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Case Report

Chest pain with bloody sputum as the main manifestation of cryptogenic organizing pneumonia: a case report and review of the literature

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Abstract: Cryptogenic organizing pneumonia (COP) is a rare disease with non-specific clinical and imaging manifestations, making it quite easy to misdiagnose. Here a case of COP is reported that was initially suspected to be malignancy because the main clinical findings were chest pain with a small amount of bloody sputum and multiple lung nodules on computed tomography. The patient was treated with oral methylprednisolone, after which respiratory symptoms disappeared and chest computed tomography showed complete absorption. Follow-up more than one year later showed no recurrence. This rare case highlights the need for careful assessment to avoid COP misdiagnosis.

Keywords: COP, chest pain, bloody sputum, malignancy

Introduction

Organizing pneumonia is a histopathological response pattern to lung inflammation. It is called secondary when it occurs in the presence of infection, drug use, allergy, radiation injury, malignancy, or connective tissue disease. In rare cases, no likely cause can be identified. In these cases, the disease is called cryptogenic organizing pneumonia (COP) [1, 2]. COP, which is considered a type of idiopathic interstitial pneumonia [3], is associated with nonspecific clinical and imaging manifestations, laboratory examinations, and pulmonary function results. It is quite common for COP to be misdiagnosed as other types of idiopathic interstitial pneumonia or even as other diseases.

COP is diagnosed on the basis of clinical, radiographic and especially pathological findings, as well as the exclusion of respiratory and other diseases associated with secondary organizing pneumonia [4]. Four imaging types of COP have been described: ground grass opacity, nodule, liner lesion or reticular lesion. Predominant symptoms in COP are malaise, cough, fever, and dyspnea [5].

Here, a case of COP is reported that was initially suspected to be malignancy because the main clinical findings were chest pain with a small amount of bloody sputum and multiple lung nodules on imaging. This report of a rare case of COP associated with chest pain and bloody sputum highlights the need for careful diagnostic assessment in order to avoid easy misdiagnosis of COP.

Case report

A 74-years-old man was treated for three days in the outpatient department of the People's Hospital of Deyang City (also known as the Affiliated Hospital of Chengdu College of Medicine) in Deyang, China. He complained of a five-day history of mild chest pain and a small amount of bloody sputum. He had no complaints of chill, fever, hot flashes, night sweats,

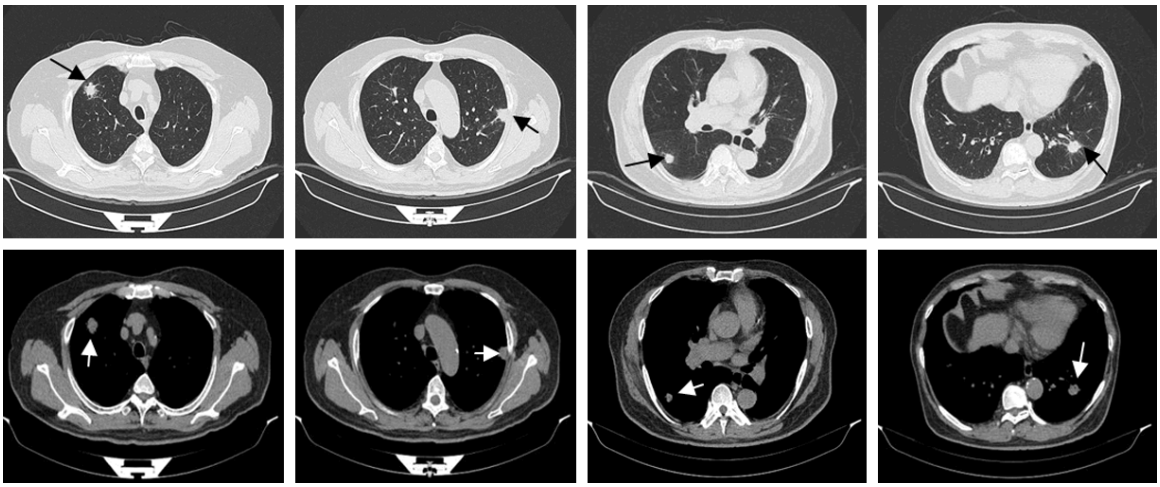

Figure 1. Initial chest computed tomography scans in the pulmonary window (*upper row*) and mediastinal window (*lower row*) showed multiple and bilateral lung nodules, particularly in the subpleural area. Some nodules had short burrs.

or dyspnea. He had a 12-year history of hypertension, for which he had been regularly taking oral anti-hypertension medication. He had been a smoker but had quit more than 30 years previously. He did not describe obvious exposure to harmful environmental agents that could have instigated or exacerbated his symptoms. He also had a history of gastrohelcosis. Chest x-ray in the outpatient department led to an initial diagnosis of pneumonia, and he was treated with oral antibiotics and hemostatic agents. However, these treatments did not obviously alleviate his symptoms.

Then the patient was admitted to the same hospital for further analysis and treatment. Physical examination revealed good general condition with a body temperature of 36.6°C; heart rate, 86 beats/minute; respiratory rate, 19/minute; blood pressure, 124/69 mmHg; and oxygen saturation, 95% in ambient air. The patient had unremarkable positive signs except bilateral basal fine moist rale. Laboratory tests showed a white blood cell count of 12.1 × 10^9/L; lymphocyte percentage, 13%; neutrophil percentage, 71.8%; eosinophil percentage, 1.8%; hemoglobin concentration, 141 g/L; and C-reactive protein level, 18.2 mg/L. The erythrocyte sedimentation rate was 48 mm/h, and results were normal for hepatic and renal function indicators, routine coagulation tests, immunological tests and tumor marker levels. Results were negative or within normal limits for IgG, IgM, IgA as well as complement C3 and C4. The patient was positive for (1, 3)-β-D-glucan but negative for galactomannan. Electrocardiography findings were normal. Pulmonary function results were as follows: FEV1 was 87% of the predicted value, FEV1/FVC ratio was 76% and DLCO was 69%. A small number of cells with heterogeneous nuclei were detected in bronchoalveolar lavage fluid (BALF), which contained 2.7% neutrophils, 0% eosinophilic granulocytes, 82.7% macrophages and 14.6% lymphocytes. Negative results were obtained for sputum culture, acid-fast staining, and a PCR-based assay for *Mycobacterium tuberculosis* DNA. Computed tomography (CT) of the chest showed bilateral and multiple lung nodules predominantly in the subpleural area, with some nodules featuring short burrs (**Figure 1**). Positron emission tomography (PET)-CT led to suspicion of malignancy.

The patient was started on piperacillin-sulbactam for possible pneumonia, but this did not alleviate clinical manifestations in the following days, nor did the lung nodules disappear. Percutaneous lung biopsy was performed, and pathology examination led to a diagnosis of organizing pneumonia (**Figure 2**). The patient was treated with oral methylprednisolone (32 mg) daily. Respiratory symptoms disappeared two weeks later, so the dose of methylprednisolone was decreased to 24 mg, then it was decreased again to 16 mg after another two weeks. Chest CT at 3 months after the start of methylprednisolone therapy showed complete

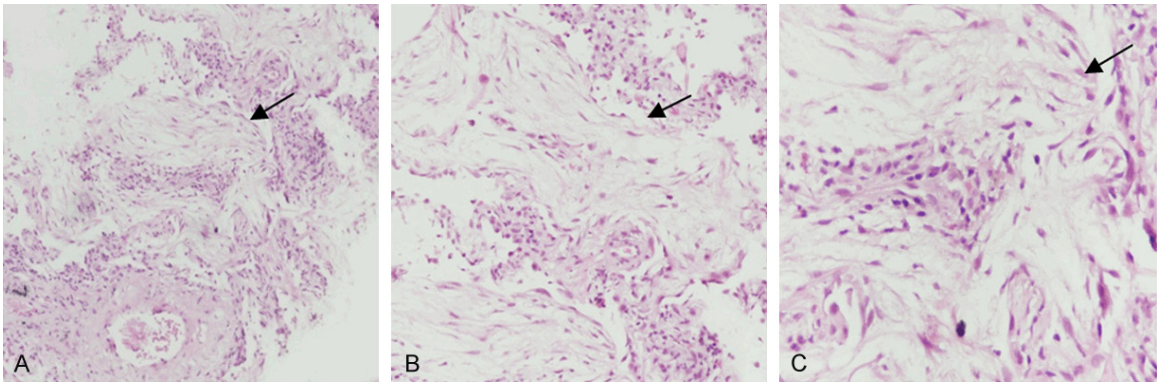

Figure 2. Histopathology confirmed the diagnosis of cryptogenic organizing pneumonia. Polypoid plugs of loose organizing connective tissue were observed within respiratory bronchioles, alveolar ducts and spaces. Tissue sections were stained with hematoxylin and eosin and viewed at magnifications of (A) × 100, (B) × 200 and (C) × 400.

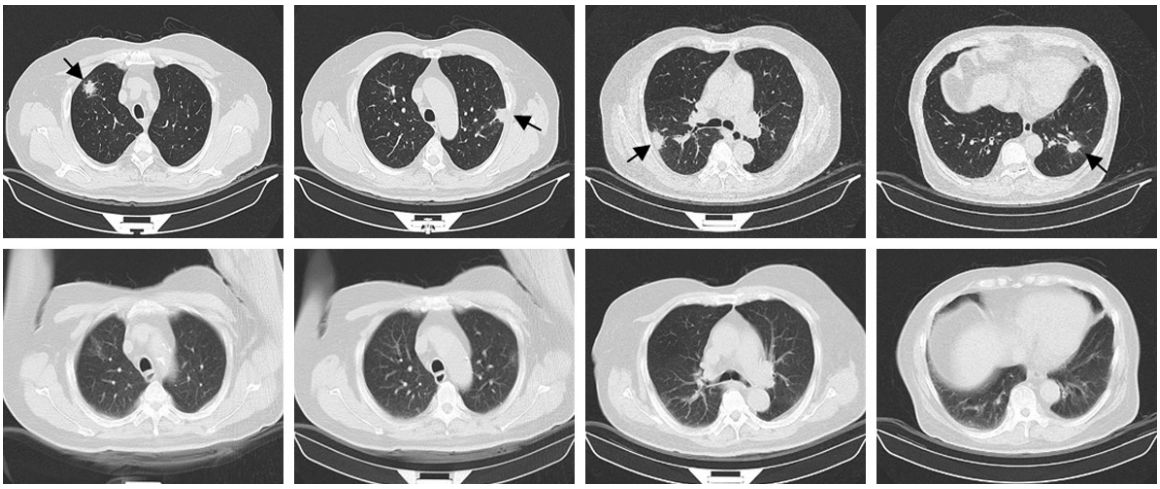

Figure 3. Comparison of chest computed tomography scanning before methylprednisolone therapy (*upper row*) and after three months of therapy (*lower row*). The treatment caused complete absorption of the multiple and bilateral lung nodules.

absorption of the previous bilateral and multiple lung nodules (**Figure 3**). Altogether, methylprednisolone therapy lasted six months. The patient showed no recurrence at follow-up more than one year later.

Discussion

Since 2002, the American Thoracic Society and European Respiratory Society have classified COP as an acute or subacute type of idiopathic interstitial pneumonia [3]. Although COP pathogenesis is poorly understood, the initial event appears to be damage to the alveolar epithelium. COP affects mainly alveoli, alveolar ducts, and distal bronchioles, but lung interstitium can also be involved [6]. COP is quite rare: mean annual incidence of organizing pneumonia is approximately 2 per 100,000, so COP incidence is expected to be substantially lower [7].

Based on COP cases in the literature, affected individuals are usually 50-60 yr old, with no apparent gender bias, and children are rarely affected [8, 9]. COP does not show a strong correlation with smoking [10]. The disease follows a sub-acute course, with symptoms developing over 2 weeks to 6 months, and the predominant clinical symptoms are non-specific and include persistent, non-productive cough and, frequently, a flu-like illness with fever, malaise, and a short history of progressive dyspnea. In some patients, COP follows a fulminant course with acute respiratory distress syndrome as the

clinical manifestation. Such patients, if not treated in time, can die of acute respiratory failure [11, 12]. Our patient presented COP with chest pain and a small amount of bloody sputum as the primary and main symptom of COP. This has rarely been reported. A rare case of COP has been reported in which the main clinical symptom was sub-massive hemoptysis [13]. Those authors concluded that COP should be taken into consideration in the differential diagnosis of severe hemoptysis.

COP is associated with nonspecific laboratory findings. Leukocyte and neutrophilic granulocytes are normal or slightly elevated, erythrocyte sedimentation rate may be elevated, and C-reactive protein may be elevated to different extents [14]. Some patients may show an obstructive ventilation defect, or they may even show normal pulmonary function. BALF shows elevated total number of leukocytes, with simultaneous increases in lymphocytes, neutrophils, and eosinophils. Lymphocytes are significantly elevated. BALF also shows elevated levels of cytokines mediated by the T-helper 1 response, including interleukin (IL)-18 and IL-12 [15].

COP shows variable manifestation by radiology and is classified into four main types: ground grass opacity, nodules, linear lesion, and reticular lesion. Lesions distribution was classified as single or double lung fields, upper or lower lung field and predominantly in the lung periphery [16]. An unusual radiological manifestation of COP is a line-shaped consolidation around the ground glass opacity. A reversed halo (or atoll) sign has been described in COP [17], but this radiological sign can be seen in other diseases, such as tuberculosis [18-20]. When CT showed multiple solid lung nodules, the PET-CT was performed because of suspected malignant disease. Although PET-CT is not well established for diagnosing COP because it can lead to false positive results, it can be used to guide invasive examination when malignancy is suspected [21]. Since CT or PET-CT cannot distinguish COP from malignant or infectious disease in most patients, the lesion must be examined histopathologically in order to diagnose COP [22]. Indeed, histopathology allowed us to correctly diagnose our patient following suspicion of malignancy. Histopathology of organizing pneumonia includes polypoid elongation of fibroblast and loose connective tissue in the alveolar cavity and distal bronchioles. In the present case, the patient was initially suspected to be malignancy because the main clinical findings were chest pain with a small amount of bloody sputum and multiple lung solid nodules on CT, and then PET-CT led to suspicion of malignancy. Finally, percutaneous lung biopsy was performed and pathology examination led to a diagnosis of organizing pneumonia. COP is a rare disease and has nonspecific clinical and imaging manifestations and laboratory examinations, thus it is often misdiagnosed early.

Uniform guidelines for treating COP do not yet exist. Glucocorticoids are the cornerstone therapy [4], but consensus is lacking on optimal dosage and duration of treatment. Glucocorticoids are usually administered orally at doses of 0.75-1.5 $mg \cdot kg^{-1} \cdot d^{-1}$. Typically, the dose is halved every 2-4 weeks to 10 mg/d or 20 mg/qod and continued for at least 6-12 months [8]. Clinical and radiological manifestations of most COP patients improve rapidly with glucocorticoids therapy, without significant sequelae. Our patient responded well to the oral methylprednisolone. In contrast, 13-58% of COP patients relapse when glucocorticoid dose is reduced or discontinued [23]. Patients may also require prolonged treatment. In addition, 10-15% of COP patients do not respond to glucocorticoids. Such patients can be given macrolides (azithromycin, clarithromycin or erythromycin) or cytotoxic agents (azathioprine, cyclophosphamide or cyclosporine A). However, at least one case has been described in which a COP patient failed to respond to glucocorticoids as well as to subsequent clarithromycin [24].

The rarity and non-specific manifestations of COP mean that it is often misdiagnosed. Here we report a patient with COP in which chest pain with bloody sputum was the main manifestation and multiple lung nodules were the major imaging finding. The patient was initially suspected of having malignancy, then histopathology allowed definitive diagnosis of COP. This case report may help improve knowledge of COP and reduce misdiagnosis.

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Disclosure of conflict of interest

None.

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