (L)		FEV_1/FVC	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Physical activity capacity						
6MWD (m)	–0.011	0.930	–0.115	0.373	0.034	0.792
IKE	–0.252	0.48	–0.163	0.207	0.117	0.365
Inflammatory biomarkers						
Fibrinogen (g/L)	0.008	0.954	0.063	0.625	–0.046	0.725
C-reactive protein (mg/L)	0.051	0.694	–0.131	0.311	–0.138	0.286
ESR (mm/h)	0.099	0.444	0.060	0.645	0.013	0.919
Cognitive capacity						
MoCA	0.042	0.748	–0.109	0.401	–0.171	0.183

Abbreviations: ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IKE, isometric knee extension; MoCA, Montreal Cognitive Assessment; 6MWD, 6-minute walking distance.

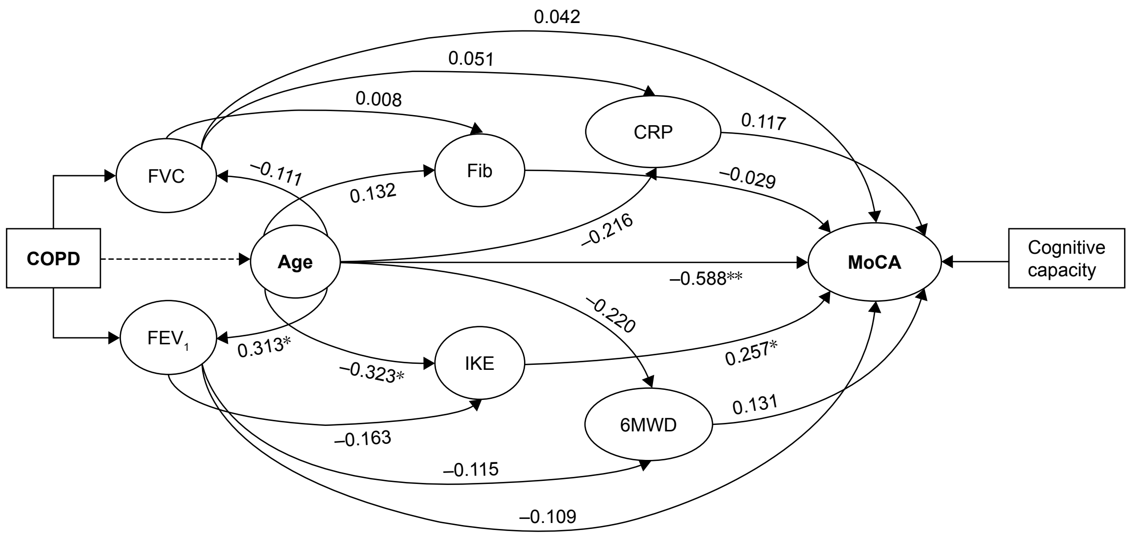

Figure 1 The correlation between the parameters of the study.
Notes: *Correlation is significant at the 0.05 level (two tailed *t*-test). **Correlation is significant at the 0.01 level (two tailed *t*-test).
Abbreviations: CRP, C-reactive protein; FEV_1, forced expiratory volume in the first second; Fib, fibrinogen; FVC, forced vital capacity; IKE, isometric knee extension; MoCA, Montreal Cognitive Assessment score; 6MWD, 6-minute walked distance.

spiral of increasing disease severity, symptoms, decreasing functional capacity and functional performance.[14]

A study that analyzed the changes in physical activity in healthy individuals and COPD patients revealed a significant decrease in activity in elderly individuals and COPD patients; in the latter ones, the decrease being worse and paralleled to the severity of the disease.[15]

We observed a significant reduced physical activity capacity evaluated by the 6MWD test in the elderly group. Our findings are consistent with those of Waschki et al who found in two longitudinal studies a decrease in physical capacity in 1.5 years follow-up. The decrease is proportional with the severity of the disease, the lowest physical activity being assessed in patients with severe COPD. The results of our study are consistent with the findings of Corlateanu et al,[16] who also compared COPD patients under and above 70 years.

Table 4 Summary of the full hierarchical multiple regression analysis

Variable	B	SE_B	β
Intercept	–51.748	22.607	
C-reactive protein	–0.108	0.043	–0.311*
Fibrinogen	1.536	0.398	0.432**
ESR	–0.044	0.033	–0.156
MoCA score	0.953	0.518	0.237
Age	0.835	0.205	0.535**
BMI	0.364	0.188	0.231

Notes: *$P<0.05$; **$P<0.0005$. B, unstandardized regression coefficient; SE_B, standard error of the coefficient; β, standardized regression coefficient.
Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; MoCA, Montreal Cognitive Assessment.

We found the same result as they did, that is, elderly COPD patients have a more severe deterioration of functional status. Age is an independent risk factor for reducing functional capacity in COPD patients.[16]

In healthy subjects, age is known to negatively affect contraction speed and muscle strength. It also induces a shift from muscle type II to type I fibers and atrophy of type II fibers. As a result, the limb muscles of elderly are smaller and contain more connective tissue and fat.[17] In patients with COPD, increasing age was found to reduce strength, and this loss of strength was more pronounced than that of age-matched healthy individuals.[18]

We observed that decreased leg muscle strength was associated with reduced exercise capacity, elderly patients walking less during the 6MWD test. Furthermore, reductions in leg muscle strength (kgf) were associated with decreased exercise capacity. Our findings are consistent with those of Hamilton et al[19] who analyzed muscle strength in patients with cardiorespiratory disorders over a period of 5 years. They demonstrated that patients with respiratory disorders have peripheral muscle weakness and that muscle strength is a significant contributor to work capacity.[19]

Cognitive impairment is an important concern for elderly because it can decrease quality of life and, in advanced stages, it might cause functional disabilities. Crişan et al[6] demonstrated in a study which compared severe COPD patients in normal and acute phases (using the same MoCA questionnaire) a significant decrease in cognitive function even in patients with a borderline hypoxemia.

Another small study suggested that cognitive impairment can occur in the absence of hypoxemia or mild disease.[20] A study from Finland found that a self-reported diagnosis of COPD in midlife was associated with increased odds of developing minor cognitive impairment in the later life.[21]

Compared to these studies we found a significant decrease in cognitive function in the elderly COPD group. Our findings confirm those of other authors who found that a longer duration of COPD (>5 years) is associated with higher odds of minor cognitive impairment and that the relationship is strongest in men.[22]

These results can be explained by the fact that longer duration of COPD could make the brain more vulnerable to hypoxic insults that can result in generation of free radicals, inflammation and neuronal damage.

The age-dependent increase in the prevalence of COPD and the dysregulation of the inflammatory and immune responses have suggested that changes related to aging may contribute to COPD pathogenesis.[2]

Several studies have shown that low-grade chronic systemic inflammation characterizes aging and that inflammatory markers are significant predictors of mortality in old individuals. Chronic inflammation has been correlated with many diseases and most of them are age related.[23]

We observed in our study that elderly patients had significantly higher inflammatory markers compared to the other group. These markers also significantly correlated with reduced walking distance and IKE force. The presence of inflammation in the skeletal muscle of patients with COPD is still a controversial issue.[24]

Our results confirm the findings of Ferrari et al,[25] who also found a significant correlation between lower limb muscle strength and inflammation markers.

In another study that divided the COPD patients into subgroups of age, Tudorache et al[26] also found significant correlations between inflammatory markers and decreased muscle strength (IKE) and exercise endurance (6MWD), with the patients aged over 70 years having the lowest results.

We have to mention that an important limitation of this study is the fact that the patients were not followed longitudinal. Although other authors have followed patients with COPD over a period of 5 years, our patients were in severe stages of the disease. Few of these patients would remain if we were to follow them over a period of 10 years. As mentioned above many factors influence the evolution of COPD but if we would extend our statistical analysis and suppose that these were the same patients we observed a decrease by 16.86%, 95% CI (13.46; 20.92) in the 6MWD, and 8.89%, 95% CI (2.61; 26.21) in the IKE, in patients older than 70 years.

Another limiting factor of this study is the absence of the control group. It would have been relevant to compare the data of the two COPD groups with at least one control group thus being able to highlight the accelerating aging process in COPD patients.

Conclusion

In summary, our findings demonstrate that elderly COPD patients have reduced exercise capacity and muscle strength, deteriorated cognitive function and increased inflammatory markers. Furthermore, inflammation markers were significantly correlated with muscle strength, walking distance and cognitive impairment. A better knowledge of the normal aging process can be essential to understand the mechanism of age-related lung diseases and thus could develop effective therapeutic strategies for lung diseases in elderly population. Besides pharmacological interventions that can have an effect on aging, exercise is the only non-pharmacological intervention associated with antiaging effect.

Disclosure

The authors report no conflicts of interest or any financial interests related to the study. The authors alone are responsible for the content and writing of the article.

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A Different Aproach of Chronic Obstructive Pulmonary Disease Severity and Plastic Medical Devices Used for Oxygenotherapy

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A very common questionnaire, used to evaluate the health status of Chronic Obstructive Pulmonary Disease (COPD) patients, COPD assessment test (CAT), was applied to finding correlations between the items of CAT and other tests used in the same category of COPD patients. A sample of 56 male COPD patients, aged between 51 and 74 years, mean 63.86 (± 5.55), half of them receiving long-term oxygen therapy, using transparent, hypoallergenic plastic masks or nasal cannulas, answered to CAT mostly choosing single items, statistically significant correlated with the Hospital Anxiety and Depression Scale scores (HADs), like walking up hills and stairs ($r = 0.412$, $p < 0.01$), doing activities at home ($r = 0.329$, $p < 0.01$), confidence leaving my home ($r = 0.409$, $p < 0.001$), sleep ($r = 0.277$, $p < 0.01$), and energy ($r = 0.387$, $p < 0.01$), but CAT item walking up hills and stairs correlated better to 6 min walking distance (6MWD) ($r = -0.581$, $p < 0.01$). The most significant correlations were found between 3 items of CAT as walking up hills and stairs, limitations doing activities at home and confidence leaving home in a most powerful and depression scores and 6MWD.

Keywords: COPD assessment test CAT, 6 min walking distance, anxiety, depression, plastic masks.

Quality of life is an important objective in the management of chronic obstructive pulmonary disease (COPD) that has been highlighted as a future research need [1]. Some of the most important systemic and pulmonary manifestations of COPD can lead to dyspnoea and physical exertion that eventually aggravate symptoms, can progressively impair the functional status and the activities of daily living [2-4]. An important recommendation has been issued by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) since 2011. This strategy highlights that the management and treatment of COPD should include beside the spirometric values, also the disease impact on future risk of exacerbations and progression [2,5,6]. Several questionnaires of the quality of life are generally used to evaluate self-reported health status in COPD patients but one of the most known questionnaires is the COPD assessment test (CAT) [7,8]. This questionnaire offers an alternative to other complex tools used for COPD patients such as the St. Georges Respiratory Questionnaire and the Chronic Respiratory Questionnaire [7]. With CAT help, the patient state can be easily understood because of its simple and extensive quality. Due to its importance, the GOLD strategy considered to create a new classification of COPD, measuring the risk of exacerbations [2]. There are still problems concerning the importance and the evidence in supporting the use of CAT questionnaire [8]. Some studies have shown that, when calculating the entire CAT score, the importance is distributed to all the single items from the questionnaire. Other studies are launching the hypothesis that single items can be more strongly related to different severity categories of the disease. As an example, phlegm and cough can be better related to respiratory related events than others. Furthermore, patients with chronic hyper-secretion are more susceptible to have exacerbations thus leading to more hospitalizations [9]. Taking into account the above mentioned facts, the *objective of the study* was to analyze and find correlations between the items of CAT and other tests usually used in COPD patients.

Experimental part

A transversal study was assessed among patients known with severe and very severe GOLD stages of COPD [1] during periodical routine control during the period 01.06 - 01.12. 2017. An informed consent was signed by all the patients before entering the study. The research was approved by the Pulmonology hospital from Constanta (number 2662-10052017). Because the great majority of hospitalized COPD cases are males, for statistical reasons, only male patients have been included. Exclusion criteria consisted in previous syncope, known cognitive impairment, postural orthostatic hypotension, severe cardiovascular disease, and/or transient ischemic attacks.

Several procedures were assessed. Lung function was evaluated by volumes obtained using MedGhraphics spirometer and maximal inspiratory/expiratory pressure (MIP, MEP) values were acquired using Jaeger (Germany) device. All cases of overlap asthma COPD or asthma COPD-like, mentioned by literature [10], were excluded. Patients with respiratory failure received long-term oxygen therapy through stationary concentrators and oxygen masks or cannulas. The medical devices used for oxygen delivery were made from hypoalergenic plastic, using polymer compounds that have been approved for biocompatibility,

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sterilization, and material physical performance. Biocompatibility of polymer compounds reffers to the absence of any adverse reaction of the human body and is demonstrated using three tests (direct contact, agar diffusion, and elution) [11].

Plastic compounds have been traditionally derived from petroleum products. More often, in the present, some of the plastic compounds are made using biobased materials, such as polymers made from renewable resources and, also, biobased additives. Biobased materials, including plasticizers, stabilizers, and lubricants, are considered more durable and environmentally friendly. Regarding the specific types of polymers, the most used polymer for medical devices was PVC, because of its many properties, including versatility, clarity, availability, kink resistance, and low price. In order to gain other enhanced properties such as resilience, chemical and abrasion resistance, there were developed PVC alloys (e.g., with polyurethane, ethylene vinyl acetate, and polyacrylonitrile) and thermoplastic elastomer (TPE) compounds, which are more flexible without containing plasticizers. [12]

Bioelectrical impedance analysis (BIA) was used to assess body composition by a body composition device, respecting the established protocol for BIA analysis [13]. Montreal Cognitive Assessment test (MoCA), used to analyse the cognitive function, evaluated the cognitive dysfunction using different domains such as memory, language, executive functions, concentration and other skills. MoCA is a 30 point test; a score below 26 points shows a mild cognitive dysfunction [14]. Functional performance was obtained through the 6 minutes walking test (6MWT), which measures the distance that a patient can quickly walk in a period of 6 minutes. It evaluates the global and integrated responses of all the systems involved during exercises, such as the pulmonary and cardiovascular systems and it assesses the sub-maximal level of functional capacity [15]. Health status was assessed with the help of the CAT questionnaire, which is commonly used in the routine practice. CAT is composed of eight questions, each item having a six point differential scale and having a maximal score of 40 points. The questions are: q1- cough, q2- phlegm, q3- chest tightness, q4- walking up hills and stairs, q5- activities doing at home, q6- confidence leaving home, q7- sleep, q8- energy. A higher score means a greater impact of the disease on the patient's health status [16]. HADs measure anxiety and depression in a general medical population of patients, including 14 items, seven related to anxiety symptoms and seven to depressive symptoms. The scores can be between 0 and 21 for each subscale: a score of 0-7 indicates a non-case, 8-10 a possible case, and 11 or higher a probable case, which may guide referral for psychological support [17]. Statistical analysis of all collected data, by using the SPSS v.17 software (SPSS Inc., Chicago, IL, USA) and R project packages for statistical computing, presented means and standard deviations for continuous variables with Gaussian distribution, median and interquartile range (IQR) for continuous variables without Gaussian distribution, or percentage (absolute frequency) for categorical variables. Continuous variable distributions were tested for normality using the Shapiro-Wilk's test and for equality of variances by using Levene's test. To assess the differences between groups, the Student's *t*-test (means, Gaussian populations), One-way ANOVA (means, Gaussian populations), Mann-Whitney *U* test (medians, non-Gaussian populations), and Pearson chi-square or Fisher's exact test (proportions) were used. The correlation between studied variables was evaluated using Spearman's rank sum correlation coefficient (non-Gaussian distributed variables), its statistical significance being assessed using the *t*-distribution score test. A *P*-value less than 0.05 was considered as the threshold for statistical significance.

Results and discussions

A sample of 56 male patients with severe and very severe forms of COPD, mean aged 63.86 (± 5.55) years (limits between 51 and 74 years), had a median CAT score of 26.00 (range 23.00-30.00). Almost a half of them (58.93%) had persistent symptoms with a total CAT score between 20 and 29 points. The median forced vital capacity (FVC) was 2.52 L (range 2.29 -2.94 L), and the median FVC [%] was decreased below 70% (64.50%; range, 60.00%-68.55%). Additionally, the median forced expiratory volume in the 1st second (FEV1) was 0.91 L (range, 0.75 - 1.15 L), and the median FEV1 [%] was 28.95% (range, 22.30 - 32.25%). More than one COPD exacerbation reported in the last 3 months were noticed among 17.90% patients. Almost a half of the patients were ex-smokers (73.20%), and 26.80% were current smokers. Half of the patients received long-term oxygen therapy through stationary concentrators and oxygen masks or cannulas, made from transparent, hypoallergenic plastic. The patients' characteristics are presented in table 1.

Higher CAT scores were associated with poor lung function and more frequent exacerbations in the last 3 months. Anxiety and depression tended to be more severe at higher CAT scores, statistically significant differences being observed between score's categories (One-way ANOVA test, $F(1.54) = 19.89$, $p < 0.001$, and $F(1.54) = 15.55$, $p < 0.001$, respectively). A severe decrease of physical activity capacity was found to be associated with higher CAT scores, differences between medium, high and very high CAT score levels being were statistically significant (One-way ANOVA test, $F(1.54) = 6.19$, $p < 0.05$) (table 2).

Lung function parameters as FVC, FEV1, FEV1/FVC were poorly correlated with total CAT score, $r = -0.105$, $p = 0.440$; $r = 0.237$, $p = 0.079$; and $r = -0.252$, $p = 0.060$, respectively. This could be explained by the diversity of factors influencing lung function such as treatment or nutrition status [16,17]. The MoCA score was also weakly correlated with the total CAT score ($r= -0.174$, $p= 0.200$). On the contrary, the HADs-anxiety statistically significant correlated with the total CAT score ($r= 0.531$, $p< 0.01$), as well as HADs-depression ($r= 0.408$, $p< 0.01$). The physical activity parameter 6MWT was statistically significant correlated with the total CAT score ($r= -0.407$, $p< 0.01$). At the same time, CRP inversely correlated with the total CAT score ($r= -0.286$, $p< 0.05$). The aim of the study was to identify correlations between single items of the CAT and the outcome parameters of COPD, such as, spirometry measures, physical activity, cognitive capacity, and health related status. So, most of the CAT items correlated alone significantly with the HAD depression scores, namely, as walking up hills and stairs ($r= 0.412$, $p< 0.01$), *doing activities at home* ($r= 0.329$, $p < 0.01$), *confidence leaving my home* ($r= 0.409$, $p< 0.001$), item *sleep* ($r= 0.277$, $p< 0.01$), and *energy* ($r = 0.387$, $p< 0.01$). CAT item *cough* poorly correlated with all the COPD measured parameters, as well as the item *breathless when walking.* CAT item *chest tightness* best correlated with FEV1 ($r= -0.314$, $p< 0.05$), fibrinogen ($r= -0.379$, $p< 0.01$), and 6MWD ($r= -0.339$, $p< 0.05$). CAT item *walking up hills and stairs* best correlated with 6MWD ($r = -0.581$, $p< 0.01$), HADs-depression ($r = 0.412$, $p< 0.01$), and HADs-anxiety (r=

Number of patients	56
Age [years][a]	63.86 (±5.55)
Height [cm][a]	171.21 (±7.64)
Weight [kg][a]	76.21 (±20.19)
BMI [kg/m²][a]	25.91 (±6.42)
LBM [kg][b]	54.70 (47.60 – 67.20)
PBF [%][b]	25.10 (16.07 - 30.05)
Smoking status[c]	
Ex-smoker	41 (73.20%)
Current smoker	15 (26.80%)
Education level (number of classes)[c]	
12 classes	45 (80.40%)
11 classes	5 (8.9%)
10 classes	6 (10.7%)
Spirometry measures	
FVC [L][b]	2.52 (2.29 – 2.94)
FVC [%][b]	64.50 (60.00 - 68.55)
FEV1 [L][b]	0.91 (0.75 – 1.15)
FEV1 [%][b]	28.95 (22.30 - 32.25)
FEV1/FVC[b]	35.00 (30.55 – 41.50)
Exacerbation (last 3 months)[c]	10 (17.90%)
HADs	
HADs-a [pts][b]	10.00 (7.00 - 12.00)
HADs-d [pts][b]	11.00 (8.00 - 14.00)
Basal PO2 [%][b]	93.00 (91.00 – 95.00)
LTOT[c]	28 (50.00%)
MoCA [pts][b]	21. 00 (20.00 – 23.00)
6MWT [m][b]	370.00 (180.00 – 450.40)
MIP [%][b]	62.35 (41.40 – 79.35)
MEP [%][b]	57.10 (44.10 – 68.05)
Inflammatory biomarkers	
CRP [mg/L][b]	3.79 (2.48 – 6.32)
Fibrinogen[b]	3.00 (2.47 – 3.52)
CAT [pts][b]	26.00 (23.00 – 30.00)

Table 1
PATIENTS BASELINE CHARACTERISTICS

[a]Continuous variables (with Gaussian distribution) are indicated by their mean and standard deviation.
[b]Continuous variables (with non-Gaussian distribution) are indicated by their median (interquartile range).
[c]Nominal variables are indicated by their absolute and relative frequencies.
Abbreviations: BMI - Body Mass Index; LBM - Lean Body Mass; PBF - Percent Body Fat; FVC - Forced Vital Capacity; FEV1 - Forced Expiratory Volume in the first second; HADs - Hospital Anxiety and Depression Scale; LTOT - Long-Term Oxygen Therapy; MoCA - Montreal Cognitive Assessment; 6MWD - 6 min Walking Distance; MIP - Maximum Inspiratory Pressure; MEP - Maximum Expiratory Pressure; CRP - C-Reactive Protein; CAT - COPD Assessment Test.

Parameter	CAT score category			*p-value*
	10-19	20-29	30-40	
Number of patients	7 (12.50%)	33 (58.93%)	16 (28.57%)	
Lung volumes				
FVC [L]	2.66 (0.48)	2.66 (0.47)	2.50 (0.36)	0.211
FEV1 [L]	0.94 (0.21)	1.01 (0.37)	0.82 (0.29)	0.081
FEV1/FVC	35.07 (4.84)	37.10 (11.39)	32.76 (10.66)	0.207
Inflammatory biomarkers				
Fibrinogen [mg/L]	2.99 (0.71)	2.99 (0.71)	3.55 (3.25)	0.886
C-reactive protein	3.19 (2.52)	3.19 (2.52)	6.59 (5.44)	0.857
Physical activity capacity				
6MWD [m]	449.57 (100.12)	449.70 (104.14)	239.44 (170.44)	**0.016**
Tests				
HADs-anxiety	9.86 (5.84)	9.12 (2.83)	13.69 (3.13)	**<0.001**
HADs-depression	9.71 (5.91)	9.30 (3.14)	13.38 (2.70)	**<0.001**
MoCA	21.43 (2.44)	21.52 (2.17)	20.63 (2.18)	0.181

Table 2
COPD PARAMETERS BY DIFFERENT CATEGORIES OF THE CAT SCORE

Abbreviations: FVC - Forced Vital Capacity; FEV1 - Forced Expiratory Volume in the first second; HADs - Hospital Anxiety and Depression Scale; MoCA - Montreal Cognitive Assessment; 6MWD - 6 min Walking Distance; CRP – C-Reactive Protein; CAT - COPD Assessment Test.

0.400, $p< 0.01$), as well as the vital capacity parameters, namely, FEV1 ($r= -0.428$, $p< 0.01$), FEV1 % predicted ($r = -0.394$, $p < 0.001$), and FEV1/FVC ($r= -0.428$, $p< 0.01$). CAT item *have lots of energy* was also correlated with HADs-anxiety ($r = 0.359$, $p < 0.01$), HADs-depression ($r = 0.387$, $p < 0.001$), and inversely weak but significant correlations were found with MoCA score ($r = -0.254$, $p < 0.05$). CAT item *limitations doing activities at home* was strongly significant correlated with 6MWD ($r = -0.631$, $p < 0.01$), HADs-depression ($r = 0.329$, $p < 0.05$) and HADs-anxiety ($r = 0.380$, $p < 0.01$). CAT item *confident leaving my home* inversely significantly correlated with 6MWD ($r = -0.558$, $p< 0.01$), HADs-depression ($r = 0.409$, $p < 0.01$) and HADs-anxiety ($r= 0.495$, $p< 0.01$). Although vital capacity poorly correlated with the total CAT score, several items statistically significant correlated, such as *walking up hills and stairs*, and *doing activities at home* (table 3).

Parameter	CAT questions							
	q1	q2	q3	q4	q5	q6	q7	q8
Vital capacity								
FVC [L]	0.049	-0.080	-0.201	-0.145	-0.193	-0.044	0.199	0.017
FVC [%]	0.006	0.018	0.080	0.066	0.024	0.033	0.144	-0.021
FEV1 [L]	0.052	-0.026	**-0.314***	**-0.428****	**-0.350****	-0.168	0.208	-0.021
FEV1 [%]	0.168	0.105	-0.161	**-0.394****	**-0.287***	-0.083	0.219	0.022
FEV1/FVC	0.064	0.085	-0.186	**-0.428****	**-0.275***	-0.254	0.049	-0.141
Maximal respiratory pressures								
MIP [%]	-0.097	-0.125	-0.239	-0.118	-0.297*	-0.221	0.134	0.045
MEP [%]	-0.338*	-0.382**	-0.136	-0.039	-0.096	-0.158	0.003	0.108
Inflammatory biomarkers								
Fibrinogen	-0.160	-0.195	**-0.379****	-0.209	-0.163	-0.194	0.050	-0.107
CRP	0.107	0.025	-0.044	-0.052	0.013	0.003	0.241	0.224
Physical activity capacity								
6MWT[m]	0.088	0.184	**-0.339***	**-0.581****	**-0.631****	**-0.558****	0.170	-0.155
Tests								
HADs-d	0.012	-0.114	0.231	**0.412****	**0.329***	**0.409****	**0.277****	**0.387****
HADs-a	0.157	0.045	**0.263***	**0.400****	**0.380****	**0.495****	**0.266****	**0.359****
MOCA[pts]	0.033	0.076	-0.080	-0.208	-0.125	-0.108	-0.201	**-0.254***

Table 3
CORRELATION COEFFICIENTS BETWEEN SINGLE ITEMS OF CAT AND MEASURED PARAMETERS

**Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed)*
Abbreviations: FVC - Forced Vital Capacity; FEV1 - Forced Expiratory Volume in the first second;
MIP -Maximum Inspiratory Pressure; MEP -Maximum Expiratory Pressure; HADs - Hospital Anxiety and Depression Scale;
MoCA - Montreal Cognitive Assessment; 6MWD - 6 Minutes Walking Distance; CRP -C-Reactive Protein;
CAT - COPD Assessment Test; q1 -item cough; q2 -item phlegm; q3 -item chest tightness; q4 -item walking up hills and stairs;
q5 -item doing activities at home; q6 - item confidence leaving my home; q7 - item sleep; q8 - item energy.

Maximal respiratory pressures were poorly correlated with CAT score, namely, MIP and CAT score ($r = -0.240$, $p = 0.075$), and MEP and CAT score ($r = -0.174$, $p = 0.200$). On the contrary, MIP was significantly correlated with CAT item *doing activities at home* ($r = -0.297$, $p < 0.05$) than MEP which was significantly correlated with items *cough* ($r = -0.338$, $p < 0.05$) and *phlegm* ($r = -0.382$, $p < 0.01$). Fibrinogen, as an inflammatory biomarker, was poorly correlated with the total CAT score ($r = 0.286$, $p = 0.033$), but it was significantly correlated with CAT item *chest tightness* ($r = -0.379$, $p < 0.01$) (fig. 1). In addition, MoCA score, poorly correlated with the CAT score ($r = -0.174$, $p = 0.200$), revealed a stronger and significant correlation with individual item *energy* ($r = -0.254$, $p < 0.05$) (fig. 1).

Recent studies have proved the sustainability of the CAT questionnaire presenting it as a reliable instrument that can measure the COPD patient's quality of life compared to other tools usually used in this disease [20]. The main objective of the study was to analyse if individual CAT items are better correlated with different tests performed in COPD patients. Exacerbation in the last three months, anxiety and depression, decreased physical capacity and poorer lung function were all found to be significantly correlated with the total CAT score. Some studies have demonstrated that CAT score correlates with exacerbation severity and its impact on the health status [20]. We found COPD patients with higher CAT total score had exacerbation in the last three months, results consistent

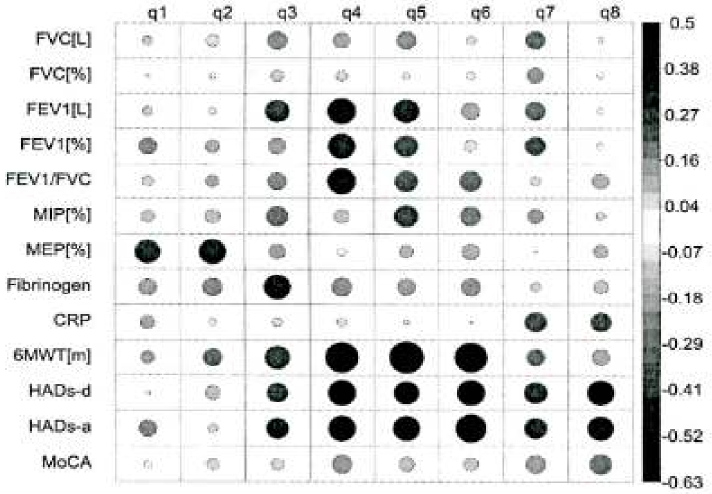

Fig. 1. Correlation coefficients between items of CAT and measured parameters
Abbreviations: FVC - Forced Vital Capacity; FEV1 - Forced Expiratory Volume in the first second; MIP – Maximum Inspiratory Pressure; MEP - Maximum Expiratory Pressure; CRP - C-Reactive Protein; 6MWD - 6 Minutes Walking Distance; HADs - Hospital Anxiety and Depression Scale; MoCA - Montreal Cognitive Assessment;.

with those of Sang-Do Lee et al, who evaluated the relationship between the higher CAT score and shorter time to the first exacerbation or risk of exacerbations [21]. Different studies have shown that anxiety and depression are co-morbidities of COPD independently associated with an increased risk of exacerbation even in stable COPD forms. Burgel et al. found depression as the most important contributor to the Saint Georges Respiratory Questionnaire total score in patients with COPD [22]. Masaki Miyazaki et al. observed depression has a more important impact on increasing the CAT score than anxiety thus highlighting the psychiatric co-morbidities of COPD [23]. Consistent with these findings, we observed that HAD depression score was significantly correlated with several CAT items as *walking up hills and stairs*, *doing activities at home*, *confidence leaving home* and *energy* compare to the score of HAD anxiety, which was significantly correlated only with the total CAT score. Consistent with Young Seok Lee et al., who found that depression was associated better with the *chest tightness*, *confidence leaving home*, *activity limitation at home*, *energy* and *sleep* [24], we observed a significant association and presented good discrimination power of *energy* item. Thus, *energy* item can be a better indicator of depression compared to other COPD symptoms such as phlegm and cough in patients with COPD. The most important symptoms that limit the daily living activities among COPD patients, reducing gradually the functional status, are fatigue and dyspnoea [25]. One of the highest predictors of mortality in these patients is the level of physical activity and a decline in functional status can have a worse impact on the health status of the patients [26]. We noticed a drastic decrease of the functional capacity at higher CAT scores. Differences between medium, high and very high CAT score levels were statistically significant. The most significant correlation between CAT item and 6MWD was *limitation doing activities at home*. Carlos H. Martinez et al. found similar results reporting that patients who had an increased CAT score and a reduced quality of life presented a shorter walking *distance* [27]. Interestingly, compared to our study, a link between dyspnoea and reduced physical capacity was described related to the first four CAT questions. Similar to our results, Martinez found significant correlation between higher CAT score and depression, leading to reduced physical activity, fatigue and poor sleep [27]. CAT score is well correlated with the functional status when it is evaluated with the help of the 6MWD test [28]. We found the same correlation between lower CAT score and increased functional status. Reduced physical activity can explain the significant correlation between MIP and CAT item *doing activities at home*. It is well known that the weakness of the respiratory musculature with reduced muscular resistance and strength can have important clinical consequences for patients with COPD, explaining partially common symptoms such as effort dyspnoea and reduced tolerance to physical exercise [29]. Patients with COPD comprise multiple comorbidities, including cognitive impairment and a greater risk of developing cognitive impairment than patients without COPD [30,31]. MOCA questionnaire is capable to detect minor cognitive impairment found that all patients with severe COPD suffered of minor cognitive impairment regardless of hypoxemia [31]. We also found cognitive impairment in COPD patients (MoCA score less than 26 points) without significant correlation between this test and total score of CAT, the only significant correlation being noticed for *energy* item. Relationship between systemic inflammation and CAT score is not very well studied with inconclusive and contradictory data about the correlation between CRP and CAT [32-34]. Compared to these studies, in our study CRP is inversely correlated with total score of CAT and the only significant correlation is between fibrinogen and CAT item *chest tightness*. One of the limitations of our study was that it had a small sample size although other studies that used COPD measurement instruments had also reduced number of patients.

Conclusions

This study demonstrated an independent association between different CAT items and other tools used in the assessment of patients with COPD. The most significant link was between CAT components related to walking up hills and stairs, limitations doing activities at home and confidence leaving home. The most powerful correlation was observed between these three questions and depression and 6MWD.

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CASE REPORT

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Pulmonary alveolar lipoproteinosis associated with emphysematous areas

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Abstract

Pulmonary alveolar lipoproteinosis, described for the first time in 1958 by Rosen SH, Castleman B and Liebow AA, is a rare pathological condition characterized by alveolar accumulation of lipoproteinaceous material. It is the result of macrophages impairment to rid the alveolar spaces of spent surfactant. This condition involves a restrictive function of pulmonary tissue, reflected in gas exchange impairment and respiratory symptoms of variable severity. Until now, about 410 cases have been reported in the literature. From these cases, 90% were represented by primary type of pulmonary alveolar lipoproteinosis. We present the case of 37-year-old male patient admitted in the Department of Internal Medicine, Emergency County Hospital, Constanta, Romania, with progressive exertional dyspnea, dry cough and perioral cyanosis. The clinical symptoms started three months before hospital admission. Based on clinical findings and imaging features, the primary pulmonary alveolar proteinosis diagnosis has been suspected. Uncharacteristic serous aspect of fluid resulting from bronchoalveolar lavage required open lung biopsy. Pathologic examination of pulmonary slice revealed features consistent with the diagnosis of pulmonary alveolar lipoproteinosis associated with emphysematous foci. The peculiarity of this case lies in the association of two pathological conditions, each of them requiring different pathways.

Keywords: pulmonary alveolar lipoproteinosis, pulmonary emphysema.

Introduction

Pulmonary alveolar lipoproteinosis, described for the first time in 1958 by Rosen SH, Castleman B and Liebow AA, is a rare pathological condition characterized by alveolar accumulation of lipoproteinaceous material. It is the results of macrophages impairment to rid the alveolar spaces of spent surfactant [1, 2].

This clinico-pathological syndrome recognizes many causes. The most frequent cause is the development of autoantibodies that neutralize GM-CSF (granulocyte-macrophage colony-stimulating factor) and in this way the macrophages functions are impaired [3, 4]. This pathway induces primary pulmonary alveolar proteinosis. The secondary type of alveolar proteinosis determined by many pathological conditions: heavy dust exposure, various enzyme defects reported in children, autoimmune disorders comprised rheumatoid arthritis, diseases characterized by immunosuppression like leukemia or lymphoma, infection with mycobacteria, *Nocardia* and anaerobes [5–7].

Until now, about 410 cases have been reported in the literature. From these cases, 90% were represented by primary type of pulmonary alveolar lipoproteinosis, less than 10% were secondary form of disease and 2% congenital form. Males are most frequently affected than females, sex ratio M/F 2.65/1. The age of diagnosis ranging from 30 to 50-year-old, with median age of 37±13.3 years. About 72% of patients diagnosed with primary pulmonary alveolar lipoproteinosis showed history of smoking [8].

Clinical features are non-specific. Most of the time, patients with alveolar proteinosis present with progressive dyspnea of gradual onset, accompanied by fatigue, weight loss, cyanosis and dry cough. Patients with this clinical syndrome have high risk to develop pulmonary infections with opportunistic pathogens like *Nocardia* sp. and *Mycobacterium tuberculosis* [9, 10].

Diagnostic methods include plain chest radiography, high-resolution CT, and also BAL (bronchoalveolar lavage). The open lung biopsy with histopathological exam remains the "gold standard" for final diagnosis of alveolar proteinosis [11, 12].

Clinical and imaging findings

We present the case of 37-year-old male (E.G.) patient admitted in the Department of Internal Medicine, Emergency County Hospital, Constanța, with progressive exertional dyspnea, dry cough and perioral cyanosis. Historical data show insidious onset of clinical symptoms three months before hospital admission, except for cyanosis, that occurred two days before admission. At the same time, personal data show 17 years smoking history, about twenty cigarettes daily. Physical exam revealed characteristic signs of respiratory insufficiency: cyanosis, dyspnea, circulation. Crackles have been found on auscultation, too, especially at bases.

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On plain chest radiography test, bilateral symmetric confluent alveolar infiltrates with extensive areas of consolidation in perihilar zones were noted. CT scan imaging showed, especially in central zones, bilateral confluent areas of alveolar consolidation with air bronchograms, and the ground-glass opacifications with interlobular septal thickening – "crazy paving" appearance (Figure 1). The presence of emphysema bubbles with unsystematic disposition was noted, too (Figure 2).

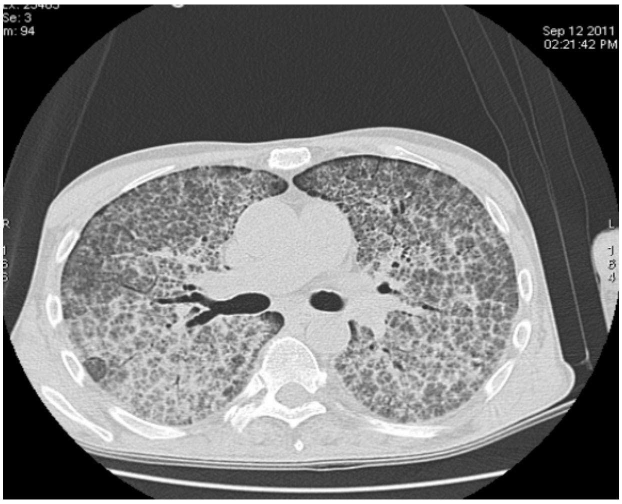

Figure 1 – ***CT scan imaging showed "crazy paving" appearance and interlobular septal thickening.***

Figure 2 – ***CT scan imaging: emphysema bubbles with unsystematic disposition.***

Arterial air gas analysis indicated 60% saturation that supports the presence of restrictive pulmonary damage. ELISA test showed the absence of HIV infection. Fluid obtained by bronchoalveolar lavage presented a serous uncharacteristic aspect.

Based on clinical findings and imaging features, the primary pulmonary alveolar proteinosis diagnosis has been suspected. To confirm this diagnosis, open lung biopsy was performed. Patient's evolution was complicated by the infection with opportunistic germ, *Acinetobacter* sp., identified in blood cultures.

Materials and Methods

The macroscopic and histopathologic assessments were performed in the Clinical Service of Pathology, Emergency County Hospital, Constanța, using standard protocols procedures. The surgical sample was macroscopically evaluated and after that, was fixed in 10% formalin. After fixation, specimen was cut into 4–5 mm slice operated with ATP1 Tissue Processor and paraffin embedded. The paraffin blocks were serially sectioned at 5 μm, stained with Hematoxylin and Eosin, van Gieson, and PAS.

Results

Macroscopic assessment of the pulmonary tissue slice, measuring 2.2×1.5×0.8 cm, showed thin, transparent pleura on the external surface. On cut surface, we noted a gray-yellowish color, a slight firm consistency, and the presence of multiple small cystic spaces of 0.1 cm in size. After compression, a small amount of opalescent fluid was discharged.

Histopathological examination showed alveolar spaces almost completely filled by an acellular, intense eosinophilic, finely granular fluid (Figure 3). Inside of this, fluid lamellar bodies and cholesterol crystal clefts were identified (Figure 4). A small number of extravasated erythrocytes was observed, too. Alveolar spaces were lined by flattened epithelium.

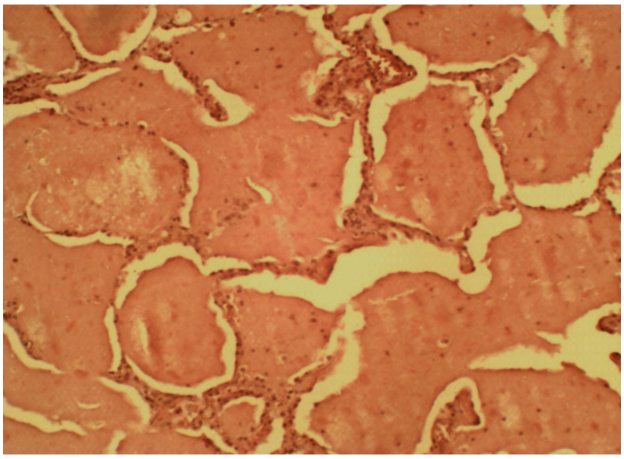

Figure 3 – ***Alveolar spaces filled by an acellular, intense eosinophilic, finely granular fluid (HE stain,***

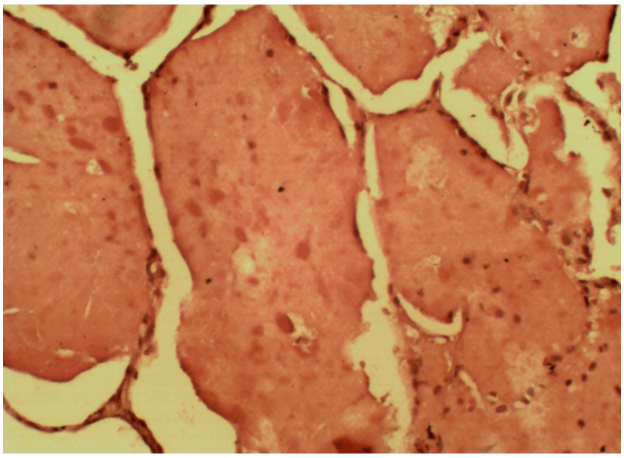

Figure 4 – ***Lamellar bodies and cholesterol crystal clefts inside eosinophilic fluid (HE stain, ob. ×20).***

In the main, microscopic assessment revealed well-preserved alveolar architecture with some exceptions. Thereby, many foamy macrophages inside the alveoli located near pleura were noticed (Figure 5). Alveolar walls were thin, interrupted in places, with emphysematous foci formation (Figure 6). Minimal fibrosis was identified in a small number of septa, too, especially near emphysematous areas. At the same time, moderate lymphocytic infiltrate of pleura was observed (Figure 7). Applying PAS stain, intra-alveolar fluid was intensely positive (Figure 8).

Based on microscopic findings, the final diagnosis of primary pulmonary alveolar lipoproteinosis associated with emphysematous foci has been confirmed.

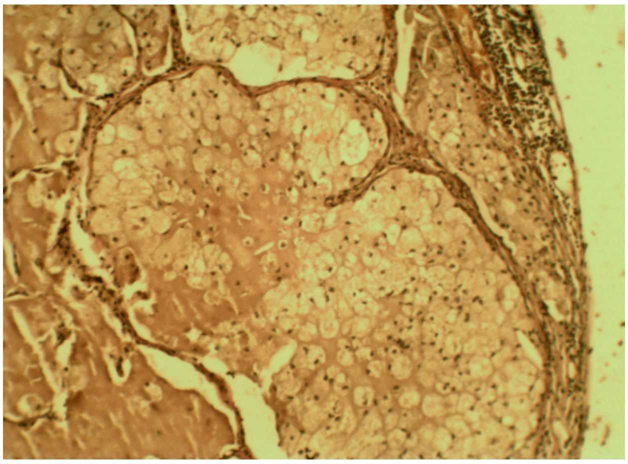

Figure 5 – ***Alveolar spaces containing foamy macrophages (van Gieson stain, ob. ×10).***

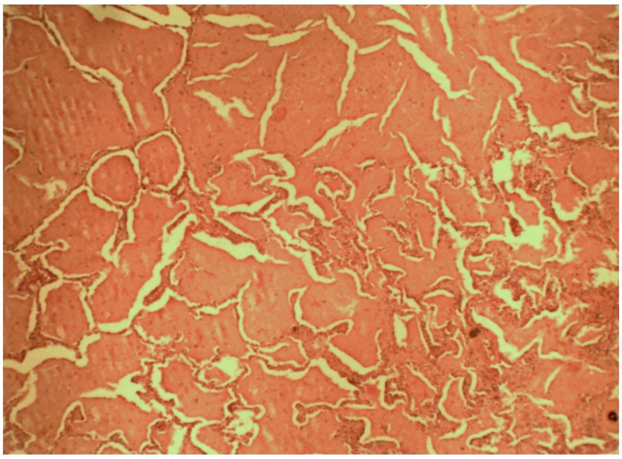

Figure 6 – ***Interrupted alveolar walls (HE stain, ob. ×4).***

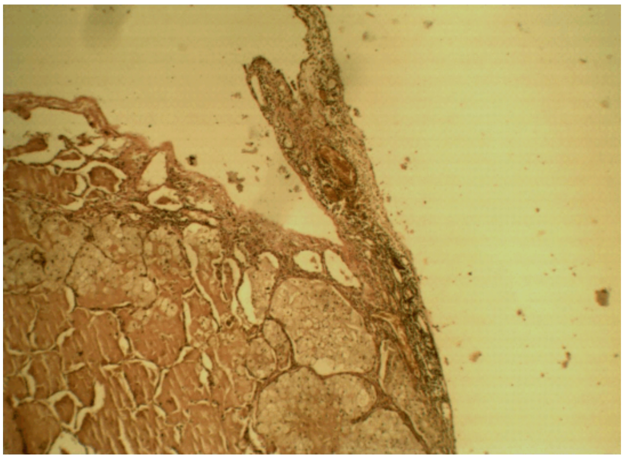

Figure 7 – ***Lymphocytic infiltrate of pleura and minimal fibrosis (van Gieson stain, ob. ×4).***

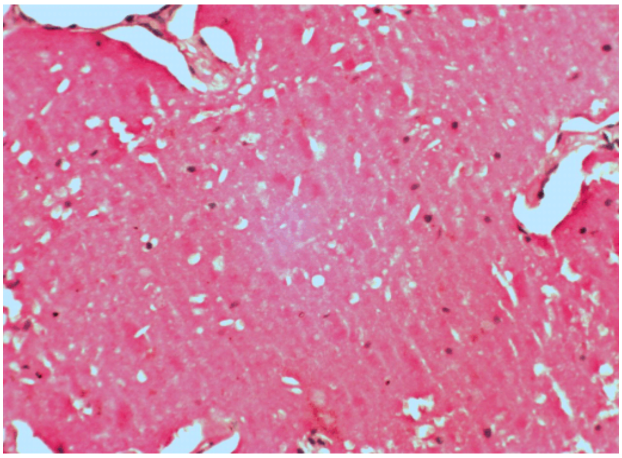

Figure 8 – ***Intensely positive intra-alveolar fluid (PAS stain, ob. ×20).***

Discussion

Pulmonary alveolar lipoproteinosis is a rare clinicopathological syndrome consisting in abnormal intra-alveolar accumulation of surfactant-derived lipoproteinaceous material of unclear origin [1, 8, 13]. It results in restrictive function of pulmonary tissue, reflected in gas exchange impairment and respiratory symptoms of variable severity.

Clinical course of this disease is variable, ranging from spontaneous resolution to death with pneumonia or respiratory failure. The most effective treatment is whole-lung lavage [2, 8, 14].

Current classification of pulmonary alveolar proteinosis includes three types of disease: primary form with unclear etiology, secondary associated with various pathological conditions, and congenital alveolar proteinosis that involve genetic disorders [2, 8]. Until now, 410 cases have been reported in literature. Primary pulmonary alveolar lipoproteinosis is the most common form of the disease, consisting in 90% of total cases. Several studies showed that this form is induced by the development of autoantibodies that neutralize GM-CSF. It results in the alveolar macrophages impairment to rid the alveolar spaces of spent surfactant containing large amount of lipids and proteins [1, 2, 15].

In our patient, uncharacteristic serous aspect of fluid resulting from bronchoalveolar lavage, required open lung biopsy. On the other hand, imaging features represented by areas of alveolar consolidation accompanied by aeric bronchogram, ground-glass opacifications and interlobular septa thickening may suggest diagnosis of pulmonary alveolar lipoproteinosis but are still nonspecific.

Histopathological examination using usual and special stains revealed pulmonary tissue changes sustaining diagnosis of alveolar lipoproteinosis. Most of these changes are consistent with the literature [1, 2, 5].

The peculiarity in this case lies in the presence of marked dilation of alveolar spaces accompanied by alveolar walls interruption. Such microscopic changes are consistent with pulmonary emphysema. The consulted literature did not mention an association between pulmonary alveolar lipoproteinosis and pulmonary emphysema. In fact, pathogenesis of pulmonary emphysema involved morphologically alveolar walls destruction accompanied by septal fibrosis and inflammatory infiltrate composed by an increased number of neutrophils, macrophages, lymphocytes and eosinophils [16]. In contrast, alveolar lipoproteinosis involve mild fibrotic degeneration and the absence of inflammatory cells.

Several studies showed that in pulmonary emphysema, interruption of the alveolar walls resulting from elastic fibers damage due to elastolytic enzymes produced by inflammatory cells like neutrophils and macrophages, in addition with MMP-3 (collagenase), MMP-9 (gelatinase), and cathepsins. Besides genetic disorders and inflammatory conditions, an important role in emphysema development is attributed to oxidative stress [16]. In our patient, presence of emphysematous foci could be related with smoking history. Experimental animal models showed that the lung exposure to cigarettes smoke, gradually increases oxidative stress and this might lead to emphysema development. At the same time, prolonged exposure to cigarettes smoke of the lung inhibits fibroblast proliferation that is essential to promote alveolar walls repair [16].

Another aspect observed in our case on microscopic exam was the presence of a large number of foamy macrophages inside alveolar spaces located near pleura. This is a characteristic feature of lipoid pneumonia, an uncommon pathological condition resulting from accumulation of exogenous or endogenous lipidic material inside the alveolar spaces. Several experimental studies showed that clinical course of alveolar lipoproteinosis may be complicated by lipoid pneumonia. Otherwise, the consulted literature mentioned cases with association between these two pathological conditions [5, 17]. In our patient, presence of this feature may be suggestive for a possible evolution of alveolar proteinosis to lipoid pneumonia.

One of the pulmonary lesions we had to exclude on microscopic exam was *Pneumocystis carinii* pneumonia. In pulmonary infection with *Pneumocystis carinii* histopathological exam showed completely filled alveolar spaces by an amorphous, pale-eosinophilic, foamy material. Occasionally, this amorphous material is accompanied by hyaline membranes. In addition, alveolar septa are thickened by an inflammatory infiltrate composed of lymphocytes and plasmocytes [5]. Unlike alveolar lipoproteinosis, PAS stain application in *Pneumocystis carinii* pneumonia revealed only the pathogen inside the alveolar spaces without the presence of the amorphous material.

Regarding *Acinetobacter* sp. infection, this was probably caused by immunosuppression in the absence of HIV infection. Consulted literature mentioned only one case of alveolar lipoproteinosis that had a secondary infection with *Acinetobacter* sp. [18]. Patients with pulmonary alveolar lipoproteinosis present an increased risk for infection with a wide range of opportunistic pathogens. Otherwise, in cases diagnosed with alveolar lipoproteinosis, more than 20% from deaths are the results of secondary infection. Most frequently, these infections are caused by *Nocardia* sp. and *Mycobacterium tuberculosis* [8–10]. In our case, secondary pulmonary infection required postponing of whole-lung lavage.

Conclusions

This is a rare case of pulmonary alveolar proteinosis associated with areas of pulmonary emphysema. The final diagnosis was established performing the histopathological exam. It may be an example of association of two pathological conditions, each of them requiring different pathways.

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Patient Preference and Adherence

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ORIGINAL RESEARCH

Inhaler technique errors in Romanian patients with asthma – a multicenter study

This article was published in the following Dove Press journal:
Patient Preference and Adherence

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Background: Non-adherence to treatment is associated with poor asthma control, increased exacerbations, decline in lung function, and decreased quality of life. M-health applications have become increasingly in the last years, but little research regarding the efficiency of the instructional videos for correct inhaler use exist. The aim of this study is to assess and improve the inhalator technique and to establish which types of errors were made more often with the help of a mobile health application.

Materials and methods: Seventy-five patients with partially controlled or uncontrolled asthma, using any of turbuhaler, diskus, pressurized metered dose inhaler (pMDI) or soft mist inhaler (SMI), were included in the study. When they first entered the study, the patient's inhaler technique was assessed by a trained medical professional and the technique errors were categorized in handling, respectively inhalation errors. After the first evaluation, the patients downloaded an application on their Smartphone and were encouraged to use the application as much as needed to remind them the correct inhalation technique. The patients were re-called every three months for evaluation, treatment, and assessment of inhalation technique.

Results: We analyzed both handling and inhalation errors for each of the four considered inhalers. We observed a significantly reduced number of inhalation technique errors after using the mobile phone application. Turbuhaler median errors were 6.00, and after six months we did not observe errors. Diskus median error was 6.00, and after six months we observed a maximum of one error. pMDI median errors were 7.00, and after six months we observed just one error. Similarly, SMI median error was 7.00, and after six months we observed just one error.

Conclusion: Although technique inhalation errors are very common among asthma patients, video instructions provided through specific mobile phone applications could improve the inhaler technique in order to achieve a better control of the disease.

Keywords: inhaler device, mobile phone application, adherence

Introduction

Asthma is a chronic respiratory disease that is highly prevalent in the overall population affecting over 334 million people worldwide.[1] Although it has a high prevalence, asthma is still under-diagnosed and under-treated, with over 50% of the patients in European countries not achieving the control of the disease.[2]

Guidelines for asthma recommend multiple medication strategies which include the use of inhaler devices such as pressurized metered dose inhalers (pMDI), soft mist inhalers (SMI), and dry powder inhalers (DPI).[1] Although there is evidence of the effectiveness of current asthma treatments, non-adherence to inhaled corticosteroids therapy remains a significant problem,[3,4] associated with poor asthma

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control, increased exacerbations, decline in lung function , and decreased quality of life.[5] The reasons for non-adherence to asthma medication are complex and various, but a common factor relates to patient behavior.[5,6]

Successful management of asthma patients includes controlling the symptoms and reducing the risk of exacerbations. There are many reasons for poor asthma control, one of the most important is the incorrect utilization of inhalers devices.[7,8] Many studies have shown that 50–80% of the investigated patients use the inhaler device incorrectly thus substantially reducing the delivery of the administrated substance and consequently the effectiveness of the medication.[9,10] Predictors of a poor inhaler technique like inadequate knowledge of the disease, increasing age, female gender, and low education have been previously reported.[11]

The main types of errors found in the inhaler technique are represented by the "critical or essential" error, which significantly impairs the delivery of adequate medication to the lung and the "non-critical" error, which results in a reduced amount of drug reaching the lungs.[12]

In the recent documents, the Global Initiative for Asthma (GINA) highlighted the importance of the assessment and correction of the poor inhalation technique before escalating drug therapy.[1] Price et al, emphasized the association between the incorrect inhaler technique and the poor clinical outcomes and increased health care costs.[12] The estimated prevalence of asthma is 4–6% which accounts for 800 thousand to 1 million Inhabitants.[13]

Since the early 80`s, Self et al, observed that patients who received personal instructions or videotape had a better inhalation technique than the patients who only read the package instructions.[14] Video education has become increasingly in the last years but little research regarding the efficiency of the instructional videos for correct inhaler use exist.

Given these facts, the aim of this study is to assess and improve the inhalation technique and to establish which types of errors were made more often with the help of a mobile health application.

Materials and methods

Study design and patients

This was an observational multicenter study that was performed over a period of one year. The study design and contract forms were approved by the Ethics Committee of the "Victor Babes" Clinical Hospital of Infectious Diseases and Pneumophtisiology, Timisoara, and of the Clinical Pneumophtisiology Hospital of Constanta (no 261/10.01.2018 and no 87/08.01.2018, respectively). No invasive procedures have been applied. All the subjects have been informed upon the research, and informed consent was obtained before the beginning of the study. This research is respecting the Declaration of Helsinki ethical principles for research regarding the safety of human subjects.

Patients were included in the analysis if the following criteria were met: age over 18 years old; diagnosed with asthma and met the standards of the GINA guidelines ;[1] received previous inhaled medication but still did not manage to control the disease; partially controlled disease or uncontrolled disease according to the physicians evaluation and GINA guidelines.[1]

In order to evaluate the recorded inhaler technique errors, we adopted a within-subject design. One of the main advantages of the present study design is that only fewer participants are required and the chance of discovering differences between the repeated measurements increases. Patients were both randomly selected and randomly assigned to evaluate an inhaler device. Although we included patients that received previous inhaled medication, none of them had experience with a mobile phone application for medical purpose.

Patients were excluded if they were younger than 18 years, illiteracy, unable to read the instructions, no available Smartphone, or no knowledge how to properly use a Smartphone.

Inhaler technique errors assessment

We chose to analyze the following devices: turbuhaler, diskus, pMDI, and SMI, because these are the most prescribed inhalers in the Romanian population with asthma.

When the patients first entered the study, the inhaler technique was assessed by a trained medical professional. The correct use was assessed by following a pre-defined checklist for each inhaler type based on instruction package from the manufacturers. We considered a checklist used by Gregiano et al.[15,16] and critical errors were noted according to van der Palen J, et al.[17]

The technique was split in handling errors and inhalation errors. A critical error was considered if it prevented the subject from inhaling any of the medications contained in the inhaler. A non-critical error was when it caused a suboptimal administration of the drug, although the subject could still inhale part of the dose. The steps were marked with "1" if the technique was correct and "0" if incorrect. The same physician evaluated the technique at every visit.

After the first evaluation, the patients downloaded an application on their Smartphone and were encouraged to use the application as much as needed to remind them the correct inhalation technique. The patients were re-called every three months for evaluation and treatment. The inhalation technique was assessed at every evaluation.

Device application description

Pneumocontrol (Figures 1–4) is an application developed by a group of medical physicians together with an IT specialist. The application was developed for the self-management of the patients with asthma and chronic obstructive pulmonary disease (COPD) and it can also be tracked on www.pneumocontrol.ro

Depending on their diagnosis (asthma or COPD), patients will complete either Asthma control test (ACT), either COPD assessment test. In this situation, patients

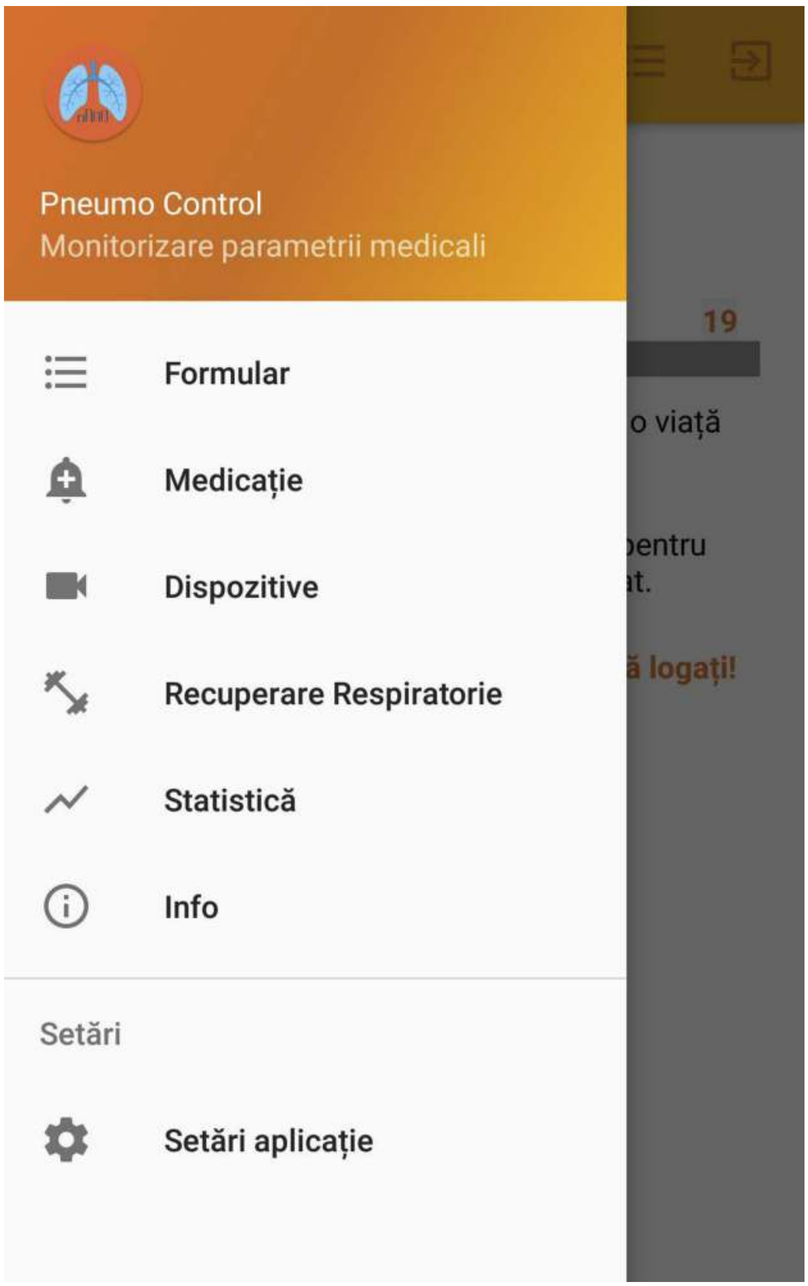

Figure 1 Application menu.

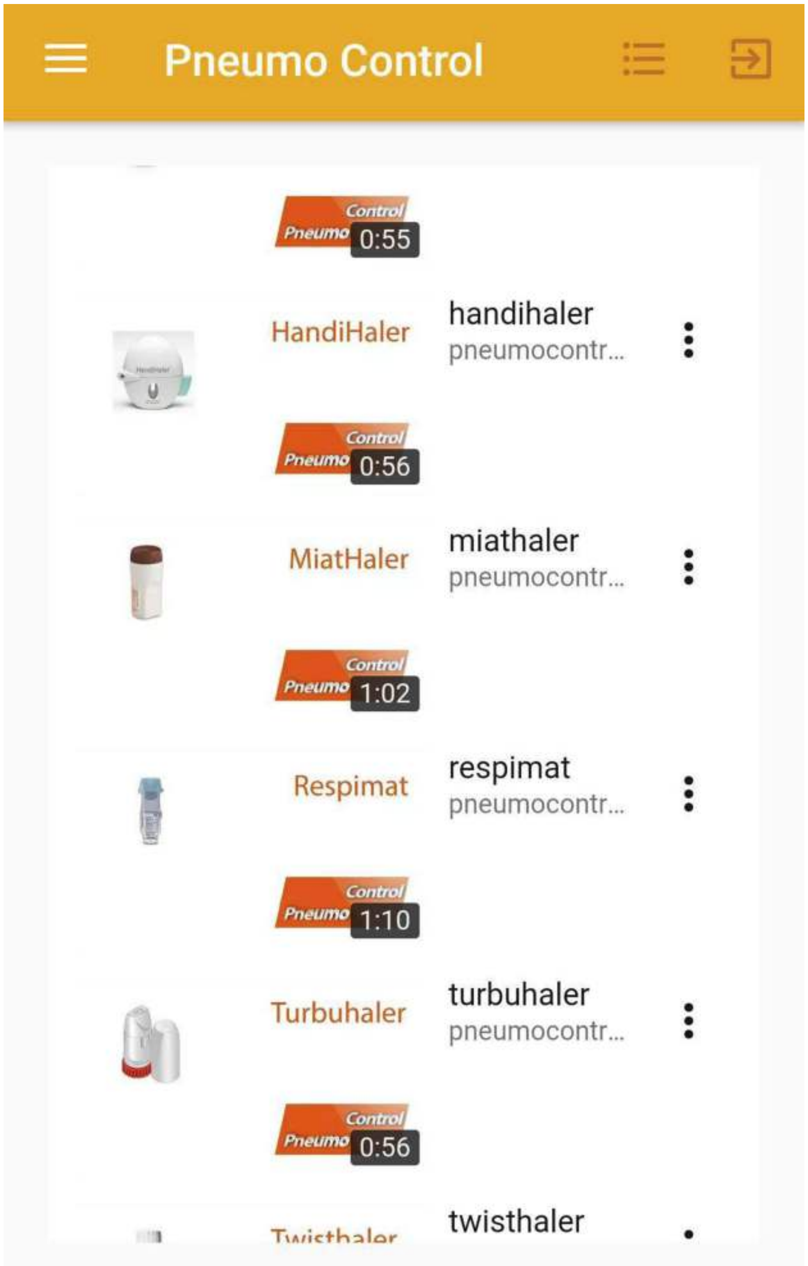

Figure 2 List of devices.

completed the ACT questionnaire. Depending on the score obtained from the questionnaire a presumptive patient classification and will display messages of: normal evolution (continue treatment), alarming evolution (need for medical consultation), and immediate medical emergencies. Medical values are automatically processed, and a graphical score will indicate patient classification according to medical standards and disease control level (scores obtained from the ACT). The mobile application allows the identification of the patient through a user account. From the first login, the patient will introduce the identification number of the current physician (which is also logged in the application) and the physician will be able to monitor the patient's evolution. Furthermore, it will save a history of the connections made, the number of completed ACT forms, and the statistical evolution of the score (ACT questionnaire total score).

The application has three specific areas: self-management plan with specific questionnaires, inhalation devices techniques with video presentation, and

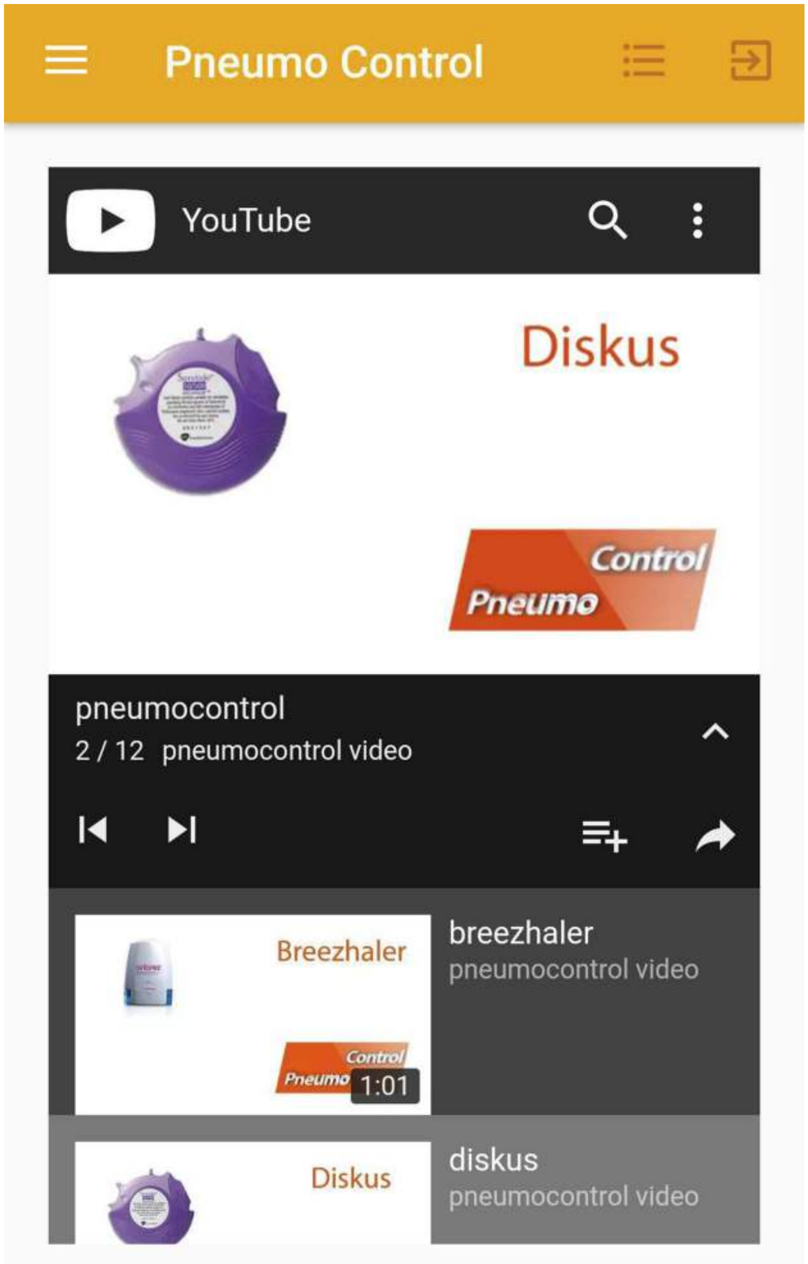

Figure 3 Device selection.

pulmonary rehabilitation exercises with video explanation and subtitles.

Statistical analysis

Collected data were presented as mean (standard deviation) for numerical continuous variables with Gaussian distribution, median (percentile 25%–percentile 75%). for numerical variables without Gaussian distribution, or absolute frequency (percentage) for categorical variables. Continuous variable distributions were tested for normality using the Shapiro–Wilk's test and for equality of variances by using Levene's test.

To assess the significance of the differences between groups, the Student's *t*-test (means, Gaussian populations), Mann–Whitney *U* test (medians, non-Gaussian populations) or Kruskal–Wallis test (medians, non-Gaussian populations), and Pearson chi-square or Fisher's exact test (proportions) were used.

To evaluate the change within-subjects, we conducted a one-way repeated measures ANOVA. The condition of

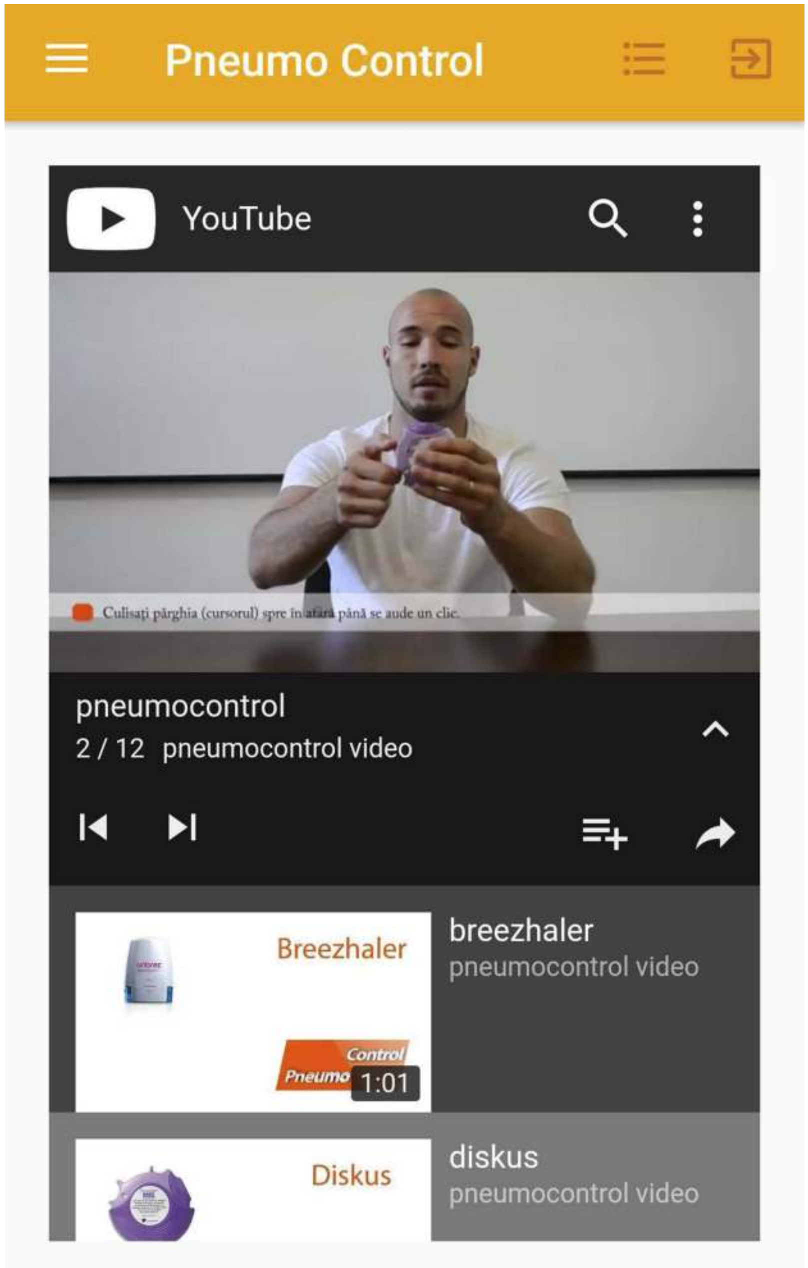

Figure 4 Instructional video.

sphericity was assessed by the Mauchly's test. When the sphericity condition was violated, we applied a Greenhouse-Geisser correction. Post-hoc analysis with a Bonferroni adjustment was applied for testing all possible pairwise combinations of levels of the within-subjects factor.

Data were analyzed using the SPSS v.17 software (SPSS Inc., Chicago, IL, USA). The graphical representations were generated using GraphPad Prism v8.0.2. A *p*-value of 0.05 was considered as the threshold for statistical significance, and a confidence level of 0.95 was considered for estimating intervals.

Results

We analyzed both handling and inhalation errors for each of the four considered inhalers, namely, Turbuhaler, Diskus, pMDI, and SMI.

In order to evaluate the errors recorded by the Turbuhaler device, we considered a sample of 25 individuals, 12 men and 13 women, aged between 22 and 64 years, mean age

Table 1 Description of collected errors using Turbuhaler (N=25) at the three evaluation moments

Errors	Evaluation time		
	0 months	**3 months**	**6 months**
Handling errors[a]			
Not removing/opening the cap	0 (0%)	0 (0%)	0 (0%)
Not shaking the device before actuation	N/A	N/A	N/A
No upright posture before inhalation	15 (60%)	0 (0%)	0 (0%)
Poor coordination of actuation and inhalation: triggering before or at the end of inspiration	N/A	N/A	N/A
Failure to pierce the capsules	N/A	N/A	N/A
Incorrect rotation	14 (56%)	0 (0%)	0 (0%)
Incorrect inhaler position	17 (68%)	1 (4%)	0 (0%)
Failure to load	N/A	N/A	N/A
Failure to open the device	N/A	N/A	N/A
Mouthpiece not enclose tightly with the lips	17 (68%)	0 (0%)	0 (0%)
Inhalation errors[a]			
Not holding breath for about 5 s after inhalation	16 (64%)	0 (0%)	0 (0%)
No complete expiration before inhalation	17 (68%)	2 (8%)	0 (0%)
Expiration into the device	0 (0%)	0 (0%)	0 (0%)
No deep and slow inspiration	N/A	N/A	N/A
No forceful and deep inspiration	21 (84%)	7 (28%)	0 (0%)
No audible vibration of the capsule during inhalation	N/A	N/A	N/A
No breathing out with pursed up lip technique after inhalation	24 (96%)	13 (52%)	0 (0%)
Total errors[b]	6.00 (5.00–6.00)	1.00 (0.00–1.00)	0.00 (0.00–0.00)
Critical errors[b]	4.00 (3.00–4.00)	0.00 (0.00–1.00)	0.00 (0.00–0.00)

Notes: [a]Values are expressed as absolute frequency (percentage); [b]Values are expressed as median (percentile 25%–percentile 75%).
Abbreviation: N/A, not available.

39.44 (±12.59), 95% CI (34.24; 44.64). The total number of errors decreased from the first evaluation to the evaluations after 3 months and 6 months (Table 1).

At the first evaluation, a total number of 7.00 errors, median 6.00 (5.00–6.00) errors were noted, and after three months, a maximum number of 3.00 errors, median 2.00 (2.00–2.00) errors were recorded, while after six months, no errors were observed. When considering only the critical errors, at the first evaluation, we noticed a maximum number of 4.00 errors, median 4.00 (3.00–4.00), while after three and six months, the number decreased to 2 errors, median 0.00 (0.00–1.00) errors, and zero errors, respectively (Figure 5).

One-way repeated measures ANOVA conducted in order to determine if the number of total errors was statistically

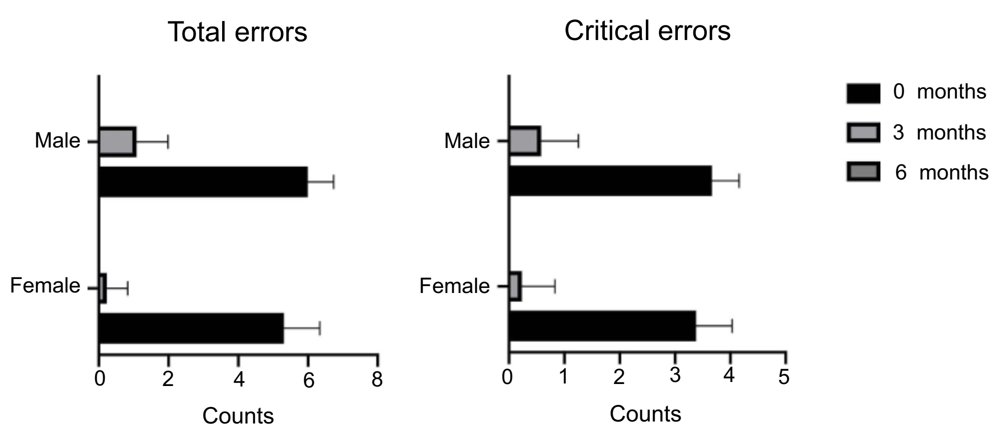

Figure 5 Representation of both total errors (left) and critical errors (right) recorded by the Turbuhaler device at the three evaluation moments when patients were grouped by gender.

significant over the course of the six-month evaluation period revealed that the data were not normally distributed, but the sphericity condition was met, Mauchly's test of sphericity, $\chi2$ (2) =2.891, p=0.236. There were not outliers, as indicated by the box-plots. The number of total errors statistically significant changed over time, F(2,48) =49.607, p<0.001, partial η^2=0.954. Post-hoc analysis with a Bonferroni adjustment revealed that the total number of errors has significantly decreased from initial evaluation to three months (4.72 (95% CI, 4.15–5.28) errors, p<0.001), from the initial evaluation to six months (5.64 (95% CI, 5.15–6.13) errors, p<0.001), and from three months to six months (0.92 (95% CI, −1.33 to 1.32) errors, p<0.001).

In addition, when comparing the number of critical errors recorded over the six-month evaluation period, we observed that the assumption of sphericity was met, as assessed by Mauchly's test of sphericity, $\chi2(2)$ =1.465, p=0.481. The number of critical errors significantly changed over time, F(2,48) =42.995, p<0.001, partial η^2=0.947. Post-hoc analysis with a Bonferroni adjustment revealed that the number of critical errors has significantly decreased from initial evaluation to three months (3.12 (95% CI, 2.47 to 3.49) errors, p<0.001), from the initial evaluation to six months (3.52 (95% CI, 3.21 to 3.82) errors, p<0.001), and from three months to six months (0.4 (95% CI, 0.12 to 0.92) errors, p=0.015).

No statistically significant difference between the number of errors at the handling the device operation "No upright posture before inhalation", or other handling and inhalation errors, in case of men vs women patients, 53.3% vs 46.7%, Chi-square test, $X^2(1)$ =0.214, p=0.775, were noted. On the contrary, when considering the age groups, patients aged between 22 and 40 years presented statistically significant lower number of errors at the handling the device operation "No upright posture before inhalation" than the patients aged between 42 and 64 years, Chi-square test, $X^2(1)$ =6.55, p=0.018.

Regarding the evaluation of the errors recorded by the Diskus inhaler, a sample of 14 individuals, nine men and five women, aged between 22 and 61 years, mean age 39.21 (±12.11) years, 95% CI (32.22; 46.21) was considered. The total number of errors decreased from the first evaluation (10.00 errors, median 6.00 (6.00–7.00) errors) to the evaluation after three months (maximum number of

Table 2 Description of collected errors using inhaler Diskus (N=14) at the three evaluation moments

Errors	Evaluation time		
	0 months	**3 months**	**6 months**
Handling errors[a]			
Not removing/opening the cap	N/A	N/A	N/A
Not shaking the device before actuation	N/A	N/A	N/A
No upright posture before inhalation	10 (71.4%)	4 (28.6%)	0 (0%)
Poor coordination of actuation and inhalation: triggering before or at the end of inspiration	N/A	N/A	N/A
Failure to pierce the capsules	N/A	N/A	N/A
Incorrect rotation	N/A	N/A	N/A
Incorrect inhaler position	10 (71.4%)	4 (28.6%)	0 (0%)
Failure to load	5 (35.7%)	0 (0%)	0 (0%)
Failure to open the device	4 (28.6%)	0 (0%)	0 (0%)
Mouthpiece not enclose tightly with the lips	14 (100%)	2 (14.3%)	0 (0%)
Inhalation errors[a]			
Not holding breath for about 5 s after inhalation	9 (64.3%)	6 (42.9%)	1 (7.1%)
No complete expiration before inhalation	10 (71.4%)	4 (28.6%)	0 (0%)
Expiration into the device	2 (14.3%)	0 (0%)	0 (0%)
No deep and slow inspiration	N/A	N/A	N/A
No forceful and deep inspiration	14 (100%)	3 (21.4%)	0 (0%)
No audible vibration of the capsule during inhalation	N/A	N/A	N/A
No breathing out with pursed up lip technique after inhalation	13 (92.9%)	7 (50%)	0 (0%)
Total errors[b]	6.00 (6.00–7.00)	5.00 (2.00–2.00)	0.00 (0.00–0.00)
Critical errors[b]	4.00 (4.00–4.00)	1.00 (1.00–2.00)	0.00 (0.00–0.00)

Notes: [a]Values are expressed as absolute frequency (percentage); [b]Values are expressed as median (percentile 25%–percentile 75%).
Abbreviation: N/A, not available.

5.00 errors, median 2.00 (2.00–2.00) errors) and six months (one error) (Table 2).

When considering only the critical errors, we noticed a maximum number of 6.00 errors, median 4.00 (4.00–4.00), at the first evaluation, while after three months and six months, the number decreased to 3 errors, median 1.00 (1.00–2.00) errors, and only one error, respectively. The number of total errors statistically significant changed over time, $F(2,26) = 50.738$, $p<0.001$, partial $\eta^2=0.956$. At the same time, the number of critical errors statistically significant changed over time, $F(2,26) = 31.509$, $p<0.001$, partial $\eta^2=0.956$. The total number of errors has significantly decreased from initial evaluation to three months (4.357 (95% CI, 3.676 to 5.039) errors, $p<0.001$), and from the initial evaluation to six months (6.429 (95% CI, 5.486 to 7.371) errors, $p<0.001$), and from three months to six months (2.071 (95% CI, 1.68 to 2.463) errors, $p<0.001$).

Additionally, we did not find significant differences between the number of errors in case of men patients vs women patients, when considering the handling and inhalation operations (Figure 6). At the same time, we did not observe significant differences between the number of errors in case of patients from different age groups.

For testing the errors recorded by the pMDI inhaler, we considered a sample of 26 individuals, 13 men and 13 women, aged between 20 and 62 years, mean age 37.81 (±11.12) years, 95% CI (33.31; 42.30). We observed that the number of errors decreased from the first evaluation to the evaluations after three months and six months (Table 3).

At the first evaluation, we found a total number of 9.00 errors, median 7.00 (6.00–8.00) errors. After three months, we observed a total number of 3.00 errors, median 2.00 (1.00–2.00) errors, while after six months, we observed just one error. When considering only the critical errors, we noticed a number of 5.00 errors, median 3.50 (3.00–4.00) at the first evaluation, while after three months and six months, the number decreased to only two errors, median 1.00 (0.00–1.00) errors, and zero errors, respectively. The number of total errors statistically significant changed over time, $F(2,50) = 49.391$, $p<0.001$, partial $\eta^2=0.963$. At the same time, the number of critical errors statistically significant changed over time, $F(2,50) = 31.601$, $p<0.001$, partial $\eta^2=0.903$. The total number of errors has significantly decreased from initial evaluation to three months (5.077 (95% CI, 4.565– 5.589) errors, $p<0.001$), and from the initial evaluation to six months (6.846 (95% CI, 6.265–7.428) errors, $p<0.001$), and from three months to six months (1.769 (95% CI, 0.98–2.143) errors, $p<0.001$).

When comparing the number of errors recorded in case of patients grouped by gender, we observed that men did significantly more errors compared to women at the handling the device operation “Mouthpiece not enclose tightly with the lips”, 76.9% vs 23.1%, Chi-square test, $X^2(1) = 7.54$, $p=0.017$. However, we did not observe significant differences between the number of errors in case of men patients vs women patients when considering the other handling and inhalation errors (Figure 7). On the contrary, when we compared the number of errors recorded in case of patients at the age group of 20–40 years vs age group of 41–62 years, we observed statistically significant differences between the number of errors at the handling the device operation “Not removing/opening the cap”, 16.7.% vs 83.3%, Chi-square test, $X^2(1) = 6.82$, $p=0.017$. When considering the other handling and inhalation errors, we did not observe significant differences between the number of errors for the two age groups.

When evaluating the inhaler technique errors recorded by the SMI, we considered a sample of 10 individuals, 6 men

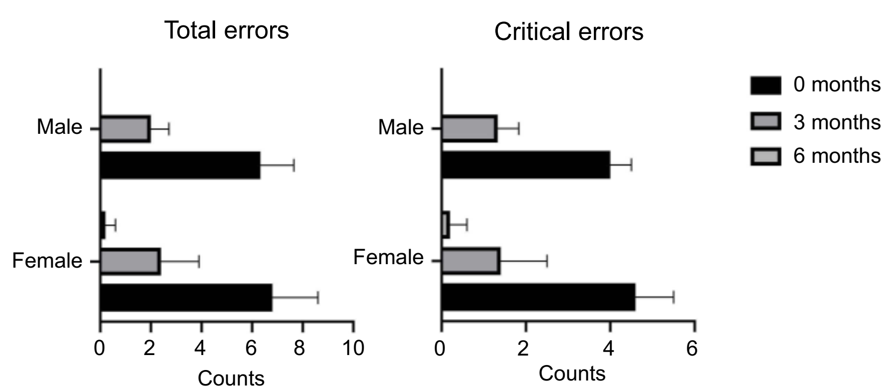

Figure 6 Representation of both total number of errors (left) and critical errors (right) recorded by the Diskus inhaler at the three evaluation moments when patients were grouped by gender.

Table 3 Description of collected errors using inhaler pMDI (N=26) at the three evaluation moments

Errors	Evaluation time		
	0 months	**3 months**	**6 months**
Handling errors[a]			
Not removing/opening the cap	6 (23.1%)	0 (0%)	0 (0%)
Not shaking the device before actuation	25 (96.2%)	0 (0%)	0 (0%)
No upright posture before inhalation	12 (46.2%)	1 (3.8%)	0 (0%)
Poor coordination of actuation and inhalation: triggering before or at the end of inspiration	25 (96.2%)	12 (46.2%)	0 (0%)
Failure to pierce the capsules	N/A	N/A	N/A
Incorrect rotation	N/A	N/A	N/A
Incorrect inhaler position	11 (42.3%)	0 (0%)	0 (0%)
Failure to load	N/A	N/A	N/A
Failure to open the device	N/A	N/A	N/A
Mouthpiece not enclose tightly with the lips	13 (50%)	0 (0%)	0 (0%)
Inhalation errors[a]			
Not holding breath for about 5 s after inhalation	15 (57.7%)	1 (3.8%)	0 (0%)
No complete expiration before inhalation	23 (88.5%)	9 (34.6%)	0 (0%)
Expiration into the device	N/A	N/A	N/A
No deep and slow inspiration	23 (88.5%)	6 (23.1%)	1 (3.8%)
No forceful and deep inspiration	N/A	N/A	N/A
No audible vibration of the capsule during inhalation	N/A	N/A	N/A
No breathing out with pursed up lip technique after inhalation	26 (100%)	18 (69.2%)	0 (0%)
Total errors[b]	7.00 (6.00–8.00)	2.00 (1.00–2.00)	0.00 (0.00–0.00)
Critical errors[b]	3.50 (3.00–4.00)	1.00 (0.00–1.00)	0.00 (0.00–0.00)

Notes: [a]Values are expressed as absolute frequency (percentage); [b]Values are expressed as median (percentile 25%–percentile 75%).
Abbreviation: N/A, not available.

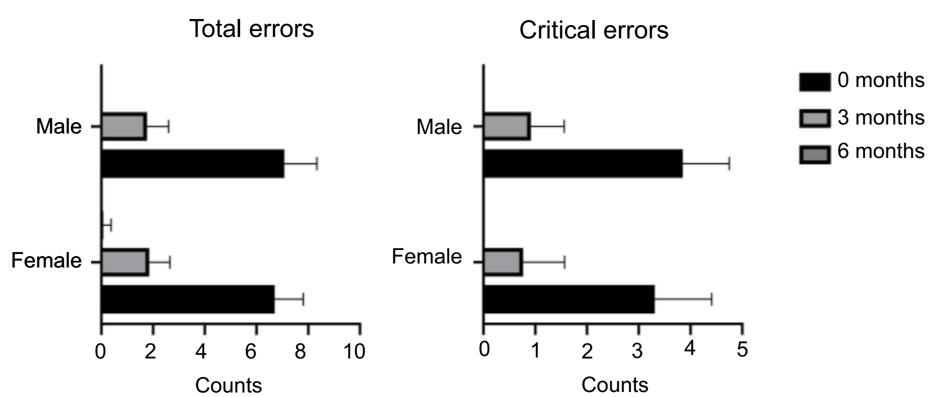

Figure 7 Representation of the total number of errors (left) and the critical errors (right) recorded by the pMDI inhaler at the three evaluation moments when patients were grouped by gender.

and 4 women, aged between 24 and 57 years, mean age 40.10 (±10.6) years, 90% CI (32.52; 47.68). We observed that the number of errors decreased from the first evaluation to the evaluations after three months and six months (Table 4).

We found a total number of 11.00 errors, median 7.00 (5.00–8.00) errors at the first evaluation. After three months, we observed a total number of 7.00 errors, median 3.00 (2.00–4.00) errors, while after six months, we observed just one error, median 0.50 (2.00–4.00) errors. When considering only the critical errors, we noticed a number of 6.00 errors, median 5.00 (3.00–5.00) at the first evaluation, while after three months and six months, the number decreased to 3 errors, median 2.00 (1.00–2.00) errors, and just one error, respectively.

We observed that the number of the total recorded errors at the three evaluation moments has significantly

Table 4 Description of collected errors using inhaler SMI (N=10) at the three evaluation moments

Errors	Evaluation time		
	0 months	**3 months**	**6 months**
Handling errors[a]			
Not removing/opening the cap	0 (0%)	0 (0%)	0 (0%)
Not shaking the device before actuation	N/A	N/A	N/A
No upright posture before inhalation	5 (50%)	3 (30%)	1 (10%)
Poor coordination of actuation and inhalation: triggering before or at the end of inspiration	10 (100%)	2 (20%)	0 (0%)
Failure to pierce the capsules	N/A	N/A	N/A
Incorrect rotation	N/A	N/A	N/A
Incorrect inhaler position	7 (70%)	1 (10%)	0 (0%)
Failure to load	N/A	N/A	N/A
Failure to open the device	0 (0%)	0 (0%)	0 (0%)
Mouthpiece not enclose tightly with the lips	9 (90%)	3 (30%)	0 (0%)
Inhalation errors[a]			
Not holding breath for about 5 s after inhalation	10 (100%)	6 (60%)	1 (10%)
No complete expiration before inhalation	7 (70%)	5 (50%)	1 (10%)
Expiration into the device	1 (10%)	0 (0%)	0 (0%)
No deep and slow inspiration	9 (90%)	4 (40%)	1 (10%)
No forceful and deep inspiration	N/A	N/A	N/A
No audible vibration of the capsule during inhalation	N/A	N/A	N/A
No breathing out with pursed up lip technique after inhalation	10 (100%)	5 (50%)	1 (10%)
Total errors[b]	7.00 (5.00–8.00)	3.00 (2.00–4.00)	0.50 (0.00–1.00)
Critical errors[b]	5.00 (3.00–5.00)	2.00 (1.00–2.00)	0.00 (0.00–0.00)

Notes: [a]Values are expressed as absolute frequency (percentage); [b]Values are expressed as median (percentile 25%–percentile 75%).
Abbreviation: N/A, not available.

decreased from the first evaluation to the third evaluation, $F(2,18)=61.127$, $p<0.001$, partial $\eta^2=0.872$. At the same time, we observed that differences between the number of critical errors at the three evaluation moments were statistically significant, $F(2,18)=85.172$, $p<0.001$, partial $\eta^2=0.904$. The total number of errors has significantly decreased from initial evaluation to three months (2.800 (95% CI, 1.660–3.940) errors, $p<0.001$), and from the initial evaluation to six months (4.300 (95% CI, 3.224 to 5.376) errors, $p<0.001$), and from three months to six months (1.500 (95% CI, 1.098–2.002) errors, $p<0.001$).

In addition, no significant differences between the number of errors recorded in case of men vs women, when considering both the handling and inhalation errors were observed (Figure 8). Moreover, no significant differences between the number of errors recorded by the inhaler when considering patients at different age groups were found.

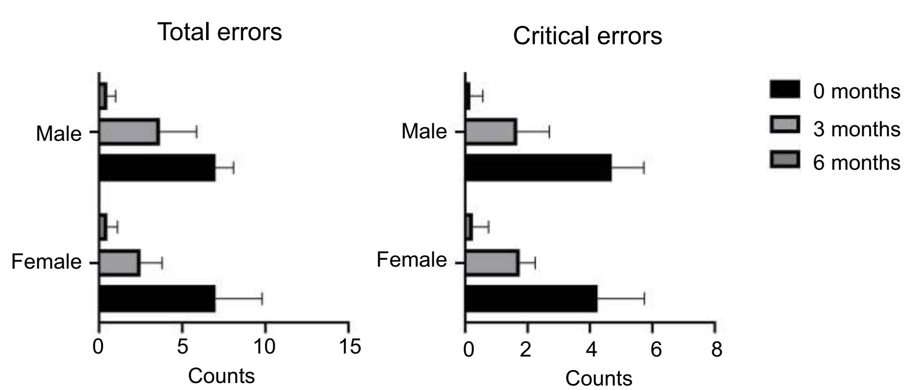

Figure 8 Representation of both total number of errors (left) and critical errors (right) of the SMI inhaler at the three evaluation moments when patients were grouped by gender.

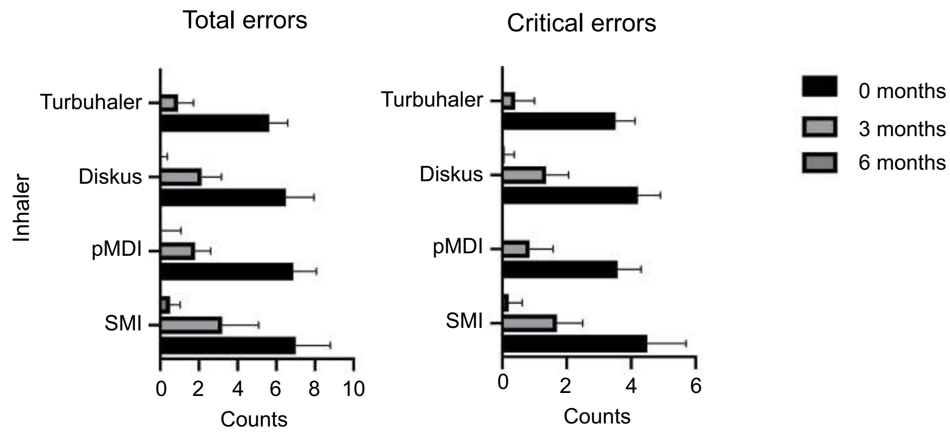

Figure 9 Representation of both total errors (left) and critical errors (right) recorded by the considered inhalers at the three evaluation moments.

The comparative representation of both total number of errors and number of critical errors recorded by the considered inhalers is shown in Figure 9. The total number of errors decreased from the first evaluation to the evaluations after both three and six months when considering all the inhalers.

Discussion

It is known that for the past 40 years, the type and the frequency of inhaler errors did not significantly change, and treatment outcomes are often reduced due to deficient inhaler technique.[18]

In this study, we analyzed the inhaler technique and the error evolution after using a specific M-health application that contains demonstrative inhaler technique videos. We compared our findings with the literature results and presented it as a valuable option in order to reduce the inhaler technique errors.

We found major inhaler technique errors in all the analyzed devices, every single one having at least four critical errors.

The CRITIKAL study, which is one of the largest studies that investigated the inhaler technique in a multinational population, the authors have observed that inspiratory effort errors were frequent in all studied device cohorts. Patients that used DPI devices inhaled insufficiently fast and forceful: 32.1% of the patients that used Turbuhaler, 38.4% of the patients using Diskus, and 47.2% in patients that used MDI devices.[19]

The most frequent errors remain the generic ones, such as dose preparation for DPIs, coordination problems with MDIs, and other current reported errors consisting in not exhaling, not holding breath and insufficient speed of inhalation.[19]

Compared to the above-mentioned studies, in the present study, 84% of the patients that used Turbuhaler device, and all the patients that used Diskus device did not inhale sufficiently fast and forceful. One explanation for our high rate of errors could be that we analyzed a significantly reduced number of patients compared to the other studies. Regardless of the number of patients, it is clear that this type of critical error remains high.

The CRITIKAL study also highlighted "exhaling into the device" as a critical MDI error.[19] Although the literature has found patients that exhaled into the device, in our study not a single patient made this error.

Sanchis et al, analyzed a large number of studies during 2000 and 2013 and found a wide variability between the subjects making errors across different studies. The most commonly made errors in pMDI across studies were failing to actuate the inhaler while breathing in slowly and failing to hold breath after inhalation. The proportion of former errors ranged between 24% and 77%, respectively 10% to 68% across different studies.[20]

Plaza et al, found that inhalation techniques remain poor in Spain, the most common error reported for the pMDI being: failing to breath out prior to inhalation, poor coordination between inhalation and actuation of the device, forgetting to shake the inhaler, and failing to hold breath after medication delivery.[21]

Compared to the result of these studies, 96% of our patients failed to actuate the inhaler while breathing in slowly, while 57% of the patients failed to hold their breath for about 5 s after inhalation.

Other authors found that the most common mistakes in DPI inhalers are failing to breathe out and away from the inhaler, and failing to hold breath. Furthermore, 30% of the subjects that used the Turbuhaler device made an error related to the inhaler position.[22]

Other studies reported that the steps with the highest error rate in DPIs were critical errors: 34% of the patients did not shake the inhaler well, 46.2% did not exhale completely away from the inhaler, and 40.9% of the studied patients did not hold the breath for 10 s.[23]

In this study, older patients operated the inhalers with multiple technique errors compared to the younger ones. Reduced dexterity and cognitive function can be some of the factors that limit their ability to correctly use the inhalers. Statistically significant differences between the age groups 22–40 and 41–64 years were observed in the Turbuhaler group regarding the handling error "no upright posture before inhalation". When we analyzed the pMDI group we found significant differences between the same group ages but this time the handling error was "not removing/opening the cap" (16.7% vs 83.3%). No handling errors were observed between the two group ages for the SMI.

A study that used video instructions to promote correct technique for DPI observed that non-verbal videos were an inadequate way of providing inhaler education for first time users of inhalers.[24]

Compared to their study, our instructional videos were verbal and had clear subtitle, this could be one reason why our subjects had an improved inhaler technique. Instead of learning how to use inhalers by reading the instructions only, visual demonstrations with the help of M-health applications can reduce the critical errors during inhaler use.

Other studies had also proved that the use of video technology can improve the patient knowledge and understanding regarding inhaler technique.[25]

It has been observed that the inhaler technique is deteriorating over time, sometimes as little as 2–3 months.[26] Thus, it is important to have repeated training in order to obtain and maintain a correct technique. Providing inhaler education via M-health applications could be suitable for this situation instead of recalling the patient to verify the technique. This option is also supported by Wilson et al, who emphasized that the use of instructional videos can promote recall on inhaler use in asthma patients.[27]

We evaluated the patients over a period of six months with a constant reminder to use the phone application when needed and thus we obtained significant result regarding the inhaler technique. After six months, all types of errors (critical and non-critical) had been significantly reduced to almost no error. For the future, it would be interesting to observe if no further reminder from the physician and no use of an M-health application can maintain the inhaler technique for a longer period of time.

One limitation of this study could be that we did not include the education level of the subjects. Education level could affect the ability to understand instructions, memorize the technique steps, and operate the inhaler.

Conclusion

Incorrect inhaler technique remains frequent among patients with asthma, and it did not improve significantly over the past years. This problem could be an important obstacle in achieving good asthma control. Careful instructions, demonstration, and repeated tuition are possible strategies that could enhance the proper inhaler technique, but new approaches should be explored. The results of this study suggest that video instructions provided through specific mobile phone applications could improve the inhaler technique in patients with asthma.

Disclosure

The authors report no conflicts of interest in this work.

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Lethal disseminated tuberculosis in patients under biological treatment – two clinical cases and a short review

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Abstract

Tumour necrosis factor (TNF)-α inhibitors are highly used in Romania for the treatment of autoimmune disorders, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel diseases, and ankylosing spondylitis. Biological therapy using TNF-α inhibitors is very effective but is associated with an increased risk of opportunistic infections, including active tuberculosis. Here, two cases are presented of patients with RA and psoriasis under biological therapy who developed very aggressive forms of disseminated tuberculosis, with a rapid progression to death. The authors conclude that patients undergoing biological therapy require thorough evaluation prior to initiating treatment, followed by continuous and rigorous monitoring by a multidisciplinary team during biological treatment, particularly in countries with a high incidence of tuberculosis.

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Keywords

Rheumatoid arthritis, psoriasis, TNF-α inhibitors, lethal disseminated tuberculosis

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Introduction

The use of tumour necrosis factor (TNF)-α inhibitor therapy in patients diagnosed with autoimmune diseases, such as rheumatoid arthritis (RA) and psoriasis, has proven highly effective in suppressing the pathologic inflammation responsible for specific symptoms and joint damage, but is associated with a decrease in host defence against opportunistic infections, including active tuberculosis (TB).[1–4] All anti-TNF drugs are associated with an increased risk of TB reactivation in patients positive for latent TB infection, with a lower risk associated with etanercept,[5,6] and a consistent number of cases have also been reported from countries with a low TB incidence (less than 20 per 100 000 population per year).[7] Cases of tuberculosis have been described in patients with known RA even before starting biological therapy, particularly in countries with high incidence of TB.[8] Only a few cases with rapid progression to death due to disseminated forms of TB have been reported to date, however.[9,10] Romania has a relatively high incidence of TB (70 per 100 000 inhabitants),[11] and like other countries, biological treatment is frequently used, thus, monitoring of the adverse effects of this therapy must be very rigorous, multidisciplinary, and well established in active national guidelines. The tuberculin skin test (Statens Serum Institut, Copenhagen, Denmark) and QuantiFERON-TB Gold in-tube assay (Cellestis Ltd, Carnegie, Victoria, Australia) are used in Romania to screen for latent TB infection.

Here, two cases are presented of patients with RA and psoriasis, treated using biological therapy, who developed very aggressive forms of disseminated tuberculosis. These cases are presented due to the unusual clinical features, unexpected severity, and fast progression to death.

Case reports

Approval to publish the present findings was provided by the Ethics committee of the Clinical Pneumology Hospital of Constanta (Case 1) and the Ethics committee of the Clinical Infectious Diseases Hospital of Constanta (Case 2) and each patient provided written informed consent on admission to hospital.

Case 1

A 72-year-old female patient was admitted to the First Internal Medicine Department of Constanta County Clinical Emergency Hospital in December 2015, for fever, chills, severe asthenia, productive cough, polyarthralgia, with symptomatology that had worsened over the previous 3 days. Medical history revealed arterial hypertension dating from 2010 and stage III seropositive RA since November 2004. The patient's RA had been initially treated with 15 mg methotrexate, oral, weekly and anti-inflammatory drugs (500 mg naproxen with 20 mg esomeprazole as gastric protection, both oral, twice daily). From June 2015, because of highly active disease (Disease Activity Score 28 for Rheumatoid Arthritis using C-reactive protein

[DAS28-CRP], 7.79), 40 mg adalimumab, subcutaneous, every other week, was added to the regimen. Before the initiation of adalimumab, chest X-ray was normal, tuberculin skin test (Statens Serum Institut) and QuantiFERON-TB Gold in-tube test (Cellestis) were negative, and enzyme-linked immunosorbent assay for human immunodeficiency virus (HIV) was negative. Following six months of adalimumab therapy, the patient was admitted into the hospital in a conscious state with normal body mass index (BMI, 21.1 kg/m^2), fever (38.6 °C), joints with specific deformities only, normal lung examination, SpO_2 of 97%, blood pressure at 120/70 mmHg, heart rate of 100 beats per min, and an enlarged abdomen with ascites. Biological tests showed normal white blood cell (WBC) count (5.910 x 10^3 cells/µl), mild chronic inflammatory anaemia (haemoglobin, 9.6 g/dl; haematocrit, 30.1 %) and systemic inflammatory syndrome (erythrocyte sedimentation rate [ESR], 36 mm/h; fibrinogen, 512 mg/dl). Bacteriological examination of blood culture was sterile and sputum samples were negative for pyogenic bacteria, fungi, and acid-fast bacillus. Standard chest X-ray (Figure 1) showed multiple micronodular and nodular pale opacities, disseminated in both lungs. The investigations were extended using thoracic computed tomography (CT) and revealed a bronchopneumonic aspect, mediastinal lymphadenopathy (between 12 and 20 mm), and straight lymph node calcifications (Figure 2). Antibiotic and antifungal treatment was initiated, comprising 1 g ceftazidinum twice daily and 400 mg/250 ml moxifloxacin once daily, plus 200 mg fluconazole once daily, all administered intravenously (i.v.). On day 4 of treatment, ceftazidinum was replaced with 1 g meropenem i.v., three times daily, and the treatment continued for a further 10 days, while previous treatment remained the same for the entire treatment duration. This treatment regimen was without good patient progression. Abdominal ultrasound, performed on the first day of hospitalization and repeated on day 5 due to poor patient progression, indicated

Figure 1. Chest X-ray from a 72-year old female patient with rheumatoid arthritis, obtained following 6 months of treatment with 40 mg/day adalimumab, every 2 weeks: X-ray shows multiple pale nodular opacities disseminated bilaterally, particularly in the upper two thirds of the thorax

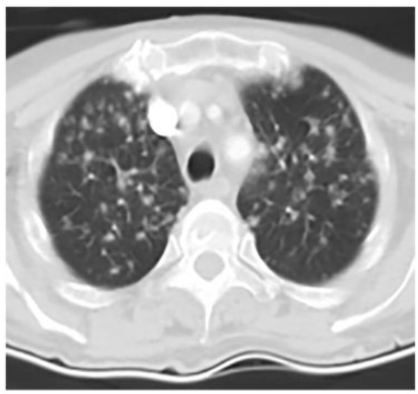

Figure 2. Thoracic computed tomography (CT) image from a 72-year old female patient with rheumatoid arthritis, obtained following 6 months of treatment with 40 mg/day adalimumab, every 2 weeks: CT image shows bronchopneumonic aspect, mediastinal lymphadenopathies between 12 and 20 mm, and straight lymph node calcifications

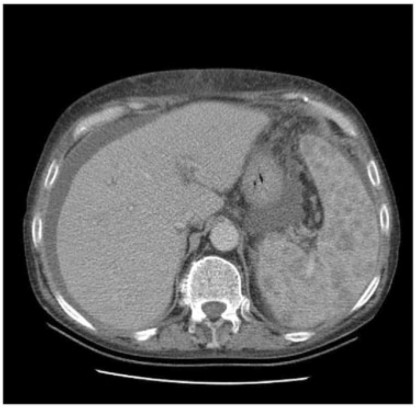

Figure 3. Abdominal computed tomography (CT) image from a 72-year old female patient with rheumatoid arthritis, obtained following 6 months of treatment with 40 mg/day adalimumab, every 2 weeks: CT image shows ascites, and a heterogeneous spleen with multiple hypoechogenic formations

splenomegaly with heterogeneous structure and multiple hypoechogenic formations, and gross ascites, confirmed by abdominal CT (Figure 3). Exploratory paracentesis revealed the presence of an exudate with protein (3.7 g/dl), lactate dehydrogenase (864 U/l), and increased adenosine deaminase (ADA; 93 U/l). At this hospitalization, the repeated QuantiFERON-TB Gold test was positive. Due to the risk of TB infection secondary to biological therapy, enforced by the patient's lung images and ADA value, a complete range of bacteriological tests were performed. Microscopic examination of sputum was negative for acid-fast bacilli. The rapid detection of *Mycobacterium tuberculosis* in liquid culture from sputum specimens and ascites liquid (tested using the BD BACTEC™ MGIT™ automated mycobacterial detection system; Becton Dickinson, Sparks, MD, USA), which were both positive after 14 days of liquid culture, confirmed the diagnosis of disseminated secondary tuberculosis, with multiple organ involvement (pulmonary, peritoneal and possibly splenic). Consequently, the patient was transferred to the Pulmonology Department, Constanta County Clinical Emergency Hospital, to undergo appropriate treatment. Due to corroboration between clinical and paraclinical factors, treatment against TB had been initiated prior to having bacteriological confirmation from sputum and ascites samples in solid culture on Lowenstein-Jensen medium, which became positive after 40 days (positive culture with 1–30 colonies of *M. tuberculosis*, antigen MPT64 positive, fully sensitive to all TB drugs, in sputum and [++] in ascites liquid). The first standard regime of treatment, in accordance with the National Programme for Prevention, Monitoring and Control of Tuberculosis,[11] was initiated with: 5 mg/kg/day isoniazid, 10 mg/kg/day rifampicin, 30 mg/kg/day pyrazinamide and 25 mg/kg/day ethambutol, all intravenous, in perfusion (approximately 30–40 min per drug), all administrated in the morning. In addition, 250 mg pyridoxine, and 20 mg esomeprazole, both oral, daily, were added. Progression was quickly and constantly unfavourable, with additional complications: upper digestive bleeding (exteriorized by haematemesis) and multiple organ failures (respiratory, kidney and liver). The patient finally died following 7 days of standard TB treatment and 21 days of hospitalization, despite all medical efforts. The family did not consent to an autopsy.

Case 2

A 65-year-old female patient was admitted to the Cardiology Department of Constanta County Clinical Emergency Hospital in February 2016, for headache, dizziness and thoracic pain with suspicion of acute myocardial infarction. This patient presented with a history of essential stage III arterial hypertension (with very high additional risk) since 2002, diabetes mellitus with nephroangiopathy and polyneuropathy treated with oral antidiabetes medications since 2006, and severe chronic psoriasis since 2009. In the previous three months the patient had received treatment for severe psoriasis with psoriatic arthritis (Psoriasis Area and Severity Index score, 23.2) comprising an anti-TNF-α agent: three doses of 5 mg/kg infliximab, i.v. (at weeks 0, 2, and 6; last dose received in December 2016), according to an approved RA protocol.[12] Physical examination did not reveal pathological signs. Biological tests were without significant or specific abnormalities: normal haemogram, fibrinogen, alanine transaminase, aspartate aminotransferase, creatine kinase-muscle/brain, creatinine, and urea, but elevated ESR (68 mm/h), blood glucose (195 mg/dl) and troponin level (199.2 μg/l). Myocardial infarction was excluded, but the patient's general condition deteriorated during hospitalization, the level of consciousness decreased, and fever with signs of meningeal irritation appeared five days following hospital admission. She was diagnosed with acute meningoencephalitis with a Glasgow coma scale score of 6 and was admitted to the Intensive Care Unit. Analyses of cerebrospinal fluid (CSF) revealed: intense positive Pandy's reaction (++++), 235 cells/μl (85% polymorphonuclear leukocytes and 15% lymphocytes), increased albumin (132 mg/dl), hypoglycorrhachia (glucose, 0.31 g/l) and hypochlorrhachia (chloride, 9.20 μmol/l [6.35 g/dl]). Bacteriological examination showed the CSF to be positive for acid-fast bacillus (Ziehl-Neelsen staining), positive for TB nucleic acid using GeneXpert (Cepheid, Sunnyvale, CA, USA) with no detection of rifampin resistance, and positive for *M. tuberculosis* in liquid culture, tested using the BD BACTEC™ MGIT™ system. Chest X-ray showed a miliary TB pattern (not shown). The patient was confirmed as a new case of disseminated TB in a patient recently treated with infliximab for psoriasis. Specific anti-TB chemotherapy with four first-line drugs, as in the previous case (5 mg/kg/day isoniazid, 10 mg/kg/day rifampicin, 30 mg/kg/day pyrazinamide and 25 mg/kg/day ethambutol), oral administration, was started. Three days following initiation of treatment for TB, the patient presented upper digestive haemorrhage exteriorized by melena. Despite all aggressive treatment, the patient died with cardiorespiratory failure after 16 days of hospitalization.

Discussion

Incidence of RA in Romania is approximately 1% of the general population, and incidence of psoriasis is approximately 2%.[12] In these population groups, the prevalence of latent TB infection remains unknown. In patients diagnosed with RA and psoriasis, TNF-α blockers are initiated only in patients who are unresponsive to conventional treatment, and after careful exclusion of latent TB infection.[2,3,12,13] Romanian guidelines stipulate that prior to administration of biological treatment, the patient should follow an algorithm to identify latent TB infection, and chemoprophylactic treatment should be administered for 9 months in patients who have a positive tuberculin skin test, (tuberculin skin test, $\geq$ 10 mm, and without signs of active disease).[11] Despite pretreatment evaluation, it is well known that the use of TNF-α inhibitor therapy is associated with an increased risk of active TB.[12–15] The current report presents the cases of two female patients, both over 65 years old, with a long history of RA and psoriatic arthritis, who were diagnosed with TB after starting biological treatment, despite both being confirmed negative for latent TB infection prior to initiation of treatment. Neither of the cases had been recently exposed to TB, making it difficult to support an exogenous reinfection mechanism for TB. The possibility of a false-negative tuberculin skin test and negative QuantiFERON-TB Gold assay need to be taken into consideration, due to immunosuppression caused by disease or chronic anterior immunosuppressive therapy,[16,17] making the reactivation of post-primary TB lesions more feasible. Moreover, use of the tuberculin skin test is more controversial for a patient with psoriasis due to the possibility of over-diagnosis or ambiguous results.[18] Despite the fact that in many national guidelines the tuberculin skin test remains the first-line tool to screen for latent TB infection in patients with psoriasis, it is recommended that the QuantiFERON-TB Gold test is also performed, either before or on the same day as the Mantoux test, to increase the accuracy of diagnosis.[18] Unusual clinical features in adults with disseminated pulmonary and extrapulmonary TB (peritoneal and meningitis), may delay diagnosis for 5 to 15 days, leading to an increased risk of mortality (authors' personal experience). In Romania, meningitis is more frequently observed as a complication of primary TB in infants and is a very rare complication in adults.[19] Knowing the paucibacillary character of serositis, the present authors consider that the positive acid-fast bacillus smear for CSF (case 2) and positive GeneXpert and liquid culture for *M. tuberculosis* for ascites (case 1) reflect the severity of the disease. Published studies report a positive rate for acid-fast bacillus smear in TB meningitis of between 37 and 58%.[20,21] For both cases reported in the current study, death was considered to be related to disseminated TB, and it is unclear whether the occurrence of superior digestive haemorrhage aggravated the patients' prognosis. The anti-TB treatment cannot be directly associated with this haemorrhage complication, as administration was intravenous in case 1, and the complication preceded the start of treatment in case 2.

Medical professionals should be aware of the unusual pattern of TB in patients undergoing biological treatment.[22] For example, extrapulmonary or disseminated tuberculosis are more frequently observed in patients treated with TNF-α inhibitors.[7,23] A review of 70 cases of TB that developed after treatment with infliximab showed an increased proportion of extrapulmonary TB (56% versus 18%) and disseminated diseases (18% versus 2%), when associated with a severe immunosuppression status (including HIV positivity).[22] The four deaths out of 70 patients in this study were related to TB,[22] however, in patients receiving biological treatment, very few deaths related to TB have been reported in the literature.[9,10]

The number of TB cases has been reported in the literature to be higher for infliximab than adalimumab,[22,24] however, two studies (one French and one English) reported that the incidence of TB was higher for adalimumab.[5,6] The interval from starting anti-TNF-α treatment until TB onset was 6 months in the present first case (treated with adalimumab), which was shorter than in a published study reporting median time to TB onset of 18.5 months for 11 patients treated with adalimumab,[6] and was more comparable with timeframes reported for patients treated with infliximab.[3,22,25] Clinical deterioration despite specific anti-TB treatment has been reported in cases of RA treated with adalimumab, due to a paradoxical reaction involving the lungs, with acute respiratory failure attributed to the recurrence of disease in the absence of biological treatment.[23,26,27] The onset of paradoxical reaction is considered one month after TB diagnosis and treatment.[23,27] In the present cases, it is difficult to maintain that death was attributed to a paradoxical reaction, because it occurred soon after starting the anti-TB treatment (7 days for case 1, and 3 days for case 2), but after 4 weeks from the last dose of adalimumab and 8 weeks from the last dose of infliximab. Unfortunately, procalcitonin level, a possible diagnostic and prognosis marker for paradoxical reaction,[23] was not tested in either case. The moment of restarting therapy with TNF-α inhibitors during or following the end of anti-TB treatment differs between guidelines. It is possible to restart after 2 months,[28] but it is mandatory to pay close attention to TB evolution during follow-up.[29]

In conclusion, because of the high endemic value of TB in Romania,[30] and given the severe forms presented by these cases, there is ongoing discussion as to whether or not chemoprophylaxis with isoniazid should be provided in all cases before anti TNF-α treatment, even if the first screening excludes latent TB infection. In addition, old age, female sex, long history of autoimmune disease, and association of other comorbidities, such as diabetes, digestive haemorrhage, and HIV infection, could be risk factors for developing disseminated and lethal forms of TB during biological treatment with infliximab and adalimumab. Etanercept may be a more beneficial anti-TNF-α treatment given its relatively low incidence rate of TB, for patients in which this therapy is mandatory.[31]

In cases at high risk of TB reactivation, the choice of a non-anti-TNF targeted biologic is advisable.[31]

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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ORIGINAL ARTICLE

THE PREVALENCE AND SPECTRUM OF *MYCOBACTERIUM TUBERCULOSIS* CHEMORESISTANCE AMONG TB PATIENTS

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Abstract

Rapid detection of *Mycobacterium tuberculosis* (MTB) chemoresistance against anti-tuberculosis drugs is a major challenge of any Pulmonology department. The aim of the study was to synthesize the epidemiological features of multidrug resistant (MDR), rifampicin resistant (RR) or extensively drug resistant (XDR) TB, for estimating the extent of MTB resistance pattern and severity of tuberculosis (TB) disease. Between 1st of March 2013 to 31st of December 2017, all 1,643 inpatients with positive diagnosis of pulmonary TB active disease were evaluated by specific methods consisting in phenotypic and genotypic investigation of MTB strains. The frequency and pattern of MTB resistance to anti-TB drugs were assessed. The prevalence of MDR-TB was low (1.95%). Delayed diagnosis of MDR-TB was frequent (71.87%) and more common in active smokers (53.12%), unemployed and uninsured patients. The secondary pattern of chemoresistance was prevalent (62.5%), but primary resistance pattern of MTB was related to younger individuals mean aged 38 years ($p < 0.03$). The prevalent broad- spectrum of MTB resistance against first line of anti-TB drugs was noticed in majority of cases (87.5%), with the predominance of isoniazid (H) and rifampicin (R) pattern (53.1%), and supplementary gaining XDR profile. Although MDR-TB prevalence was low and HR pattern dominated the spectrum of MTB resistance, the progressive extension of MDR to XDR profile of resistance occurred.

Rezumat

Detectarea rapidă a chimiorezistenței dezvoltate de *Mycobacterium tuberculosis* (MTB) la medicamentele antituberculoase este o provocare majoră pentru orice departament de pneumologie. Scopul studiului a fost evaluarea caracteristicilor epidemiologice ale tuberculozei multirezistente (TB-MDR), rifampicin rezistente (RR) sau extensiv rezistente (XDR), necesitând conturarea profilului chimiorezistenței și severității bolii tuberculoase. Intre 1 Martie 2013 si 31 Decembrie 2017, toate cazurile de TB pulmonara spitalizate si confirmate bacteriologic (n = 1.643) au fost evaluate prin metode fenotipice si genotipice. Au fost determinate frecvența și profilul chimiorezistenței MTB. Prevalența TB-MDR a fost scăzută (1,95%). Diagnosticul TB-MDR a fost frecvent tardiv (71,87%), mai ales la fumătorii activi (53.12%), persoane neasigurate și fără ocupație. Modelul chimiorezistenței secundare al MTB predomină (62,5%), iar chimiorezistența primară se asociază cu vârsta medie tânără (sub 38 ani) a adulților ($p < 0,03$). Prevalența crescută a chimiorezistenței la medicamentele antiTB de prima linie a fost observată la majoritatea cazurilor (87,5%), cu predominanța rezistenței la izoniazidă (H) și rifampicină (R) (53,1%) și dobândirea chimiorezistenței extensive (XDR). Deși prevalența TB-MDR e redusă și HR domină spectrul chimiorezistenței, survine extensia progresivă de la MDR la XDR.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, chemoresistance, MDR-TB, XDR-TB

Introduction

Drug resistant tuberculosis (DR-TB) forms of active disease represent a serious public health threat, with an incidence and mortality continuously growing worldwide. The resistant pattern of *Mycobacterium Tuberculosis* (MTB) strains to the drugs used to treat the disease can be achieved by an incorrect or inappropriate administration of antiTB drugs, in terms of association, dosage, or duration. DR-TB can be acquired through person to person transmission, or through deficient management of TB treatment. Multidrug resistant (MDR) TB is more difficult to treat than drug-susceptible TB, requiring much longer and more expensive therapies with a higher rate of adverse events and even mortality. In 2016, globally, approximately 600.000 persons developed MDR or rifampicin resistant (RR) TB, and 6.2% of MDR-TB cases had additional drug-resistance, known as extensively drug-resistant (XDR) TB [1]. In Romania, in 2015, there were 14.225 notified TB cases, of which 4.8$^{o}/_{oooo}$ were MDR/RR-TB cases [2]. Although Romania made substantial improvements in diagnosing MDR-TB, the number of notified cases is below the estimated value considered by World Health Organization (between 800 and 1000 new MDR-TB cases) [3]. The main reason of this discrepancy is represented, from time to time, by partial and intermittent testing of the bacteriologically confirmed TB cases and lack of necessary equipment. Considering the negative impact of TB drug resistance phenomenon on the treatment efficiency, with direct consequence on spreading the resistant MTB, the aim of the study was to analyse the epidemiological profile of MTB, defining the primary and secondary type of chemoresistance among TB case-patients in Constanța County, Romania.

Materials and Methods

Patients and sample processing

A prevalence study, approved by the Ethics Committee of Clinical Pneumophthysiology Hospital of Constanța, Romania, was conducted from January 1st of 2013 to December 12th of 2017, using the electronic database of all notified TB in patients (n = 1,643). TB diagnosis was sustained by positive sputum smears and cultures. Inclusion criteria consisted in the evidence of *Mycobacterium tuberculosis* resistant strains against rifampicin (R) and/or isoniazid (H). All patients signed an informed consent before enrolling in the study.

Identification tests of multidrug resistant forms of TB

The identification tests of multidrug resistant forms of TB needed genetic and phenotypic methods with mandatory drug testing (DST), which were recommended in accordance with national and international guidelines (two sputum specimens were collected from each patient and then processed for TB diagnosis by smear microscopy and culture) [4-7]. Each sputum sample was decontaminated using sodium hydroxide method, followed by neutralization and centrifugation. Sediment was examined by Ziehl-Neelsen staining and cultured in Löwenstein-Jensen slope and/or into a *Mycobacteria* Growth Indicator Tube (MGIT), according to the manufacturer's instructions (BACTEC MGIT 960 system BD Diagnostics Systems, Sparks, MD).

Drug sensitivity testing

The resistance against rifampicin (R) and/or isoniazid (H) was tested using the rapid detection molecular tests, such as Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and a rapid line probe assay (LPA) (Hain Lifescience GmbH, Nehren, Germany). All subcultures showing drug resistance of MTB to HR were later transported to the national reference laboratory in Bucharest for an extensive DST to pyrazinamide, ethambutol, streptomycin, ethionamide, ofloxacin, para-aminosalicylic acid, and to the second-line injectable drugs (amikacin, kanamycin and capreomycin). HR resistance was defined as resistance revealed either by the rapid molecular tests or the conventional culture-based susceptibility test. According to the international [8] and national [9] guidelines, all definitions were considered: primary (initial) resistance of MTB if resistance was detected in TB patients who had never received, or received under one month of any anti-tuberculosis treatment; secondary (acquired) resistance of MTB, if resistance was detected in previously treated cases with more than 1 month prior to the detection of the resistance; mono drug-resistance (DR) when resistance to a single anti-TB drug is determined (excluding Rifampicin resistance -RR- which represents a special form of mono-resistance, considered a prior form of MDR, whereas in 85% of cases it can also associate resistance to isoniazid); multidrug resistant tuberculosis (MDR-TB) defined as resistance to both HR; and extensively drug resistant tuberculosis (XDR-TB) defined as MDR-TB with additional fluoroquinolone and second-line injectable agent resistance.

Statistical analysis

Data on demographics, previous TB exposure or treatment, risk factors, clinical and radiological features, bacteriological status, comorbidities and evolution under anti-TB treatment were recorded and analysed, including multivariate logistic regression models by IBM SPSS Statistics version 19.

Results and Discussion

During the study period of almost 4 years, 1,643 patients were hospitalized and diagnosed with pulmonary active TB disease (PTB), of which 32 were identified with different drug resistant strains of MTB. The overall prevalence of hospitalized MDR-TB was low (1.95%), with higher values of new cases and relapses in 2016 (Figure 1). This value is lower than those reported by a Brazilian study, that involved 2176 patients diagnosed with pulmonary TB between 2000-2004 in the city of Santos, Brazil, where the drug resistant TB was found in 15% of the cases, mostly on males (78%) and with a lower median age at diagnosis (39.2 versus 47 years) [10].

Demographic, clinic and radiologic features of MDR-TB patients revealed a mean age of 47 ± 15.14 years and an increased prevalence (46.8%) among cases between 40 and 59 years. MDR-TB disease occurred more frequently in males (71.8%), smokers and former smokers (68.75%), uninsured (46.9%) and people living in urban areas (62.5%) (Table I).

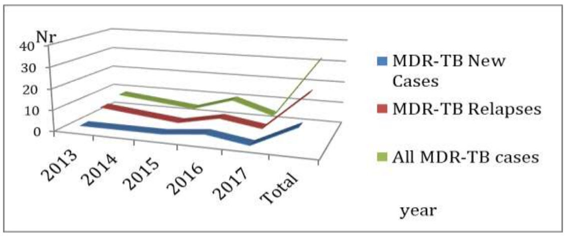

Figure 1.
The distribution of annually hospitalized MDR-TB by epidemiological categories of disease (new cases and relapses)

Table I
Demographic, clinic and radiologic features of MDR-TB patients

Characteristics	MDR-TB patients (n =, %)
Total	32 (1.95)
Gender	
male	23 (71.87)
female	9 (28.12)
Age (mean)	47 ± 15.14
Residence	
urban	20 (62.5)
rural	12 (37.5)
Exogenous risk factors*	17 (53.12)
Smoking status	
smokers & ex-smokers	22 (68.75)
non-smokers	10 (31.25)
Constitutional symptom	
cough	7 (21.87)
hemoptysis	1 (3.1)
fever	1 (3.1)
night sweats	3 (9.37)
body weight loss	4 (12.5)
nausea, vomiting	2 (6.25)
Comorbidities	
Diabetes mellitus	2 (6.25)
Cardiovascular diseases	5 (15.62)
COPD	2 (6.25)
Bronchiectasis	2 (6.25)
Chronic liver disease	2 (1.6)
Radiological appearances	
cavitation	14 (43.75)
nodules	5 (15.62)
ulceration	13 (40.62)

* poor living conditions, homeless, institutionalized patients or not having medical insurance

The symptoms of TB are variable, generally non-specific, but closely related to the extent, location and character of the TB lesions, as well as aggravated comorbidities. Due to the fact that the MTB has a slow rate multiplication, the onset is frequently insidious, with a gradual deterioration of the health status. The main manifestations, such as weight loss, low fever, nocturnal sweating, fatigue, and persistent cough, were present in 87.5% of patients (Table I), similar to other reported studies [10-12]. The clinical manifestations of pulmonary MDR-TB had an insidious pattern of the onset (78.1%). The most common radiological appearance of PTB included cavities (43.75%) and ulcerated lesions (40.62%) (Table I) and, in 71.4%, of cases the size of cavitary lesions was ≥ 4 cm. Previous published data [10, 13] documented an association between the clinical suspicion of anti-TB drug resistance and the presence and persistence of a greater number of pulmonary cavitary lesions. Drug resistant TB represents, all over the world, even in countries with a low burden of TB [14], a significant health problem and a real epidemiological challenge in obtaining reliable information on the real prevalence and spectrum of MTB resistant strains among TB patients. Delayed diagnosis of TB and/or severe comorbidities can have an important unfavourable impact on the survival [15-17]. In the particular case of MDR-TB, the delayed diagnosis of MDR-TB can influence dramatically the outcomes of any TB control program.

Most of the patients (n = 23/32; 71.87%), had any known exposure to a TB source of infection. Almost a third of MDR-TB patients (n = 9/32; 28.1%) were actively diagnosed within the contact investigation of TB patients previously identified (3 of them being in contact with MDR-TB patients). A third of MDR-TB cases (n = 11/32; 34.37%) represented new cases of TB active disease, not previously reported or ever treated. Regarding the history of sensitive TB treated disease, the rest of the cases (n = 21/32; 62.5%) received at least once TB treatment (maximum 4 relapses *per* patient). Non-compliance to previous anti-TB regimens (n = 11/32; 34.37%) and frequent relapses (n = 10/32; 31.25%) were the main risk factors for the occurrence of drug resistance phenomenon. The prevalence of smoking exposure (n = 22/32; 68.75%) was significantly higher than other comorbidities of TB (n=13/32; 40%) (OR = 3.154; RR = 1.6923; χ^2 = 5.0276, p < 0.025) (Table I). Regarding the risk factors for the occurrence of drug resistance, our study showed that majority of patients with MDR-TB were smokers and former smokers (68.75%), similar to a study from Georgia conducted on 591 TB patients, reporting a lower risk of developing MDR-TB in non-smokers and former smokers comparing with active smokers [18]. Smoking is a known risk factor not only for obstructive lung diseases [19] or lung cancer [20], but even for pulmonary TB, and, in the absence of adequate treatment, in terms of dosage, duration, association of drugs, it evolves in severe cavitary forms [21]. New cases of MDR-TB occurred after a large interval of time 72.28 ± 97.33 months (range 1 - 444 months) from the first episode of TB active disease, irrespective of the primary or secondary pattern of resistance. In acquired (secondary) type of MDR-TB, the mean time from the first diagnosis of TB disease until the occurrence of resistance was much higher, of 115.65 ± 100.879 months (range 10 to 444 months). The main risk factor for the secondary pattern of MDR is the poor adherence to previous TB treatments. In contrast with Coelho's study [11], which showed similar values of primary and secondary resistance, our study showed a higher proportion of acquired resistance (62.5%), with a median duration between the first TB diagnosis and appearance of MDR-TB of 72 months, revealing previous deficiencies in administering directly observed therapy. Similar data, documented, in 2016, by WHO Report, revealed approximately 3% of new cases and 12% of TB relapses as MDR-TB cases [1].

Patients with primary type of MDR were significantly much younger than those with secondary type, according to ANOVA analysis: 38.36 ± 11.673 years (range: 24 - 59 years) compare to 50.9 ± 15.718 years (range: 23 - 83 years); F = 5.341; p = 0.028. The quality of life is severely affected, in all independent domains, (physical health, psychological, social and environmental) [22]. In other chronic pulmonary diseases, only the total score of the quality of life was related with the physical indicators [23]

Bacteriological exam of sputum specimens revealed the presence of acid-fast bacilli (AFB) in 90.6% of MDR-TB cases, 96.9% positive MGIT cultures and 100% positive Löwenstein-Jensen cultures (solid media). Xpert testing was not available in the first 2 years of study (between 01.01.2013 - 30.09.2014). So, only 21 patients (65.62%) were tested and rifampicin resistance (RR) was detected in 85.71% cases (n = 18/21). The level of RR revealed by GeneXpert was a moderate one in 84% of cases. LPA was available for less cases (n = 18/32; 56.25%), but it had a higher rate of HR detection (n = 17/18; 94.4%) with an obvious KatG MUT pattern in 82.35% (n = 14/17) Overall, using drug sensitivity testing (DST), by both phenotypic and genotypic tests results, the MTB resistant spectrum was polymorphic with the predominance of resistance to the first line antiTB drugs (n = 28/32; 87.5%), mostly double HR profile of resistance (n = 17/32; 53.1%) (Table II).

Table II

The distribution of the initial MDR profile of resistance

Initial Drug Sensitivity Testing	Nr. of cases	(%)
INH+ RMP	17	53.1%
INH+ RMP+ EMB+ SM	3	9.4%
INH+ RMP+ EMB+ PZA+ SM	2	6.3%
INH+ RMP+ EMB	2	6.3%
INH+ RMP+ SM	2	6.3%
INH+ RMP+ PZA+ SM	1	3.1%
INH+ RMP+ EMB+ PZA	1	3.1%
INH+ RMP+ PAS	1	3.12%
INH+ RMP+ EMB+ OFX	1	3.1%
INH+ RMP+ SM+ KM	1	3.1%
INH+ RMP+ SM+ KM+ AK	1	3.1%
Total cases	32	100%

INH = isoniazid, RMP = rifampicin, PZA = pyrazinamide, EMB = ethambutol, SM = streptomycin, KM = kanamycin; AK = amikacin; OFX = ofloxacin; PAS = para-aminosalicylic acid

Accessibility to rapid phenotypic and genotypic tests facilitates an early diagnosis of MDR-TB [24]. In the present study, the accessibility to fast methods of detection of drug resistance was increased for the BACTEC MGIT method (n = 31/32; 96.9%), but lower for molecular methods (between 56.2 and 65.6%). Molecular tests cannot be substituted of phenotypic ones, but may be useful in the screening of MTB and anti-TB drug resistance, as well as in the identification of silent mutations that are not identified by phenotypic methods and are considered to be false-positive [24]. The accessibility to Xpert testing was higher (n = 21/32; 65.6%), but with more frequent negative outcomes (n = 3/21; 14.9%), compared to LPA genotyping, which showed positive results in the majority of tested patients (n = 17/18; 94.4%). BACTEC MGIT 960 is extremely important due to the possibility of drug susceptibility testing (DST) for both the first and the second line of anti-TB drugs [25]. In this study, the results regarding MTB distribution pattern of resistance are similar with those identified in the north-eastern part of Romania [25], where the MDR pattern associates additional resistance to the second line of anti-TB medication. A lower proportion of MDR patients included in this study (9.4%) developed XDR, compared to the study of Lunca *et al.* [26], where 17% of MDR patients developed XDR. A study conducted in the Romanian National Pulmonology Institute of Bucharest, involving a large number of molecular tests (872 LPA and 1,580 GeneXpert), reported MTB detection in 88.64% of LPA testing with 126 cases diagnosed with MDR-TB, while 19.87% of GeneXpert tests detected MTB, of which 14 cases were MDR-TB [27].

Evolution under treatment was generally favourable for 84.37% of patients (n=27), only 3 patients developed, during the 4-year study, an extension of MDR pattern to acquired resistance to ofloxacin (floroquinolone) and amikacin (a second-line injectable anti-TB drug), representing XDR-TB new cases. In one case the treatment failed and another one was considered a chronic form of MDR-TB. Sometimes, surgical therapy is required for resolving MDR-TB cases [28]. Considering the high burden of TB in Romania [29], a properly performed bacteriological exam can facilitate the early diagnosis and therapy of new cases of MDR-TB. Reducing the impact of human errors and increasing the adherence to standardized regimens of therapy, the occurrence of MDR-TB can be prevented. Without a sustained supervision of administration and periodic monitoring of adequate anti-TB treatment and therapeutic adherence, the extent of MDR can lead to XDR forms of TB disease.

Conclusions

The prevalence of hospitalized MDR-TB was 1.95%, with the predominance of acquired resistance pattern. The spectrum of MTB resistance was dominated by the HR pattern, with progressive extension of MDR to XDR profile of resistance. MDR-TB occurrence and extension can be prevented by rapid new molecular methods of diagnosis and a better adherence to therapy.

Conflict of interest

The authors declare no conflict of interest.

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PROBLEME DE ETICĂ ÎN COMUNICAREA CU PACIENTUL ONCOLOGIC

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Rezumat
Numeroase modificări au apărut în ultimile decade în îngrijirea pacienților cu cancer. În mijlocul progreselor diagnostice şi terapeutice, o modificare importantă de atitudine a apărut în comunicarea medic-pacient oncologic. În urmă cu câteva decade, medicii nu discutau cu pacienții diagnosticul de cancer. În prezent o asemenea abordare este de neconceput. Modelul paternalist al relației medic-pacient în care în mod tradițional diagnosticul de cancer nu era comunicat pacientului, a fost înlocuit de decizia medicală comună, în care pacientul este informat pentru a putea participa activ în strategia terapeutică. Conform acestui model întrebarea nu este dacă să spunem pacientului, ci care este modalitatea optimă de informare privitoare la diagnostic şi prognostic. Probabil că modalitatea optimă de comunicare este una individualizată, în care medicul este sensibil la nevoile particulare ale pacientului, furnizându-i acestuia într-un mod corespunzător şi onest informațiile necesare unei bune decizii medicale.

Cuvinte cheie: *cancer, aspecte etice, paternalism, autonomie, comunicare.*

Introducere

Comunicarea dintre clinicieni şi pacienți este un concept multi-dimensional care implică conținutul dialogului, componenta afectivă (ceea ce se petrece la nivel emoțional între medic şi pacient) şi comportamentul non-verbal.

Cancerul este o afecțiune amenință-toare de viață şi, deşi progresele terapeutice s-au asociat cu creşterea speranței de vindecare, diagnosticul de cancer se asociază cu teama şi

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nesiguranța. Din acest motiv, comunicarea medicului cu pacientul şi familia acestuia este extrem de importantă [20].

Problemele legate de diagnosticul de malignitate îi vizează şi pe oncologi, care se confruntă frecvent cu comunicarea veştilor proaste şi cu decesul pacienților. Nevoia de informare a pacienților a crescut, iar aceştia îşi consideră medicul curant ca fiind principala sursă de sprijin psiho-emoțional. Pe de altă parte însă oncologii nu sunt pregătiți din punct de vedere profesional pentru comunicare şi pentru dimensiunile interpersonale ale îngrijirii pacientului oncologic [20, 27].

Cercetările legate de comunicare în oncologie au demonstrat asocierea dintre comunicare şi satisfacția pacientului, complianța la tratament, înrolarea în trialuri clinice, o mai bună tranziție de la tratamentul curativ la cel paliativ şi o scădere a stresului medicului oncolog şi implicit a incidenței sindromului de oboseală cronică (burnout) [13, 22].

Comunicarea diagnosticului şi a prognosticului

Etica clinică este o disciplină practică care contribuie la procesul de îngrijire a pacientului centrându-se pe importanța preferințelor pacientului în cadrul relației medic-pacient şi pe obligațiile morale fundamentale ale medicului, care includ onestitatea, competența, compasiunea şi respectul față de pacient. Punctul de start al analizei etice îl reprezintă întâlnirea medic-pacient, întâlnire care defineşte atât scopurile relației medic-pacient, cât şi drepturile şi responsabilitățile mutuale. Din acest punct de vedere, stabilirea principiilor etice în oncologie începe cu înțelegerea semnificației cuvântului “cancer” de către pacienți, familiile lor, medici şi societate. Majoritatea percepțiilor pacienților se bazează pe o combinație a imaginilor din cultura populară cu imaginile experiențelor anterioare ale prietenilor sau membrilor familiei diagnosticați sau tratați pentru cancer. Cei mai mulți pacienți asociază cuvântul “cancer” cu decesul. Datorită variațiilor largi ale percepției cancerului, clinicienii trebuie să exploreze cu grijă implicațiile şi semnificația diagnosticului de cancer [11] pentru fiecare pacient în parte.

Comunicarea adevărului este un factor important al interacțiunii medic-pacient şi implică influențe sociale şi culturale care modulează procesul de înțelegere al bolii atât de către pacient, cât şi de către medic.

În ultimile decade, schimbările apărute în procesul de comunicare cu pacientul oncologic reflectă modificările în relația medic-pacient, de la atitudinea anterioară care considera pacientul un participant pasiv, la atitudinea actuală în care pacientul constituie în majoritatea cazurilor un participant activ la decizia medicală [1, 26]. Apariția unei noi discipline, etica medicală (bioetica) [3, 9], a contribuit la tranziția de la modelul tradițional paternalist al comunicării medic-pacient la modelul actual bazat pe creşterea autonomiei pacientului [1, 11]. De asemenea, doctrina legală a consimțământului informat a catalizat şi promovat aceste schimbări ale relației medic-pacient. Consimțământul informat a impus comunicarea adevărului despre boală şi obținerea permisiunii atât în ceea ce priveşte deciziile terapeutice, cât şi participarea în trialuri clinice. Ca urmare, evaluarea succesului tratamentelor anti-neoplazice a început să includă criterii precum calitatea vieții şi capacitatea funcțională, în asociație cu criteriul tradițional al supraviețuirii. Aceste modificări coincid cu centrarea pe pacient a practicii medicale.

Comunicarea medic-pacient oncologic a progresat de la modelul paternalist din anii 1950-1960, la cel al comunicării complete a adevărului de la sfârşitul anilor '70. Conform modelului paternalist pacientul era subiectul pasiv, având rolul de "copil", dependent de medic, care era considerat ca fiind subiectul activ cu rol de "tată". Din această poziție medicul era cel care decidea pentru pacient şi fără a lua în considerare valorile personale, culturale şi religioase ale acestuia, modelul paternalist presupunea că beneficiul pacientului este echivalent cu beneficiul medical.

Datele din literatură publicate în perioada 1950-1960 sugerează că aproximativ 88% dintre medici, bazându-se pe conceptul paternalist, nu discutau cu pacienții despre diagnosticul de cancer, justificând lipsa comunicării, cel puțin pentru cazurile cu prognostic nefavorabil, prin menținerea speranței pacienților [21]. Spre deosebire de atitudinea medicilor, studiile au arătat că cel puțin 81% dintre pacienți doreau să cunoască detalii despre diagnosticul de cancer [16, 24].

Schimbările apărute în societate în ultimele decade au influențat paradigma paternalistă a relației medic-pacient, astfel că pacienții au început să se implice activ în luarea deciziilor medicale, iar decizia medicală a devenit comună, aparținând atât medicului, cât şi pacientului. Un nou concept de respectare a autonomiei pacientului a înlocuit modelul paternalist şi conform acestui model, prin respectarea valorilor şi deciziilor pacientului, beneficiul acestuia a devenit distinct de beneficiul medical. Ca urmare, pentru ca autonomia pacientului să fie respectată, acesta trebuie informat asupra diagnosticului, prognosticului şi opțiunilor terapeutice. În plus, progresele înregistrate de metodele diagnostice şi strategiile terapeutice, cât şi îmbunătățirea prognosticului unor afecțiuni neoplazice au dus la necesitatea unei informări corecte a pacientului, cu scopul de a creşte complianța la tratament.

Schimbările apărute în comunicarea medic-pacient oncologic sunt subliniate şi de faptul că în prezent un mic procent dintre medici nu comunică pacienților diagnosticul de cancer, atitudine care conform studiilor de etică medicală nu are justificare [14].

Cultura de tip vestic se centrează pe principiul autonomiei. Ca urmare pacienții cu acest fenotip cultural solicită în general o informare completă privitoare la boală şi prognostic şi se implică activ [8, 14] în decizia medicală.

Actualmente, în America de Nord şi în majoritatea țărilor Europei de Vest, relația medic-pacient oncologic implică comunicarea diagnosticului de cancer, dar majoritatea medicilor nu discută despre prognostic decât dacă sunt întrebați [10]. În schimb în Europa de Sud, inclusiv Italia şi Spania şi în Europa de Est persistă încă reținerea de a discuta despre prognostic cu pacienții [19] terminali.

Pentru pacienți necomunicarea diagnosticului se poate asocia cu apariția izolării, anxietății, pierderea autonomiei sau controlului, abandon psihologic, neîncredere, suspiciune şi sentiment de trădare. Pe de altă parte însă, o discuție deschisă despre diagnostic diminuează sentimentul de nesiguranță şi stimulează participarea activă în luarea deciziilor medicale, permite accesul la sprijinul psiho-emoțional şi de asemenea permite pacientului să-şi facă planuri [2] de viitor.

Deşi comunicarea onestă a diagnosticului poate avea un impact emoțional negativ pe termen scurt, majoritatea pacienților se adaptează odată cu trecerea timpului. Linişte şi gratitudine, atitudine pozitivă, scăderea anxietății şi o mai bună acomodare sunt beneficiile pe care le raportează pacienții ca urmare a comunicării diagnosticului de către medicul curant. Când veştile rele sunt comunicate cu tact, onestitate şi într-o manieră suportivă, experiența conversației este mai puțin stresantă pentru pacient. În ceea ce priveşte experiența comunicării diagnosticului de cancer, un studiu efectuat pe un număr de 497 de pacienți [17] a semnalat că predictorii satisfacției pacienților au inclus: perceperea medicului curant ca fiind implicat personal, înțelegerea informației furnizate, modalitatea corespunzătoare de furnizare a informației (cabinetul medicului) şi un interval de timp suficient alocat comunicării. În ceea ce priveşte preferințele pacienților în comunicarea veştilor rele legate de diagnosticul de cancer sau recidivă, un studiu efectuat pe un număr de 351 de pacienți [23] a subliniat că principalele elemente importante pentru pacienți au fost: pregătirea profesională corespunzatoare a medicului, astfel încât acesta să fie la curent cu ultimile noutăți în domeniu, informarea asupra modalităților optime de tratament, alocarea unui interval suficient de timp pentru a răspunde la întrebări, onestitatea medicului referitor la severitatea bolii, utilizarea unui limbaj simplu şi clar, furnizarea directă a informației şi acordarea unei atenții corespunzătoare pacientului.

Majoritatea pacienților diagnosticați cu cancer se prezintă la medic datorită faptului că sunt simptomatici. Un mic număr de pacienți sunt diagnosticați în cadrul evaluărilor de screening. Deoarece speranța are un rol important în reacția pacientului la boală, clinicienii trebuie să țină cont de starea de spirit a pacientului când discută diagnosticul, prognosticul şi opțiunile de tratament. Pacienții simptomatici de mult timp sau care prezintă simptome severe sunt mai puțin surprinşi şi pregătiți pentru diagnosticul de cancer, comparativ cu pacienții asimptomatici în momentul diagnosticului. Unii pacienți pot experimenta o senzație de eliberare după un diagnostic clar, care urmează unei perioade de incertitudine. Comunicarea cifrelor statistice ale supraviețuirii în momentul diagnosticului trebuie contrabalansată de doi factori importanți şi anume: în momentul diagnosticului oncologul nu poate predicționa întotdeauna istoria naturală a bolii sau categoria de pacienți care răspund la tratament, iar în cursul perioadei dificile care urmează comunicării diagnosticului trebuie susținute resursele psihologice şi spirituale ale pacientului şi familiei sale. Ca urmare, deşi comunicarea adevărului este importantă, este mai important de a şti cum şi când să fie comunicat diagnosticul.

Un model optim de comunicare a veştilor rele constă în următoarele etape [7]: stabilirea interviului (dată, locație), evaluarea percepției pacientului privitoare la boală, obținerea invitației pacientului (obținerea permisiunii pacientului de a i se furniza explicații referitoare la boală), furnizarea de cunoştințe şi informație, furnizarea de răspunsuri empatice corespunzătoare emoțiilor pacientului (care survin în cursul comunicării veştilor rele sau a planului de tratament), strategie şi sumar (pentru familie şi pacient). Clinicienii trebuie să inițieze discuția de informare a pacientului referitoare la diagnostic, opțiunile de tratament şi prognostic şi trebuie să încurajeze pacienții şi membrii familiei să pună întrebări, la care să ofere răspunsuri oneste, dar medicii trebuie să respecte prerogativele pacienților de a refuza informația. În acest fel clinicienii trebuie să evite dezvăluirile exhaustive necesare nevoilor personale psihologice şi morale şi să ofere informaţii care sunt corespunzătoare nevoilor pacientului. Prin încurajarea pacienților să pună întrebări la care doresc răspunsuri, medicii promovează un model individualizat al comunicării în beneficiul pacientului şi care respectă obligațiile morale ale comunicării adevărului.

În timp ce majoritatea medicilor din țările vestice comunică pacienților diagnosticul de cancer, informațiile legate de prognostic sunt prezentate mult mai puțin frecvent. În schimb, majoritatea pacienților raportează că informațiile prognostice au o mare importanță pentru ei. Dacă pacienții sunt încurajați activ să pună întrebări, atunci majoritatea întrebărilor puse sunt legate de prognostic [10]. Cu toate acestea necesitățile informaționale ale pacienților care vizează prognosticul variază larg, iar pacienții cu cancere avansate solicită mai puțin frecvent detalii legate de speranța de viață [15]. Studiile au arătat că atât medicii, cât şi pacienții cu cancere avansate supraestimează frecvent probabilitatea de supraviețuire [14], ceea ce ridică controverse asupra modalităților de discutare a prognosticului [4-6, 12, 15] cu pacienții.

Gradul de speranță furnizat de clinician este influențat de datele obiective şi de interpretarea subiectivă a acestor date. Oncologul trebuie să integreze constant în cât de mult comunică pacientului factorii obiectivi şi subiectivi. Deşi dezvăluirea completă a informațiilor medicale este cea mai uşoară modalitate, această strategie reprezintă abdicarea de la responsabilitățile medicului. Pacienții aşteaptă de la medicii lor interpretarea şi filtrarea informațiilor comunicate, iar medicii trebuie să respecte această obligație. În plus, față de obligația de a fi onest cu pacientul, există obligația de a furniza o speranță rezonabilă pacientului cu cancer. Câtă speranță ar trebui să ofere oncologul în discuțiile cu pacientul şi familia acestuia? Răspunsul la întrebare îl reprezintă specificul fiecărui caz în parte, iar factorii care trebuie luați în considerare includ: tipul şi stadiul bolii, vârsta pacientului, co-morbiditățile şi momentul în tratamentul şi evoluția bolii în care are loc discuția. De asemenea, discuțiile legate de îngrijirea paliativă nu ar trebui să fie parte a comunicării inițiale medic-pacient deoarece diminuează optimismul şi speranța pacientului [25].

O altă caracteristică importantă a relației medic-pacient este încrederea. Pacienții oncologici sunt de obicei vulnerabili şi au o nevoie disperată de clinicieni în care să aibă încredere. Deşi unii dintre pacienții cu cancer doresc să-şi exercite autonomia şi să controleze complet deciziile medicale, alții preferă să-şi lase medicii să decidă pentru ei. Majoritatea pacienților se încadrează între cele două extreme, dar toți beneficiază din dezvoltarea unei relații bazate pe încredere cu medicul curant. Importanța încrederii în relația medic-pacient şi vulnerabilitatea chiar şi a pacienților educați este ilustrată într-o lucrare a Dr. Franz Ingelfinger, un distins medic şi academician. Într-un articol intitulat "Aroganța", Dr. Ingelfinger a relatat experiența sa despre multiplele opinii care i-au fost comunicate privitoare la cel mai bun tratament al cancerului de care suferea şi a descris imensa uşurare pe care a simțit-o în momentul în care a primit de la un prieten următorul sfat: "Ai nevoie doar de un doctor". Înțelepciunea sfatului acestui comentariu se aplică tuturor pacienților cu cancer: aceştia au nevoie de un doctor şi este de preferat unul în care să aibă încredere [11].

În modelul contemporan de îngrijire a

pacientului oncologic, care se bazează pe decizia medicală comună, problema principală nu o constituie comunicarea în sine a diagnosticului de cancer, ci cât de mult trebuie spus pacientului privitor la boala sa. Un studiu național efectuat în USA în 1982 a semnalat faptul că 96% dintre pacienți doreau să li se comunice diagnosticul de malignitate, iar 85% dintre ei doreau şi o estimare corectă a speranței de viață, în special dacă aceasta era sub 1 an. Studiul a arătat că în cazul pacienților cu prognostic nefavorabil doar 13% dintre medici comunicau un prognostic real [18]. Cifrele sugerează că, deşi pacienților li se comunică diagnosticul de cancer, de multe ori informațiile necesare luării unei decizii medicale comune sunt trunchiate.

Concluzii

Practica medicală curentă impune respectarea autonomiei pacientului. Ca urmare, pentru a putea lua decizii, pacientul trebuie informat într-un mod corespunzător. În acest model de interacțiune medic-pacient problema principală nu o constituie comunicarea în sine a diagnosticului de malignitate, ci modalitatea optimă de informare privitoare la boală şi prognostic.

În unele culturi diagnosticul de cancer constituie un stigmat negativ şi cunoaşterea impactului psihosocial al termenului este esențială. Ca urmare, utilizarea unor termeni ca "tumoră malignă" este mai puțin traumatizantă şi mai uşor de acceptat.

Probabil că în aceste condiții conduita optimă medicală este una individualizată şi impune ca medicul să fie sensibil la nevoile particulare şi valorile personale, culturale şi religioase ale fiecărui pacient, astfel încât să fie capabil să ofere într-un mod onest şi eficient informațiile necesare unei bune decizii medicale.

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The Triad Nocturia, Smoking and Obstructive Sleep Apnea

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In patients with obstructive sleep apnoea (OSA), a consequence of the intermittent hypoxia is nocturia. The frequency of nocturia related OSA is increased because many pathological pathways are present simultaneously. The aim was to assess the prevalence of nocturia among OSA patients and to identify the relationship with OSA and its comorbidities. A transversal study determining the prevalence of OSA's comorbidities and nocturia related OSA and smoking was assessed, from 2011 to 2015, in 2 Romanian centres of Somnology, in Constanta county. All patients suspected of sleep breathing disorders were investigated by polygraphy and all patients diagnosed with OSA were recruited. Demographic and clinical characteristics were assessed, including the onset of nocturia. The comparison between groups with and without nocturia was performed using SPSS software, using Anova for numerical outcomes and χ^2 test for the categorical ones. Nocturia was highly prevalent (62.75 %) among 204 OSA patients, especially in elderly ($p < 0.00001$). High blood pressure (hypertension), obstructive pulmonary disease (COPD), smoking exposure were more frequently reported in the OSA patients presenting nocturia ($p < 0.05$). Type 2 diabetes and cardiac failure were also frequent, but did not reach a significant threshold of 95%. In conclusion, the nocturia is a frequent symptom and it is influenced by the OSA severity and comorbidities as hypertension and COPD. A further multidisciplinary approach in these patients is justified, especially in smokers.

Key words: nocturia, obstructive sleep apnoea, smoking, COPD

More than half of the patients with obstructive sleep apnoea (OSA) have nocturia [1], a complaint defined by a void preceded and followed by sleep [2]. Behind the low tract infections, nocturia is classified as a global polyuria, nocturnal polyuria and reduced bladder capacity and all these 3 entities might be present in OSA. Therefore, nocturia is classified as a mixt disorder associated with OSA. Directly related to the pathophysiology of the sleep apnoea is the intermittent hypoxia, with an increase of the sympathetic tonus and a decrease of the parasympathetic one, determining an alteration of the bladder contractility and detrusor instability. The intermittent collapse of the upper airways increases the negative intrathoracic pressure that opposes to the obstruction [2].

Consequently, the transmural left ventricular pressure rises and the afterload increases. So, the negative intrathoracic pressure augments the venous return and right ventricular load, while the hypoxic pulmonary vasocontriction augments the right ventricle afterload. The higher intraventricular pressure triggers the secretion of the natriuretic peptides [3]. Through its extensive influence on metabolic and vascular inflammation, OSA impairs the renal concentration function and induces hormonal changes, which both contribute to the nocturia [4].

Experimental part

In a cohort of new OSA cases, the study proposed to assess the prevalence of nocturia in relation with the OSA's comorbidities. The recruitment methodology included all patients with suggestive sleep breathing symptoms, but not previously diagnosed with OSA, examined by cardio-respiratory sleep polygraph in Constanta Somnology centre, Romania, between October 2011 to April 2015. Patients with central sleep apnoea, obesity-hypoventilation syndrome and upper airways resistance syndrome were excluded from the analysis and 204 OSA patients were included. Using a standard examination protocol interview, all signs and symptoms of OSA, chronic diseases related OSA and smoking exposure were assessed as previous analysis reported [5]. The body mass index (BMI) was calculated as weight (kg)/height (m)^2. The apnoea-hypopnea index (AHI) and oxygen desaturation index (ODI) were extracted from the polygraph datasheets. ODI represents the hourly average number of desaturation episodes; a desaturation episode is recorded for each least 4% decrease in saturation from the average saturation in the preceding 2 min that lasts for more than 10 seconds [6]. According to the AHI value, cases were grouped in mild (AHI = 5-14.9), moderate (15-29.9) and severe (AHI> 30) forms of OSA. Classes of OSA severity were, also, defined according to the ODI values, as following: mild (ODI: 5-14.9); moderate (ODI = 15-29.9) and severe (ODI> 30). Patients were divided in 2 groups: group 1 included the patients with nocturia and group 2 the patients without nocturia. COPD severity was considered as stages I-IV, according to the Global Initiative for Chronic Obstructive Lung Disease [7].The statistical analysis of the data recorded was performed with SSPS software (StatPlus for Mac, Analyst Soft Inc. version V6, 2016). Comparison between categorical and numerical variables was

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performed using chi^2 test and Kruskal Wallis Anova. The threshold for the statistical significance was set at 95%.

Results and discussion.

The prevalence of nocturia among adult OSA patients was high (n= 128/204; 62.75%). Nocturia was not reported by 76 patients (37.25 %). Patients with nocturia were older than those without (55.37 + 9.39 years versus 48.59 + 11.22 years; p< 0.00001) and the distribution of cases by age revealed the predominance of nocturia among patients older than 50 years (fig. 1). From the total number of 204 OSA patients, mean aged 52.84 + 10.61 years, 160 (78.43%) were men and 44 (21.57%) women, but gender did not influenced the occurrence of nocturia (p< 0.7) (table I).

Smoking exposure was higher in OSA patients (67.65%), counting similar values in both groups with and without nocturia (p< 0.9) but the distribution of OSA comorbidities among groups was totally different (table 1). A significantly higher prevalence of high blood pressure (p< 0.00001) and COPD (p< 0.04) was noticed in patients with nocturia compared with no significance among patients with OSA and diabetes (p< 0.07) (table I). Considering the stages of high blood pressure (HBP), the majority of cases were in stage 2 in both groups. However, the distribution of the HPB stages in the 2 groups was statistically significant (p = 0.024), with more severe cases in group 1. COPD was diagnosed in 28.91% of the patients from group 1 and in 21.06% of the patients in group 2. Almost ¾ of OSA patients were diagnosed with moderate COPD in both groups (28/37 patients in group 1 and 12/16 patients in group 2), without differences of distribution by the severity of lung function decline between groups (p = 0.78). Among 60 patients with ENT disorders, the most prevalent disease in both groups was nasal polyposis (8 cases in group 1 and 7 cases in group 2), followed by the nasal septum deviations (6 cases in group 1 and 7 cases in group 2), the great majority of them with previously surgical treatment (70.58% of cases in group 1 and 85% in group 2). Difference in the distribution of the ENT disorders was not statistically significant (p = 0.19), but there were more patients with associated ENT disorders in group 1 (31% versus 20% in group 2). Patients with nocturia had more severe forms of OSA revealed by higher values of AHI and ODI, and lower average saturation with minimal values of O_2 saturation. The distribution of cases among groups, by the severity of AHI, was significantly different (p= 0.0012) with a lower proportion of mild OSA (7.08%) in group 1 compared to

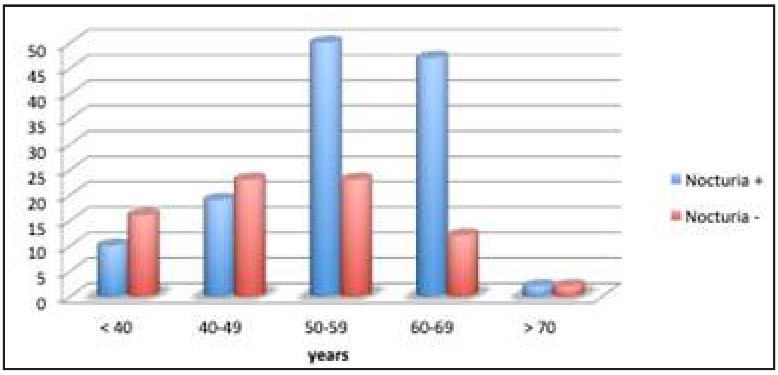

Fig. 1. Age distribution of OSA cases by nocturia

	Total	Group 1	Group 2	P<
Number; %	204 (100%)	128 (62.75%)	76 (37.25%)	
Age (years)	52.84 $\pm$ 10.61	55.37 $\pm$ 9.39	48.59 $\pm$ 11.22	0.00001
Sex (M/F)	160/44	99/29	61/15	0.7
BMI	35.21 $\pm$ 6.72	35.77 $\pm$ 6.83	34.26 $\pm$ 6.44	0.2
Smokers (No/%)	138 (67.65%)	87 (67.97%)	51 (67.1%)	0.9
Current smokers	81	48	33	
Ex smokers	57	39	18	
Non smokers (No/%)	66 (32.35%)	41 (32.03%)	25 (32.9%)	
Comorbidities				
T2D	31	24	7	0.07
HBP	130	95	35	0.00001
Cardiac failure	24	19	5	0.08
COPD	53	37	16	0.04
ENT disorders	60	35	25	0.4
OSA characteristics				
AHI	45.91 $\pm$ 23.91	49.82 $\pm$ 23.59	39.302 $\pm$ 23.12	0.002
ODI	48.04 $\pm$ 26.98	51.71 $\pm$ 27.10	41.86 $\pm$ 25.79	0.002
Av SO_2	91.21 $\pm$ 4.001	90.99 $\pm$ 4.09	91.59 $\pm$ 3.85	0.4
Min SO_2	72.96 $\pm$ 7.69	72.52 $\pm$ 7.63	73.63 $\pm$ 7.82	0.4

Legend: BMI = body mass index; T2D = type 2 diabetes; HBP = high blood pressure; COPD = chronic obstructive lung disease; ENT= Ear Nose Throat; OSA = obstructive sleep apnoea; AHI = apnoea-hypopnea index; ODI = oxygen desaturation index; Av SO_2 = average saturation in O_2; Min SO_2 = minimal level of saturation in O_2

Table I
CHARACTERISTICS OF THE STUDY GROUP

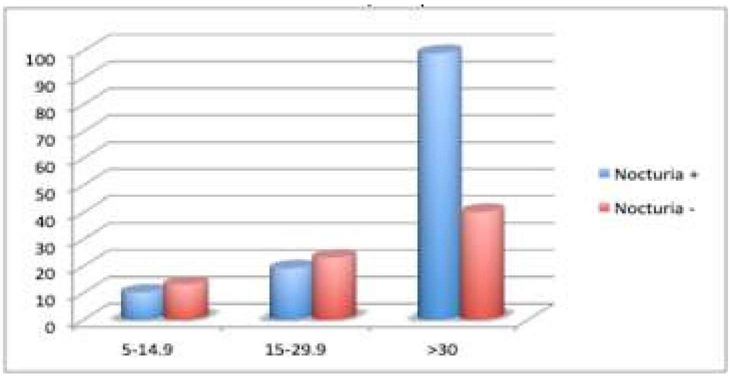

Fig.2. Severity of obstructive sleep apnoea among groups, according to the apnoea hypopnea index (AHI).

17.1% in group 2, and higher proportion of severe OSA in group 1 (77.34%) than in group 2 (52.63%) (fig. 2). These significant differences in evaluating the severity of OSA forms are maintained when using ODI as criteria for severity (p= 0.00196).

This study found a high prevalence of nocturia in OSA patients, in accordance with other previously reported data [8,9]. Two biases of the reported symptom of nocturia in OSA were described: the awaken time during sleep that could initiate the reflex of voiding and the significant contribution of aging [10]. The influence of age was also confirmed in our study, by mostly cases in their fifth and sixth decade of age having nocturia. Aging is associated with different modifications that can ultimately contribute to nocturia, such as: impairment of the circadian rhythm decreasing the nocturnal arginine-vasopression (AVP) secretion as well as the nephron response to AVP [11], and augmentation of the collagen to smooth muscle ratio of the bladder wall limiting the bladder capacity [12]. Despite these, the intervention by continuous positive airway pressure (CPAP) in reducing the number of the nocturnal voiding [9] is a strong argument for an independent existing relation between nocturia and OSA. Sometimes more efficient measures and therapies have to be associated in OSA patients as smoking cessation, losing weight by exercise and hypocaloric diet, or even dental interocclusal thermoformed appliances for preventing other risk factors of sleep disturbances [13,14]. We also found a significant incidence of comorbidities, as previously reported in other OSA studies [15], some of them having a direct effect on the nocturnal, intermittent obstruction, while others only sharing common pathogenic pathways [16] or being therapy related [17]. Nocturia related to OSA revealed a significant association with HBP and COPD, while other OSA comorbidities as cardiac failure and diabetes were not significantly associated. All of these OSA comorbidities are sharing common pathophysiological mechanisms as activation of the sympathetic neuronal system, of the renin-angiotensin axis (RAA) [18] and a high level of arginin-vasopression (AVP). In late stage of hypertension [19] and cardiac failure, abnormal high atrial and brain natriuretic peptides (ANP and BNP) levels are reported. The triggers of these pathophysiological mechanisms are complemented by specific neuro-hormonal pattern of OSA. Concerning the RAA axis, it is important to underline that primary hyperaldosteronism is more prevalent in OSA, particularly in the hypertensive patients [19]. A recent meta-analysis found an increased plasma levels of angiotensin II and aldosterone in OSA [20], consistent with a high prevalence. A predominant renal effect of the RAA activation was noticed in OSA; this effect is reflected by a lower effective renal basal flow, a higher filtration fraction and a blunted reno-vascular response to angiotensin II [21]. All these mechanisms can contribute to the progression to the chronic renal disease and accelerate the loss of kidney function [22], explaining the urine concentration impairment and the diminished response to AVP. The subclinical vascular inflammation and the atherogenic process in OSA [23] will also contribute to the impairment of renal flow, eventually leading to nocturia. Aldosterone retention of sodium and water manifested during the daytime expend the body volume of fluid. The nocturnal rostral shift of this fluid towards the neck, increases the severity of OSA [24], but also enhances the secretion of the ANP and BNP. The negative pressure generated to overpass the upper airways obstruction promotes the venous return. Intermittent hypoxia and pulmonary vasoconstriction increases the atrial transmural pressure, aggravating the atrial stretch and the natriuretic peptides release. Indeed, an increased fraction of sodium excretion was recorded, particularly in the hypertension patients [25]. Saturation in O_2 correlates positively with basal and pulse secretion of ACTH and cortisol; the hippocampal damage and sympathetic nervous activation presumably impair the normal control feedback of the hormonal secretion [26]. Nocturia is related to severe forms of OSA (p< 0.002) as Mansour et al, also, showed [27]. Several factors are referred to the quality of life in OSA patients, among which diurnal somnolence, dyspnoea and nocturia are most frequently cited. Although lung function can be impaired, particularly among the obese patients [28], the quality of life might be earlier affected, as well as for other lung diseases [29,30]. Nocturia affects the quality of life of OSA patients by further decreasing the duration of sleep, the proportion of REM sleep and the sleep efficiency. CPAP therapy provides an important improvement of the symptoms [31], but it does not entirely eliminate the nocturnal voiding.

Conclusions

Nocturia is high prevalent among OSA cases, influenced by OSA severity and its comorbidities as hypertension and COPD. Although smoking exposure is the main risk factor of COPD and it was prevalent among OSA patients. Interdisciplinary collaboration is mandatory in order to explore better the mechanisms of nocturia in OSA and to identify specific biomarkers for severe OSA forms for providing an efficient, individualized and patient-centered treatment.

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Partea a II-a – TRATAMENT

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CUVÂNT INTRODUCTIV

Ghidul pentru managementul cancerului pulmonar, partea a II-a, cuprinde tratamentul cancerului pulmonar şi este continuarea firească a primei părţi, cea de diagnostic şi stadializare.

Acest ghid se doreşte a fi un punct de referinţă al medicului practician care tratează pacienţii cu cancer bronho-pulmonar şi se situează alături de celelalte ghiduri naţionale şi internaţionale în vigoare.

Pe de altă parte, beneficiul pacientului cu cancer bronhopulmonar constă într-un tratament aplicat conform standardelor internaţionale, unitar în toată ţara, cu criterii şi indicaţii bine stabilite.

Progresele înregistrate în ultimii ani în tratamentul cancerului bronhopulmonar au adus în lumină noi opţiuni terapeutice pe care atât practicianul, cât şi pacientul trebuie să le cunoască.

AUTORII

GHID PENTRU MANAGEMENTUL CANCERULUI PULMONAR

Partea a II-a – TRATAMENT

TRATAMENTUL CANCERULUI BRONHOPULMONAR

Tratamentul cancerului bronhopulmonar (CBP), în special al celui fără celule mici (NSCLC), a înregistrat progrese importante în ultimii ani, ca urmare a cercetării fundamentale ale cărei rezultate s-au reflectat în predicţia răspunsului la tratament şi în dezvoltarea terapiilor ţintite.

Tratamentul CBP se face diferenţiat, în funcţie de tipul histologic, stadializare, comorbidităţi.

De reţinut!
Evaluarea multidisciplinară ar trebui să concluzioneze decizia terapeutică în maxim 4 săptămâni de la prima evaluare!

1. TRATAMENTUL CBP CU CELULE MICI (SCLC)

Carcinomul bronhopulmonar cu celule mici (SCLC) reprezintă aproximativ 15% din cancerele bronho-pulmonare [1]. Comparativ cu CBP fără celule mici (NSCLC), SCLC prezintă un timp de dedublare mai rapid, o rată de creştere mai mare şi o metastazare precoce.

Aproximativ 2/3 din pacienţii cu SCLC se prezintă cu boală extinsă, doar 1/3 cu boală limitată [2]. Sensibilitatea SCLC la chimio- şi radioterapie este extrem de mare, însă cu toate acestea majoritatea pacienţilor decedează din cauza recurenţei bolii [3, 4]. Chimio- şi radioterapia (RT) pot avea viză curativă pentru un număr mic de pacienţi cu boală limitată [5, 6]. Chimioterapia are rol paliativ şi poate prelungi supravieţuirea pentru majoritatea pacienţilor cu boală extinsă [7, 8].

1.1. Tratamentul bolii limitate la torace (stadiile I-IIIB)

Pentru toţi pacienţii cu SCLC, indiferent de stadiu, chimioterapia este un element esenţial al planului terapeutic [9, 10]. Chirurgia plus chimioterapia adjuvantă poate fi indicată la cazurile T1-2 N0-1 M0, alternativa fiind chimio-radioterapia concomitentă.

Pentru pacienţii cu SCLC în stadiu limitat şi cu un status de performanţă (PS) bun (0-2), tratamentul constă în chimio-radioterapie (RT) toracică concomitentă [6, 11, 12]. Pacienţii cu SCLC stadiu limitat trebuie trataţi cu combinaţii de etoposid/sare de platină (cisplatin sau carboplatin), în combinaţie cu RT toracică.

Pacienţii cu boală limitată sunt potenţial curabili. Meta-analizele şi studiile randomizate, care au utilizat chimio-RT concomitentă, raportează rate de supravieţuire la 5 ani de 20-25% [13]. La pacienţii cu boală în stadiu limitat, EP plus RT toracică determină rate de răspuns de 70-90% [14], cu o supravieţuire medie de 14-20 de luni; rata de supravieţuire la 2 ani este de aproximativ 40% [15]. Radioterapia toracică creşte cu 25-30% controlul local la această categorie de pacienţi şi se asociază, de asemenea, cu o creştere de 5-7% a ratei de supravieţuire la 2 ani [11, 12].

Pentru SCLC în stadiu limitat, RT trebuie utilizată concomitent cu chimioterapia şi trebuie să înceapă precoce (ciclul 1 sau 2 de chimioterapie), la o doză de 1,5 Gy x 2/zi (hiperfracţionare), până la doza totală de 45 Gy în 3 săptămâni sau la o doză de 2 Gy/zi (fracţionare standard), până la doza totală de 60-70 Gy [11, 16-22]. La pacienţii cu un PS bun (0-2), chimio-RT este superioară terapiei secvenţiale [23, 24].

Standardul minim pentru iradierea toracică constă în RT tridimensională (3D) conformaţională (RT 3D-conformaţională) [1], cu câmpuri multiple (ideal ≥4). În cazuri selecţionate pot fi utilizate tehnici IMRT (Intensity-Modulated Radiation Therapy)/IGRT (Image Guided Radiation Therapy) [25, 26].

Peste 50% din pacienţii cu SCLC dezvoltă metastaze cerebrale. Acest fapt a determinat utilizarea iradierii craniene profilactice (PCI). O meta-analiză a tuturor studiilor randomizate PCI a raportat o scădere cu 25% a incidenței la 3 ani a metastazelor cerebrale, de la 58,6%, în grupul de control, la 33,3% în grupul PCI [27]. Astfel, PCI pare să prevină şi nu doar să întârzie apariţia metastazelor cerebrale. Această meta-analiză a raportat, de asemenea, un plus de 5,4% în supravieţuirea la 3 ani la pacienţii trataţi cu PCI, de la 15,3% în grupul de control, la 20,7% în grupul PCI [27].

PCI este indicată atât la pacienţii cu SCLC stadiu limitat cu remisiune completă, parţială sau boală staţionară după chimio-radioterapie. [28, 29]. Regimul recomandat pentru PCI este 25 Gy în 10 fracţiuni (2,5 Gy/fracţiune) [1, 28, 29]. Administrarea PCI nu trebuie făcută în acelaşi timp cu chimioterapia sistemică, din cauza riscului crescut de neurotoxicitate.

De reţinut!
Cel mai frecvent regim de chimioterapie, utilizat în SCLC în stadiu limitat, este combinaţia etoposid/ derivat de platină (cisplatin sau carboplatin).
Chimio-RT concomitentă precoce este superioară terapiei secvenţiale.
La pacienții cu răspuns obiectiv sau boală stabilă, PCI previne apariţia metastazelor cerebrale, cu creşterea supravieţuirii şi a calităţii vieţii.

1.2. Tratamentul bolii extinse (stadiul IV)

Două treimi din pacienţii cu SCLC au în momentul diagnosticului boală extinsă.

Pentru pacienţii cu boală extinsă, tratamentul recomandat constă în chimioterapie (etoposid/cisplatin). RT poate fi utilizată în cazuri selecţionate, pentru paliaţia simptomelor cauzate de tumori primare şi boli metastatice (metastaze cerebrale, epidurale, osoase) [1].

La pacienţii cu boală avansată, chimioterapia se asociază cu rate de răspuns de 60-70% [14]. Din păcate, supravieţuirea medie este de 9-11 luni, iar rata de supravieţuire la 2 ani este de sub 5% [15].

Iradierea profilactică craniană este indicată şi la pacienţii cu boală extinsă, cu remisiune completă sau parţială a bolii sub tratament citostatic [28, 29]. Regimul recomandat pentru PCI este 25 Gy în 10 fracţiuni (2,5 Gy/fracţiune) [1, 28, 29].

Au fost evaluate multiple strategii terapeutice, având ca scop ameliorarea rezultatelor obţinute cu tratamentul standard şi creşterea supravieţuirii pe termen lung, prin folosirea de triplete de chimioterapie, utilizarea de regimuri intensificate, terapie de menţinere, regimuri chimioterapice alternante fără rezistenţă încrucişată. Niciuna dintre aceste strategii, însă, nu a reuşit să aducă avantaje semnificative, comparativ cu abordarea standard [1].

De reţinut!
Pentru pacienţii cu SCLC în stadiu avansat, tratamentul recomandat constă în chimioterapie (etoposid/cisplatin sau etoposid/carboplatin), urmată de iradiere craniană profilactică la pacienţii cu răspuns obiectiv la chimioterapie.

1.3. Tratamentul bolii recidivate

Pacienţii cu recădere au indicaţie de chimioterapie de linia a doua. Candidaţii ar trebui selectaţi pe baza răspunsului la terapia de primă linie, intervalului de timp de la încheierea primei linii de tratament, toxicităţii reziduale a terapiei de primă linie şi PS, deoarece probabilitatea de răspuns la linia a doua de chimioterapie depinde de toţi aceşti factori [13].

Deşi SCLC este extrem de responsiv la tratamentul iniţial, majoritatea pacienţilor cu recădere sunt relativ rezistenţi la terapie [30]. Aceşti pacienţi au o supravieţuire medie sub chimioterapia de linia a doua de numai 4-5 luni. Probabilitatea de răspuns la chimioterapia de linia a doua depinde de intervalul de timp dintre tratamentul iniţial şi recidivă: dacă acest interval este sub 3 luni (boală refractară sau rezistentă), răspunsul la majoritatea agenţilor citostatici sau regimurilor de chimioterapie este slab (≤ 10%); în cazul în care acest interval este de peste 3 luni (boală sensibilă), sunt aşteptate rate de răspuns de aproximativ 25% [1]. Cu cât intervalul până la recădere este mai lung, şansele de a obţine o nouă remisiune utilizând acelaşi regim care a fost utilizat în linia întâi (etoposid/cisplatin sau etoposid/carboplatin) sunt mai mari. Topotecanul oral a ameliorat supravieţuirea, calitatea vieţii şi controlul simptomelor faţă de placebo într-un studiu randomizat de faza a III-a, în care jumătate din pacienţi aveau boală rezistentă la chimioterapia de linia întâi [31]. Într-un studiu randomizat mai vechi, topotecan i.v. a fost echivalent în termenii ratei de răspuns, ai timpului până la progresia bolii şi ai supravieţuirii globale cu protocolul CAV (ciclofosfamidă + doxorubicină + vincristin), monoterapia având însă o toleranţă mai bună. Topotecanul oral şi intravenos s-au dovedit la fel de eficiente, într-un studiu randomizat, dar cu un profil de toxicitate întrucâtva diferit. În consecinţă, la pacienţii cu reşută sensibilă sau rezistentă, tratamentul recomandat este topotecanul fie oral, fie i.v, iar protocolul CAV constituie o alternativă. Cazurile cu reşută chimio-sensibilă pot beneficia şi de reintroducerea tratamentului utilizat în linia întâi (etoposid/platină). Alegerea chimioterapiei de linia a doua trebuie să ţină seama de preferinţele şi confortul pacientului, precum şi de toxicitate [13].

Alţi agenţi cu activitate moderată în studiile de fază II includ docetaxel, paclitaxel, irinotecan, vinorelbină, gemcitabină, ifosfamidă şi etoposid oral, care pot constitui opţiuni pentru o terapie ulterioară la pacienţii cu status de performanţă care se menţine bun [1].

Chimioterapia de linia a doua trebuie efectuată până la două cicluri după obţinerea celui mai bun răspuns, până la progresia bolii sau dezvoltarea unor toxicităţi inacceptabile.

De reţinut!
Pacienţii cu recădere au indicaţie de chimioterapie de linia a doua.
Majoritatea pacienţilor cu recădere sunt relativ rezistenţi la terapie.
Topotecanul oral s-a dovedit superior faţă de placebo şi echivalent cu topotecanul intravenos, în studii randomizate.
Topotecanul i.v. s-a dovedit la fel de eficient, dar mai bine tolerat decât regimul CAV.

2. TRATAMENTUL TUMORILOR PULMONARE NEUROENDOCRINE

Carcinoamele pulmonare neuroendocrine (LNT) se clasifică în: 1) carcinoame neuroendocrine cu grad înalt de malignitate (SCLC şi carcinoame neuroendocrine cu celulă mare [LCNEC]); 2) carcinoame neuroendocrine cu grad intermediar de malignitate (tumori carcinoide atipice); 3) carcinoame neuroendocrine cu grad scăzut de malignitate (tumori carcinoide tipice) [1, 32, 33].

Majoritatea LNT aparţin histotipului SCLC şi sunt tratate ca atare. LCNEC este tratat ca şi NSCLC [1, 34].

LNT cu grad intermediar şi scăzut de malignitate reprezintă 1-2% din CBP şi, în general, sunt diagnosticate în stadii precoce (stadiul I). Metastazele în ganglionii limfatici regionali (stadiile II, III) sunt întâlnite mai frecvent în cazul tumorilor cu grad intermediar.

Comparativ cu alte tipuri histologice de carcinoame pulmonare, prognosticul este excelent pentru mulţi pacienţi diagnosticaţi cu tumori carcinoide atipice/tipice. Pentru pacienţii diagnosticaţi cu LNT cu grad intermediar/scăzut în stadiile I, II, IIIA este recomandată intervenţia chirurgicală.

În cazul carcinoidelor tipice fără extensie în parenchimul pulmonar, limitate la axul bronşic, sunt de ales rezecţiile bronho-anastomoză. Rezecţiile de bronşie primitivă sau chiar de carină, cu reconstrucţia continuităţii aeriene prin diverse procedee, au un prognostic foarte bun pe termen lung. Chiar şi când extensia tumorii vizează parenchimul pulmonar, intervenţia chirurgicală trebuie să evite pe cât posibil pneumonectomia, mai ales atunci când afecţiunea este situată pe partea dreaptă.

Ratele de supravieţuire la 5 şi 10 ani sunt de peste 90% pentru pacienţii cu carcinoide tipice şi de 50-70% pentru pacienţii cu carcinoide atipice [1, 35-37]. Interesarea ganglionilor limfatici scade supravieţuirea pe termen lung [1, 35-37].

Dacă chirurgia nu este fezabilă, pentru LNT cu grad scăzut stadiul III este indicată RT externă, iar pentru LNT cu grad intermediar stadiul III este recomandată chimio-RT.

Terapia sistemică (cisplatin/etoposid, temozolomidă, sunitinib sau everolimus) este recomandată pacienţilor cu boală nerezecabilă sau cu stadii avansate, dar ratele de răspuns sunt modeste [1, 28-43].

Terapia cu octreotide este indicată în cazuri selecţionate, pentru pacienţii cu octreoscan pozitiv sau simptomatologie datorată sindromului carcinoid [1].

De reţinut!
Majoritatea LNT aparţin histotipului SCLC şi sunt tratate ca atare.
LCNEC este tratat ca şi NSCLC.
LNT cu grad intermediar şi scăzut de malignitate în stadiile I, II, IIIA beneficiază de intervenţie chirurgicală, iar pacienţii cu boală nerezecabilă sau în stadii avansate beneficiază de terapie sistemică.

3. TRATAMENTUL CBP FĂRĂ CELULE MICI (NSCLC)

CBP prezintă cea mai mare rată de mortalitate dintre toate neoplaziile şi constituie a doua localizare neoplazică ca frecvenţă la ambele sexe (după cancerul mamar la sexul feminin şi după cancerul de prostată la sexul masculin). CBP este agresiv, iar tratamentul constituie o provocare.

Descoperirea şi dezvoltarea în ultima decadă a terapiilor ţintă moleculare au avut un impact major asupra tratamentului CBP fără celule mici (NSCLC) avansate, în prezent existând o paletă de terapii personalizate incluse în tratamentul acestei neoplazii.

Toţi pacienţii diagnosticaţi cu NSCLC avansat sunt potenţial candidaţi pentru studiile care evaluează noi terapii [44, 45].

NSCLC reprezintă 80-85% din formele de CBP şi include ca şi principale tipuri histologice carcinomul scuamos şi carcinoamele non-scuamoase (adenocarcinomul şi carcinomul cu celule mari). Carcinomul epidermoid (scuamos) este mai strâns corelat cu fumatul şi este frecvent localizat la nivelul bronhiilor mari. Incidenţa acestui tip histologic este în scădere (în România el ocupă încă primul loc cu circa 40% din cazuri). Adenocarcinomul este responsabil de circa 35% din toate cazurile de CBP, are o incidenţă în creştere şi este cel mai frecvent tip de CBP la nefumători. Carcinoamele cu celule mari (5-10%), reprezintă un grup heterogen de tumori maligne nediferenţiate cu origine în celulele epiteliale [45].

NSCLC este o boală heterogenă, evoluţia sa fiind specifică pentru fiecare pacient în ceea ce priveşte caracteristicile clinice, prognosticul, răspunsul şi toleranţa la tratament.

Identificarea mutaţiilor în NSCLC a condus la dezvoltarea de terapii moleculare ţintite, în special în adenocarcinoame [44].

Utilizarea terapiilor moleculare ţintite a dus la creşterea supravieţuirii la pacienţii cu boală metastatică [46]. Trei modificări genetice au fost identificate relativ frecvent în adenocarcinoamele pulmonare: mutaţii ale KRAS (la 20-25% din cazuri), mutaţii activatoare ale EGFR (epidermal growth factor receptor, la 10%, cel mai frecvent în exonii 19 şi 21), şi rearanjări ale genei ALK (anaplastic lymphoma kinase, la 4%). Inhibitorii de tirozin-kinaze anti-EGFR (erlotinib, gefitinib, afatinib) şi inhibitorii ALK (crizotinib, ceritinib) sunt intraţi în terapeutica clinică. Până în prezent nu există niciun medicament înregistrat pentru pacienţii cu mutaţii KRAS [44].

Intervenţia chirurgicală, RT şi chimioterapia (inclusiv terapia moleculară ţintită) sunt cele trei modalităţi terapeutice utilizate frecvent în tratamentul NSCLC şi pot fi utilizate în monoterapie sau în combinaţie, în funcţie de stadiul bolii [47].

Un număr mic de pacienţi cu NSCLC sunt diagnosticaţi în stadii precoce, beneficiind, în consecinţă, de tratament cu potenţial curativ (chirurgie, RT). Intervenţia chirurgicală rămâne opţiunea terapeutică cu cel mai mare potenţial curativ în boala localizată. Chimioterapia adjuvantă postoperatorie poate aduce beneficii suplimentare pentru pacienţii cu NSCLC rezecat (stadiile II-III). radioterapia adjuvantă are beneficii limitate la cazurile pN2. Majoritatea pacienţilor se prezintă în stadiul III local-avansat (30-40%) şi au indicaţie de chimio-radioterapie combinată şi respectiv în stadiul IV (40%) având indicaţie de chimioterapie/ terapie moleculară.

La pacienţii cu boală în stadiu avansat, chimioterapia sau inhibitorii tirozin-kinazici (TKI) ai receptorului factorului de creştere epidermal (EGFR) se asociază cu o ameliorare modestă a supravieţuirii medii, supravieţuirea generală (OS) fiind în general scăzută [45, 48, 49]. Ratele de supravieţuire la un an pentru NSCLC avansat sunt în creştere (mediană ~12-18 luni), însă ratele de supravieţuire la 5 ani au rămas în jur de 15% [45, 50].

De reţinut!
Intervenţia chirurgicală, RT şi chimioterapia/terapia moleculară ţintită sunt cele trei modalităţi terapeutice utilizate frecvent în tratamentul NSCLC.
Intervenţia chirurgicală rămâne singura opţiune terapeutică cu potenţial curativ în boala localizată. Chimioterapia adjuvantă ameliorează supravieţuirea faţă de chirurgia singură în stadiile II-III operate radical.
Beneficiul radioterapiei adjuvante este limitat la categoria pN2.
Pentru boala avansată loco-regional (stadiile III) chimio-radioterapia concomitentă reprezintă tratamentul standard.
NSCLC în stadiu avansat (stadiul IV) beneficiază de chimioterapie şi terapie moleculară.

În momentul diagnosticului, pacienţii cu NSCLC pot fi împărţiţi în trei grupe, care reflectă extensia bolii şi modalităţile terapeutice [45]:

a) cu tumori rezecabile (stadiile I şi II şi categorii selectate de pacienţi cu stadiul III – T3N1):
   - acest grup prezintă cel mai bun prognostic;
   - pacienţii cu boală rezecabilă, dar la care intervenţia chirurgicală este contraindicată, sunt candidaţi pentru radioterapie cu intenţie curativă;
   - combinaţiile citostatice adjuvante pe bază de cisplatin oferă un avantaj în supravieţuire pentru pacienţii cu stadiile II şi IIIA rezecate.

b) cu tumori avansate local (T3/T4) şi/sau regional (N2/N3):
   - tratamentul standard este chimio-radioterapia asociată (asocierea concomitentă superioară celei secvenţiale);

- pacienţii selectaţi cu T3 sau N2 (găsit intraoperator) beneficiază de intervenţie chirurgicală şi chimioterapie preoperatorie sau postoperatorie, fie chimio-RT.

c) cu boală metastatică (M1):
- statusul de performanţă bun (PS), sexul feminin şi un singur sediu de boală metastatică se asociază cu un avantaj în supravieţuire [50, 51];
- combinaţiile citostatice (dublete pe bază de sare de platină cu o moleculă de generaţia a III-a în linia întâi de tratament) se asociază cu un avantaj în supravieţuire şi paliaţia simptomatologiei cu ameliorarea calităţii vieţii;
- pentru carcinoamele non-scuamoase, dubletul cisplatin + pemetrexed confer o supravieţuire mai lungă decât cisplatin + gemcitabină şi, respectiv, asocierea bevacizumab la dubletul paclitaxel + carboplatin este superioară combinaţiei fără bevacizumab.
- terapia cu EGFR-TKI, la cazurile cu mutaţii activatoare ale EGFR, ameliorează supravieţuirea fără progresia bolii faţă de chimioterapia pe bază de cisplatin.
- terapia de întreţinere cu pemetrexed sau erlotinib ameliorează supravieţuirea faţă de strategia de urmărire fără tratament de întreţinere.
- pacienţii cu progresie, trataţi anterior cu combinaţii citostatice pe bază de sare de platină pot beneficia de controlul simptomelor şi ameliorarea supravieţuirii prin terapia de linia a doua/ a treia cu docetaxel, pemetrexed (exclusiv carcinoame non-scuamoase) sau inhibitorii EGFR.
- pacienţii cu boală metastatică pot beneficia de radioterapie paliativă în cazuri individuale (ex. iradierea metastazelor cerebrale, a metastazelor osoase dureroase sau iradierea decompresivă pentru sindroamele de compresiune a venei cave superioare sau compresiune medulară).

3.1. Tratamentul CBP-NSCLC în stadiu localizat/local-avansat

3.1.1. Tratamentul chirurgical

Intervenţia chirurgicală este opţiunea terapeutică cu cel mai mare potenţial curativ în NSCLC.

Intervenţia chirurgicală este precedată de evaluarea funcţională respiratorie, care are ca scopuri [52]:
- predicţia complicaţiilor post-operatorii: *se poate opera?*;
- planificarea îngrijirilor peri-operatorii;
- estimarea funcţiei pulmonare în postoperator, pentru a permite o calitate rezonabilă a vieţii (QoL): *cât se poate rezeca?*

Evaluarea funcţională include:

a) spirometrie, curbe flux-volum:
- capacitatea vitală fortaţă (FCV):
    - <50% din prezis sau <1,5 l asociată cu risc operator crescut;
- VEMS (volumul expirator maxim pe secundă):
    - VEMS postoperator se calculează după următoarea formulă:

      VEMS postoperator = VEMS preoperator x (1-y/19),

  unde y reprezintă numărul segmentelor care vor fi rezecate, iar 19 reprezintă numărul total de segmente; se pierd 5,5-6% pentru fiecare segment rezecat;
- MEF_{50} (debitul expirator maxim instantaneu la 50% CV);
- FEF_{25-75} (debitul expirator maxim pentru jumătatea CV forţate);
- MVV (ventilaţia voluntară maximă):

  - testează parenchimul pulmonar, căile aeriene, musculatura respiratorie, cooperarea voluntară şi este un predictor mai bun pentru complicaţiile postoperatorii comparativ cu debitele expiratorii;
  - măsurare indirectă: VEMS x 35 (sau 40);
  - măsurare directă: inspir + expir;

b) test bronhodilatator – risc mai mic dacă există reversibilitate a obstrucţiei;
c) analiza gazelor sangvine:
   - PaO_2<50 mmHg şi $PaCO_2$>45 mmHg se asociază cu creşterea morbidităţii şi mortalităţii operatorii;
   - $PaCO_2$>45 mmHg este cel mai bun indicator gazometric pentru riscul postoperator;

d) factorul de transfer (capacitatea de difuziune a monoxidului de carbon – D_LCO) – nu ameliorează predicţia privind complicaţiile postoperatorii, dar este obligatorie efectuarea sa pentru stabilirea rezecabilităţii;
e) testele de efort:
   - prezic cu acurateţe mai bună riscul postoperator, comparativ cu testarea de repaus, cu care nu se corelează;
   - VO_2 max (nivelul maxim de O_2 în ml/kg pe care o persoană îl poate folosi într-un minut):
     - >20 ml/kg/min: risc postoperator mic;
     - <15 ml/kg/min: complicaţii întotdeauna;
     - <10 ml/kg/min: inoperabil;
     - <40% prezis: deces în 50% din cazuri;

f) scintigrafia pulmonară:
   - permite, alături de spirometrie, estimarea funcţiei pulmonare postoperatorii:
     - VEMS postoperator = VEMS preoperator x % din perfuzia zonelor nerezecate;
     - nu se rezecă dacă VEMS postoperator <800 ml;
   - scintigrafia de perfuzie (Q): se realizează cu I^{131} sau agregate de albumină serică marcată cu Tc^{99}; defectele de perfuzie se traduc prin aspecte lacunare unice sau multiple;
   - scintigrafia de ventilaţie (V): permite studii cantitative ale ventilaţiei, global pe cei doi plămâni, diferenţiat stânga/dreapta sau regional (baze, vârfuri);

g) presiunea de ocluzie în artera pulmonară:
   - pneumectomia determină redirecţionarea întregului debit cardiac din VD într-o singură arteră pulmonară; se cateterizează artera pulmonară, care se va rezeca, iar ocluzia fluxului sangvin cu balon determină creşterea presiunii în cealaltă arteră;
   - se poate face pneumectomie dacă presiunea de ocluzie este <35 mmHg.

Evaluarea preoperatorie a funcţiei pulmonare, a riscului operator şi indicaţia de pneumectomie sunt redate în tabelele 1 şi 2.

Tabelul 1. *Evaluarea preoperatorie a funcţiei pulmonare şi a riscului operator:*

Test	Risc operator crescut	Risc operator mare
FVC	<50% din valoarea predicţionată	< 1,5 l
VEMS	<50% din valoarea predicţionată sau 2 l/s <40% din valoarea predicţionată sau 1,6 l/s	< 1 l
FEF_{25-75}	<50% din valoarea predicţionată	
MVV		<50% din valoarea predicţionată sau <50 l/min
$PaCO_2$		>45 mmHg
VO_2max	15-20 ml/kg/min	<15 ml/kg/min

Tabelul 2. *Evaluarea preoperatorie a funcţiei pulmonare şi indicaţia de pneumectomie:*

Test	Poate face pneumectomie
VEMS	>2 l
MVV	<50% din valoarea predicţionată
VO_2max	>20 ml/kg/min
VEMS postop	>800 ml/s sau >700 ml/s
Presiunea de ocluzie în artera pulmonară	<35 mmHg

Tipul intervenţiei chirurgicale (pneumectomie, lobectomie, rezecţii limitate) depinde de extensia bolii şi rezervele cardiovasculare ale pacienţilor [47]; la pacienţii cu funcţie pulmonară compromisă, vârstă avansată, comorbidităţi asociate sunt indicate rezecţiile limitate [53]. Trialurile clinice au semnalat faptul că rata de recidivă locală este mai mică în cazul lobectomiei, comparativ cu rezecţiile mai limitate [54-56].

În ceea ce priveşte managementul ganglionilor limfatici loco-regionali, trialurile randomizate nu au reuşit să rezolve controversele legate de tratamentul optim şi anume sampling ganglionar versus disecţie ganglionară sistematică, cele două opţiuni nefiind diferite în ceea ce priveşte rata complicaţiilor, dar datele sunt contradictorii în ceea ce priveşte supravieţuirea generală (OS) [57, 58].

Gradul disecţiei ganglionare este, prin urmare, dictat în principal de obţinerea unui status de rezecţie "R0"; acest status este definit de IASLC (International Association for the Study of Lung Cancer) ca un minim de şase staţii, dintre care trei trebuie să fie mediastinale, inclusiv staţia sub-carinală [47].

Intervenţia chirurgicală rămâne principala modalitate terapeutică în NSCLC în stadii precoce (I şi II) şi la pacienţi selectaţi cu std. IIIA (T3N1) [53]. Lobectomia, inclusiv rezecţia şi mapping-ul N1 şi N2 (sampling a cel puţin 3 staţii N2 sau disecţie ganglionară completă), este considerată standard în NSCLC stadiile I şi II, rezultând într-o supravieţuire la 5 ani care variază de la 69% la 89% pentru pIA, de la 52% la 75% pentru pIB, de la 45% la 52% pentru pIIA şi de 33% pentru pIIB [47, 58]. Disecţia ganglionară mediastinală ipsilaterală formală este indicată în stadiul IIIA (N2).

Intervenţiile chirurgicale variază ca indicaţie şi extensie în funcţie de stadiul bolii, statusul de performanţă generală al pacientului (PS), precum şi de rezerva funcţională respiratorie. Rezecţiile includ o paletă largă: de la rezecţii atipice şi segmentectomii tipice până la pneumectomii cu rezecţie de carină, acolo unde statusul funcţional o permite şi unde prin mediastinoscopie sau PET-CT au fost eliminate posibilităţile de afectare a grupelor ganglionare mediastinale (N2). În stadiile T3 cu implicarea peretelui toracic, a diafragmului, pleurei mediastinale, pericardului parietal, aceste structuri vor fi rezecate în bloc cu parenchimul pulmonar afectat tumoral, recurgându-se la diverse procedee de plastie ale acestora. Pot fi rezecate şi structuri vasculare, vena azygos sau vena cavă superioară, pentru aceasta din urmă recurgându-se la înlocuirea cu proteză sintetică sau cu pericard bovin.

Cele mai frecvente rezecţii sunt lobectomiile, ele neafectând esenţial performanţa respiratorie a pacientului. Ori de câte ori se poate, trebuie evitată pneumectomia dreaptă; ea poate fi înlocuită de cele mai multe ori cu rezecţii ce implică şi axul bronşic principal, aşa-numitele lobectomii cu rezecţii bronho-anastomoze.

Limfadenectomia ipsilaterală este obligatorie.

Rezecţiile pulmonare în stadiul IV al bolii sunt acceptate atunci când metastazele unice sunt controlabile chirurgical sau oncologic sau când, în ciuda prezenţei metastazelor, există o afecţiune perfect rezecabilă din punct de vedere tehnic (rezecţie atipică sau lobectomie), care pune în pericol viaţa prin complicaţiile sale (hemoptizii, supuraţie, invazia structurilor nervoase cu sindrom algic intens) sau creează un disconfort greu de suportat de către pacient.

Mortalitatea operatorie raportată este în medie de 3,7% şi variază de la 1% la 7,6% [45, 58]. Mortalitatea în centrele specializate este de aşteptat să fie în mod clar < 2% [58].

În mod clasic, intervenţia chirurgicală se realizează printr-o toracotomie laterală. În prezent, tendinţa este de utilizare a unor tehnici mai puţin invazive, şi anume lobectomie minim invazivă video-asistată/lobectomie toracoscopică (VATS), din ce în ce mai frecvent utilizată pentru tumori cu diametrul < 5cm [58]. O meta-analiză recentă a raportat rate de recidivă loco-regională similare pentru VATS şi lobectomia clasică, dar rate mai mici de recurenţă sistemică (P=0,03) şi o ameliorare a ratelor de supravieţuire la 5 ani (P=0,04) pentru VATS. De asemenea, lobectomia VATS este asociată cu morbiditate, complicaţii şi o durată de spitalizare mai reduse şi cu o frecvenţă mai mică a sindroamelor algice acute/cronice, comparativ cu lobectomia clasică [58].

Rolul intervenţiei chirurgicale în NSCLC stadiul IIIA (N2) documentat histopatologic este controversat, în principal din cauza heterogenităţii acestui grup de tumori, în ceea ce priveşte dimensiunea tumorală şi gradul afectării mediastinale [47, 53, 58]. Stadiul IIIA include tumori cu extensie limitată la plămânul afectat (T3N1), dar şi pacienţi cu afectare medistinală ganglionară ipsilaterală (T1-3N2). Aproximativ 10-15% din cazurile de NSCLC nou diagnosticate sunt încadrate în stadiul IIIA-N2, iar prezentarea clinică variază de la tumori aparent rezecabile cu metastaze nodale oculte, la tumori nerezecabile cu afectare multinodală voluminoasă şi extinsă [58].

Indicaţia de intervenţie chirurgicală este considerată oportună pentru pacienţii cu ganglionii mediastinali certificaţi – fie prin PET-CT sau mediastinoscopie – ca negativi preoperator şi un singur ganglion pozitiv (< 3cm) diagnosticat în cursul toracotomiei; intervenţia chirurgicală este contraindicată la pacienţii cu multiple metastaze ganglionare (> 3cm), confirmate histopatologic, această categorie de pacienţi având indicaţie de chimio-RT definitivă [47]. Tratamentul neoadjuvant este indicat în cazuri selecţionate şi constă în chimioterapie sau chimio-RT neoadjuvantă [47].

De reţinut!
Intervenţia chirurgicală trebuie precedată de evaluarea funcţională respiratorie.
Tipul intervenţiei chirurgicale depinde de extensia bolii, statusul de performanţă, rezerva funcţională respiratorie şi statusul cardiovascular.
Gradul disecţiei ganglionare este dictat de obţinerea unui status de rezecţie “R0”.

3.2. Chimioterapia

3.2.1. Chimioterapia adjuvantă

Datele trialurilor randomizate şi a meta-analizelor de chimioterapie adjuvantă au schimbat standardul de tratament pentru pacienţii cu NSCLC complet rezecat, confirmând beneficiul de supravieţuire obţinut cu chimioterapia adjuvantă.

În 2004 trialul IALT (*International Adjuvant Lung Cancer Trial*) a raportat rezultatele celui mai mare trial de chimioterapie adjuvantă efectuat pe un număr de 1.867 de pacienţi cu NSCLC rezecat, în stadiile I-III, pacienţi randomizaţi într-un braţ de chimioterapie adjuvantă pe bază de cisplatin şi într-un braţ de urmărire, cu o durată medie de monitorizare de aproximativ 56 de luni. O rată de supravieţuire semnificativ mai mare (45% vs. 40% la 5 ani; HR pentru mortalitate=0,86; 95% CI, 0,76-0,98; $P<0{,}03$) şi o supravieţuire fără semne de boală (DFS; 39% vs. 34% la 5 ani; HR=0,83; 95% CI, 0,74-0,94; $P<0{,}003$) au fost observate la pacienţii din braţul de chimioterapie adjuvantă [1, 57]. Datele trialului IALT semnalează ameliorarea supravieţuirii la 5 ani la pacienţii cu NSCLC complet rezecat, care efectuează chimioterapie adjuvantă pe bază de cisplatin [47]. În trialul IALT, 37% dintre pacienţi erau în stadiul I, 24% în stadiul II şi 39% în stadiul III; la pacienţii în stadiul III s-a obţinut cel mai mare beneficiu în urma chimioterapiei adjuvante [58].

O meta-analiză a 4.584 de pacienţi (LACE – Lung Adjuvant Cisplatin Evaluation) a arătat creşterea supravieţuirii la pacienţii cu NSCLC rezecat care au beneficiat de chimioterapie adjuvantă: de la 64% la 67% pentru stadiul IB, de la 39% la 49% pentru stadiul II şi de la 26% la 39% pentru stadiul III, cu o perioadă medie de urmărire de 5,1 ani. Beneficiul în supravieţuire a variat în funcţie de stadiu şi a fost maxim la pacienţii cu stadiul II şi IIIA de boală. Ameliorarea supravieţuirii nu a atins semnificaţie statistică la pacienţii cu stadiul IB, iar în cazul pacienţilor cu stadiul IA meta-analiza a confirmat efectul detrimental al chimioterapiei [58, 59].

În 2007, o meta-analiză a datelor din 30 de trialuri clinice, incluzând un număr de 8.147 de pacienţi, a demonstrat un beneficiu semnificativ în supravieţuire pentru chimioterapia adjuvantă pe bază de cisplatin, cu un beneficiu absolut de 4% la 5 ani (de la 60% la 64%) [58].

În concluzie, studiile indică un potenţial beneficiu în supravieţuire pentru pacienţii cu NSCLC rezecat, care efectuează chimioterapie adjuvantă pe bază de cisplatin.

Pe baza acestor date s-a constituit un consens. Mai exact, tratamentul citostatic adjuvant, constând în dublet pe bază de cisplatin, îmbunătăţeşte supravieţuirea fără semne de boală (DFS) şi supravieţuirea generală (OS) la 5 ani, la pacienţii cu NSCLC stadiile II-IIIA, complet rezecat [58].

Singurele combinaţii recomandate astăzi pentru utilizare adjuvantă, ca urmare a utilizării lor în studii clinice cu rezultate pozitive, sunt cisplatin cu vinorelbină şi cisplatin cu etoposid [47].

3.2.2. Chimioterapia neoadjuvantă

Numeroase trialuri clinice semnalează beneficiul chimioterapiei neoadjuvante la pacienţii cu boală IIIA-N2 [47, 58, 60-62], iar beneficiul obţinut este comparabil cu cel obţinut de chimioterapia adjuvantă [47, 58].

Chimioterapia neoadjuvantă realizează un downstaging clinic la un procent de 40-60% dintre pacienţi şi o rată de răspuns complet în 5-10% din cazuri [58].

Combinaţiile citostatice neoadjuvante sunt similare celor adjuvante dar experienţa acumulată în studiile clinice este mult redusă, comparativ cu chimioterapia adjuvantă [47].

De reţinut!
Tratamentul citostatic adjuvant (cisplatin + vinorelbină, cisplatin + etoposid) îmbunătăţeşte supravieţuirea fără semne de boală (DFS) şi generală (OS) la 5 ani în NSCLC stadiile II-IIIA, complet rezecat.
Chimioterapia neoadjuvantă aduce beneficii în NSCLC stadiul IIIA-N2, iar combinaţiile citostatice sunt similare celor adjuvante.

3.3. Radioterapia

Radioterapia poate fi utilizată ca şi:
1) RT adjuvantă/postoperatorie (PORT) la pacienţii cu NSCLC rezecabil, care nu au contraindicaţii pentru intervenţia chirurgicală;
2) RT definitivă sau SABR/SBRT (RT stereotactică) la pacienţii cu contraindicaţii pentru intervenţia chirurgicală [47].

Standardul minim în RT îl constituie RT 3D-conformaţională.

3.3.1. Radioterapia definitivă sau SBRT

Radioterapia constituie o oportunitate rezonabilă pentru pacienţii care nu sunt candidaţi pentru intervenţie chirurgicală din cauza comorbidităţilor sau refuzului acesteia. Rata de recidivă locală a fost iniţial de aproximativ 40%, iar supravieţuirea medie a fost cuprinsă între 18 şi 33 luni, dar rezultatele sunt în prezent ameliorate prin utilizarea tehnicilor moderne de RT (RT 3D-conformaţională), astfel că rata de recurenţă locală a fost redusă la aproximativ 14,5% [58].

SABR/SBRT utilizează cicluri scurte de RT cu doze mari şi este indicată la pacienţii cu NSCLC stadiul I cu contraindicaţie chirurgicală sau care refuză intervenţia [47, 58]; supravieţuirea la această categorie de pacienţi este mai mare, comparativ cu RT 3-D conformaţională [47, 63-65]. SABR se asociază cu o supravieţuire medie de 32 luni şi o rată de supravieţuire la 3 ani de ~ 43% la pacienţii în stadiul I [47, 66].

3.3.2. RT adjuvantă/postoperatorie (PORT)

Nu există niciun indiciu că radioterapia postoperatorie (PORT) ameliorează prognosticul pacienţilor cu boală N0 sau N1 complet rezecată, o meta-analiză, de fapt, demonstrând un efect negativ asupra supravieţuirii în aceste cazuri [67, 68]. Drept urmare, PORT nu este recomandat pacienţilor cu NSCLC în stadii precoce, complet rezecat, dar poate fi indicată în cazul rezecţiilor incomplete (R1 sau R2) [67] sau boală IIIA-N2 [47, 67, 69].

De reţinut!
Standardul minim în RT îl constituie RT 3D-conformaţională.
RT definitivă este indicată în NSCLC stadiul I cu contraindicaţie chirurgicală sau care refuză intervenţia.
RT adjuvantă este indicată în NSCLC rezecat incomplet sau stadiul IIIA-N2.

3.4. Chimio-radioterapia neoadjuvantă

NSCLC local-avansat potenţial rezecabil este definit, în urma evaluării de către o echipă multidisciplinară, ca un stadiu de boală care poate fi complet rezecat (R0) după tratamentul de inducţie.

Tratamentul NSCLC local-avansat potenţial rezecabil rămâne o chestiune în dezbatere [67, 70]. Lung Intergrup Trial 0139 a randomizat pacienţi cu boală rezecabilă IIIA-N2 astfel: RT la o doză de 45Gy şi chimioterapie concomitentă cu cisplatin/etoposid, urmate de intervenţie chirurgicală sau chimio-RT concomitentă definitivă la o doză de 61Gy [67, 71]. Nu s-a observat nicio diferenţă semnificativă în OS (P=0,24), dar supravieţuirea fără semne de progresie a bolii (PFS) a fost semnificativ mai bună în braţul de terapie trimodală (P=0,017).

Ca urmare a diferenţelor nesemnificative între opţiunile de tratament, planul optim terapeutic trebuie discutat în board multidisciplinar. Atât chimio-RT definitivă, cât şi terapia de inducţie urmată de intervenţie chirurgicală constituie opţiuni viabile. Un studiu randomizat de fază III, care a comparat chimio-RT de inducţie la o doză de 45Gy, urmată de intervenţie chirurgicală şi chimioterapia de inducţie, urmată de chirurgie şi RT postoperatorie nu a semnalat diferenţe între cele două braţe de tratament [67, 72].

De reţinut!
Chimio-RT neoadjuvantă constituie o opţiune terapeutică în NSCLC local-avansat potenţial rezecabil.

3.5. Chimio-radioterapia definitivă

NSCLC local-avansat nerezecabil este definit, în urma evaluării de către o echipă multidisciplinară, ca un stadiu de boală care nu poate fi complet rezecat (R0), chiar şi după tratamentul de inducţie.

Tratamentul NSCLC local-avansat nerezecabil, inclusiv stadiul IIIB (T1-3N3, T4N2-3), constă în chimio-RT concomitentă definitivă (RT în doză de 60Gy, în fracţiuni de 2Gy), concomitentă cu două cicluri de chimioterapie [47, 67].

Mai multe studii clinice de fază III şi o meta-analiză au comparat chimioterapia de inducţie urmată de RT (chimio-RT secvenţială; 60-66 Gy în 30-33 fracţiuni în 6-7 săptămâni), cu chimio-RT concomitentă la aceeaşi doză [67, 73]. Chimio-RT concomitentă s-a asociat cu rate mai mari de supravieţuire la 5 ani, dar cu incidenţă mai mare a esofagitei.

Ca urmare chimio-RT concomitentă constituie tratamentul standard al NSCLC local-avansat nerezecabil la pacienţii cu un status de performanţă (PS) bun [67].

În schimb, pentru pacienţii în vârstă sau cu comorbidităţi, chimio-RT secvenţială constituie o opţiune terapeutică rezonabilă [67], iar studiile au raportat rate de supravieţuire mai bune în cazul în care s-au utilizat scheme accelerate de RT (administrate pe perioade de timp mai scurte, 66 Gy în 24 fracţiuni) [67, 74].

Regimurile citostatice care pot fi utilizate pentru toate tipurile histologice în concomitenţă cu RT includ cisplatin/etoposid sau cisplatin/vinorelbină [47].

De reţinut!
Chimio-RT concomitentă constituie tratamentul standard al NSCLC local-avansat nerezecabil la pacienţii cu un status de performanţă bun.
Chimio-RT secvenţială este indicată doar pacienţilor cu NSCLC local-avansat nerezecabil, în vârstă sau cu comorbidităţi.

3.6. Tratamentul CBP NSCLC metastatic

3.6.1. Chimioterapia

Strategia terapeutică trebuie să ia în considerare histologia, patologia moleculară, vârsta, statusul de performanţă (PS), comorbidităţile şi preferinţele pacientului.

Terapia sistemică ar trebui să fie oferită tuturor pacienţilor cu NSCLC stadiul IV (chimioterapia clasică restrânsă la pacienţii cu un PS de 0-2, iar pentru terapia moleculară ţintită, de tip EGFR-TKI, PS 0-3 [75].

În orice stadiu al NSCLC, trebuie încurajată renunţarea la fumat, deoarece abandonarea fumatului ameliorează prognosticul [75].

Chimioterapia rămâne piatra de temelie a tratamentului pentru pacienţii cu NSCLC stadiul IV. O meta-analiză, care a inclus 16 studii randomizate de fază III şi 2714 pacienţi, a demonstrat că tratamentul citostatic oferă un beneficiu în supravieţuirea generală (OS), cu o îmbunătăţire absolută a supravieţuirii de 9% la 12 luni (de la 20% la 29%), comparativ cu tratamentul simptomatic (*best suportive care* – BSC) [53, 76].

Dubletele de chimioterapie sunt superioare, în linia I [53, 77, 78], monochimioterapiei iar tripletele, comparativ cu dubletele, nu oferă niciun beneficiu în ceea ce priveşte OS [53, 78].

ASCO (American Society of Clinical Oncology) recomandă dubletele pe bază de cisplatin, deoarece acestea sunt asociate, comparativ cu regimurile fără platină, cu un beneficiu marginal în supravieţuirea la un an [53, 79].

Standardul actual de chimioterapie la pacienţii cu un PS bun (0-2) constă într-o combinaţie dintre un agent citotoxic de generaţia a treia ca de exemplu gemcitabină, vinorelbină sau taxani (paclitaxel, nab-paclitaxel, docetaxel) cu un compus de platină [50]. Regimurile fără platină, cu chimioterapice de generaţia a treia (gemcitabină/vinorelbină, gemcitabină/docetaxel) reprezintă o alternativă la pacienţii care nu pot tolera o combinaţie pe bază de cisplatin. La pacienţii cu un PS care nu permite administrarea combinaţiilor citostatice se utilizează monochimioterapia cu vinorelbină, gemcitabină, pemetrexed sau taxani.

Comparaţia directă a mai multor dublete în studii clinice randomizate de fază III la începutul anilor 2000 nu a reuşit să demonstreze superioritatea unui dublet comparativ cu altul [53, 80], astfel că niciun regim nu a fost recomandat ca “standard de aur” [53].

Studiul de fază III publicat de Scagliotti et al [53, 81] a fost primul studiu care a demonstrat în mod clar o interacţiune importantă între eficacitatea tratamentului şi histologia tumorală. Trialul a randomizat 1.725 de pacienţi chimio-naivi cu NSCLC în stadiile IIIB/IV, într-un braţ de cisplatin/gemcitabină şi într-un braţ de cisplatin/pemetrexed. OS pentru combinaţia cisplatin/pemetrexed a fost non-inferior, comparativ cu OS pentru combinaţia cisplatin/gemcitabină (supravieţuire medie 10,3 versus 10,3 luni) în toată cohorta de pacienţi. Cu toate acestea, OS a fost statistic superior pentru combinaţia cisplatin/pemetrexed versus cisplatin/gemcitabină la pacienţii cu adenocarcinom (n=847, 12,6 versus 10,9 luni) şi la pacienţii cu histologie cu celule mari (n=153, 10,4 versus 6,7 luni). La pacienţii cu histotip scuamos, a existat o îmbunătăţire semnificativă în supravieţuire pentru pacienţii cu combinaţia cisplatin/gemcitabină versus cisplatin/pemetrexed (n=473; 10,8 versus 9,4 luni).

În ceea ce priveşte compusul de platină optim pentru tratamentul NSCLC, mai multe meta-analize au arătat rate de răspuns (RR) mai mari pentru combinaţiile pe bază de cisplatin, comparativ cu cele pe bază de carboplatin. OS este semnificativ superioară pentru cisplatin în subgrupul de tumori non-scuamoase şi la pacienţii trataţi cu regimuri care includ agenţi citotoxici de generaţia a treia [50, 75, 82], însă cisplatinul se asociază cu cele mai multe efecte adverse.

Pemetrexed este preferat gemcitabinei la pacienţii cu tumori non-scuamoase, studiile arătând un beneficiu în supravieţuire [75, 82]. Utilizarea pemetrexed este limitată la NSCLC non-scuamoase, în orice linie de tratament [75, 83, 84].

Numărul de cicluri de chimioterapie de linia I indicat pacienţilor cu NSCLC avansat/metastatic, care prezintă boală staţionară sau răspund la terapia de primă linie, este de 4-6 cicluri [47].

Pentru pacienţii care progresează sub tratamentul de primă linie este indicată terapia de linia a doua.

De reţinut!
În orice stadiu al NSCLC, trebuie încurajată renunţarea la fumat.
Standardul actual de chimioterapie la pacienţii cu un un status de performanţă bun (PS 0-2) constă într-o combinaţie între un agent citotoxic de generaţia a treia cu un compus de platină.

3.7. Terapii ţintite

Identificarea mutaţiilor în NSCLC a condus la dezvoltarea de terapii moleculare ţintite, în special în adenocarcinoame [44]. Utilizarea terapiilor moleculare ţintite a dus la creşterea supravieţuirii la pacienţii cu boală metastatică [46, 46].

3.7.1. Anticorpii monoclonali anti-VEGF

3.7.1.1. Bevacizumab

Bevacizumab este un anticorp monoclonal recombinant care blochează factorul de creştere endotelial vascular (VEGF – *vascular endothelial growth factor*). Bevacizumab a fost aprobat în 2006 de către FDA /EMA în tratamentul NSCLC non-scuamos inoperabil sau metastatic [47].

Două trialuri de fază III, care au evaluat rolul bevacizumab în combinaţie cu chimioterapia (dublet) în tratamentul NSCLC în primă linie de tratament, au demonstrat un beneficiu clinic în ceea ce priveşte PFS (supravieţuirea fără semne de progresie a bolii) (Avastin in lung [Avail] study şi Eastern Cooperative Oncology Group [ECOG] 4599 study) [85, 86] şi OS [86]. Ca urmare a rezultatelor studiilor clinice, ECOG recomandă bevacizumab în combinaţie cu paclitaxel şi carboplatin la pacienţii cu NSCLC non-scuamos avansat.

Pentru a beneficia de tratament cu bevacizumab, pacienţii cu NSCLC trebuie să îndeplinească următoarele criterii: histologie non-scuamoasă şi să nu aibă istoric recent de hemoptizie. De asemenea, orice regim citostatic cu risc crescut de trombocitopenie, şi prin urmare şi de sângerare, trebuie utilizat cu precauţie în combinaţie cu bevacizumab [47].

Ca urmare bevacizumab în combinaţie cu chimioterapia (paclitaxel/carboplatin) reprezintă una din opţiunile terapeutice la pacienţii cu NSCLC non-scuamos [47, 86].

3.7.2. Inhibitorii tirozin-kinazici ai EGFR

Receptorul factorului de creştere epidermal (EGFR) este un receptor transmembranar supraexprimat în NSCLC [53, 87].

Inhibitorii tirozin-kinazici (TKI) ai EGFR se leagă de domeniul catalitic tirozin-kinazic intracelular al EGFR, împiedicând autofosforilarea şi activarea.

3.7.2.1. Erlotinib şi gefitinib

Erlotinib şi gefitinib sunt TKI cu administrare orală [47].

Studiile au arătat că mutaţiile la nivelul domeniului tirozin-kinazic al genei EGFR (exonii 18-21) se asociază cu răspunsul la TKI (rate de răspuns de 70-90%, PFS de 7-13 luni) [88-90]. Cele mai frecvente mutaţii EGFR la pacienţii cu NSCLC sunt deleţiile la nivelul exonului 19 (45% din pacienţi) şi mutaţia L858R la nivelul exonului 21 (40% din pacienţi). Ambele mutaţii rezultă în activarea domeniului tirozin-kinazic şi se asociază cu răspunsul terapeutic la TKI, cum sunt erlotinib, gefitinib, afatinib; prin urmare, aceste mutaţii sunt denumite mutaţii activatoare EGFR. Mutaţiile activatoare EGFR se regăsesc la aproximativ 10% dintre pacienţii caucazieni cu NSCLC şi la peste 30% dintre pacienţii asiatici cu NSCLC. Rezistenţa primară la tratamentul cu TKI se asociază cu mutaţiile KRAS şi rearanjările ALK, iar rezistenţa dobândită la TKI se asociază cu mutaţii particulare ale EGFR (ex. T790M), cu transformarea histologică din NSCLC în SCLC şi cu tranziţia de la histotipul epitelial la cel mezenchimal [47].

Studiile au demonstrat superioritatea TKI comparativ cu chimioterapia în ceea ce priveşte PFS la pacienţii cu mutaţii activatoare EGFR (10,4 versus 5,5 luni pentru gefitinib versus paclitaxel/carboplatin, respectiv 13,1 luni versus 4,6 luni pentru erlotinib versus gemcitabină/carboplatin) [53, 91, 92].

O meta-analiză a cinci trialuri a arătat că pacienţii cu NSCLC avansat (stadiile IIIb şi IV) cu mutaţii activatoare EGFR, care beneficiază de TKI, prezintă rate de răspuns (RR) de 67% şi OS de 24 de luni [47, 93].

Aceste date sprijină utilizarea TKI la pacienţii cu mutaţii EGFR activatoare. În cazul în care statusul mutaţiilor EGFR este negativ sau necunoscut, este preferată chimioterapia [53, 79].

ASCO recomandă testarea pacienţilor cu NSCLC avansat pentru mutaţii EGFR. Ghidurile NCCN (National Comprehensive Cancer Network) şi ESMO (European Society of Medical Oncology) recomandă ca testarea EGFR să se facă doar pentru pacienţii cu histologie non-scuamoasă (d.e. adenocarcinom, carcinom cu celule mari, NSCLC NOS – not otherwise specified) [47]. Este puţin probabil ca pacienţii cu histologie scuamoasă pură să prezinte mutaţii activatoare EGFR; cu toate acestea cei cu histotipuri mixte (adenoscuamos) pot prezenta mutaţii [47, 94].

În 2004, FDA a aprobat erlotinib în tratamentul NSCLC avansat sau metastatic, după eşecul a cel puţin un regim de chimioterapie. Erlotinib este, de asemenea, recomandat în primă linie pacienţilor cu NSCLC avansat, recurent sau metastatic, care prezintă mutaţii activatoare EGFR, indiferent de PS, iar această recomandare se bazează pe rezultatele studiilor care arată ameliorarea supravieţuirii fără progresia bolii (PFS) şi a calităţii vieţii (QoL), comparativ cu chimioterapia, la această categorie de pacienţi [47].

3.7.2.2. Afatinib

Afatinib este un inhibitor tirozin-kinazic oral care inhibă întreaga familie de receptori Erb/HER, inclusiv EGFR şi HER2.

Un trial de fază III a semnalat îmbunătăţirea PFS la pacienţii cu adenocarcinoame pulmonare metastatice cu mutaţii activatoare EGFR în tratament cu afatinib, comparativ cu cisplatin/pemetrexed (11,2 versus 6,9 luni) [47, 95].

FDA şi EMA au aprobat recent afatinib în tratamentul de primă linie al pacienţilor cu NSCLC metastatic non-scuamos, cu mutaţii activatoare EGFR.

3.7.3. Inhibitorii tirozin kinazici ai ALK

Rearanjările ALK sunt prezente la aproximativ 2-7% dintre pacienţii cu NSCLC. Aceşti pacienţi sunt rezistenţi la EGFR-TKI, prezintă caracteristici similare cu ale pacienţilor cu mutaţii EGFR (histologie de adenocarcinom, nefumători/ fumători ocazionali) şi tind să fie în special bărbaţi cu vârste tinere. Rearanjările ALK nu sunt prezente de obicei în asociere cu histologia scuamoasă, dar pot apărea rar în cazul histologiilor scuamoase mixte [47].

3.7.3.1. Crizotinib

Crizotinib este un TKI oral al ALK, ROS1 şi MET, aprobat de FDA și EMA în tratamentul pacienţilor cu NSCLC avansat sau metastatic, cu rearanjări ALK, studiile arătând îmbunătăţirea semnificativă a RR (> 60%) sub tratament cu crizotinib [47].

Mutaţiile EGFR şi rearanjările ALK sunt mutual exclusive, din acest motiv erlotinib (sau gefitinib) nu sunt recomandaţi în tratamentul de linia a două la pacienţii cu rearanjări ALK care au recidivat/progresat sub crizotinib.

3.7.3.2. Ceritinib

Un inhibitor tirozin-kinazic de generaţie nouă, care vizează în mod specific NSCLC pozitiv pentru rearanjări ALK a fost aprobat recent de FDA. Noul medicament, ceritinib, este indicat pacienţilor cu NSCLC ALK-pozitiv, cu boală în progresie sub tratament cu crizotinib sau care prezintă intoleranţă la crizotinib.

De reţinut!
Bevacizumab în combinaţie cu chimioterapia reprezintă o opţiune terapeutică în NSCLC non-scuamos, PS 0-1.
Erlotinib, Gefitinib şi Afatinib sunt indicate în prima linie de tratament în NSCLC non-scuamos avansat, recurent sau metastatic, cu mutaţii activatoare EGFR, indiferent de PS.
Crizotinib este indicat în NSCLC avansat sau metastatic, cu rearanjări ALK.
Ceritinib este indicat în NSCLC ALK-pozitiv, cu boală în progresie sub tratament cu crizotinib sau cu intoleranţă la crizotinib.

3.8. Terapia de întreţinere

Terapia de întreţinere este un concept relativ nou intrat în arsenalul terapeutic al NSCLC. Terapia de întreţinere se referă la tratamentul sistemic care poate fi administrat pacienţilor cu NSCLC avansat, după 4-6 cicluri de chimioterapie de linia I [47].

Terapia de întreţinere a fost dezvoltată pentru a îmbunătăţi efectul tratamentului de inducţie, fie prin comutare la tratament cu un compus diferit faţă de cei din regimul de inducţie (*switch maintenance*), fie prin continuarea tratamentului cu unul din compuşii regimului de inducţie (*continuation maintenance*), la pacienţii care au răspuns sau cel puţin au prezentat boală stabilă sub tratamentul de inducţie [50].

Selectarea tipului de terapie de întreţinere depinde de o serie de factori: histologia tumorală, prezenţa mutaţiilor/rearanjărilor genice, PS. Terapia de întreţinere nu este considerată standard terapeutic pentru toţi pacienţii cu NSCLC şi nu este recomandată pacienţilor cu PS 3-4 şi celor cu progresie.

3.8.1. Terapia de întreţinere de continuare (*continuation maintenance*)

Terapia de întreţinere de continuare creşte supravieţuirea fără semne de progresie a bolii (PFS), şi supravieţuirea generală (OS) şi ameliorează calitatea vieţii (QoL) comparativ cu urmărirea fără tratament. Tratamentul este continuat cu unul din compuşii din regimul de inducţie (cel mai puţin toxic) până la progresia bolii sau apariţia toxicităţii inacceptabile.

Terapia de întreţinere de continuare este recomandată pacienţilor cu NSCLC non-scuamos, care au prezentat răspuns terapeutic sau boală stabilă sub tratamentul de inducţie şi include ca opţiuni: bevacizumab, pemetrexed [47, 96-100].

3.8.2. Terapia de întreţinere secvenţială (*switch maintenance*)

Terapia de întreţinere secvenţială include opţiunile: pemetrexed şi erlotinib. Studiile au arătat un beneficiu în PFS şi OS în cazul tratamentului cu pemetrexed sau erlotinib după 4-6 cicluri de chimioterapie, la pacienţi cu NSCLC fără semne de progresie a bolii.

Terapia de întreţinere secvenţială cu pemetrexed poate fi iniţiată la pacienţii cu histologie non-scuamoasă cu răspuns obiectiv sau boală staţionară după chimioterapia iniţială [47, 83, 101].

Terapia de întreţinere secvenţială cu erlotinib poate fi iniţiată la pacienţii cu boală staţionară după chimioterapia iniţială [47, 102].

De asemenea, orice pacient cu mutaţii activatoare EGFR are indicaţie de terapie de întreţinere /switch cu EGFR-TKI (dacă nu a primit această terapie în primă linie) [75].

De reţinut!
Terapia de întreţinere se referă la tratamentul sistemic care poate fi administrat în NSCLC avansat, după 4-6 cicluri de chimioterapie de linia I, la pacienţii care nu au progresat sub tratamentul de inducţie.

3.9. Tratamentul de linia a doua

Pacienţii care progresează clinic sau radiologic după prima linie de chimioterapie, cu un status de performanţă bun (PS 0-2), au indicaţie de terapie de linia a doua, indiferent de administrarea anterioară a terapiei de întreţinere sau adjuvantă. Până recent s-a considerat că regimurile combinate nu aduc beneficii comparativ cu monochimioterapia [75, 103], însă înregistrarea recentă a ramucirumab ca tratament de salvare, alături de docetaxel, a modificat acest concept.

Opţiunile comparabile din punct de vedere al terapiei de linia a doua constau în docetaxel, indiferent de subtipul histologic [75, 104] şi pemetrexed pentru histologia non-scuamoasă [75, 105].

Erlotinib ameliorează supravieţuirea generală (OS) în linia a doua sau a treia de tratament la pacienţii cu NSCLC, indiferent de histologie, care nu sunt eligibili pentru chimioterapie, inclusiv la pacienţii cu un PS de 3 [75, 106].

Erlotinib este echivalent ca supravieţuire cu pemetrexed sau docetaxel ca tratament de linia a doua la pacienţii cu boală refractară (progresie în cursul celor patru cicluri de chimio-terapie standard pe bază de dublet de platină) pe o populaţie neselectată [75, 107]. Erlotinib este însă inferior chimioterapiei ca supravieţuire fără semne de boală la o populaţie cunoscută ca fiind EGFR wild-type.

Gefitinib s-a fost dovedit non-inferior docetaxel într-un studiu randomizat [108], cu un profil mai bun de toxicitate şi al calităţii vieţii (QoL) [75]. De asemenea, datele arată rezultate comparabile pentru pemetrexed şi erlotinib [75, 109].

Pacienţii cu tumori cu mutaţii activatoare EGFR au indicaţie de TKI EGFR în linia a doua de terapie, dacă nu au primit anterior tratament cu TKI.

În cazul pacienţilor cu rearanjări ALK, trebuie luată în considerare terapia de linia a doua sau a treia cu crizotinib şi ulterior ceritinib, dacă nu au beneficiat deja de aceste tratamente [75].

Nu există reglementări cu privire la durata tratamentului de linia a doua, tratamentul poate fi prelungit atât timp cât boala este controlată şi toxicitatea este acceptabilă [75].

De reţinut!
NSCLC cu progresie clinică sau radiologică după prima linie de chimioterapie, are indicaţie de terapie de linia a doua: chimioterapie (PS 0-2) sau TKI (orice PS).

3.10. Radioterapia paliativă

Radioterapia are rol în controlul simptomelor, în caz de metastaze osoase şi cerebrale. De asemenea, este eficientă în tratamentul durerii secundare invaziei tumorale (d.e. de ţesuturi moi), sindroamelor de compresie medulară, hemoptizie, compresia/obstrucţia căilor respira-torii, etc. [75].

De reţinut!
Radioterapia are rol în controlul simptomelor, în NSCLC metastatic.

3.11. Rolul bifosfonaţilor

Acidul zoledronic reduce frecvenţa evenimentelor scheletale (fracturi în os patologic, compresie medulară) şi este recomandat în NSCLC stadiul IV cu metastaze osoase [75].

Denosumab tinde să fie superior acidului zoledronic în ceea ce priveşte prevenţia evenimentelor scheletale [75, 110] şi OS (9,5 vs 8 luni) [47, 111].

De reţinut!
Bifosfonaţii sunt indicaţi în NSCLC cu metastaze osoase.

3.12. Tratamentul NSCLC oligometastatic

Pacienţii cu NSCLC stadiul IV, cu metastaze solitare localizate la nivel cerebral, glande suprarenale sau pulmonar, pot fi trataţi cu intenţie curativă. Acest lucru necesită însă evaluare individuală şi ţine cont de: momentul apariţiei metastazelor în raport cu tumora primară (boala metacronă are prognostic mai bun comparativ cu cea sincronă) [47, 112], PS, comorbidităţile şi extensia locală a tumorii primare.

În cazul metastazelor cerebrale solitare tratamentul constă în rezecţie chirurgicală urmată de radioterapie cerebrală (WBRT – *whole brain* RT) sau radio-chirurgie cu/fără WBRT. WBRT după intervenţia chirurgicală prelungeşte OS [47, 113], în timp ce acest beneficiu nu a fost reprodus după radiochirurgie [47, 114]. Radio-chirurgia combinată cu WBRT este superioară WBRT la pacienţii care se prezintă cu până la trei metastaze cerebrale [47, 115].

În cazul metastazelor solitare de suprarenale (diagnostic confirmat histologic), studiile au semnalat prelungirea supravieţuirii după rezecţia suprarenalei şi a tumorii primare [47, 116].

Leziunile solitare în plămânul contralateral trebuie considerate, în cele mai multe cazuri, ca tumori primare secundare sincrone şi tratate, dacă este posibil, chirurgical şi eventual cu chimioterapie adjuvantă, radioterapie definitivă sau chimio-RT.

De reţinut!
Pacienţii cu NSCLC stadiul IV, cu metastaze solitare (la nivel cerebral, al glandelor suprarenale sau pulmonare), pot fi trataţi cu intenţie curativă.

3.13. Opţiunile terapeutice în NSCLC în funcţie de stadiu

3.13.1. <u>Tratamentul stadiilor I şi II [47]:</u>

- Intervenţia chirurgicală – toracotomie deschisă sau VATS;
- Lobectomia este preferată rezecţiilor limitate (d.e. segmentectomie);
- Disecţia ganglionilor limfatici trebuie să fie conformă cu specificaţiile IASLC;
- Chimioterapia adjuvantă este indicată pacienţilor cu NSCLC stadiile II şi III rezecate şi pacienţilor cu stadiul IB rezecat şi tumori primare > 4 cm;
- Pentru chimioterapia adjuvantă sunt preferate dubletele pe bază de cisplatin. În studiile clinice randomizate, doza cumulativă de cisplatin a fost de 300 mg/m², administrată în 3-4 cicluri de chimioterapie, iar cel mai studiat regim a fost cisplatin/vinorelbină;
- Tratamentul non-chirurgical al NSCLC în stadiul I este radioterapia stereotactică (SABR). SABR se asociază cu efecte adverse reduse la pacienţii cu BPOC şi la cei în vârstă;
- Pentru tumorile > 5 cm şi/sau localizate central este recomandată RT, utilizând fracţionare convenţională sau accelerată;
- Radioterapia postopreatorie (PORT) nu este recomandată în NSCLC în stadii incipiente, complet rezecat. Ea poate fi însă indicată după rezecţiile chirurgicale incomplete.

3.13.2. <u>Tratamentul stadiului III [47]:</u>

- Tratamentul NSCLC local-avansat inoperabil constă în chimio-RT concomitentă definitivă;
- RT toracică definitivă trebuie administrată în doză de 60Gy, în fracţiuni de 2Gy;
- Chimioterapia este indicată tuturor pacienţilor cu NSCLC local-avansat, care o pot tolera;

- Sunt recomandate dubletele pe bază de cisplatin (d.e. cisplatin/etoposid sau cisplatin/ vinorelbină) administrate concomitent cu RT. Studiile care au utilizat carboplatin/ paclitaxel sau alte combinaţii pe bază de carboplatin au arătat, în general, rezultate inferioare, dar aceste combinaţii pot fi alese în mod individual în funcţie de comorbidităţi. Numărul de cicluri este de 2-4, iar doza de cisplatin per ciclu este în medie de 80 mg/m^2;
- Pacienţii care nu pot beneficia de chimio-RT concomitentă au indicaţie de terapie secvenţială cu intenţie curativă;
- În cazul terapiei secvenţiale, tratamentul constă într-un dublet pe bază de platină, cu un număr de cicluri de 2-4;
- Pentru NSCLC local-avansat rezecabil (IIIA-N2), atât chimio-RT definitivă, cât şi terapia de inducţie urmată de chirurgie reprezintă opţiuni fezabile;
- Utilizarea de rutină a PORT (radioterapie post-operatorie) poate fi luată în considerare la pacienţii cu N2 şi după o intervenţie chirurgicală incompletă.

3.13.3. Tratamentul stadiului IV [47]:

- Strategia de tratament trebuie să ia în considerare histologia, patologia moleculară, vârsta, statusul de performanţă (PS), comorbidităţile şi preferinţele pacientului;
- Deciziile de tratament trebuie discutate în board tumoral multidisciplinar;
- Terapia sistemică este indicată tuturor pacienţilor în stadiul IV, cu un PS 0-2 (chimioterapie), orice PS (terapie moleculară ţintită);
- În orice stadiu trebuie încurajată abandonarea fumatului, deoarece se asociază cu ameliorarea prognosticului.

3.13.3.1 Tratamentul de primă linie:

- În subgrupul de tumori non-scuamoase şi la pacienţii trataţi cu regimuri de generaţia a treia, inclusiv gemcitabină şi taxani, cisplatinul este opţiunea de elecţie;
- Pemetrexed este preferat gemcitabinei la pacienţii cu tumori non-scuamoase. Utilizarea pemetrexed trebuie limitată la NSCLC non-scuamos, în orice linie de tratament;
- Bevacizumab în asociere cu paclitaxel/carboplatin este indicat pacienţilor cu NSCLC non-scuamos şi PS 0-1;
- Regimurile fără platină, cu chimioterapice de generaţia a treia, reprezintă o alternativă la pacienţii care nu pot tolera o combinaţie pe bază de cisplatin;
- Pentru majoritatea pacienţilor se recomandă 4-6 cicluri de chimioterapie;
- Pacienţi cu PS ≥ 2:
    - Chimioterapia prelungeşte supravieţuirea şi, eventual, îmbunătăţeşte calitatea vieţii (QoL), comparativ cu tratamentul suportiv (BSC – *best suportive care*);
    - Monochimioterapia cu gemcitabină, vinorelbină sau taxani reprezintă o opţiune fezabilă;
    - Pacienţii cu NSCLC, fără mutaţii activatoare EGFR, cu PS 3-4, beneficiază de BSC.
- Pacienţi vârstnici:
    - Chimioterapia pe bază de platină poate fi utilizată la pacienţii vârstnici cu un PS 0-1 şi fără comorbidităţi.
    - Monochimioterapia reprezintă o variantă acceptabilă la pacienții vârstnici, în special cei cu comorbidităţi.
- Utilizarea TKI:
    - Tratamentul de primă linie cu TKI (erlotinib, gefitinib, afatinib) este indicat pacienţilor cu tumori cu mutaţii activatoare EGFR, indiferent de PS;
    - La pacienţii fără mutaţii activatoare EGFR (EGFR-WT), terapia cu TKI EGFR nu este recomandată ca tratament de primă linie, fiind inferioară chimioterapiei;
    - Pacienţii cu NSCLC cu rearanjare ALK au indicaţie de terapie cu crizotinib.
- Tratamentul metastazelor cerebrale:
    - WBRT (*whole brain RT*) rămâne tratamentul standard în cazul în care nu sunt posibile abordări locale.

3.13.3.2. Tratamentul de întreţinere:

- La pacienţii cu histologie non-scuamoasă terapia de întreţinere secvenţială cu pemetrexed, după patru cicluri de chimioterapie pe bază de platină, se asociază cu ameliorarea supravieţuirii fără semne de progresie a bolii (PFS) şi supravieţuirii generale (OS);
- Terapia de întreţinere secvenţială cu erlotinib în NSCLC, indiferent de histologie, se asociază cu ameliorarea PFS şi OS la pacienţii cu boală stabilă după tratamentul de inducţie;
- Pacienţii cu tumori cu mutaţii activatoare EGFR au indicaţie de terapie de întreţinere cu TKI EGFR, în cazul în care nu au beneficiat de TKI în primă linie;
- Terapia de întreţinere /continuare cu pemetrexed după finalizarea chimioterapiei de primă linie cu cisplatin/pemetrexed este recomandată pacienţilor cu histologie non-scuamoasă.

3.13.3.3. Tratamentul de linia a doua:

- Pacienţii cu PS 0-2, care progresează clinic sau radiologic după chimioterapia de primă linie au indicaţie de chimioterapie de linia a doua;
- Opţiunile comparabile în linia a doua constau în pemetrexed pentru histologia non-scuamoasă sau docetaxel (oricare histologie);
- Asocierea ramucirumab la docetaxel a prelungit supravieţuirea pacienţilor în linia a doua de tratament faţă de docetaxel singur (studiul REVEL).
- Erlotinib reprezintă o opţiune suplimentară la pacienţii EGFR-WT, cu PS 0-3;
- Pacienţii cu tumori cu mutaţii activatoare EGFR au indicaţie de terapie cu TKI EGFR în linia a doua de tratament, în cazul în care nu au beneficiat de TKI în primă linie;
- Tratamentul poate fi prelungit atât timp cât boala este controlată şi toxicitatea este acceptabilă.

3.13.3.4. Terapii minim-invazive:

- În caz de obstrucţie simptomatică a căilor respiratorii sau infecţie post-obstrucţie, pot fi utile dezobstrucţia endoscopică cu laser, crioterapia sau plasarea de stenturi;
- Endoscopia poate fi utilă în tratamentul hemoptiziei (ghidarea embolizării endovasculare);
- În compresia de venă cavă superioară poate fi utilă plasarea de stenturi vasculare;
- Revărsatele pleurale recurente pot fi gestionate prin pleurodeză. Agentului sclerozant preferat este talcul, mai eficient comparativ cu bleomicina sau tetraciclina.

3.13.3.5. Radioterapia:

- Are rol în controlul simptomelor, în caz de metastaze osoase şi cerebrale;
- Este eficientă în tratamentul durerii secundare invaziei tumorale (d.e. de ţesuturi moi), sindroamelor de compresie medulară, hemoptizie, compresia/obstrucţia căilor respiratorii, etc.

3.13.3.6. Bifosfonaţii:

- Acidul zoledronic reduce frecvenţa evenimentelor scheletale (fracturi în os patologic, compresie medulară) şi este recomandat în NSCLC std. IV cu metastaze osoase;
- Denosumab tinde să fie superior acidului zoledronic în ceea ce priveşte prevenţia evenimentelor scheletale.

3.13.3.7. Tratamentul paliativ:

- Se recomandă iniţierea precoce a îngrijirilor paliative, în paralel cu terapia oncologică standard.

3.13.3.8. Tratamentul NSCLC oligometastatic:

- Pacienţii cu stadiul IV NSCLC, cu metastaze solitare localizate la nivel cerebral, glande suprarenale sau pulmonar, pot fi trataţi cu intenţie curativă;

- În caz de metastaze cerebrale solitare, rezecţia chirurgicală urmată de radioterapie cerebrală (WBRT) sau radiochirurgie ± WBRT constituie opţiuni fezabile;
- În cazul metastazelor solitare de suprarenale (diagnostic confirmat histologic), studiile au semnalat prelungirea supravieţuirii după rezecţia suprarenalei şi a tumorii primare;
- Leziunile solitare în plămânul contralateral trebuie considerate, în cele mai multe cazuri, ca tumori primare secundare sincrone şi tratate, dacă este posibil, chirurgical şi eventual cu chimioterapie adjuvantă, radioterapie definitivă sau chimio-RT.

Notă:
În momentul trimiterii ghidurilor către tipar, următoarele medicamente la care se face referire în material sunt autorizate pentru utilizare de către FDA şi/sau EMA şi/sau ANMDM, dar nu sunt deocamdată rambursate prin Programul Naţional de Oncologie: afatinib, ceritinib, crizotinib, gefitinib, ramucirumab.

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