A Cryptogenic Case of Fulminant Fibrosing Organizing Pneumonia

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Abstract

Cryptogenic organizing pneumonia (COP) generally responds well to corticosteroids with a favorable outcome. Rare cases of organizing pneumonia are rapidly progressive. Yousem et al. studied pathologic predictors of idiopathic bronchiolitis obliterans organizing pneumonia/COP with an unfavorable prognosis. Beard-sley and Rassl proposed the name fibrosing organizing pneumonia (FOP). A 74-year-old female non-smoker presented with a 2-week history of dry cough followed by dyspnea and a fever. The clinical course was fulminant, but we successfully performed bronchoscopy. After the diagnosis of FOP, we treated the patient with mechanical ventilation and high-doses of steroids/immunosuppressants, which improved the disease.

Key words: cryptogenic organizing pneumonia (COP), fibrosing organizing pneumonia (FOP), rapidly progressive bronchiolitis obliterans organizing pneumonia, bronchoscopy

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Introduction

Cryptogenic organizing pneumonia (COP) is synonymous with idiopathic bronchiolitis obliterans organizing pneumonia (idiopathic BOOP), although COP is the preferred term. COP is a characteristic clinicopathologic disease condition that generally responds to steroids with a good outcome (1-3). Histopathologically, COP is defined by the filling of distal airways, alveolar ducts, and adjacent alveoli with fibromyxoid plugs of granulation tissue without findings characteristic of other diseases, such as hyaline membranes or abundant fibrin (3). It has been documented that COP usually responds to corticosteroid therapy with favourable outcomes (2-4). However, some patients exhibit a rapidly progressing disease that is often refractory to steroids and associated with poor outcomes (5-8). About 10% to 15% of idiopathic BOOP/COP patients are steroid-resistant and progressive (9, 10).

Rare cases previously classified as idiopathic BOOP/COP can progress to respiratory failure and death (3). Some of these cases present additional features of diffuse interstitial fibrosis, suggesting an alternative diagnosis, including organizing pneumonia superimposed on an unusual interstitial pneumonia lesion (3). The 2013 statement of the international multidisciplinary classification of the idiopathic interstitial pneumonias mentioned “a fibrosing variant of OP” in the section of COP and pointed out that some patients with this pattern of mixed fibrosis and organizing pneumonia have underlying polymyositis or antisynthetase syndrome (11). In 2013, Beardsley and Rassl used the term fibrosing organizing pneumonia (FOP) alluding to the histologic features of steroid-resistant idiopathic BOOP/ COP (9, 11, 12). Some articles reported cases of COP with
severe prognoses (5, 9, 10). Therefore, it is essential and important to establish a rapid histologic diagnosis. The clinical course of rapidly progressive idiopathic BOOP/COP is fulminant, and we have not been able to evaluate the lung disease by surgical lung biopsies. Bronchoscopy is a less invasive procedure tool than a biopsy and may prove useful in such cases (13).

We herein report a case of rapidly progressive idiopathic BOOP/COP histologically diagnosed as FOP by transbronchial lung biopsy (TBLB) specimens with a favourable outcome by prompt drug therapies.

Case Report

A 74-year-old woman presented in September 2014 with a 2-week history of dry cough followed by progressive dyspnea and a fever. She was diagnosed with bacterial pneumonia 10 days later, for which she had received treatment with levofloxacin (500 mg/day orally) for 2 weeks, and was referred to our hospital with complaints of worsened dyspnea. She was a never-smoker and had not been exposed to known toxins. On an examination, she was alert and did not seem to be overtly sick. Her body temperature was 38.2°C. Pulse oximetry showed an oxygen saturation of 94% on ambient air. Fine crackles were heard in the bilateral lung fields without wheezing. Physical examination findings were negative for signs of connective tissue disease such as heliotrope rash or Gottron’s sign.

Chest X-ray films showed right-sided predominant bilateral pulmonary infiltrates (Fig. 1). High-resolution computed tomography (HRCT) of the chest revealed bilateral and progressive multiple areas of subpleural and peribronchial patchy consolidation with ground glass opacities (Fig. 2).

An arterial blood gas analysis on room air revealed marked hypoxemia [partial pressure of oxygen (PaO₂) 56.8 mmHg]. Blood and serologic examinations revealed leukocytosis (15.1×10⁴ cells/μL) and mild eosinophilia (510 eosinophils/μL); markedly increased values of C-reactive protein (CRP) (23.34 mg/dL), erythrocyte sedimentation rate (ESR; 115 mm/60 minutes), and ferritin (1,725 ng/mL; normal female range: 3.6-11.4); and mildly-to-moderately increased values of surfactant protein-D (SP-D) (141.9 ng/mL; normal <110) and surfactant protein-A (SP-A) (92.3 ng/mL; normal <43.8). There was no notable increase in the value of Krebs von den Lungen-6 (KL-6) (Table and Fig. 3).

On the fourth hospital day when the patient was transferred to the respiratory care unit, we managed to perform bronchoscopy under a clinical suspicion of organizing pneumonia. Bronchoalveolar lavage fluid (BALF) from the right B₁ showed a cell count of 1.14×10⁵ cells/mL, and a cellular analysis of the BALF revealed increased neutrophils (23.8%) and lymphocytes (5.2%), with a CD4⁺/CD8⁺ ratio of 3.2. No pathogens were cultured. A TBLB obtained two samples from the right upper lobe (rtB₂) and right lower lobe (rtB₈ and rtB₉), and the TBLB specimens revealed histologic features of FOP (Fig. 4). One specimen from the right upper lobe showed hyalinisation and fibrosis of the central core of the Masson body, and another sample also from the right upper lobe showed granulation tissues mainly in the alveolar ducts without adhesions of the alveolar duct walls. Another
Table. Results of a Blood Examination at Admission.

<table>
<thead>
<tr>
<th>WBC</th>
<th>15.1×10^9 /L</th>
<th>KL-6</th>
<th>290 U/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>81.9 %</td>
<td>SP-D</td>
<td>141.9 ng/mL</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>9.4 %</td>
<td>SP-A</td>
<td>92.3 ng/mL</td>
</tr>
<tr>
<td>Monocytes</td>
<td>5.1 %</td>
<td>Ferritin</td>
<td>1,725 ng/mL</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3.4 %</td>
<td>CRP</td>
<td>24.34 mg/dL</td>
</tr>
<tr>
<td>Hb</td>
<td>8.8 g/dL</td>
<td>ESR</td>
<td>115 mm/h</td>
</tr>
<tr>
<td>Ht</td>
<td>31.9 %</td>
<td>ANA antibody</td>
<td>negative</td>
</tr>
<tr>
<td>Plt</td>
<td>5.280×10^9 /L</td>
<td>ss-A antibody</td>
<td>negative</td>
</tr>
<tr>
<td>TP</td>
<td>6.9 g/dL</td>
<td>ss-B antibody</td>
<td>negative</td>
</tr>
<tr>
<td>Alb</td>
<td>2.1 g/dL</td>
<td>anti-Jo 1 antibody</td>
<td>negative</td>
</tr>
<tr>
<td>BUN</td>
<td>12.9 mg/dL</td>
<td>anti-synthetase antibody</td>
<td>negative</td>
</tr>
<tr>
<td>Crea</td>
<td>0.62 mg/dL</td>
<td>anti-neutrophil cytoplasmic antibody</td>
<td>negative</td>
</tr>
<tr>
<td>LDH</td>
<td>241 U/L</td>
<td>anti-cyclic citrullinated peptide antibody</td>
<td>negative</td>
</tr>
</tbody>
</table>


Sample from the right lower lobe showed fibrination in the alveolar ducts and infiltration of a few neutrophils in the fibrin. The fibrination did not show organization. We considered the possibility of an artificial effect from the transbronchial biopsy (not shown). None of the four lung specimens showed any malignant cells, granulomas, or significant infiltration of eosinophils or neutrophils (Fig. 4).

Empirical broad-spectrum antibiotics were initially administered. However, during the subsequent four days, the patient’s condition continued to deteriorate, with worsening of
Figure 3. The clinical course of the present case between Days 1 and 150. A bronchoscopic examination with a TBLB and BAL was performed on Day 4, and drug therapy of methylprednisolone pulse therapy and intravenous cyclophosphamide was started on Day 8 (dotted line: CRP, solid line: KL-6). KL-6: Krebs von den Lungen-6, IV-CY: intravenous cyclophosphamide, CsA: cyclosporine, PSL: prednisolone, BF: bronchoscopy.

chest radiograph findings (Fig. 1, 2) and hypoxemia. She developed dyspnea on the seventh hospital day. On the eighth hospital day, mechanical ventilation and intravenous methylprednisolone treatment (1,000 mg per day for three consecutive days) was started (Fig. 3). On the seventh hospital day, a histopathologic diagnosis of FOP was rendered by the lung pathologist of this article (Fig. 4). The patient received 750 mg/day cyclophosphamide (CY) intravenously in addition to corticosteroid therapy. Initially, despite these regimens, her chest radiograph findings and hypoxemia did not stop deteriorating. Therefore, 100 mg (2.0 mg/kg) cyclosporin A (CsA) was added. The chest radiograph findings and hypoxemia gradually improved, and she was successfully extubated on hospital day 22. The peribronchovascular consolidation revealed by chest radiography resolved steadily. She was discharged on hospital day 73 when prednisolone was tapered to 20 mg/day (Fig. 3). Her symptoms and the HRCT findings of the lungs improved during the follow-up 150 days later. She was fine 500 days later and did not develop any symptoms or signs of connective tissue disease (Fig. 3).

Discussion

To our knowledge, there have been no previous reports of idiopathic rapidly progressive idiopathic BOOP/COP confirming the histopathologic features of FOP by TBLB specimens in the English literature. The prompt histopathologic diagnosis of FOP by TBLB enabled us to make a treatment decision on the eighth hospital day (Fig. 3).

Colby listed four findings as the major histologic features of BOOP in 1992: 1) patchy bronchiolitis obliterans with organizing pneumonia, 2) interstitial mononuclear cell infiltrates, variable in density, 3) alveolar space foam cells, and 4) absence of honeycombing or extensive interstitial fibrosis (14). Yousem et al. compared 10 cases of steroid-responsive idiopathic BOOP/COP (Group I) and 9 cases of steroid-resistant idiopathic BOOP/COP (Group II) to determine the histopathologic predictors (18 open lung biopsies and 1 lobectomy cases) (9). They pointed out the poor prognostic findings and listed the findings of the presence of background remodelling of the pulmonary parenchyma (scarring/interstitial fibrosis) and dense eosinophilic hyalinization of the fibromyxoid plugs of air space collagen (9).

The 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias described the histologic features of organizing pneumonia as follows: 1) intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli); 2) patchy distribution; 3) preservation of lung architecture; 4) uniform temporal appearance; and 5) mild interstitial chronic inflammation. Among the seven pertinent negative findings for organizing pneumonia, the characteristic of “lack of interstitial fibrosis (except for incidental scars or apical fibrosis)” was noted (3). Beardsley and Rassl proposed FOP to include the hist-
Figure 4. A transbronchial lung biopsy was performed for the right upper and lower lobes. (a-d) Tissue from the rtSb. (a) The tissue showed granulation tissues (Masson bodies) formed in the alveolar ducts and adjacent alveoli. (b) The tissue showed hyalinous thickening of alveolar walls. (c, d) The tissue showed hyalinisation of the central core of the Masson body. (e-h) The tissue taken from the rtSb. (e) The tissue showed granulation in the alveolar ducts and adjacent alveolar spaces, as well as accumulation of foamy cells in the alveolar spaces (lower centre). Relatively normal alveolar walls were noted in the adjacent area of organizing pneumonia. (f) A higher magnification of the rectangular area of (e); the alveolar duct was obliterated with granulation tissue and the alveolar duct walls were adhesive due to intervening granulation tissue (arrowed). (g) An elastic tissue stain showed granulation tissues and foamy cells in the alveolar ducts and alveolar spaces. (h) A higher magnification of the rectangular area of (g); an alveolar duct was obliterated due to the presence of granulation tissue with adhesion of alveolar duct walls (arrowed). Because of the findings (a-d) and (e-h), we made a histologic diagnosis of fibrosing organizing pneumonia (FOP). The findings of (a-h) showed an organizing pneumonia pattern. However, obliterative alveolar duct fibrosis was not observed in previously reported cases of steroid-responsive idiopathic BOOP/COP (9, 17, 23, 24). Staining methods: a-f: Hematoxylin and Eosin staining; g, h: Weigert’s elastic van Gieson stain. Magnification: a, e, g×4; c, ×10; b, d, f, h×40. Bar=1 mm.
ologic characteristics of dense hyalinisation and fibrosis of the central core of the Masson bodies and hyalinated fibrotic lesions of alveolar septa, as well as the obliterative fibrotic processes mainly in the alveolar ducts with loss of normal alveolar structure, based on the 1997 report of Yousem, Lohr, and Colby (9, 12). Some severe cases of OP have been published, most of which were diagnosed histologically by high-risk open-lung biopsies (9, 15, 16). Beardley and Rassl pointed out that collagenised Masson bodies become incorporated into the interstitium mainly at the alveolar duct level. To distinguish their diagnosis from diffuse alveolar damage, they showed the histologic finding of relatively normal adjacent alveolar walls in the obliterating fibrotic lesions at the level of the alveolar ducts [see Fig. 6 of Ref 12].

We propose the following histological definition of FOP (3, 11, 12, 14, 17, 23, 24): 1) intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli); 2) patchy distribution; 3) preservation of lung architecture without honeycombing, even in the area of extensive obliterative alveolar duct fibrosis when observed by an elastic tissue stain; 4) uniform temporal appearance; 5) mild interstitial chronic inflammation; and 6) obliterative alveolar duct fibrosis with adhesions of alveolar duct walls due to the presence of air-space granulation tissues.

In the present case, the fibrotic lesions due to obliterative alveolar duct fibrosis were mild and focal that was observed in one focus as shown in Fig. 4e-h. This was considered to be due to the small size of the lung biopsy samples obtained by the tranbronchial biopsy.

The 16 cases of idiopathic BOOP reported by Nagai et al. belonged to steroid-responsive idiopathic BOOP/COP according to the 1997 idiopathic BOOP/COP classifications by Yousem et al (9). The BAL data of those steroid-responsive cases showed a high lymphocytes percentage (44.4±7.3%) with a low CD4/CD8 ratio (0.97±1.35). However, the BALF data from 4 of 6 cases of rapidly progressive BOOP showed ≥26% neutrophils (5 cases from Cohen et al. and 1 case from Lee et al.) (10, 15). The present case also increased an increased neutrophil proportion (23.8% of nucleated cells) with an increased CD4/CD8 ratio (3.2). Therefore, the BALK cell analysis suggested that steroid-responsive and steroid-resistant idiopathic BOOP/COP were different disease conditions. Cases of COP, according to the 2002 ATS/ERS classification of idiopathic interstitial pneumonias, mainly corresponded to those of steroid-responsive idiopathic BOOP/COP, similar to the 1997 description by Yousem et al. (9, 15, 17). High percentages of neutrophils in the BALF might suggest characteristics of steroid-resistant idiopathic BOOP/COP or FOP in the clinical setting of COP.

Bronchoscopy is a useful and low-invasive diagnostic tool. We performed BAL and a TBLB for this case study. A TBLB is commonly performed to confirm the tissue diagnosis of interstitial pneumonia (IP) (18) and appears to be an important diagnostic tool for the diagnosis of IPs; however, the diagnostic yield of its histopathologic assessment varies and is influenced by factors such as the size of samples and the presence of crush artefacts due to the use of biopsy forceps (19). The accurate diagnostic yield of a TBLB of COP is low (20), and it is difficult to confirm the preservation of normal alveolar structure in the entire lung tissues due to the small size of the samples obtained with a TBLB.

The proposal of FOP is not yet well-defined and is still a relatively new concept. Its definition must be discussed further using more cases successfully histopathologically diagnosed as FOP by a surgical lung biopsy or TBLB. However, we were able to detect dense hyalination and fibrosis of the central core of the Masson body and hyalinated fibrotic lesions of alveolar septa in addition to the obliterative fibrotic lesions in the lumen of alveolar ducts (obliterative alveolar duct fibrosis) (Fig. 4). Therefore, we were able to make a diagnosis of FOP based on the clinical and radiological findings. One possible reason for our successful diagnosis using TBLB specimens was the fact that we performed the TBLB when the patient’s pulmonary condition was worsening. Bronchoscopy may be a useful diagnostic tool in the clinical setting when encountering rapidly progressive idiopathic BOOP/COP or FOP.

Minimal data have been reported regarding alternative immunosuppressive agents in cases of corticosteroid-refractory OP or rapidly progressive idiopathic BOOP/COP (5-7). Some reports have suggested that early treatment with CY and CsA might be effective, especially in patients that failed to respond to treatment with corticosteroids alone (5, 6). We obtained a good outcome with CY and CsA in the FOP patient. Delayed treatment in rapidly progressive patients receiving steroid therapy can lead to poor outcomes. In our case, a TBLB by bronchoscopy contributed to an accurate pathologic diagnosis of FOP and a prompt decision on therapy. CY and CsA may be beneficial in FOP patients even without a rapid response to steroid treatment. These drug regimens should therefore be considered early for therapeutic trials in these cases.

Patients with connective tissue disorders seem to have a poorer prognosis than COP patients (21). The serologic tests conducted in the present case were all negative (Table). However, due to the unavailability of commercial anti-melanoma differentiation-associated gene 5 (MDA5) antibodies, we were unable to check for MDA5 antibodies, which are myositis-specific antibodies identified in the sera of patients with clinically amyopathic dermatomyositis (C-ADM) (22). The characteristics of anti-CADM-140-positive dermatomyositis-associated interstitial lung disease are high levels of ferritin, which is a known prognostic factor; a ground glass attenuation (GGA) pattern, a random GGA pattern, or low consolidation; and the absence of interlobular reticular opacities (22). Although the levels of ferritin were increased significantly in the present case, the radiological findings were not similar to those of anti-CADM-140-positive dermatomyositis-associated interstitial lung disease. We were therefore able to exclude this from our differential
diagnosis.

In summary, we presented a rapidly progressive case of FOP diagnosed based on TBLB specimens, including a histologic finding of obliterative alveolar duct fibrosis. The present case responded to drug treatment with high-dose methylprednisolone, CYC, and CsA (Fig. 3). She remained idiopathic and well 500 days after the initial presentation in September 2014. The present case is important, as it suggests that bronchoscopic examination, including a TBLB and BAL, may be an important diagnostic tool for a prompt diagnosis and adequate therapy, as well as for predicting the prognosis of OP of unknown etiology.

The authors state that they have no Conflict of Interest (COI).

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