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MULTIMORBIDITY IN A PATIENT WITH COPD: HARD TO OVERCOME CHALLENGES

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Rezumat

Pacienții cu boală obstructivă pulmonară cronică (BPOC) suferă frecvent de multimorbiditate, definită ca prezența a două sau mai multe comorbidități la un pacient, cele mai frecvente dintre acestea fiind boala cardiovasculară și cerebrovasculară, cancerul pulmonar, diabetul zaharat, slăbiciunea musculară, osteoporoza, anxietatea și depresia. La pacienții cu BPOC, comorbiditățile se pot dezvolta sindemic, adică pot evolua concomitent ca răspuns la factorii de risc comuni și prin mecanisme patogenetice comune. Autorii prezintă cazul unui pacient cu multimorbiditate, cu prezența în antecedente a unui factor de risc comun (fumatul) pentru câteva din comorbiditățile care le asociază și provocările care au apărut în abordarea terapeutică a acestuia.

Cuvinte cheie: *boală obstructivă pulmonară cronică (BPOC), multimorbiditate, tratament*

Abstract

Patients with chronic obstructive pulmonary disease (COPD) frequently suffer from multimorbidity, defined as the presence of 2 or more comorbidities in a patient, the most common of which are cardiovascular and cerebrovascular disease, lung cancer, diabetes, muscle weakness, osteoporosis, anxiety and depression. In patients with COPD, comorbidities can develop syndemically, that is, they can evolve simultaneously in response to common risk factors and through common pathogenetic mechanisms. The authors present the case of a patient with multimorbidity, with a history of a common risk factor (smoking) for some of the associated comorbidities and challenges occurred in his therapeutic approach.

Keywords: *chronic obstructive pulmonary disease (COPD), multimorbidity, therapy,*



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Introduction

Chronic obstructive pulmonary disease (COPD) represents a group of lung conditions, such as emphysema, chronic bronchitis and asthma, that cause breathing difficulties due to inflammation of the lungs and narrowing of the airways. Typical symptoms of COPD include shortness of breath, persistent cough with sputum, frequent lower respiratory tract infections and wheezing. COPD is a classic model of complex pathology, it can start at a young age, progresses very slowly and is often diagnosed when patients are in their 6th or 7th decade of life.

According to WHO estimates, COPD will become the third leading cause of death worldwide by 2030, probably due to difficulties in early and accurate diagnosis[6].

The classification of causes of death published by the WHO lists individual chronic diseases as the sole causes responsible for the event. The reality is different, as multimorbidity, defined as the presence of two or more chronic diseases, is seen in almost 50% of adults[2].

Patients with chronic obstructive pulmonary disease (COPD) frequently suffer from multimorbidity, the most common of which are cardiovascular and cerebrovascular disease, lung cancer, diabetes, muscle weakness, osteoporosis, anxiety and depression. These comorbidities are not only more common, but also appear 1-2 decades earlier than in patients without COPD[3].

Most patients with chronic obstructive pulmonary disease (COPD) have at least one additional, clinically relevant chronic disease. Those with the most severe airflow obstruction will die from respiratory failure, but most COPD patients die from non-respiratory disorders, particularly cardiovascular disease and lung cancer. Since many chronic diseases have common risk factors (for example, aging, smoking, pollution, sedentary lifestyle and poverty), some authors support the idea, that to move forward in the prevention, diagnosis and management of chronic diseases, it is necessary to move from to the current paradigm according to that COPD is considered a single disease with comorbidities, to one in which COPD is considered part of a multimorbid condition - with comorbidities that may share common pathobiological mechanisms[4].

The term **syndemic** is used to describe the co-occurrence of diseases with common mechanisms and risk factors, this new concept that the authors propose contributes to explaining the occurrence of certain groups (clusters) of co-morbidities in patients diagnosed with COPD.

The most accurate estimates of the frequency of comorbidities in COPD have been reported by Vanfleteren et al., 2013, who noted that they appear earlier in life in

patients with COPD, and often remain undiagnosed and untreated in patients with COPD, compared with individuals without COPD, suggesting that multimorbidity is an essential characteristic of people who develop COPD.

They performed an observational, prospective clinical study, to cluster 13 clinically important objectively identified comorbidities, and to characterize the comorbidity clusters in termsof clinical outcomes and systemic inflammation. A total of 213 patients with were included prospectively. Thirteen comorbidities were identified in all patients based on predefined cut-offs: chronic kidney disease (estimated glomerular filtration rate , 60 ml/min); anaemia (haemoglobin level , 8.1 mmol/L in men and ,7.5 mmol/L in women); hypertension (systolic blood pressure .140 mm Hg or diastolic pressure .90 mm Hg); obesity (BMI >30 kg/m2); underweight (BMI ,21 kg/m2); muscle wasting (fat free mass index ,16 kg/m2 for men or ,15 kg/m2 for women); hyperglycaemia (fasting glucose level .5.6 mmol/L); dyslipidaemia (triglyceride level .1.7 mmol/L or high-density lipoprotein cholesterol level ,1.03 mmol/L in men or ,1.29 mmol/L in women); osteoporosis (t-score less than 22.5); symptoms of anxiety and depression (HADS score >10 points); atherosclerosis (c-IMT .0.9 mm); and myocardial infarction (CIIS >20).

A total of 97.7% of all patients had one or more comorbidities and 53.5% had four or more comorbidities. Five comorbidity clusters were identified: Cluster 1 (less comorbidity cluster) had significantly fewer comorbidities compared with theother clusters. Cluster 2 (cardiovascular cluster) had a significantly higher prevalence of hypertension and atherosclerosis compared with the other clusters. However, dyslipidaemia, hyperglycaemia, underweight, and muscle wasting were less prevalent compared with the other clusters. Cluster 3 (cachectic cluster) had a higher prevalence of underweight, muscle wasting, osteoporosis, and renal impairment, whereas obesity and atherosclerosis were less often identified. This cluster 3 had a high number of comorbidities.

Cluster 4 (metabolic cluster) also had a higher number of comorbidities.

This cluster contained more patients with obesity, atherosclerosis, dyslipidaemia, hyperglycaemia, and hypertension, but fewer patients with anxiety, underweight, muscle wasting, and osteoporosis. Finally, cluster 5 (psychological cluster) had the highest proportion of patients with psychological disorders (anxiety and depression),but also the highest prevalence of myocardial infarction. It has been concluded, that multimorbidity is common in patients with COPD, and different comorbidity clusters can be identified in such patients[11].

Case report

We report a clinical case of a 78-year-old male patient from the urban environment, a former chronic smoker (cigarette-smoking for about 40 years, about 20 cigarettes/day, in abstinence for 7 years), who worked as a chemical laboratory technician at a textile industry company, pre-professional activity involving occupational contact with chemical dyes, organic solvents, cotton fibre dust. He was admitted to the cardiovascular rehabilitation clinic for a specialised evaluation in preoperative setting for bladder tumour, presenting NYHA class III dyspnoea, pronounced asthenia, fatigue, pain in the limb muscles when walking distances below 200 m.

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Figure 1. *Fingernails in the patient with COPD*



Figure 2. *Toenails in the patient with COPD*

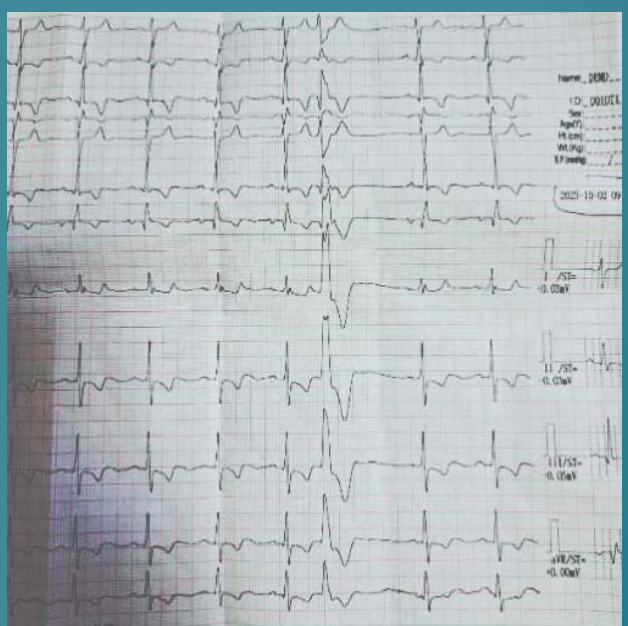


Figure 3. *EKG changes in patient with COPD. SR=sinus rhythm, VES=ventricular extrasystoles, VA=ventricular allure, LV=left ventricle*

From the personal pathological antecedents, we mention the cardiovascular ones (Essential arterial hypertension grade III high additional risk, Chronic ischemic heart disease, Chronic heart failure class III NYHA, Chronic venous insufficiency class 2 CEAP, Peripheral arterial disease stage IIb), pulmonary (COPD stage III GOLD, Bilateral pulmonary fibrosis, Pulmonary emphysema, Bilateral bronchiectasis, Chronic respiratory failure, Chronic O2-therapy at home), nephrological (Chronic kidney disease stage G3a), oncological (lung nodules in LSL and RIL, Suspect malignant opacity in the lingula, Obs. Bladder tumour), gastroenterological (Chronic liver disease), degenerative osteoarticular disease (Spondylodiscarthrosis).

The patient, known with COPD and arterial hypertension, being on chronic treatment with bronchodilators, antihypertensives and vasodilators, developed macroscopic hematuria in July 2023, which raised the suspicion of the presence of a neoplasm of the urinary tract, confirmed by abdominal-pelvic ultrasound, which identified a tumoral formation in the bladder. Following the specialized consultation, the surgical resection of the tumour was recommended, with preoperative pulmonary and cardiovascular evaluation. The chest CT, performed during the pulmonary evaluation, revealed: bilateral pulmonary fibrosis, retractile consolidations with intracavitary bronchial distortions, nodular formation suspicious for malignancy at the level of the lingula, pulmonary nodules in LSL and RIL (require follow-up at 3 months), mediastino-pulmonary lymph nodes mostly with reactive appearance, congestive liver, vertebral arthrosis.

Medication on admission: Trimbow 2 puffx2/day, Ventolin 100 mg as needed, O2-therapy with a flow rate of 2 l/min, 16/24h.

Clinical examination on admission: patient with influenced general condition, afebrile, with normal weight (BMI=22.9 kg/m2). Teguments with a gray tint, labial cyanosis, upper limbs - fingernails with an hourglass appearance, cyanosis of the nail beds (Figure 1); lower limbs - venectasia, onycholysis, onychodystrophy (Figure 2).

Chest slightly cyfortic, symmetric costal excursions, with reduced amplitude, vesicular breathing decreased bilaterally, crepitant and subcrepitant rales bilaterally, BF=18/min, SpO2=80% a.a. spontaneous and SpO2 =94% a.a. under external oxygen supply.

Rhythmic heart sounds, apparently without extra murmurs, BP=100/66 mmHg, VA=75 bpm, the pulsation on the pedic artery and the posterior tibial artery was difficult to detect bilaterally. Slow intestinal transit, altered urination (nicturia, pollakiuria, hyperchromic urine).

The paraclinical examination revealed: quasinormal HLG, moderate inflammatory syndrome, sideropenia, hyperglycaemia with values of HgA1c at the upper limit of normal value, moderate liver cytolysis and cholestasis syndrome, nitrogen retention, mixed dyslipidaemia (increased LDL-c and triglycerides), NT-proNP=6691 pg/ml, pro-thrombotic status (increased D-dimers and fibrinogen), pathological urine summary (proteinuria, leukocyturia, microscopic haematuria).

EKG: SR with single VES, VA=65 bpm, QRS axis with right deviation, R>S in D2, signs of LV overload, terminal phase changes (Figure 3).

Heart ultrasound: RV dilatation, paradoxical movement of IVS, posterior mitral annulus calcification, more echodense mitral and aortic valves, with preserved opening, TAPSE=17 mm, IVC=21.8 mm, with inspiratory collapse present.



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Ankle-brachial index = 0.6 – medium arterial obstruction.

By corroborating the clinical and paraclinical data, the following diagnoses were established: Chronic ischemic heart disease, non-painful, Chronic heart failure class III NYHA, Chronic venous insufficiency class 2 CEAP, Peripheral arterial disease stage IIb, Extra systolic ventricular arrhythmia, Mixed dyslipidaemia, Modified basal blood glucose, COPD stage III GOLD, Bilateral pulmonary fibrosis, Pulmonary emphysema, Bilateral bronchiectasis, Chronic respiratory failure, Chronic O2-therapy at home, Chronic kidney disease stage G3b, lung nodules in LSL and RIL, Suspect malignant opacity in the lingula, Bladder tumour, Chronic liver disease.

The natural evolution of the case involves the progressive worsening of pulmonary suffering, cardiovascular decompensation, progression of chronic kidney disease, oncological pathology and peripheral vasculopathy.

Complications *occurred*: chronic respiratory failure, chronic global heart failure, chronic kidney disease. *Probable*: decompensated chronic pulmonary heart. *Possible*: cor pulmonale acute, acute myocardial infarction, stroke, acute or chronic pulmonary thrombo-embolism, complications of neoplastic disease.

During hospitalization patient received O2-therapy, diuretics, antiplatelet therapy and statins. The evolution during hospitalization was stable, the patient being afebrile, normotensive.

At discharge patient received following recommendations:

- Hypo sodic, hypoglycaemic diet, with reduced amount of animal fats and proteins
- Adequate hydration (2 l of water per day, fractional)
- Avoid intense physical activity, stress and extreme temperatures
- Smoking and alcohol consumption are prohibited
- Respiratory gymnastics at home
- BP monitoring at home
- Chronic treatment with: Aspenter 75 mg 1 tab/day, Furosemide 40 mg 1 tab every 2 days, Atorvastatin 10 mg 1 tab/day, Pentoxifylline 400 mg 1 tabx2/day
- Follow the recommendations and continue the medication prescribed by the pulmonologist
- Oncological and nephrological monitoring
- Cardiovascular reassessment in 3 months or as needed.

The particularity of the case

We have a patient:

- with multimorbidity: COPD, cardiovascular, oncological, nephrological, metabolic pathologies, which includes all 3 main causes of death in these patients

(COPD, cardiovascular disease, lung cancer);
- with a common risk factor for COPD, lung cancer and cardiovascular diseases in anamnesis (smoking);
- being hard to approach therapeutically due the coexistence of predisposing conditions and risk factors for CV, respiratory, thromboembolic and haemorrhagic complications (chronic hypoxia, systemic inflammation, dyslipidaemia, hyperglycaemia, pro-thrombotic status, neoplastic pathology, forced sedentary lifestyle).

Discussions

Complications

Pulmonary fibrosis exacerbation may represent a possible complication. In the pulmonary fibrosis guideline, the definition criteria of acute exacerbation of pulmonary fibrosis are the following previous or present diagnosis of idiopathic pulmonary fibrosis (IPF), worsening or unexplained onset of dyspnoea in the last 30 days, High Resolution Computer Tomography with new areas of ground glass or condensation processes superimposed on the changes of usually interstitial pneumonia type, lack of infection (proved by tracheal aspirate or broncho-alveolar lavage), exclusion of alternative causes (left heart failure, pulmonary thromboembolism, acute pulmonary injury of known cause).

Acute exacerbation is the main cause of hospitalization and mortality of patients with IPF with a post-exacerbation survival between 26 days and 4.2 months, in-hospital mortality between 27 and 96%, significantly reduced 5-year survival. The treatment used among these patients is broad-spectrum antibiotics and high-dose steroid therapy (intravenous methylprednisolone 0.5-1g per day - 3 days). The combined treatment with anticoagulant and steroids is cited as favourable in the survival of patients with IPF exacerbation. It is important to evaluate the evolution of acute exacerbations under treatment in the first 10 days after the initiation of treatment, a clinical improvement being cited in the situation where we have an increase in PaO2 by more than 10mmHg, an increase in SpO2 by more than 5% or a decrease in oxygen therapy by more than 3L/minute[9].

Chronic cor pulmonale could represent another significant complication in the patient case. The Chronic Pulmonary Cord Guide attests to the following typical EKG changes in pulmonary hypertension, which correlate with the EKG changes of the patient in question, pulmonary P (P greater than 0.25mV in D II), right axial deviation (QRS axis over 90 degrees or undeterminable), left ventricle hypertrophy, complete or incomplete right bundle branch block, right ventricle overload with ST depression, T inversion in right leads V1-V4 and lower II, III aVF, prolonged QTc (non-specific). Transthoracic echocardiographic parameters detected on echocardiography are also showing right ventricular pressure. Regarding the functional WHO classification of patients diagnosed with pulmonary hypertension, high risk factors that determine a high prognosis of mortality at one year, summed up in our patient are the signs of HF, walking distance in 6 minutes less than 165m, NT- proBNP greater than 1100ng/L[4].

The therapeutic approach to thromboembolic and haemorrhagic risk in the case of lung and bladder neoplasia requires careful examination. Patients with neoplasia can present high thromboembolic risk. On the



other hand, the haemorrhagic risk is also increased, so a careful evaluation is needed to provide a treatment indication adapted to the patient's profile (patient's risk, type of neoplasia, risk factors and comorbidities, weight, renal function)[8].

The Khorana score is used to quantify the indication for anticoagulation in neoplastic patients at risk of venous thrombosis (location of neoplasia, level of platelets, leukocytes, haemoglobin, body mass index). A Khorana score greater than 2 indicates a patient at intermediate or high risk of venous thromboembolism who may benefit from oral anticoagulants. In the neoplastic patient who needs antithrombotic treatment, we have an indication of antivitamin K direct oral anticoagulants or low molecular weight heparins[5].

Oxygen therapy

Regarding the indication of oxygen therapy at home, it is important to state that the therapeutic target of SpO2 for oxygen therapy is 92-96% or even 90-94%. Normal SpO2 values among young people are 95-100%, and for patients over 73 years old the value can drop to 93%. Supplementation with O2 produces decrease of dyspnoea, the increase in the level of daily physical activity, the improvement of the quality of life, increases the life span by reducing cardiac work.

The studies concluded a mortality of 1% when comparing a liberal administration of oxygen therapy with a more conservative administration approach among acute hospitalized patients. Indication for oxygen therapy administration is a decrease in SpO2 below 90%[10].

It is important to avoid the administration of additional O2 in patients with a saturation greater than 92% and to avoid increasing SpO2 more than 96% in patients under oxygen therapy, because in patients with chronic hypercapnia, oxygen therapy can worsen alveolar hypoventilation, hypercapnia and respiratory acidosis.

At risk pathologies include COPD, cystic fibrosis, neuromuscular diseases, obesity-hypoventilation syndrome and chest wall diseases. Cardiovascular mechanisms that compensate for hypoxemia are tachycardia, increased cardiac output and moderate increase in blood pressure. After the compensation mechanisms are overcome, the patient may have episodes of arterial hypotension, changes in blood pressure when changing position, bradycardia, arrhythmias.

Criteria for establishing long-term oxygen therapy are PaO2 lower than 55mmHg (measured in arterial blood) or a SpO2 level lower than 88% (measured by pulse oximeter) in ambient air. Patients must be instructed to administer oxygen at least 15 hours a day[7].

Following a study carried out regarding the respiratory recovery of patients with Pulmonary Fibrosis and COPD, the importance of supplementing with oxygen during physical exercises of these patients was certified, due to the increased endurance and intensity, compared to those who did not use oxygen during physical exertion. Oxygen saturation must be measured both at rest and during exertion. The recording of oxygen saturation must be done in a Holter system, in the case of the walking test, to track the time until the patient desaturates as well as the level of desaturation[1].

Respiratory gymnastics

Respiratory gymnastics is a form of respiratory physiotherapy through which the patient learns to control and work the thoracic and abdominal respiratory muscles. It improves air ventilation in the lungs, blood oxygenation and muscle work and the possibility of physical exertion.

Breathing exercises have the role of strengthening the intercostal muscles, increasing the vital and functional capacity of the lungs, the elasticity of the chest, favouring the movements of the diaphragm.

Respiratory gymnastics increases the respiratory capacity and helps the oxygenation of the tissues, prevents ventilatory dysfunction, decreases the contracture of the inspiratory muscles and the associated pain, increases the flexibility of the joints responsible for the respiratory process, determines the efficient permeability of the respiratory paths, prevents respiratory diseases complications, exercise training and help with the elimination of bronchial secretions. To be effective, the recovery program must be carried out for a period of 6-8 weeks, 3 sessions per week.

Conclusions

- Strategies for the primary prevention of COPD and its multimorbidity should focus on modifying risk factors, including those related to unhealthy lifestyle and environmental exposures, and developing policies to address the social determinants of health.
- Health care providers should consider COPD as part of a multimorbid condition in the approach to each patient, from the first encounter; this paradigm requires a shift from a single-disease approach to a person-centred, holistic and integrated approach.
- While we await evidence on interventions that could improve the duration and quality of life of patients with COPD and multimorbidity, it is time to provide clinical recommendations based on the treatable traits approach, including patient-centred management criteria for identified components of multimorbidity.

References

1. Branson RD (2018) Oxygen therapy in COPD. Respiratory care 63:734-748.

2. Decramer M and Janssens W (2013) Chronic obstructive pulmonary disease and comorbidities. The Lancet Respiratory medicine 1:73-83.

3. Divo M and Celli BR (2020) Multimorbidity in patients with chronic obstructive pulmonary disease. Clinics in chest medicine 41:405-419.

4. Galie N and Humbert M (2016) ESC/ERS Guidelinesforthe Diagnosisand Treatmentof Pulmonary Hypertension. RevEspCardiol (EnglEd) 69:177.

5. Howard L (2019) Acute pulmonary embolism. Clinical Medicine 19:243.

6. Nikolaou V, Massaro S, Fakhimi M, Stergioulas L and Price D (2020) COPD phenotypes and machine learning cluster analysis: A systematic review and future research agenda. Respiratory Medicine 171:106093.

7. O'driscoll B, Howard L, Earis J and Mak V (2017) BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 72:ii1-ii90.

8. Poenou G, Dumitru Dumitru T, Lafaie L, Mismetti V,



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Ayoub E, Duvillard C, Accassat S, Mismetti P, Heestermans M and Bertoletti L (2022) Pulmonary embolism in the cancer associated thrombosis landscape. Journal of Clinical Medicine 11:5650.

9. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM and Martinez FJ (2022) Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. American Journal of Respiratory and Critical Care Medicine 205:e18-e47.

10. Siemieniuk RA, Chu DK, Kim LH-Y, Güell-Rous M-R, Alhazzani W, Soccal PM, Karanicolas PJ, Farhoumand PD, Siemieniuk JL and Satia I (2018) Oxygen therapy for acutely ill medical patients: a clinical practice guideline. Bmj 363.

11. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, Rutten EP, Op't Roodt J, Wouters EF and Franssen FM (2013) Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 187:728-735.