

Case Report

Cryptogenic organizing pneumonia in patient with Crohn's disease: a case report and literature review

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Abstract: Crohn's disease is a chronic granulomatous illness associated with a number of extra-intestinal manifestations that may be involved with many organ systems. Cryptogenic organizing pneumonia (COP) has been considered as relatively rare extra-intestinal manifestation of Crohn's disease. In this case, we described the whole diagnostic and therapeutic process in a Crohn's patient with cryptogenic organizing pneumonia, reviewed articles describing such cases reported in PubMed and summarized its clinical characteristics. The main common symptoms in all 13 reported cases are dyspnea, cough, fever and chest pain. One patient just showed imaging changes without symptoms. No similar case was reported in children. The common imaging manifestations are diffuse ground-glass opacities, multiple nodular consolidation or bilateral infiltrates. Majority of the patients were diagnosed as pulmonary infection and prescribed empirical antibiotics initially and ineffectively. 7 in 13 patients was received treatment with glucocorticoids, 3 with infliximab. 3 patients showed spontaneous remission. All the 13 patients had a wonderful improvement of pulmonary disease. One in 13 patients developed severe organizing pneumonia because of initiation of azathioprine. In conclusion, COP is a pulmonary interstitial disease which demands us to exclude all possible or potential factors to develop organizing pneumonia (OP) such as drugs, infection, connective tissue disease especially mesalazine, azathioprine. Clinical characteristics of cryptogenic organizing disease are extremely similar to infectious pneumonia. Sometimes, its manifestation may be respiratory failure. We deemed that combination of careful history review, evaluation of disease and lung biopsy is imperative to obtain a definite diagnosis. Moreover, physicians should be alert to asymptomatic pulmonary disease especially when Crohn's disease remains active continually despite treatment of various medications. Corticosteroid is the standard treatment. However, treatment with infliximab infusion rituximab or macrolides may be appropriate choices when corticosteroid therapy is non-effective.

Keywords: Crohn's disease, cryptogenic organizing pneumonia, clinical feature, differential diagnosis, treatment

Introduction

Crohn's disease (CD) is a chronic granulomatous inflammatory disease, mainly involving gastrointestinal tract with a series of extra-intestinal manifestations that could affect almost every organ system, such as joint, skeletal, dermatologic, ocular, hepatobiliary systems etc [1]. The occurrence of extra-intestinal manifestations has been reported to more than 25% in CD, more common than in ulcerative colitis (UC) [2]. Furthermore, pulmonary manifestations, a comparatively rare extra-intestinal complication in CD, occur in 0.4% of patients with CD by the statistics, which is far less than in UC [3]. Of note, the reports describing cryptogenic organizing pneumonia (COP), a type of

organizing pneumonia (OP) without the presence of evident etiology, gradually increased as a relatively uncommon respiratory involvement in patients with CD, in recent years. The clinical symptoms and imaging features of COP are both nonspecific [4]. Therefore, until now, it is often involved in a diagnostic and therapeutic dilemma for physicians to differentiate it from drug-induced lung diseases, infectious pneumonia or other lung diseases and to diagnose and treat it earlier and definitely in order to avoid misdiagnosis, mistreatment, destructive and irreversible lung lesions. Herein, we reported a case of a CD patient with COP received in our hospital and summarized clinical characteristics of this disease in all presenting literature to deepen our understanding with such cases.

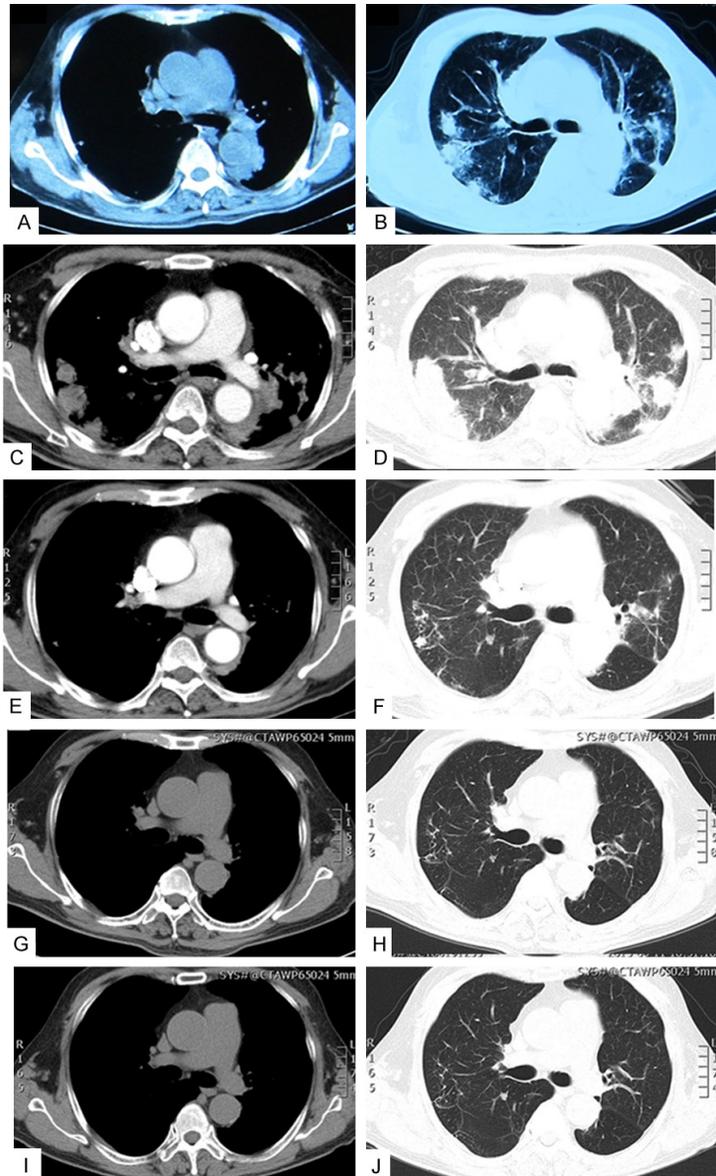


Figure 1. A, B: pulmonary CT (performed in the local hospital) showing patchy and nodular opacities, distributed along the bronchovascular bundle and subpleural area in bilateral lung. C, D: CT (after treatment with antibiotics for more than 10 days) showing worsening lesions, with increased bilateral, multiple, diffuse patchy hyperdensities and nodular consolidations with air bronchogram. E, F: CT (given predisone for 10 days) showing obvious improvement of pulmonary lesions. G, H: Follow-up CT (2 months post-treatment with predisone) showing almost complete resolution of lung lesions. I, J: CT (finished the treatment with predisone) showing normal imaging.

Case report

A 66-year-old nonsmoking man was admitted to our department because of dyspnea and nonproductive cough for one month without fever, chest pain, hemoptysis and digestive

symptoms. Prior to coming to our hospital, the patient had been taken to the local hospital. A computed tomography (CT) scan of the chest had revealed nodular and patchy opacities distributed along the bronchovascular bundle and sub-pleural area in bilateral lung (**Figure 1A, 1B**). Then he had been diagnosed with infectious pneumonia and treated with piperacillin-tazobactam and cephalosporins, while the symptoms had never been improved. So the patient was admitted to our ward.

He was diagnosed with CD by ileocolonoscopy 8 months ago when he presented with abdominal pain, diarrhea and mild-moderate fever, and treated initially with mesalazine without any pulmonary side effects. Because of no improvement in gastrointestinal symptoms, mesalazine treatment was discontinued and the therapy with episodic infliximab infusion (0, 2, 8 weeks) at a dose of 5 mg/kg was initiated. For sub-optimal response, he was also given oral methylprednisolone 40 mg/d after 2 months. Throughout those managements, his worrisome symptoms were obviously relieved. And subsequent gradual taper were also administered. By the end of last month before admission, methylprednisolone was completely withdrawn and azathioprine was started at a dose of 100 mg/d. That is to say, he was in clinical remission of CD at admission.

A physical examination revealed inspiratory crackles at both lung bases. Otherwise the remainder of his physical examination was normal. Laboratory findings revealed white blood cell count of $7.21 \times 10^9/L$ (74.5% neutrophils, 2.8% eosinophils), and increased erythrocyte sedimentation rate (ESR) of 87 mm/h. Arterial blood gas analysis revealed hypoxia, a partial pressure of oxygen of 69 mmHg, a par-

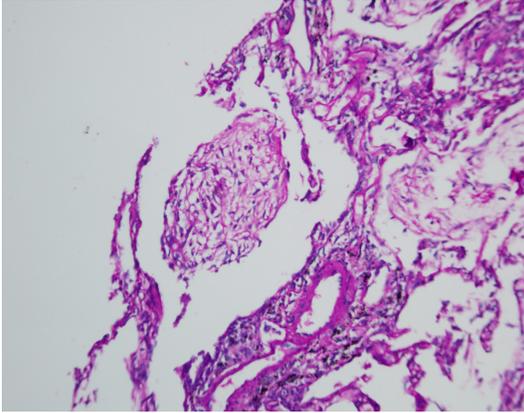


Figure 2. The pathological tissue (Hematoxylin and eosin staining, magnification $\times 100$) showing multiple non-necrotic and non-caseating granulomatous nodules. Loose fibroblasts showed within some alveolar lumen.

tial pressure of carbon dioxide of 36 mmHg and oxygen saturation of 95% while he was resting on 2 L/min of oxygen. A tuberculin skin test was non-reactive, and sputum stains for *Mycobacterium tuberculosis* were negative. Sputum stains for fungus, G test, CN-Ag (*Cryptococcus neoformans* Antigen) and T.SPOT-TB test were negative. Sputum cultures of the pulmonary specimens for bacteria and fungus were negative. The examinations about connective tissue disease, such as Anti-DNA antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase (MPO), protease 3 (PR3), Glomerular Basement Membrane (GBM), rheumatoid factor (RF) and C3 were all in the normal range. Serology for cytomegalovirus, rubella virus, Herpes simplex virus type 1, Toxoplasma, Coxsackie virus and EB (Epstein-Barr) virus were negative, too.

Upon admission, the patient was managed with antibiotic, cefoselis 1.0 g q8h and azathioprine, 100 mg/d continually. Despite treatment for a week, his symptoms did not alleviate at all. And a repeated high resolution CT scan of the chest demonstrated evident progression (**Figure 1C, 1D**). Therefore, a CT-guided percutaneous trans-thoracic needle biopsy in the lower right lung where the lesions is the most obvious and severe was performed. The histological examination of lung biopsy revealed multiple non-necrotic and non-caseating granulomatous nodules. Loose fibroblasts showed within some alveolar lumen (**Figure 2**). According to the histopathological features, combination with all

the CT scans and case history, we evaluated the patient as COP. So the patient was initiated oral prednisone 50 mg/d. After 10 days of treatment, extraordinary improvement on his symptoms, physical examination and radiological imaging was observed (**Figure 1E, 1F**). In addition, repeated laboratory examinations also revealed signs of improvement, with reduced ESR and increased partial pressure of oxygen. The patient was discharged after 2 weeks. After two months of therapy, the patient was asymptomatic. And a follow-up CT scan showed almost complete resolution of pulmonary opacities (**Figure 1G, 1H**). To date, the patient has been followed-up for more than one year. The treatment with prednisone was completed 5 months ago and the diseases have not relapsed (**Figure 1I, 1J**).

Discussion

This case represented a rare extra-intestinal disease, COP, in CD. Pulmonary manifestation is exceptionally uncommon in CD. Pulmonary involvements in patients with CD has been described in various forms including airway diseases, lung parenchymal diseases, pleural diseases, drug-induced complications (non-infectious cause, opportunistic infections), or sub-clinical alterations [5]. The pathogenesis of pulmonary manifestations occurring in CD is still unclear. The underlying mechanisms include the existence of circulating immune complexes and auto-antibodies [6], common embryological progenitor of the respiratory and gastrointestinal tract [7], the shared common susceptibility loci [8], analogous immune systems involved in pulmonary and gastrointestinal mucous membrane [9], negative side effects of some drugs [10] and the shared antigen of these two organ systems [11].

COP, formerly referred to bronchiolitis obliterans with organizing pneumonia (BOOP), is a type of OP without any identifiable cause, such as infection, connective tissue disease or other associated diseases [12]. COP occurring in children is extremely uncommon [13]. The average onset age is 50 to 60 years old. We searched on PubMed and found 12 reported cases of COP or BOOP in patients with CD [11, 14-22]. We summarized the clinical characteristics of current 13 cases with COP in CD in **Table 1**. It consists of 10 men and 3 women, whose ages ranged from 17 to 84 years old (median age of

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Table 1. Clinical characteristic review of cryptogenic organizing pneumonia occurring in Crohn's disease reported in literature

Refer	NO patient	Age/gender	Duration Of CD (year)	Clinical symptoms	CT/Radiology	Biopsy type	Drug treatment Of CD	Treatment of COP	Outcome of lung lesion
Dinneen HS, 2014	1	64/M	10	Dyspnea, productive cough	Diffuse ground glass nodular opacities in bilateral perihilar and lower lung region	TB	Mesalamine	Prednisone	CR
Carratu P, 2005	1	29/M	1	Dyspnea, dry cough, fever	Peripheral subpleural opacities in the upper and middle lobes, mainly in the right lung	OL	Mesalamine	Methylprednisolone, prednisone	CR
Gil-Simon P, 2008	1	41/M	2	Dyspnea, cough, expectoration, fever	Bilateral patchy alveolar infiltrates in the right lung base, then extensive parenchymal consolidation in the upper right lobe, resolution in lower right lobe	TB	No maintenance treatment	Prednisone	CR
Basseri B, 2010	1	56/M	30	Dyspnea, cough, fever	Worsening bilateral lung infiltrates and a nodular density in the right mid-lung field	TS	Mesalamine	Prednisone	RI
5*	1	66/M	8 months	Dyspnea, nonproductive cough	Patchy and nodular opacities in bilateral lungs	PTNB	Azathioprine	Prednisone	CR
Ananthakrishnan AN, 2007	1	71/M	1	Dyspnea, nonproductive cough, fever	Ground glass opacities predominantly in the upper lobes bilaterally	OL	Azathioprine	Discontinuation of azathioprine, high-dose corticosteroids	CR
Alrashid AI, 2001	1	66/F	1	Dyspnea, nonproductive cough;	Multiple nodules in the left lung without lymphadenopathy	OL	Mesalamine	Infliximab	CR
Pedersen N, 2009	1	35/F	11	Without pulmonary symptoms	Bilateral peribronchial and perivascular nodular opacities parenchymal infiltrates and pleural effusions	PTNB	Corticosteroids	Infliximab	CR
Krishnan S, 2006	1	17/M	4	Fever, chest pain	Bilateral basal infiltrates and bilateral small-to-moderate pleural effusions	TS	Mesalamine, 6-MP	Infliximab	RI
Camus P, 1993	1	26/F	8	Dyspnea, dry cough, fever, chest pain	Focal consolidation	OL	Sulfasalazine, low-dose steroids	Intravenous steroids	CR
Casey MB, 2003	3	75/M	6	Dyspnea, cough	Diffuse right-sided infiltrates	TB	Mesalamine	None	RI
		84/M	5	Dyspnea	Upper lobe infiltrates	TB	None	None	RI
		70/M	16	Fever, chills	Diffuse right lung infiltrates	TB	Prednisone	None	RI

Abbreviations: NO (number); M (male); F (female); CD (Crohn's disease); NA (not available); TB (transbronchial lung biopsy); OL (open lung biopsy); WB (wedge biopsy); TS (thoracoscopic lung biopsy); PTNB (CT-guided percutaneous transthoracic needle biopsy); 5-ASA (5-aminosalicylic acid products); 6-MP (6-mercaptopurine); CR (complete resolution); RI (rapid improvement); Refer (reference); *the present case.

64-year-old). No similar case has been reported in children. Pulmonary disease of all 132 patients happened posterior to the onset of CD. The median history of CD is 7.3 years. And 2 in 13 patients had definite history of smoking. 5 patients are non-smoker. Other subjects smoking histories are unavailable.

The primary manifestations of COP are nonspecific, such as mild fever, progressive dyspnea, cough, anorexia and weight loss [12]. The common symptoms in all 13 described cases are dyspnea, cough, fever and chest pain. However, some patients might even reveal respiratory failure and severe pneumonia [14]. Focal crackles can be heard in the related lesions. Five in 13 patients had inspiratory crackles at the lung bases. In the aspect of laboratory investigations, blood, urine and bronchial secretion culture for bacteria, fungus and tubercle bacillus were all negative within the reported cases. Besides, the examinations related to virus and connective tissue disease are normal. It is noteworthy that one patient did not present any pulmonary symptom rather than radiographic changes with nodular opacities, parenchymal infiltrates and pleural effusions, which indicated that asymptomatic COP could be involved in CD especially when the bowel disease are still active under the use of various typical drug.

The most common CT manifestations of COP are multiple, peripheral, peribronchovascular and patchy opacities, whose density ranging from ground glass to consolidation distributed along subpleural area and bilaterally, which is faced with a challenge to differentiate from infectious pneumonia, tuberculosis, interstitial lung disease and other respiratory disease [23-25]. Solitary opacity and infiltrative opacities are the relatively less frequent imaging pattern, which is similar to lung cancer and round pneumonia [23, 26]. However, a migratory imaging change should be highly considered the diagnosis of COP [12]. In the population of 13 represented patients, the most frequent imaging manifestations are diffuse ground-glass opacities, multiple nodular consolidation or bilateral infiltrates. Meanwhile, given that many patients are might taking immunosuppressant, doctors tend to evaluate such cases as infectious pneumonia. More than 6 patients were diagnosed as pulmonary infection and treated with antibiotics initially and ineffectively in those referred reports. In order to avoid misdiagnosis

and reach a conclusive diagnosis, lung biopsy is recommended for those presenting with atypical clinical and radiographic features [24]. In the present cases, all the patients were diagnosed by lung biopsy, including transbronchial, thoracoscopic, open lung biopsy and percutaneous transthoracic needle biopsy. The characteristic histopathologic manifestation of OP is the existence of buds of granulation tissue consisting of fibroblasts and myofibroblasts involved in connective tissue [12]. It is well known that respiratory manifestation of CD are frequently related to concurrent use of typical drugs to treat the disease, such as sulfasalazine, mesalazine, methotrexate [27], azathioprine and infliximab [28], which were contributed to eosinophilic pneumonia more frequently [10]. Drug-induced OP, such as mesalazine [29] and azathioprine [14], had been reported by physicians. In addition, infectious agents, hematologic malignancies, cancers and post-thoracic radiotherapy and autoimmune disease such as rheumatoid arthritis, lupus, Wegener granulomatosis etc, could also lead to OP [12, 25]. Therefore, it is significant for clinicians to exclude all the factors that may result in OP before making diagnosis with COP. In our case, we analyzed the stage when the patient took mesalazine and azathioprine carefully. The patient had stopped taking mesalazine for more than 5 months prior to the onset of lung disease. And though the patient did not stop taking azathioprine, his clinical manifestations were improved rapidly under the treatment of corticosteroid (CS). So drug secondary OP was excluded. The clinical symptoms, CT imaging, pathologic features and treatment outcomes were all suggestive of COP in the present case. Nine patients were taking drug treatment of CD, such as mesalazine, azathioprine, CS, 6-mercaptopurine, at the time of respiratory manifestations. Only one in thirteen patients was evaluated as drug-induced lung disease. He developed severe organizing pneumonia because of initiation of azathioprine.

It is acknowledged that CS therapy is the most classical treatment. The clinical symptoms and imaging performance could be improved rapidly under the treatment for 1-3 weeks and disappeared completely for 3-6 months for majority of COP patients [12, 23]. In spite of the absence of confirmed evidence, increased patients with lung involvement were treated with infliximab (a monoclonal antibody to tumor necrosis factor α) successfully in recent years, which is given

more commonly in other extra-intestinal disease of IBD [19]. In our cases, 7 in 13 patients was received treatment with CS. And 3 patients were given infliximab because of unfavorable or adverse response to CS. The above patients all revealed rapid improvement of lung disease. Other patients showed spontaneous remission with no treatment. All the 13 patients had a wonderful outcome of pulmonary disease. In addition, it is suggested that if the patient could not stand corticosteroids or reveals little reaction to CS, immunosuppressive therapy, rituximab or macrolides probably is also an alternative effective treatment, although their benefit on the outcome of COP has not been confirmed exactly [30, 31]. However, no patient was given macrolides in the reported cases.

COP is a pulmonary interstitial disease which demands us to exclude all possible or potential factors to develop OP. The most common symptoms of COP involved in CD are dyspnea, cough, fever and chest pain, which are nonspecific manifestations of pulmonary diseases. Moreover, imaging findings of COP are also atypical and various. Diffuse ground-glass opacities, multiple nodular consolidation or bilateral infiltrates are the most frequent features in such cases. COP seldom occurs in the children and the onset of CD usually predates COP. Therefore, it is easy for us to be involved with dilemma to make an exact diagnosis. Considering that clinical characteristics of COP are extremely similar to infectious pneumonia and other respiratory disease, a careful history review and evaluation of disease are imperative to definite diagnosis. It is notable that some patients may present as respiratory failure. Timely and earlier histopathological examination would be optimal when we deal with such patients with pulmonary lesions. Moreover, physicians should also watch out for asymptomatic pulmonary disease especially when CD remains active continually despite treatment of medication. CS is the preferred choice for patient with COP. When CS therapy shows inefficacy or adverse reaction in CD patient with COP, infliximab infusion, rituximab or macrolides could also be appropriate treatments.

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Written informed consent was acquired from the patient. The patient agreed to use his personal and medical information for the publication of this case report and any accompanying images.

Disclosure of conflict of interest

None.

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