Original Article
Clinicopathological findings of focal organizing pneumonia: a retrospective study of 37 cases

Zhen Huo1, Ruie Feng1, Xinlun Tian2, Haibo Zhang3, Li Huo4, Hongrui Liu1

1Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China; 2Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China; 3Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China; 4Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

Received November 13, 2014; Accepted December 24, 2014; Epub January 1, 2015; Published January 15, 2015

Abstract: Background and objective: Focal organizing pneumonia (FOP) is an uncommon disease. The etiology, and in particular the disease’s relationship with infection and the incidence of idiopathic FOP, is relatively unknown. The aim of this study is to review clinical, radiological and pathological features of patients with organizing pneumonia (OP) presenting solitary lesions and to analyze possible causes. Methods: We retrospectively reviewed 37 surgical lung biopsy or resection cases of pathologically confirmed FOP over a period of 10 years. Results: Microscopically, 17 cases showed OP with neutrophilic infiltration or abscess, 11 with epithelioid cell granulomas or scattered multinucleated giant cells, 2 with greater eosinophilic infiltration, and the remaining 7 cases met the diagnostic criteria for pathological cryptogenic OP (COP). The 37 cases of FOP included 22 men and 15 women, aged 29-76 years, and 17 cases had a history of smoking. Cough, fever, sputum, chest or back pain and hemoptysis were the main symptoms. Seven cases were asymptomatic. The diameters of the lesions ranged from 0.2-6.0 cm (median, 3.0 cm). Fever (9/30), high-sensitivity C-reactive protein elevation (9/17) and abnormalities in pulmonary function test (8/24) existed in focal secondary OP (FSOP) patients, but these symptoms were rarely observed in focal COP (FCOP) (0/7, 1/7 and 0/7 cases, respectively). However, no statistically significant differences were found between the FSOP and FCOP. Conclusions: Histologically, secondary factors exist in the majority of FOP cases. Idiopathic FOP is found in a minority. With respect to secondary FOP, acute infection and granulomatous inflammation are the main causes. Surgical resection alone appears sufficient for the management of FOP.

Keywords: Focal organizing pneumonia, secondary, cryptogenic

Introduction

Organizing pneumonia (OP) is a well-known histopathological entity characterized by loose plugs of proliferating fibroblasts and myofibroblasts within the alveolar ducts and airspaces, accompanied by varying degrees of bronchiolar involvement. OP can be classified into two categories: known causes and idiopathic. Secondary OP (SOP) with known causes can be associated with infection, collagen vascular disease, malignancies, drugs, among others. The idiopathic entity, also called cryptogenic OP (COP) [1], occurs in approximately 50% to 55% of OP cases [2, 3]. COP usually presents as multiple patchy bilateral lung opacities on computed tomography (CT) images of the chest and is located in the peripheral zone or distributed along the bronchial vascular bundle, often accompanied by air bronchogram [2]. However, OP sometimes manifests as solitary lesions, which is known as focal organizing pneumonia (FOP). FOP is relatively rare, and patients may be asymptomatic. FOP sometimes may need to be differentiated from lung neoplastic lesions, and some FOP patients have been suspected of having lung cancer before surgical resection [4, 5].

Studies regarding FOP in the literature were very limited and mostly emphasized the radiological aspects and differentiation of FOP from lung cancer [3, 4, 6-10]. Whether idiopathic FOP has a specific clinical pathological entity and
Clinicopathologic findings of focal organizing pneumonia

any associated characteristics are still debatable. More studies are needed to clarify the ambiguity of FOP causes, particularly the disease’s relationship with infection and the proportion of idiopathic FOP. Thus, the principal objective of our study is to report histological findings in 37 cases of FOP, to further analyze its relative causes and to compare the clinical, radiological and pathological features of focal COP (FCOP) and focal SOP (FSOP).

Materials and methods

We reviewed all surgical lung biopsy or resection records in our hospital from January 1, 2004 to April 31, 2014 and identified a total of 102 cases of histopathologically diagnosed OP. The 102 cases were comprised of 42 cases of lobectomy, 30 cases of partial lobectomy or segmentectomy, and 28 cases of thoracoscopic lung biopsy (or wedge resection). Patient clinical data were reviewed, and 5 patients had been ruled out because they had a history of malignancy (2 cases of lung cancer; 1 case of renal cell carcinoma; 1 case of esophageal cancer; 1 case of extramedullary plasmacytoma). In total, there were 37 cases with unifocal lung lesions based on chest CT report forms prior to operation. All samples were fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin. Hematoxylin-eosin stained sections were observed using optical microscopy. In accordance with the international consensus on organizing pneumonia pathological diagnostic criteria for idiopathic interstitial pneumonia [11, 12], the slides of 37 patients were reviewed independently by three pathologists. In the event of disagreement, the findings were discussed before a final diagnosis was made. We gathered follow-up data by phone or outpatient follow-up of all patients (or their families). We obtained Ethics Approval and patient consent for this study.

Data analysis was performed using SPSS 20.0 statistical software. Fisher’s exact Chi square analysis was used to assess measures of univariate association in frequency tables. A P value below 0.05 was considered statistically significant. Statistical tests were based on a two-sided significance level.

Results

Clinical presentation and pulmonary function studies

The 37 reviewed cases of FOP included 22 men and 15 women aged between 29 and 76 years (median, 57 years); 17 cases included patients with a history of smoking. Patients were symptomatic in 30 cases, with symptoms including cough (20/30), sputum (10/30), fever (9/30), chest pain (9/30), hemoptysis (7/30) and dyspnea (3/30). Meanwhile, 7 cases were asymptomatic with the lesion discovered by routine health examination. The time from onset of symptoms to surgical resection was 7-180 days (median, 30 days), with a mean time of 40 days. No patients had any history of drug therapy, organ transplantation, autoimmune disease or malignancy. Of the 37 patients, 13 cases were considered for lung cancer before resection.

There were 4 cases of lymphocytosis and 3 cases of leukocytosis. Serum high-sensitivity
Clinicopathologic findings of focal organizing pneumonia

C-reactive protein (hs-CRP) checks were performed in 22 cases, with 11 cases having elevated levels. Preoperative pulmonary function tests were performed in 31 cases and spirometry was included in all cases. Spirometry results were normal in 24 patients, and obstructive defects were detected in 6 cases. Two cases showed mixed ventilatory dysfunction. However, all 7 cases with FCOP had normal spirometry results.

The clinical manifestations of FCOP and FSOP are shown in Table 1. There were some differences between FSOP and FCOP with respect to the clinical manifestations of fever, serum hs-CRP level and pulmonary function, but these differences did not reach statistical significance.

Radiological findings

CT chest scans were performed in all 37 cases before surgery. Among the 37 cases, the lesions were located in the right lung in 28 patients, with 11 in the upper lobe, 4 in the middle lobe, and 13 in the lower lobe; the other 9 cases were located in the left lung, with 6 in the upper lobe, and 3 in the lower lobe. In thirty-three cases, lesions were located in the lateral 1/3 of the peripheral lung, and in 4 cases, lesions were located in the middle 1/3 of the lung. The diameters of the lesions on chest CT scans ranged from 0.2 cm to 6.0 cm (median, 3.0 cm). Twenty-eight cases had lesions with irregular margins, 15 with spicular signs, and 16 with pleural tags (Figure 1).

Microscopic findings

Among the 37 lesions, loose connective tissue polyps in the alveolar lumen, lymphocytic infiltration in the alveolar septum, and slightly widened alveolar septum were commonly observed. There was no structural damage to the lung tissue. Part of the peripheral airways also showed fibroblasts, myofibroblasts and loose fibrous connective tissue; the structure of the lung tissue surrounding the lesions was normal. Of the 37 FOP lesions, 17 cases showed predominant OP with increased neutrophilic infiltration or abscess (Figure 2); 11 cases

Figure 1. CT scan of the chest, a 18.0 mm × 16.0 mm opacity with spiculated margins was present in the basal segment of the right lower lobe.

Figure 2. FSOP showing connective tissue polyps in the alveolar lumen in the lesion, but neutrophilic infiltration can be observed in the lesion (the upper left corner). (H & E, × 150).

Figure 3. Another FSOP case, with the same morphologic features as FIG 2, but scattered multinucleated giant cells can be observed in the lesion (the lower left corner). (H & E, × 150).
Clinicopathologic findings of focal organizing pneumonia

Table 2. Histopathological findings of FOP including 5 cases with malignancy

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP with neutrophilic infiltration or abscess</td>
<td>17</td>
</tr>
<tr>
<td>OP with granulomas or scattered multinucleated giant cells</td>
<td>11</td>
</tr>
<tr>
<td>OP accompanied with malignancies</td>
<td>5</td>
</tr>
<tr>
<td>OP with eosinophilic infiltration</td>
<td>2</td>
</tr>
<tr>
<td>Meet the diagnostic criteria for COP</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
</tr>
</tbody>
</table>

There was no hyaline membrane or vascular inflammation in any of the 37 patients.

Treatment and follow-up

All 37 cases of FOP were treated using surgical resection; wedge resection was performed in 12 cases; segmentectomy in 9 cases; and lobectomy in 16 cases. Follow-up data were available in 30 cases (range: 3-125 months, median: 60 months), no patients received other treatment after surgical resection, and all patients were cured without recurrence. Seven patients were lost to follow-up after resection.

Discussion

OP can be idiopathic or secondary. When making a diagnosis of idiopathic/cryptogenic OP (COP), we need to exclude secondary factors, including any significant infiltration of neutrophils, abscesses, granulomas, multinucleated giant cells, eosinophils, hyaline membrane, or vascular inflammation, tumor cells, and so on [11, 12]. In contrast, the existence of those lesions suggests that a lesion is secondary OP (SOP). There are few published studies on the pathological characteristics of FOP and the factors associated with secondary FOP. This is the largest report of serial cases focusing on the pathological characteristics of FOP, and we found that approximately 81.08% of FOP cases had secondary factors, while unknown causes (idiopathic) accounted only for 18.91%. Research related to FOP is rare in the literature. Maldonado et al [13] reported on 26 cases of FOP, including 3 cases (12%) due to infection. The remaining 88% (23 cases) were idiopathic. One of the differences between the previous study and ours is that the results of the former study were based on biopsy and microbiological culture examination. However, our research is based on morphological features alone. Some microorganisms are difficult to culture, so infective disease may be negative in culture examination.

With respect to specific secondary factors in our research, 17 cases showed more neutrophilic infiltration and aggregation in pulmonary interstitial, suggesting the presence of acute active infection; 11 cases exhibited granulomas or some multinucleated giant cells, suggesting the presence of granulomatous inflammation; another 2 cases with lesions had increased eosinophilic infiltration. There were also 5 cases of FOP excluded from the series for being accompanied by malignancy. According to the data, among the secondary factors in FOP, acute infections and granulomatous
Clinicopathologic findings of focal organizing pneumonia

inflammation were predominant with proportions of 66.66%. With results similar to our findings, Watanabe [6] et al. reported on 14 cases of FOP after excluding other secondary factors (such as granulomas). There were 10 cases (71.4%) with neutrophil aggregates in airways and/or pulmonary parenchyma.

Clinically, FOP is more common in men aged 55 to 65 years old (58%-77%). The majority of patients have a history of smoking (50%-76%) and mainly manifest with cough, chest pain, fever, or dyspnea; 20%-62% of patients are asymptomatic [5, 8, 9, 13]. In our study, the FOP patients were a median age of 57 years and had a male to female ratio of 22:15. Male smokers were more common (only one female). The main symptoms were cough, sputum, fever, chest pain and hemoptysis. Seven patients (18.9%) were asymptomatic. The mean time of diagnosis from the onset of symptoms was 40 days. The patients with FCOP, when compared to those with FSOP, seemed to lack the clinical manifestations of fever, and their serum Hs-CRP were generally not increased; however, this finding did not reach statistical significance.

The radiological features of FOP are typically characterized by ill-defined nodular shadow, mainly distributing in the outer of the peripheral region of the lung [5, 7, 13], particularly the right side lobe [5, 8], and some lesions show elevated metabolism on PET/CT examination [8]. A few studies have found masses located in the left upper lobe [6]. Some lesions have spicular signs, or present with pleural tag or pleural thickening. The radiological features of FOP cannot be easily distinguished from the characteristics of primary lung cancer, particularly peripheral lung cancer [4, 5, 10]. In particular for lesions less than 3 cm in diameter, it is difficult to differentiate between FOP and lung cancer using radiological features [10]. In our study, the CT characteristics of 37 cases of FOP were evaluated, and there was a trend towards consistency to those reported in literature. First, the most common location of the lesions was the lateral 1/3 of the peripheral lung, particularly the right lobe (75.6%). Second, the margin of the lesions was ill-defined in most cases, with visible spicular signs and pleural involvement.

In our study, follow-up data on 30 patients were available; 23 FSOP patients and all 7 FCOP patients underwent surgical lung resection and received no other treatment after surgery. These 30 patients received postoperative follow-up for 3 to 125 months (median, 60 months) and were cured without recurrence. The results of our study suggest that the prognosis of FOP is good and that surgical resection is enough without further therapy; this finding is consistent with the literature discussing treatment of FCOP [13].

The study has some limitations. First, the number of samples in the study was relatively small. Second, because it was a retrospective study, some data were not readily available. For example, microbiological cultures of biopsy specimens were not performed, so we could not identify which type of infection each patient had. Third, the patients in the study were those who had been suspected of having lung neoplastic lesions or lung cancer, which might introduce a major bias into the sample selection. Prospective studies should be performed in the future to verify our findings.

In conclusion, histologically, secondary factors exist in a majority of reviewed FOP patients, and a few are idiopathic. Of the secondary factors, acute active infection and granulomatous inflammation are the main causes. Some patients may have fever and high Hs-CRP level, which were commonly observed in the FSOP pattern in this study, though this finding did not reach statistical significance. Pathological diagnosis to differentiate between cryptogenic and secondary OP is important. Surgical resection alone appears sufficient for the management of FOP.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ruie Feng, Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 1 Shuaifuyuan, Wangfujing Street, Dongcheng District, Beijing 100730, China. Tel: 0086-010-69159373; Fax: 0086-010-69159373; E-mail: fengruie1@163.com

References

[1] Lohr RH, Boland BJ, Douglas WW, Dockrell DH, Colby TV, Swensen SJ, Wollan PC, Silverstein MD. Organizing pneumonia. Features and

Clinicopathologic findings of focal organizing pneumonia


