Haemoptysis as a primary manifestation of cryptogenic organizing pneumonia (COP)

Hemoptizia ca primă manifestare a pneumoniei criptogenice în organizare

Abstract

Cryptogenic organizing pneumonia (COP), previously called bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathological disorder of unknown aetiology but increasingly reported. It usually presents with symptoms of dyspnea, cough, fever, weight loss accompanied by the presence of alveolar opacities on chest radiograph. Haemoptysis, described as blood streaking has only rarely been reported as primary presentation of COP. Herein, we report a case of COP in which submassive haemoptysis was the main clinical manifestation. The clinical, radiological, pathological, and therapeutic aspects of the disease are briefly discussed. Cryptogenic organizing pneumonia should be taken into consideration in the differential diagnosis of severe haemoptysis.
Keywords: *cryptogenic organizing pneumonia, haemoptysis, corticosteroids*

Rezumat

Pneumonia criptogenică în organizare (COP), numită anterior bronșiolotă obliterantă cu pneumonie în organizare (BOOP) este o entitate clinicopatologică de etiologie necunoscută, dar cu prevalență în creștere. Tabloul clinic cuprinde simptome ca dispnee, tuse, febră, pierdere în greutate, cu apariția opacităților de tip alveolar pe radiografia toracică. Hemoptizia a fost rar descrisă ca prim semn în COP. Raportăm cazul unui pacient cu COP la care hemoptizia masivă a fost principala manifestare clinică. Prezentăm particularitățile clinice, radiologice, patologice și terapeutice. COP trebuie luată în considerare ca diagnosticul diferențial în hemoptizia masivă.
Cuvinte-cheie: *COP, hemoptizie, corticoterapie*

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Introduction

Cryptogenic organizing pneumonia (COP), previously known as bronchiolitis obliterans organizing pneumonia (BOOP), is a clinico-pathological entity characterized by excessive proliferation of granulation tissue within small airways and alveolar ducts, associated with chronic inflammation in the surrounding alveoli[1]. The disorder is considered to be cryptogenic/idiopathic when a definite cause or characteristic associated context is not present. Nevertheless, there is "secondary" form of organizing pneumonia to a known causative agent (infections, drugs and radiation therapy) and systemic or predisposing conditions. The cardinal clinical features are cough and dyspnea, which can develop acutely or sub-acutely. It most often mimics viral infection, with flu-like symptoms including fever, malaise, fatigue and weight loss. Haemoptysis (small or large quantity of expectorated blood) as major presenting symptom of COP has only rarely been described[2,3]. In this article, we present a case of COP in which submassive haemoptysis was the primary presenting manifestation.

Case presentation

A 61-year-old male, ex-heavy smoker (135 p/y, smoking cessation 1yr ago), was admitted to our department presenting haemoptysis (about 100ml of bright red blood daily) for 5 consecutive days prior to hospital admission. He denied any additional symptoms. His past medical history included combined emphysema-pulmonary fibrosis syndrome and one-vessel coronary artery disease under percutaneous transluminal coronary angioplasty (PTCA). His outpatient medication was aspirin, atenolol and inhaled formoterol/budesonide. He was a retired military officer with no known occupational exposures and no history of allergies. He had developed atypical pneumonia syndrome caused by C. burnetii 6 months before his admission with complete recovery after receiving appropriate antibiotic treatment.

Vital signs on hospital admission showed temperature of 36.9°C, respiratory rate of 16 breaths/min, heart rate of 85 bpm and arterial blood pressure of 140/70 mmHg. Chest physical examination revealed end-inspiratory crackles at the left lower lung field. The rest of the clinical examination was unremarkable.

Initial laboratory studies showed a WBC count of 9.500/μL with normal differential count, haemoglobin was 14.4g/dL, haematocrit was 43.4% and platelet count was 184.000/μL. Erythrocyte sedimentation rate (ESR) was elevated (59 mm/h). C-reactive protein, serum biochemistry tests and urinalysis were within normal range. ECG showed normal sinus rhythm with no acute ST-T wave changes. Tests for antinuclear antibody, rheumatoid factor, complement, antiglomerular basement membrane antibody and antineutrophil cytoplasmic antibody as well as the tuberculin skin test were negative. Arterial blood gas analysis on room air revealed a pO_2:99 mmHg, pCO_2:23.3 mmHg, pH: 7.49, HCO_3:18 mmol/lt. Chest radiograph revealed left middle lung field diffuse infiltrates with reticular pattern. Chest

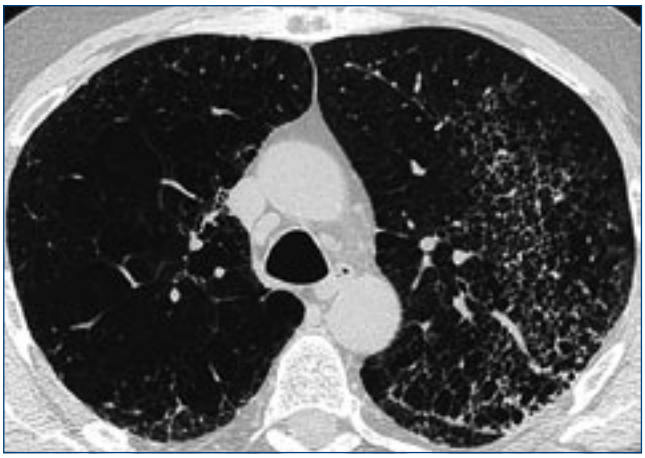

Figure 1. *High resolution computed tomography (HRCT) of the chest on admission showing intralobular septal thickening, as well as bronchial wall thickening and dilatation in the left upper lobe.*

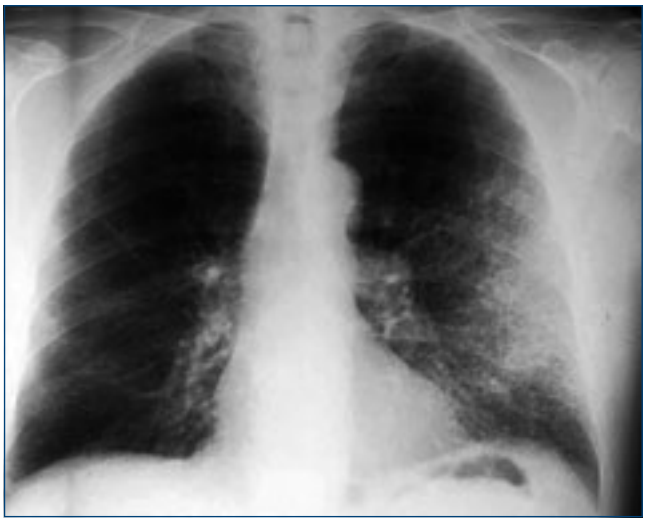

Figure 2. *Chest radiograph showing left middle/lower lung field diffuse infiltrates with associated reticular pattern.*

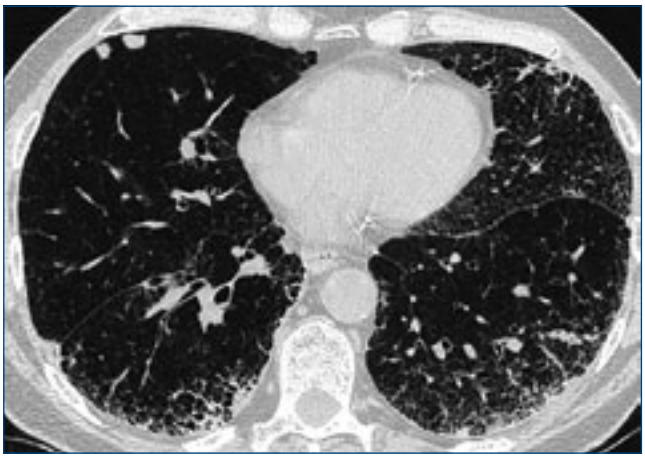

Figure 3. *Chest HRCT revealing bibasilar and left upper lobe intralobular septal thickening and bronchial wall thickening and dilatation.*

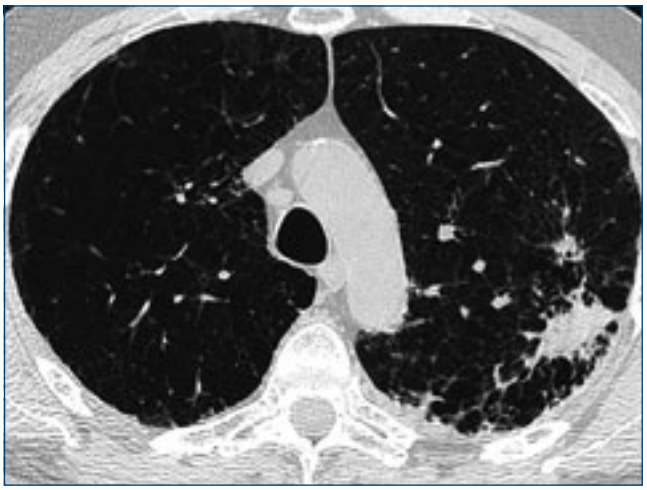

Figure 4. *Chest HRCT 18 days after admission showing consolidation in the posterior segment of the left upper lobe.*

CT demonstrated intralobular septal thickening, as well as bronchial wall thickening and dilatation, mainly in the left upper lobe (Figure 1). Spiral CT pulmonary arterial angiography performed simultaneously was negative for emboli in pulmonary arterial trunk and the following branching system.

The patient underwent fiberoptic bronchoscopy showing blood of moderate quantity in the lingula. No intraluminal lesions were found. Bronchoalveolar lavage (BAL) showed a large percentage of haemosiderin-laden macrophages. BAL was negative for mycobacteria and other common pathogens as well as cytologic examination.

The patient continued to expectorate a moderate amount of blood (20-30cc daily) and developed further deterioration of his clinical condition thus exhibiting low-grade fever (38.5°C), bibasilar end-inspiratory crackles, dyspnea on exertion and acute hypoxemic respiratory failure (ABG's,FiO2=50%:pO_2:54mmHg,pCO_2:22mmHg pH:7.50, HCO_3:17mmol/lt) on the 18th day of admission. New laboratory studies showed WBC count of 18.300/μL with neutrophil predominance (89.7%), haematocrit:33.4%, Hb:10,9g/dL, platelet count of 187.000/μL, ESR of 108 mm/h and C-reactive protein of 98mg/l. A new frontal chest radiograph showed left middle/lower lung field diffuse infiltrates with associated reticular pattern (Figure 2). In addition, high-resolution chest CT showed further aggravation with bibasilar and left upper lobe intralobular septal thickening, bronchial wall thickening and dilatation (Figure 3), as well as consolidation in the posterior segment of the left upper lobe (Figure 4).

His regular medications as well as an empirical broad-spectrum antibiotic scheme that started on the date of admission were discontinued. Left thoracotomy was then performed to facilitate diagnosis. Microscopic examination of specimens revealed areas of normal parenchyma alternating with well-defined fibrosed areas. More specifically, fibroblastic foci were noted within the alveolar air spaces accompanied by mild interstitial chronic inflammation with septal thickening (Figure 5). There was an accumulation of foamy macrophages within dilated alveoli. Evidence

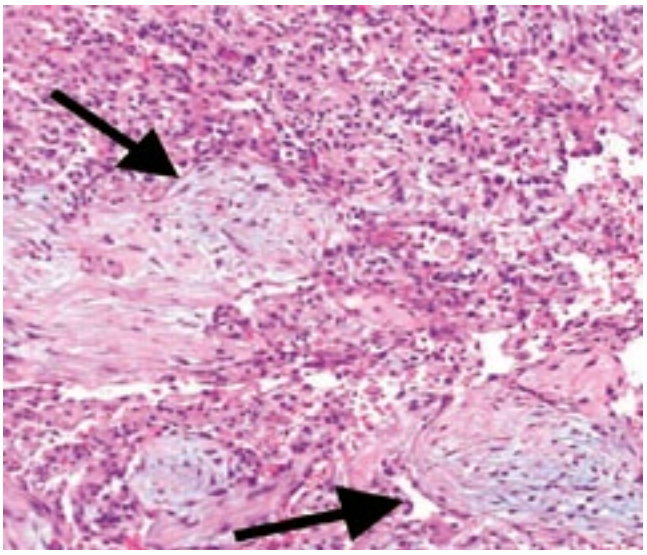

Figure 5. *An open lung biopsy specimen showing fibroblastic foci within the alveolar air spaces (arrows)(Haematoxylin & Eosin, original magnification X100)*

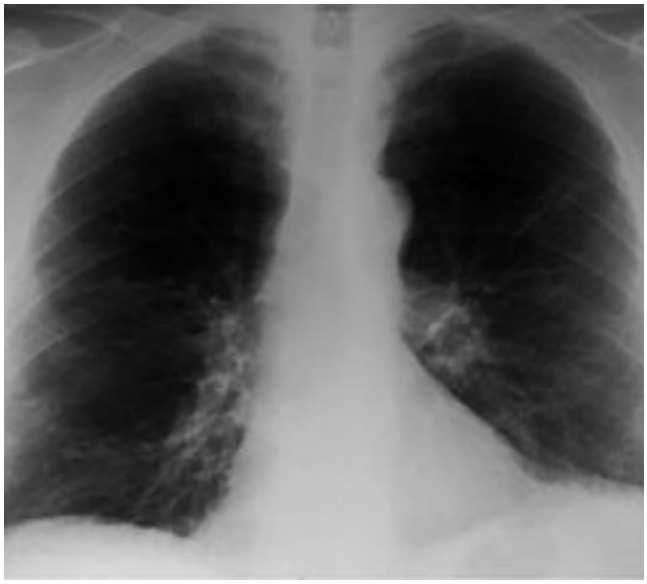

Figure 6. *Chest X-ray at one year follow-up showing complete resolution of radiographic findings*

of recent and old haemorrhage with haemosiderin-laden macrophages was also noted. Alveolar capillaries displayed endothelial degeneration/ sclerosis and consequential focal luminal stenosis. The histological features were in keeping with an organizing pneumonia.

Corticosteroid treatment was initiated (50mg/day prednisone) with rapid improvement of the patient's symptoms, gas exchange, and chest imaging findings. The initial prednisone dose was effectively tapered down over a period of several months, with a schedule of the steroid therapy completion in the sixth month. At one year follow-up, he has remained asymptomatic with complete resolution of radiographic features (Figure 6).

Discussion

It was only during the last two decades that COP was individualized as a distinct clinicopathological entity, after the reports of Davison et al.[4] and Epler et al.[1], who could correlate an idiopathic clinicoradiological syndrome with the typical pathological lesions of organising pneumonia. Despite its relative rarity, it rapidly became a common disorder that was especially gratifying for the clinician due to its prompt improvement under corticosteroid treatment. The previous terminology of bronchiolitis obliterans with organizing pneumonia (BOOP) was abandoned because the major process is organising pneumonia, with bronchiolitis obliterans being only a minor and accessory finding (which may even be absent)[5,6].

Since the time COP was established as a clinical entity, several reports have been published underpinning its various clinical manifestations. It has neither sex nor age predominance (mean age of onset 50-60 yrs) and is not related to smoking. The typical presenting symptoms are cough, dyspnea, malaise, weight loss, fever, often following a mild flu-like syndrome. Haemoptysis as a presenting feature is rare, and seldom severe. In particular, scanty haemoptysis has been described in cases of COP[1,7-10]. However, there are only three cases of COP in the current literature presenting with large quantity of haemoptysis, one of them exhibiting fatal massive haemoptysis[2,3].

The main characteristic imaging pattern of COP consists of bilateral patchy airspace consolidation, with a subpleural or peribronchial distribution, with or without ground-glass opacities. Additional abnormalities are rounded areas of ground glass with central clearing (reverse halo or atoll sign), peribronchovascular nodules and linear opacities, bronchial wall thickening and dilation in the consolidation areas[11]. The latter finding was markedly seen in the present case, as well as the migratory aspect of imaging findings in COP.

Haemoptysis can be classified as mild, moderate or massive, depending on the amount of blood expectorated: < 100 mL in 24 h (mild); 100-600 mL in 24 h (moderate); and > 600 mL in 24 h or > 30 mL/h (massive)[12,13]. Our patient had persistent haemoptysis for three weeks prior to diagnostic surgical procedure, with an estimated total expectorated blood volume of 400 to 450 mL. Though massive haemoptysis was not documented in the present case, moderate haemoptysis was noted, as it occurred only in another old-published descriptive study[2].

There was no clinical or laboratory evidence to support conditions that are associated with organizing pneumonia (infections, systemic diseases, drugs). More specifically, failure to isolate any organism on repeated cultures made infectious aetiology unlikely. In addition, negative vasculitis/connective tissue diseases screen and no vasculitic process on histological examination were detected. Drug-induced organising pneumonia was also impossible since there was no temporal association between the long-term administration of aspirin and Atenolol and the onset of haemoptysis. Neither of the medications withdrawal led to patient's clinical and radiological improvement, nor did their resumption cause haemoptysis. The Naranjo algorithm (Naranjo Causality Scale for Adverse Drug Reactions)

was also employed and the case scored a zero, which translates into a negative causal relationship between patient's medication and the development of COP.

The histopathological hallmark of COP is the presence of granulation tissue plugs within the lumen of distal bronchioles extending into alveolar ducts and alveoli[1,14]. Inflammation, either as an integral part of COP or as a result of some unidentified infectious/noxious agent, might be the cause of parenchymal damage and resultant bleeding. Myers and Katzenstein especially described extensive areas of epithelial necrosis and denudation of the epithelial basal laminae in nine cases of COP[15]. There was evidence of endothelial damage to alveolar capillaries in seven of these cases, with some demonstrating endothelial necrosis and extravasation of erythrocytes into the interstitium.

Although the pulmonary lesions in COP are mainly intra-alveolar, COP may be confused with other forms of idiopathic interstitial pneumonias (idiopathic non-specific interstitial pneumonia and idiopathic pulmonary fibrosis), especially when the imaging pattern is infiltrative[5]. However, the main histopathological findings suggestive of NSIP include temporal and spatial homogeneity, mild-to-moderate interstitial inflammation (usually lymphocytic) with intra-alveolar organising fibrosis (minor component) and lack of interstitial fibrosis (cellular NSIP pattern) or dense/loose interstitial fibrosis with mild or moderate interstitial chronic inflammation (fibrosing NSIP pattern). Architectural destruction, temporal and spatial heterogeneity (areas of normal lung present), interstitial fibrosis with honeycombing and fibroblastic foci comprise the characteristic features of IPF. Mild interstitial inflammation is present in areas of organizing pneumonia, and foamy alveolar macrophages are present in those alveoli that are not filled by buds. It must be highlighted that the mere presence of some buds is not sufficient to make the diagnosis of organising pneumonia as the organisation of intra-alveolar exudates is a non-specific process that may occur in various inflammatory lung diseases including Wegener's granulomatosis, eosinophilic pneumonia, hypersensitivity pneumonitis, pneumonia distal to obstruction (especially of neoplastic origin), abscesses, aspiration pneumonia, cystic fibrosis, organizing diffuse alveolar damage of any cause, pneumoconiosis , or in the vicinity of pleural plaques[5,16].

Therapeutic goals in the treatment of haemoptysis include the cessation of bleeding, aspiration prevention and management of the underlying cause. As with any potentially serious condition, evaluation of the "ABCs" (i.e., airway, breathing, and circulation) is the initial step. If the underlying cause (i.e., pneumonia, mass, etc.) is identified, the standard treatment approach for the underlying condition should be performed. If haemoptysis does not resolve or recurs, further treatment (medical, endovascular, and surgical) should be considered[17]. Strictly speaking, bronchial artery embolisation is the most effective and minimally invasive technique for managing massive and recurrent haemoptysis. Additionally, bronchoscopic use of iced saline lavage, topical agents such as thrombin or fibrinogen-thrombin glue, endobronchial balloon catheter tamponade and laser photocoagulation has been demonstrated favourable results. Antifibrinolytic agents (e.g. tranexamic acid) have successfully been administered via intravenous and inhalation routes, and even bronchoscopically[18,19]. Nowadays, surgery is usually only the treatment of choice in select cases, such as chest trauma and iatrogenic pulmonary artery rupture.

COP responds favorably to corticosteroid treatment in more than 80% of cases[20]. However, relapses are common upon stopping or reduction of corticosteroids, thus often leading to prolonged treatment. Although rapidly fatal COP is rare, respiratory failure leading to death may occur in up to 5% of patients[21].

In conclusion, we present a case of histologically confirmed COP, whose primary presenting symptom was large quantity haemoptysis. This entity should be considered in any patient presenting with haemoptysis and persistent migratory radiographic infiltrates. ■

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