Prognosis in Adult Patients with Idiopathic Pulmonary Hemosiderosis

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Abstract

Background  Diffuse alveolar hemorrhage (DAH) of unknown cause has been characterized as idiopathic pulmonary hemosiderosis (IPH). IPH is a rare disease, which has a high prevalence in children and shows a poor prognosis. However, in adults, since there are few reports about collective cases, the details remain to be determined.

Methods  Between January 2003 and June 2008, consecutive adult patients strictly defined as unknown cause DAH by chest images, fiberoptic bronchoscopy, autoantibody testing, and exclusion of systemic disease were enrolled. We investigated the clinical characterization and course of the enrolled patients.

Results  Nine patients were included. All patients were middle-aged men (56.1 ± 4.2 year-old) with sudden onset. They did not present with anemia (the hemoglobin level was 13.9 ± 0.5 g/dL) despite the quantity of bleeding. In bronchoalveolar-lavage fluid analysis, the cell count was increased (7.6 ± 1.6×10⁵ cells/mL) with neutrophilia (33.3 ± 13.3%). The illness resolved within 2 weeks with or without corticosteroid therapy. All of the patients were alive without recurrence during the follow-up period (45.2 ± 6.2 months) after diagnosis.

Conclusion  Adult IPH patients showed good prognosis. However, the present patients are clinically slightly different from the previously characterized IPH.

Key words: idiopathic pulmonary hemosiderosis, adult patients, diffuse alveolar hemorrhage, unknown etiology


Introduction

Diffuse alveolar hemorrhage (DAH) is a rare but a potentially fatal condition. Most DAH patients have underlying diseases, including connective tissue disorders, systemic vasculitis, or predisposing lung disease. DAH of unknown etiology has been recognized as idiopathic pulmonary hemosiderosis (IPH). Virchow initially described IPH in 1864 (1), and a more detailed characterization of IPH was reported in 1931 by Ceelen, who published autopsy findings of two children who were found with large amounts of hemosiderin in their lungs (2). The disease was subsequently defined as a clinical triad of hemoptysis, pulmonary infiltrates, and anemia of unknown etiology (3). Epidemiologically, IPH is a rare disease. Overall, 80% of cases occur in children, most being diagnosed in the first decade of life (3, 4). The remaining 20% of cases are adult-onset IPH, most of which are diagnosed before 30 years of age. Based on the literature, IPH has been characterized as an iron-overload disorder as a result of the accumulation of hemosiderin-laden macrophages in the alveolar space by chronic or recurrent DAH that is sometimes fatal, with a high prevalence in children (5-7); however, to date, there are few reports on adult cases. Here, we enrolled consecutive adult patients with unknown etiology DAH using strict ex-

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Received for publication October 19, 2010; Accepted for publication May 10, 2011

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1803
Table 1. Patients Characteristics

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GGO; ground-glass opacity
BE; bronchiectasis

Conclusion criteria, and then investigated the clinical characterization and course.

Patients and Methods

Between January 2003 and June 2008, we included consecutive patients fulfilling the following diagnostic criteria: (I) symptoms compatible with pulmonary hemorrhage such as hemoptysis, hemosputum, fever, or dyspnea (II) diffuse pulmonary infiltrates on chest images, (III) pulmonary hemorrhage confirmed by fiberoptic bronchoscopy, (IV) negative for auto-antibody including myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA), proteinase 3 (PR-3)-ANCA, anti-glomerular basement membrane (GBM)-antibody, anti-nuclear-antibody, anti-DNA-antibody, anti-double-stranded DNA-antibody, rheumatoid factor (RF), anti-Ro/SS-A-antibody, anti-La/SS-B-antibody, anti-RNP-antibody, anti-Sm-antibody, anti-cardiolipin-antibody, and lupus anticoagulant (V) absence of predisposing lung disease including bronchiectasis, interstitial pneumonia, emphysematous change, and neoplasms, (VI) absence of nephropathy and cardiovascular disease, (VII) no use of well-known alveolar hemorrhage-inducing drugs such as penicillamine, amiodarone, diphenylhydantoin, retinoic acid, propylthiouracil, etc. (8), (VIII) no use of anticoagulants including warfarin and antiplatelets, and (IX) exclusion of diseases of similar presentation, such as idiopathic acute interstitial pneumonia (IAIP), acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), and idiopathic acute eosinophilic pneumonia (AEP). Furthermore, pulmonary infection with various agents was carefully excluded as follows: Gram and acid-fast bacilli stains; aerobic, anaerobic and acid-fast bacilli cultures of bronchoalveolar lavage (BAL) fluid were carried out. Polymerase chain reaction (PCR) tests of BAL fluid for Pneumocystis jirovecii and cytomegalovirus were performed. Additionally, serum paired complement-fixing antibody tests for respiratory syncytial virus (RSV), adenovirus, parainfluenza virus types 1, 2, and 3, influenza virus A and B, Mycoplasma pneumoniae, and Chlamydia pneumoniae were performed at admission and 2-4 weeks after admission.

All patients underwent fiberoptic bronchoscopy under local anesthesia. Sequential bronchoalveolar lavage (BAL) was performed as previously described (9). Cardiovascular conditions were evaluated by ultrasound-cardiography. The results are expressed as the mean ± SE. This study was approved by the ethics committee of our institution, and informed consent was obtained according to the institutional guidelines.

Results

Patient characteristics

Nine patients met the criteria. Notably, all of the patients were men 56.1 ± 4.2 (38-76) years old who showed sudden onset (Table 1). Six were previous smokers and three were current smokers. None had been diagnosed as having anemia. Six had a stable past history which was not associated with this episode. Regarding the initial clinical presentation, hemoptysis or hemosputum was present in 8, fever in 2, and dyspnea in 2. None of the patients showed clinical evidence of any collagen vascular disease or systemic vasculitis throughout the course.

Laboratory findings

Initial chest CT findings are summarized in Table 1. Seven showed bilateral and 2 unilateral infiltration (representative cases; Fig. 1). Seven patients showed a diffuse pattern. Ground-glass opacity with or without consolidation was found in all patients. Traction bronchiectasis, honeycomb, and pleural effusion were not seen in any patient. As shown in Table 2, the PaO2/FiO2 (P/F) ratio was 284 ± 39 mmHg. WBC count (11,346 ± 1,955/μL) and C-reactive protein (CRP) level (0.93 ± 0.41 mg/dL) were slightly ele-
Peripheral WBC morphologic abnormalities were not seen. None had clinically significant anemia (the hemoglobin level was 13.9 ± 0.5 g/dL). Erythrocyte mean corpuscular volume (MCV) was 92.9 ± 1.2 fL). All had normal platelet counts (24.4 ± 0.9 × 10^4/μL) as well as normal coagulation tests. Blood urea nitrogen (BUN)(14.7 ± 1.6 mg/dL), serum creatinine levels (0.94 ± 0.07 mg/dL), and urinalysis produced normal findings. The gamma-globulin level (IgG; 1070 ± 48 mg/dL, IgM; 56 ± 6 mg/dL, IgA; 286 ± 35 mg/dL) was within normal limits. Serum levels of lactate dehydrogenase (LDH) and KL-6 were 258 ± 22 IU/L and 217 ± 12 U/mL, respectively.

**Bronchoalveolar lavage**

Bronchoscopic observation was done in all patients. Subsequently, sequential bronchoalveolar lavage (BAL) was performed at the middle lobe in 7 patients, and then hemorrhagic fluid and the presence of hemosiderin-laden macrophages were confirmed. Two patients did not undergo sequential BAL because of massive hemorrhage. Of 7 patients who underwent sequential BAL, 6 did so before starting steroid therapy. When the BAL fluids of pretreated patients were analyzed (Table 3), the cell count was increased (7.6 ± 1.6 × 10^5 cells/mL) with neutrophilia (33.3 ± 13.3%).

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**Table 2.** Laboratory Findings on Admission

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<th>Cr/ mg/dL</th>
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11346±1955 13.9 ±0.5 92.9 ±1.2 24.4 ±0.9 14.7 ±1.6 0.94 ±0.07 0.93 ±0.41 258 ±22 217 ±12 284 ±39

mean±SE
alveolar spaces, as well as alveolar walls (capillaritis-like finding) (Fig. 2a). Iron stains showed a few of hemosiderin-laden macrophages in the lung tissue (Fig. 2b).

**Treatment and outcome**

As shown in Table 4, six patients received corticosteroids and the remaining three received only symptomatic treatment. All 6 patients were treated with steroid pulse therapy (SP) [iv methylprednisolone (1,000 mg/body/day) administered for 3 consecutive days]. Four of the patients were then converted to oral prednisone therapy (0.5-0.75 mg/kg/day), followed by tapering every 2-4 weeks. In two of the 6 corticosteroid-receiving patients, mechanical ventilation was required. All 9 patients showed complete remission of symptoms and chest infiltration within 2 weeks (Fig. 1). The duration of subsequent treatment was 11.5 ± 2.7 months. The follow-up period was 45.2 ± 6.2 months after diagnosis. All of the patients are alive without relapse.

**Discussion**

It is difficult to evaluate the prognosis of IPH because of the lack of a large patient series and inadequate follow-up. There is a tendency that in children and adolescent patients it appears to have a severe course and poor prognosis with severe anemia or respiratory failure; however, in adults, the details remain to be determined. In our cohort study, we found that adult IPH patients had a favorable prognosis even with acute respiratory failure. The mortality rate was 0% and the mean survival duration was 45.2 ± 6.2 months.

Iron deficiency anemia because of recurrent or chronic hemoptysis is the most important manifestation of IPH (5-7). Interestingly, the present patients showed an absence of iron deficiency anemia despite the quantity of bleeding; they also had acute onset. Iron staining lung tissue showed a few of hemosiderin-laden macrophages. This finding is limited data but may contribute to the reason for an absence of anemia. To our knowledge, this condition was slightly different from previously characterized IPH. The present patients showed male dominance. Epidemiologically, in childhood, IPH occurs with equal frequency in both genders, whereas in adults it appears to be more frequent in men (4, 10); this result may depend on race or ethnicity.

When the diagnosis of DAH is established, it is important to determine underlying diseases because they influence the treatment and prognosis. Major causes of DAH are autoimmune diseases, such as ANCA-associated vasculitis (Wegener’s granulomatosis, microscopic polyangitis (MPA), and Churg-Strauss syndrome), Goodpasture’s syndrome, and systemic lupus erythematosus (SLE) (11). The diagnosis of autoimmune diseases is established by clinical assessment and autoantibody testing. MPO-ANCA and PR-3-ANCA for ANCA-associated vasculitis, anti-GBM-antibody for Goodpasture’s syndrome, anti-nuclear-antibody and anti-DNA-antibody for SLE are useful and highly sensitive serological tests (12, 13); however, this raises concerns about the presence of neutrophils and macrophages into biologic examinations including bacterial, mycobacterial, fungal and viral pathogens and cytology were all negative.

**Transbronchial biopsy**

Since the present patients obviously showed alveolar hemorrhage, we were concerned about post-biopsy bleeding. Thus, TBLB was performed in only 3 (patients 5-7) of the 9 patients with informed consent. Pathological examination showed infiltration with neutrophils and macrophages into

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*performed after steroid therapy

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**Figure 2.**  a. The alveolar spaces are filled with neutrophils and macrophages. The alveolar walls are thickened by infiltration of neutrophils and macrophages. b. Iron stains show a few hemosiderin-laden macrophages in lung tissue.
ence of seronegative conditions. Generally, patients with autoimmune disease, even in a seronegative condition, present with persistent fever, joint pain, skin rash, proteinuria and neuropathy, accompanied by recurrent and catastrophic systemic complications, such as severe anemia and glomerulonephritis, leading to high mortality (14-22). Thus, we believe that the present patients were not seronegative autoimmune disease-related DAH.

Little is known about cell analysis for BALF in patients with DAH. In our study, we found that the percentage of neutrophils in BALF was increased. There are several possible causes for a high neutrophil count and a basic cause could be acute infection. We excluded the possibility of already-known microbial pathogen infections by microbiologic examinations. Another cause could be neutrophilic inflammation of alveolar capillaries. In fact, in our pathological findings from transbronchial lung biopsy (TBLB), neutrophils infiltrated the alveolar interstitium. It is known that neutrophilic inflammation is involved in alveolar hemorrhage; however, it is necessary to obtain more information by performing surgical biopsy, such as video-assisted thoracic surgical lung biopsy or open lung biopsy.

BAL eosinophilia was observed in one patient (patient 4: 17.0%). The peripheral blood eosinophils on admission were 1.4% and did not become elevated throughout the course. Although drug-induced pneumonia or vasculitis (Churg-Strauss syndrome; CSS) was excluded by our diagnostic criteria, idiopathic eosinophilic pneumonia, including acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP), should be considered in the differential diagnosis. According to Allen’s criteria (23), the patient was suspected to have AEP rather than CEP. AEP is caused by be a variety of possible antigens, such as cigarette smoke (24), environmental agents (25) and drugs (26). As in our recent report (24), etiologically it is accepted that cigarette smoke is potentially related to the onset of AEP. High-resolution (HR) CT findings, such as interlobular septal thickening, bronchovascular bundle thickening, and pleural effusion, helped to diagnose AEP (24, 27). The present patient 4 had no exposure to smoking or environmental agents before onset and did not present with such HRCT findings. Furthermore, hemorrhagic fluid on BAL was not observed in our reported AEP patients (24). Taken together, we consider that this finding was a non-specific response. Basically, CEP has a different clinical characterization from AEP (28), regarding peripheral blood eosinophils (high levels before therapy), chest imaging (multiple non-segmental consolidation), and the clinical course (possible relapse); thus, we could also exclude CEP.

IPH, the HRCT features of which are bilateral consolidation and/or ground-glass attenuation (7), might be confused radiologically with AIP, ALI/ARDS, AEP, progressive organizing pneumonia (OP), acute multilobar infectious pneumonia, bronchioalveolar carcinoma (BAC), and pulmonary alveolar proteinosis (PAP). In particular, severe IPH should be distinguished from AIP and ALI/ARDS. Our IPH patients showed prompt response to steroid therapy and had a good prognosis, as opposed to the low rate of steroid responsiveness and the high mortality rate in ARDS and AIP (29). Furthermore, while it has been reported that the interstitial pneumonia marker, KL-6, serum levels are increased in most patients with AIP and ALI/ARDS (30), none of the present patients showed KL-6 elevation. Thus, we could exclude AIP and ALI/ARDS.

Generally, therapy for DAH consists of treating the autoimmune destruction of the alveolar capillary membrane, as well as the underlying condition (11). Long-term corticosteroids and immunosuppressants are the most effective therapy for patients with idiopathic as well as certain-cause DAH (6); however, in the present patients, not only continuous corticosteroid therapy, but also only steroid pulse therapy or symptomatic therapy induced remission despite the degree of severity. It was also noted that our cases showed marked improvement within 2 weeks and a favorable clinical course. The duration of corticosteroids and immunosuppressants remains controversial and depends on the specific circumstances.

In conclusion, we investigated 9 adult patients with idio-
ophathic DAH. The present patients were characterized by sudden onset, male dominance, absence of anemia, and a good prognosis, slightly different from previously categorized IPH. However, the boundaries between idiopathic acute alveolar hemorrhage and idiopathic pulmonary hemosiderosis are unclear and there is no formal comparison that could help to differentiate the two entities.

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

References