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Case report

A case of idiopathic pulmonary hemosiderosis with seasonal recurrence

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= Abstract =

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease affecting mostly children. This disorder is characterized by recurrent episodes of hemoptysis, bilateral diffuse pulmonary infiltrates, and iron-deficiency anemia. An acute fulminant alveolar hemorrhage can be fatal due to respiratory failure, while chronic hemorrhage leads to hemosiderin-laden macrophages and pulmonary fibrosis. Genetic, autoimmune, allergic, environmental, and metabolic mechanisms of pathogenesis have been suggested, but the etiology of IPH remains unknown. We report on a 9-year-old girl with idiopathic pulmonary hemosiderosis who showed seasonal recurrences without cause. (Korean J Pediatr 2009;52:256-260)

Key Words : Idiopathic pulmonary hemosiderosis; Seasonal recurrence

Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a chronic disease characterized by recurrent diffuse alveolar hemorrhage (DAH) without an identifiable cause. IPH is a rare disease first described as "brown lung induration" by Virchow in 1864[1]. There are six case of IPH reported in Korea[2-6]. The triad of hemoptysis, bilateral diffuse pulmonary infiltrates and iron-deficiency anemia are characteristic findings. Clinical manifestations include cough, hemoptysis, dyspnea, fever, pallor, and fatigue. Genetic, autoimmune, allergic, environmental, and metabolic hypotheses have been suggested as etiologic mechanisms; however, none has been confirmed to date. The diagnosis is made by demonstrating hemosiderin-laden macrophages in the sputum, bronchoalveolar or gastric lavage, or on lung biopsy. In addition, the known causes of pulmonary hemosiderosis must be excluded.

We describe a 9-year-old girl with IPH who had an acute episode every spring and fall for two years.

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Case report

In April 2005, a 9-year-old girl presented to the emergency department with a chief complaint of dyspnea. The patient had a mild fever, cough, dizziness, and fatigue for 3 days prior to the visit. She was previously healthy without any illness and her growth percentiles were within normal range. The family history was unremarkable. There was no history of chest trauma or foreign body aspiration.

The physical examination revealed tachypnea (45/min), tachycardia (140/min), low-grade fever (37.7℃), and a normal blood pressure (90/60 mmHg). The patient appeared pale and had anemic conjunctivas. The breathing sounds were coarse with bilateral crackles in the lower lung fields. There was no hepatosplenomegaly.

The laboratory tests showed a microcytic hypochromic anemia (hemoglobin 6.1 g/dL, hematocrit 19.8%, MCV 60.3 fL, MCH 18.5 pg, MCHC 30.7 g/dL) and reticulocytosis (3.33%). The white blood cell count was 12,900/mm^3, platelet count 281,000/mm^3 and erythrocyte sedimentation rate (ESR) 32 mm/hr. The prothrombin time, partial thromboplastin time and bleeding time were normal. The blood chemistry and urinalysis showed no abnormalities, except for an elevated C-reactive protein (CRP, 22.5 mg/L). The arterial blood gas analysis on room air demonstrated a mild hypoxemia (oxygen tension 57.9 mmHg and oxygen saturation 90.9%) with

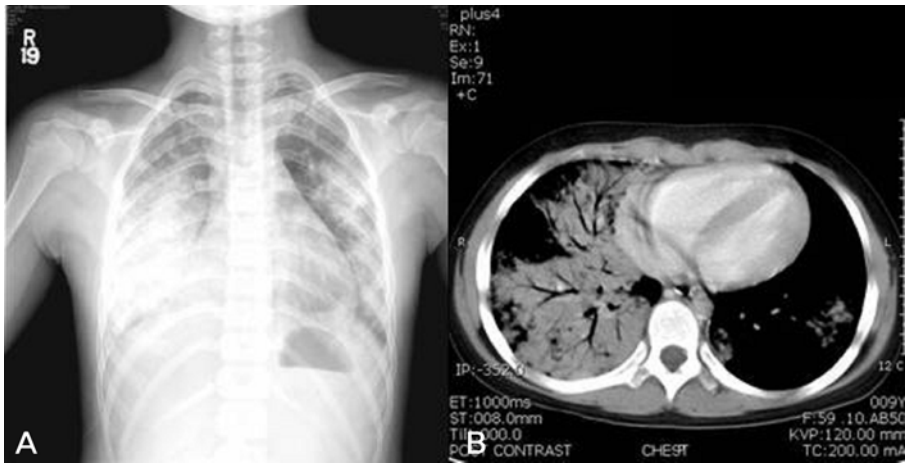

Fig. 1. Bilateral diffuse opacities are seen in the postero-anterior chest radiograph (A). Chest CT reveals multiple ground glass opacities and consolidation in both lung fields (B).

a normal pH, carbon dioxide and bicarbonate levels. The serum iron was decreased (25 g/dL) and the iron-binding capacity increased (481 μg/dL). The ferritin was 63.8 ng/mL. The direct and indirect Coombs tests were negative (Table 1).

The chest radiograph showed bilateral diffuse alveolar infiltrates and the computed tomography demonstrated multiple ground-glass opacities and consolidation of both lung fields (Fig. 1). The electrocardiography was unremarkable.

The patient was admitted to the intensive care unit where she received oxygen supplementation, red blood cell transfusions, intravenous antibiotics and oral roxithromycin. On the second hospital day, small amounts of hemoptysis were noted. The sputum smear and culture for bacteria and tuberculosis were negative. Tuberculin skin test was negative. The blood and urine bacterial cultures yielded no growth. The anti-mycoplasma antibody test, on the hemagglutination test, was positive (1:160), as well as the cold agglutinin titer (1:128). The serology examination for adenovirus revealed positive IgG and negative IgM antibodies, and the adenoviral culture showed no growth. The markers for autoimmune diseases, antinuclear antibody (ANA), rheumatoid factor, anti-glomerular basement membrane antibody (anti-GBM Ab), and antineutrophil cytoplasmic antibody (ANCA) were all negative. The patient was thought to have mycoplasma pneumonia and iron-deficiency anemia. On the seventh day of admission, the cough and dyspnea persisted and the chest radiograph showed no improvement. Oral prednisolone was started and clinical improvement followed. Eleven days after admission, the breath sounds were clear and the infiltrates on the chest radiograph were resolved (Fig. 2). The patient was discharged home with roxithromycin and iron supplements.

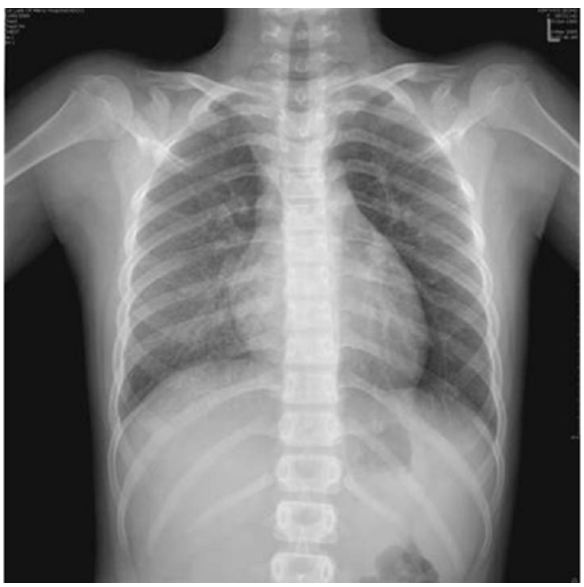

Fig. 2. Chest radiography on the eleventh day of hospitalization showed marked resolution of both lung field infiltrates after treatment with prednisolone.

In September of 2005, the patient was admitted again with hemoptysis. The chest radiograph showed diffuse bilateral alveolar infiltrates. The laboratory findings revealed iron-deficiency anemia and reticulocytosis. The ESR and CRP were negative. The anti-mycoplasma antibody was positive (1:160) again. The triad of hemoptysis, diffuse bilateral infiltrates on chest x-ray and iron-deficiency anemia, as well as recurrent illness suggested pulmonary hemosiderosis. The

Table 1. Initial Laboratory Findings on Each Admission

	1st admission Apr. 2005	2nd admission Sep. 2005	3rd admission Apr. 2006	4th admission Sep. 2006
Hemoglobin (g/dL)	6.1	7.0	8.1	11.0
MCV (fL)	60.3	68.6	69.2	80.6
MCH (pg)	18.5	22.5	23.0	27.5
Reticulocyte (%)	3.33	4.24	6.61	3.14
Iron (g/dL)	25	27	25	23
PT (second)	12.3 (96%)	14.3 (87%)	14.6 (87%)	13.4 (93%)
PTT (second)	37.5	42.5	39.5	40.1
Anti-GBM antibody (EU)	0.01	0.41	<5.0	<5.0
ANCA	Negative	Negative	Negative	Negative
FANA	Negative	Negative		Negative
RF	Negative	Negative		Negative
Tuberculosis culture	No growth		No growth	
Anti-mycoplasma antibody	Positive (1:160)	Positive (1:160)	Positive (1:80)	Positive (1:80)
Cold agglutinin	1:128	1:16	1:8	1:8
Total IgE (IU/mL)	30.1	25.5	40.4	42.9
IgE to cow's milk protein		Negative		

Abbreviations : MCV, mean corpuscular volume; MCH, mean corpuscular hematocrit; PT, prothrombin time; PTT, partial thromboplastin time; Anti-GBM, anti-glomerular basement membrane; ANCA, antineutrophil cytoplasmic antibodies; FANA, fluorescent anti-nuclear antibody; RF, rheumatoid factor; IgE, immunoglobulin E

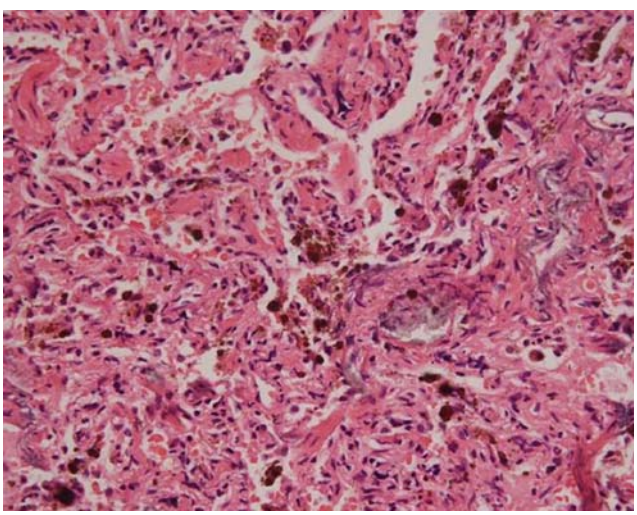

Fig. 3. Open lung biopsy showed numerous hemosiderin-laden macrophages within alveolar spaces (hematoxylin and eosin stain, ×400).

sputum, blood and urine bacterial cultures were negative. The tests for ANA, anti-GBM Ab and ANCA were negative. The serum immunoglobulin and complement levels were normal. Multiple radioallergosorbent tests (MAST), for antigen-specific immunoglobulin E, including cows milk protein were negative (Table 1). The stool occult blood was positive, but there were no abdominal symptoms. Because we could not identify an etiology for the suspected pulmonary hemosiderosis, the disease was considered idiopathic and prednisolone was initiated. The clinical manifestations resolved after two weeks of hospitalization.

In April of 2006, the patient presented to the emergency department with a cough and dyspnea. Bilateral pulmonary infiltrates on chest radiography and iron deficiency anemia were present again. Hemoptysis developed after admission. The sputum examinations for bacteria, tuberculosis and malignancy were negative. The anti-mycoplasma antibody was weakly positive (1:80) (Table 1). The patient was successfully treated with prednisolone and then maintenance therapy with alternate-day prednisolone was started.

The patient was well without respiratory symptom for several months. Then in September of 2006, the patient was readmitted due to hemoptysis without iron deficiency anemia. The arterial blood gas analysis, ESR and CRP were normal. The chest radiograph again showed bilateral diffuse infiltrates. The anti-mycoplasma antibody was again weakly positive (1:80) (Table 1). An open lung biopsy of the right middle lobe was performed; hemorrhage and infiltration of hemosiderin-laden macrophages in the alveolar spaces and interstitial fibrosis were identified (Fig. 3). With daily prednisolone treatment, the hemoptysis and pulmonary infiltrates subsided. The patient was discharged on alternate-day prednisolone, and has been followed by regular outpatient visits for 17 months without recurrence.

Discussion

DAH can occur in a variety of conditions, including systemic vasculitis, connective tissue disease, cardiac disease, infection, coagulopathy, malignancy, and exposure to exogenous toxins[7]. Pulmonary hemosiderosis is a term reserved for cases with repetitive DAH. When an etiology is not identified, the pulmonary hemosiderosis is considered idiopathic. IPH, Goodpasture syndrome and Heiner syndrome are classified as primary pulmonary hemosiderosis disorders, while the remaining conditions are considered secondary disorders. IPH is a rare disease with an annual incidence of 0.24 and 1.23 per million children in Sweden[8] and Japan[9], respectively. In Korea, the first case report of IPH was published in 1985[2] and since then, there have been five more case reports of IPH in Korea[2-6].

Although the etiology of IPH is not known, immunological processes are likely involved in the pathogenesis. The fact that immunosuppressive therapy is effective for the treatment of this disorder suggests an immunological component. A long-term follow-up study of 15 patients with IPH showed that about one quarter of the IPH patients developed autoimmune diseases such as rheumatoid polyarthritis[10]. Some of the known causes of pulmonary hemosiderosis are immune-mediated. In patients with Goodpasture syndrome, circulating autoantibodies against type IV collagen, in the glomerular basement membrane, produce acute glomerulonephritis and pulmonary hemorrhage. In patients with Heiner syndrome, plasma antibodies to cows milk protein are observed. The coexistence of celiac disease and pulmonary hemosiderosis was reported in more than ten patients, and their pulmonary disease as well as intestinal manifestations could be managed with a gluten-free diet[11].

The symptoms of IPH usually occur early in childhood, before the age of ten years[7]. Clinical manifestations vary from asymptomatic iron-deficiency anemia[12] to acute attacks of fulminant hemoptysis. During the acute phase, cough, dyspnea, hemoptysis, and sometimes respiratory failure are observed due to bleeding into the alveolar spaces. In the chronic phase between the acute exacerbations, patients may demonstrate signs of anemia, bilateral crackles or failure to thrive. Our patient had dyspnea and hemoptysis with diffuse bilateral infiltrates during each exacerbation, while she was symptom-free during the chronic phase of the disease. The specific duration of the acute and chronic phases is usually unpredictable[13].

The diagnosis of IPH is made by demonstrating hemosiderin-laden macrophages in the sputum, bronchoalveolar or gastric lavage samples, or on lung biopsy findings. Extensive examination to exclude the known causes of pulmonary hemosiderosis is essential. We performed evaluation to exclude bacterial and viral infection, tuberculosis, cardiac disease, allergy to cows milk protein, and autoimmune diseases and could not identify an etiology for the pulmonary hemosiderosis in our patient. The timing of acute exacerbations in April and September, for two years, suggested seasonal recurrence and raised the suspicion of an allergy-related origin. However, the total IgE and eosinophil counts were normal and the specific IgEs to more than 30 allergens by MAST were negative.

Because our patient was school-aged, older than the mean age of onset for IPH, and the chest x-rays showed bilateral infiltrates, we screened the anti-mycoplasma antibody titer by the hemagglutination test. A positive anti-mycoplasma antibody titer was obtained during each exacerbation of the pulmonary hemosiderosis. An association between *M. pneumoniae* and pulmonary hemosiderosis has not been previously reported. Cimolai and Seear[14] reported an immune response to a previously unknown *M. pneumoniae* antigen in a 13-year-old male with IPH, which mimicked anti-P1 IgM immunoblotting[14]. However, the investigators did not implicate *M. pneumoniae* in the development of the pulmonary hemosiderosis; instead, they suggested that there might be a specific antigenic stimulus that cross-reacted with the *M. pneumoniae* antigen. This result cannot be directly compared with ours because the methods used for antibody detection in each study were different. *M. pneumoniae* is known to induce the release of cytokines, such as IL-1β, IL-2, IL-6, TNF-α, and IFN-α from human peripheral blood mononuclear cells[15]. *M. pneumoniae* may cause exacerbation of asthma by triggering cytokine production from the mononuclear cells at the airway surface[16].

Effective treatment may be achieved using corticosteroids and other immunosuppressive drugs such as azathioprine, hydroxychloroquine, cyclophosphamide, and methotrexate. During an acute episode, blood transfusion, oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygenation may be necessary. Following recovery from an acute exacerbation, maintenance therapy is important. In contrast to an older study that reported an average survival of 2.5 years after the onset of symptoms[17], a 5-year

survival of 86% was reported in a more recent study; the improved prognosis was due to long-term immunosuppressive treatment[1]. Success with corticosteroid inhalation as maintenance therapy has been reported.

In conclusion, we report a 9-year-old girl with IPH who had seasonal recurrences during spring and fall for two years.

한 글 요 약

계절성으로 재발한 특발성 폐 혈철 침착증 1예

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곽가영 · 이나영 · 이문희 · 이수영 · 정승연 · 강진한 · 정대철

특발성 폐 혈철 침착증은 반복되는 객혈, 흉부 X-선상 양측성 폐침윤, 철분 결핍성 빈혈을 특징으로 하는 질환으로 주로 소아에서 발생한다. 매우 드문 질환으로 국내에서는 현재까지 6편의 증례가 보고되었다. 유전, 자가면역, 알레르기, 환경, 대사 등과 관련된 병인에 제시되었으나 아직까지 확실히 밝혀지지 않았다. 본 환자는 9세 여아로 2년간 매 봄, 가을에 객혈, 호흡곤란을 주소로 4차례 입원하였다. 청진 시 양폐야에서 나음이 들렸고 흉부 X-선 검사 및 CT에서 양측성 폐포성 침윤이 확인되었으며 혈액검사에서 철분 결핍성 빈혈이 관찰되었다. Anti-GBM Ab, ANCA, FANA, RF, cow's milk protein에 대한 IgE 등의 항체검사는 모두 음성이었고 응고 검사, 면역글로불린, 보체는 모두 정상이었다. 세균에 대한 객담과 혈액 배양 및 결핵에 대한 피부반응검사, 객담 도말 및 배양 검사는 모두 음성이었다. 폐생검에서 폐포내 출혈과 혈철소 함유 대식 세포(hemosiderin-laden macrophage) 및 간질의 섬유화 소견을 보여 폐 혈철 침착증을 확진 하였다. 매 악화 시마다 경구용 스테로이드 투여 후 임상양상이 호전되어 퇴원하였다. 현재 외래에서 유지요법으로 스테로이드 복용 중이며 17개월간 재발 없는 상태이다.

저자들은 이전에 국내에서 보고되었던 환자들과는 달리 학동기에 처음 발병하여 매년 봄과 가을에 뚜렷한 원인 없이 재발하는 양상을 보인 특발성 폐 혈철 침착증 1예를 보고하는 바이다.

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