Med Pregl 2026; LXXIX(1-2): 53-57. Novi Sad: januar-februar.

EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AS AN INITIAL MANIFESTATION OF LUNG CARCINOMA – A CASE SERIES

EGZACERBACIJA HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA KAO INICIJALNA MANIFESTACIJA KARCINOMA PLUĆA – SERIJA PRIKAZA SLUČAJEVA

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Case report
Prikaz slučaja
UDK 616.24-008.4-06:616.24-006.6]-07
https://doi.org/10.2298/MPNS2602053L

Abstract

Introduction. Chronic obstructive pulmonary disease is frequently accompanied by exacerbations that significantly worsen patients' clinical status. Although infections are the most common trigger, atypical, recurrent, or treatment-resistant exacerbations may indicate other underlying pathologies, including lung carcinoma. Early recognition of malignancy in patients with chronic obstructive pulmonary disease is crucial for timely initiation of therapy and improved outcomes. **Case Reports.** We present two patients with established chronic obstructive pulmonary disease in whom worsening respiratory symptoms were initially interpreted as exacerbations of the underlying disease. In the first case, chest computed tomography and bronchoscopy revealed a well-differentiated squamous cell carcinoma (stage IIIB), while in the second case histopathological analysis confirmed lung adenocarcinoma (stage IIIA). In both cases, the absence of response to standard therapy and the atypical clinical course raised suspicion of malignancy. **Conclusion.** Lung carcinoma in patients with chronic obstructive pulmonary disease patients may clinically manifest as an apparent exacerbation of the primary disease, potentially leading to diagnostic delay. Any atypical, frequent, or therapy-refractory exacerbation should prompt further diagnostic evaluation, particularly radiological assessment. Recognition of clinical "red flags," such as unexplained weight loss, hemoptysis, new-onset chest pain, or radiological changes not attributable to infection, is essential for early cancer detection and improved prognosis. Early implementation of radiological diagnostics, supported by a multidisciplinary approach, represents a key component of successful patient management.

Key words: Pulmonary Disease, Chronic Obstructive; Symptom Flare Up; Lung Neoplasms; Liquid Biopsy; Diagnosis, Differential; Early Diagnosis; Signs and Symptoms; Disease Progression; Risk Factors

Sažetak

Uvod. Hronična opstruktivna bolest pluća često je praćena egzacerbacijama koje značajno pogoršavaju kliničko stanje bolesnika. Iako su infekcije najčešći uzrok pogoršanja, atipične, učestale ili terapijski rezistentne, egzacerbacije mogu ukazivati na postojanje drugih patoloških procesa, uključujući i karcinom pluća. Pravovremeno prepoznavanje maligniteta u ovoj populaciji od suštinskog je značaja za ishod lečenja. **Prikaz slučajeva.** Prikazana su dva pacijenta sa potvrđenom dijagnozom hronične opstruktivne bolesti pluća kod kojih se pogoršanje respiratornih simptoma inicijalno tretiralo kao egzacerbacija osnovne bolesti. Kod prve pacijentkinje, nalaz kompjuterizovane tomografije i bronhoskopija otkrili su skvamozno-celularni karcinom pluća (stadijum IIIB), dok je kod drugog pacijenta dijagnostikovan adenokarcinom pluća (stadijum IIIA). U oba slučaja, odsustvo odgovora na standardnu terapiju i atipičan tok bolesti bili su ključni za sumnju na malignitet. **Zaključak.** Karcinom pluća kod bolesnika sa hroničnom opstruktivnom bolešću pluća može se klinički manifestovati kao prividno pogoršanje osnovne bolesti, što dovodi do dijagnostičkog kašnjenja. Svaka atipična, učestala ili na terapiju refraktorna egzacerbacija treba da pobudi sumnju na malignitet i zahteva dodatnu dijagnostičku obradu, naročito radiološku. Prepoznavanje „crvenih zastavica" kao što su gubitak telesne mase, hemoptizije, novonastali bol u grudima ili radiološke promene, koje se ne mogu pripisati infekciji, od suštinskog je značaja za rano otkrivanje tumora i poboljšanje prognoze. Pravovremeno sprovođenje radiološke dijagnostike, uz multidisciplinarni pristup, predstavlja ključni element uspešnog lečenja ovih bolesnika.

Ključne reči: hronična opstruktivna bolest pluća; egzacerbacija bolesti; neoplazme pluća; tečna biopsija; diferencijalna dijagnoza; rana dijagnoza; znaci i simptomi; progresija bolesti; faktori rizika

Introduction

Chronic obstructive pulmonary disease (COPD) represents one of the leading global health problems, associated with substantial morbidity. It is characterized by progressive and largely irreversible airflow limitation, accompanied by recurrent exacerbations that significantly impair patients' quality of life [1,2]. Exacerbations of COPD are most commonly triggered by respiratory infections, exposure to air pollution, or inadequate pharmacotherapy. However, atypical, frequent, or treatment-resistant exacerbations may indicate the presence of additional pathological processes, including respiratory malignancies

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Abbreviations

COPD	– chronic obstructive pulmonary disease
CT	– computed tomography
FEV_1	– forced expiratory volume in 1 second
FVC	– forced vital capacity
GOLD	– Global Initiative for Chronic Obstructive Lung Disease
IASLC	– International Association for the Study of Lung Cancer
LDCT	– low-dose computed tomography
NLST	– National Lung Screening Trial

[3]. Lung carcinoma remains one of the most common and lethal malignancies worldwide. Despite significant advances in prevention, diagnosis, and treatment, it continues to account for the highest number of cancer-related deaths globally [4]. In patients with COPD, lung cancer may clinically manifest through worsening of underlying respiratory symptoms, often leading to diagnostic delay due to overlapping clinical presentations [5]. Early tumor detection in this high-risk population is essential, as it enables timely initiation of appropriate treatment and may significantly improve clinical outcomes [6]. A strong pathophysiological association exists between COPD and lung carcinoma, primarily based on shared mechanisms of chronic inflammation, oxidative stress, and genetic susceptibility [7–9]. Chronic airway inflammation in COPD patients results in epithelial injury, fibroblast proliferation, and dysplastic changes, thereby creating a microenvironment favorable for carcinogenesis [7]. Furthermore, oxidative stress supports the concept that COPD is not merely a smoking-related risk factor but also an independent pathophysiological condition that may promote malignant transformation [8,9]. The aim of this study was to present two clinical cases in which COPD exacerbation represented the initial manifestation of newly diagnosed lung carcinoma, with particular emphasis on the importance of differential diagnosis and clinical suspicion of malignancy in patients with an atypical disease course.

Case 1

A 60-year-old woman, a long-term smoker with a 40 pack-year history, who had been treated for COPD for the previous nine years, presented to our institution with progressive dyspnea lasting fifteen days. The symptoms were accompanied by a dry, non-productive cough, without fever or signs of infection. She had previously received bronchodilator therapy and oral antibiotic for five days in an outpatient setting without clinical improvement and was therefore referred for pulmonology evaluation. At admission, the patient was receiving triple inhalation therapy consisting of an inhaled corticosteroid, long-acting beta-agonist, and long-acting anticholinergic. Her medical history included hypothyroidism and depression. She had experienced three previous COPD exacerbations, two managed on an outpatient basis and one requiring hospitalization 14 months earlier. Laboratory testing revealed elevated D-dimer levels (980 μg/L), while inflammatory markers remained within normal limits. Spirometry demonstrated severe obstructive ventilatory impairment with FEV_1 32%, FVC 67%, and Tiffeneau index 52%, corresponding to GOLD stage III. Physical examination revealed dyspnea at rest with the use of accessory respiratory muscles, while auscultation showed diffusely diminished breath sounds and prolonged expiration. Arterial blood gas analysis indicated partial respiratory insufficiency. Chest radiography demonstrated a new inhomogeneous opacity in the projection of the right middle lung field, which had not been present on imaging performed eight months earlier. Subsequent chest computed tomography revealed a soft-tissue mass surrounding the bronchus of the middle lobe, measuring 29 × 68 mm, with a central hypodense area and enlarged lymph nodes in the right hilum (up to 15 mm) and 4R mediastinal group (up to 35 mm). Bronchoscopy demonstrated an endobronchial lesion partially obstructing the bronchial lumen of the middle lobe. Histopathological examination of biopsy specimens confirmed a well-differentiated squamous cell carcinoma of the lung (stage IIIB, T3N2M0).

Case 2

A 68-year-old man, an active smoker with a 30 pack-year history, previously diagnosed with COPD three years earlier, presented with progressively worsening exertional dyspnea, more frequent cough, and unintentional weight loss of approximately 3 kg over the preceding three months. His medical history included arterial hypertension, cardiomyopathy, and myocardial infarction two years earlier. Initially, he was treated in an outpatient setting for a presumed COPD exacerbation with bronchodilators, systemic corticosteroids, and antibiotics, but without significant clinical improvement. Over the following weeks, his dyspnea progressively worsened. Notably, the clinical course differed from his previous exacerbations (two since the initial COPD diagnosis), both of which had responded well to outpatient therapy. Upon admission, the patient was dyspneic at rest, and auscultation revealed diminished breath sounds over the lower right lung field. Spirometry showed FEV_1 41%, FVC 70%, and Tiffeneau index of 56%, consistent with severe obstructive ventilatory impairment (GOLD stage III). Chest radiography demonstrated a new inhomogeneous opacity in the right basal re-

gion, which had not been present on routine imaging performed seven months earlier. Chest computed tomography revealed a non-homogeneous retrocardiac infiltrative lesion in the right lower lobe, measuring 60 × 50 × 60 mm, associated with disruption of the pulmonary parenchymal architecture and segmental bronchiectasis. The pleural space appeared clear, and mediastinal lymph nodes were not enlarged. Bronchoscopy demonstrated irregular mucosal architecture above the entrance to the upper lobe bronchus, suggestive of tumorous granulation tissue. The orifice of the posterobasal segment was completely obstructed by tumor tissue. Biopsy samples obtained from the lesion and the right basal region were submitted for histopathological analysis, which confirmed lung adenocarcinoma, stage IIIA (T3N0M0).

Discussion

In addition to the diagnostic challenges illustrated by our cases, epidemiological data strongly support the role of chronic obstructive pulmonary disease (COPD) as one of the most important high-risk conditions for lung cancer. COPD is highly prevalent in many European countries, including Serbia, and frequently coexists with long-term tobacco exposure. Beyond this shared smoking-related risk, COPD itself represents an independent carcinogenic environment characterized by chronic inflammation, oxidative stress, and structural airway remodeling, all of which contribute to malignant transformation [9,10].

These observations have important implications for lung cancer screening strategies. Although a formal national low-dose computed tomography (LDCT) screening program has not yet been implemented in Serbia, clinical practice increasingly relies on evidence derived from large randomized trials such as the National Lung Screening Trial (NLST) and the NELSON study, which demonstrated a significant reduction in lung cancer–specific mortality among high-risk smokers. Subsequent analyses have shown that patients with COPD represent a subgroup that derives particularly pronounced benefit from LDCT screening, as lung cancers are detected more frequently and at earlier, potentially curable stages compared with smokers without airflow obstruction. Data from a regional lung cancer screening initiative conducted in Vojvodina, Serbia, further highlight the importance of organized screening and the high prevalence of smoking-related risk factors among participants [11–13].

Several international recommendations, including GOLD guidelines, suggest that LDCT screening should be considered in patients with COPD and a significant smoking history, given the disproportionally high incidence of lung cancer in this population. From a clinical perspective, these findings support the concept that COPD should not be regarded merely as a comorbidity but rather as a central risk determinant when selecting candidates for lung cancer screening, alongside age and cumulative tobacco exposure [1].

In routine clinical practice, particular attention should be given to COPD patients with advanced disease (GOLD stages III–IV), frequent exacerbations, accelerated decline in lung function, or poor response to standard therapy. In such individuals, the threshold for performing additional radiological diagnostics, including LDCT, should be low, especially when the clinical course deviates from the patient's usual exacerbation pattern. In both of our presented cases, the absence of the expected therapeutic response represented the key trigger for extending the diagnostic evaluation [13].

Beyond conventional imaging, emerging diagnostic approaches may further enhance early lung cancer detection in patients with COPD. Artificial intelligence–assisted image analysis and radiomics allow quantitative assessment of subtle morphological and textural features, potentially improving the differentiation between malignant lesions and inflammatory or emphysematous changes that often complicate CT interpretation in COPD. In parallel, liquid biopsy techniques, including the analysis of circulating tumor DNA and circulating tumor cells, have demonstrated promising results in detecting malignancy even before clear radiological abnormalities become evident.

Although these advanced techniques are not yet integrated into routine clinical algorithms, their future combination with LDCT screening may prove particularly valuable in high-risk COPD populations, in whom structural lung alternations and recurrent inflammation frequently obscure early tumor manifestations. Such multimodal diagnostic strategies may help reduce diagnostic delays and improve oncological outcomes in this vulnerable patient group [14,15].

The presented cases further illustrate that lung carcinoma in patients with COPD may clinically manifest as an apparent exacerbation of the underlying disease. Such exacerbations, particularly when unresponsive to standard therapy, pose a considerable diagnostic challenge, as symptoms such as cough, dyspnea, fatigue, and functional decline are often attributed to COPD itself. Recent studies have shown that comorbidities such as COPD may significantly prolong the time to lung cancer diagnosis. An analysis conducted in England demonstrated that patients with at least one coexisting disease capable of explaining respiratory symptoms experienced, on average, a diagnostic delay of more than one month compared

with individuals without such conditions [16]. This finding underscores the importance of maintaining a high level of clinical suspicion in every atypical COPD exacerbation. Research over the past decade has further confirmed the association between frequent COPD exacerbations and an increased risk of developing lung cancer. The Norwegian HUNT study demonstrated that patients with at least one acute COPD exacerbation had nearly a threefold higher risk of subsequently developing lung carcinoma [13]. These findings suggest that exacerbations may represent not only a marker of more severe disease but also an indicator of ongoing inflammatory processes and parenchymal injury contributing to carcinogenesis. Similarly, a Danish cohort study of outpatients with COPD reported that lung carcinoma was detected more frequently – and at earlier stages – in patients undergoing regular follow-up, including annual chest radiography and prompt imaging in the event of exacerbations [17]. These observations highlight the importance of systematic monitoring and preventive diagnostics in COPD populations, which may facilitate earlier cancer detection and improve treatment outcomes [13]. Published case reports have also described patients repeatedly hospitalized for presumed COPD exacerbations in whom lung carcinoma was ultimately identified as the underlying cause [18,19]. Such observations emphasize the need for further diagnostic evaluation in patients whose clinical condition fails to improve as expected, particularly in the presence of warning signs such as unexplained weight loss, hemoptysis, chest pain, or persistent radiological abnormalities unresponsive to standard therapy. The pathophysiological link between COPD and lung carcinoma has long been recognized. Current understanding emphasizes the role of chronic inflammation, oxidative stress, structural airway remodeling, epigenetic changes, and impaired immune surveillance in the development of both diseases [20,21]. Persistent inflammatory processes in COPD may result in irreversible epithelial damage and accumulation of genetic mutations that facilitate tumor development. Recent studies indicate that LDCT screening may be particularly beneficial for patients with COPD, as the incidence of lung carcinoma in this population is substantially higher than in the general population of smokers. Prospective analyses by de Torres et al. [22,23] demonstrated that among patients with documented airway obstruction enrolled in LDCT screening programs, lung tumors were detected more frequently and at earlier stages compared with individuals without COPD. This so-called *stage-shift effect* may be explained by chronic inflammation and structural parenchymal changes in COPD that increase the likelihood of detecting clinically relevant lesions. These findings support the implementation of LDCT screening programs in carefully selected COPD patients – particularly those with a long smoking history and frequent exacerbations (defined as two or more per year requiring additional therapy or one requiring hospitalization) – while adhering to principles of rational use and individualized risk-benefit assessment.

In this context, bronchoscopy remains a pivotal diagnostic modality in patients with COPD presenting with atypical or therapy-refractory exacerbations. It enables direct visualization of endobronchial pathology and timely histopathological confirmation, thereby significantly reducing diagnostic delay. According to current recommendations, bronchoscopy should not be postponed in patients with persistent or unexplained radiological abnormalities and an unusual clinical course of exacerbation, as delayed diagnosis may directly influene disease stage and overall prognosis [6].

Conclusion

Lung carcinoma in patients with chronic obstructive pulmonary disease may clinically manifest as worsening of the underlying disease, which can lead to significant diagnostic delay because patients often cannot distinguish the symptoms of a newly developing malignancy from those related to their baseline respiratory condition. Therefore, in patients with atypical, frequent, or therapy-refractory chronic obstructive pulmonary disease exacerbations, it is essential to maintain a high level of clinical suspicion for malignancy and to promptly initiate additional diagnostic procedures, particularly radiological imaging. Early implementation of radiological diagnostics, supported by a multidisciplinary approach, represents a key component of effective management in these patients. Furthermore, growing evidence suggests that low-dose computed tomography screening in carefully selected chronic obstructive pulmonary disease patients can facilitate earlier detection of lung cancer and reduce disease-specific mortality. Integration of thorough clinical assessment with modern diagnostic modalities should therefore become an integral part of chronic obstructive pulmonary disease follow-up in order to minimize the risk of missed malignancies and improve long-term outcomes.

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Rad je primljen 3. XI 2025.
Recenziran 12. II 2026.
Prihvaćen za štampu 12. II 2026.
BIBLID.0025-8105:(2026):LXXIX:1-2:53-57.