Anemia as the Sole Presenting Symptom of Idiopathic Pulmonary Hemosiderosis: Report of Two Cases

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Idiopathic pulmonary hemosiderosis (IPH) is a rare disease in children and has an unknown etiology. It is characterized by the triad of hemoptysis, pulmonary infiltrates on chest radiograph (CXR) and iron deficiency anemia. We report two young children, aged 3 and 4 years, were admitted due to pale-looking appearance but without hemoptysis or other respiratory symptoms. Pallor was the sole presenting feature in these 2 children with IPH and which was unusual. CXR obtained on admission led to the suspicion of pulmonary hemorrhage. The diagnosis of IPH was confirmed based on the presence of many hemosiderin-laden macrophages in bronchoalveolar lavage fluid obtained by flexible bronchoscopy. Steroid was initiated after the diagnosis of IPH was established; the both of them have been well and received regular follow-up in our outpatient department. IPH may not be diagnosed because of difficulty in diagnosis. Anemia may be the only presenting feature of IPH, which was due to occult pulmonary hemorrhage. Initial treatment with corticosteroids has been successful in our patients for a period of 6 and 8 months of follow up respectively. *(Chang Gung Med J 2004;27:824-9)*

Key words: idiopathic pulmonary hemosiderosis, hemosiderin-laden macrophages, anemia, bronchoalveolar lavage fluid.

Idiopathic pulmonary hemosiderosis (IPH) is a rare and potentially lethal disorder in children. The estimated incidence was 0.24[1] and 1.23[2] cases per million in selected populations. A recent case series showed only five patients in a tertiary children's hospital in northern Taiwan over a 25-year period.[3] The diagnosis of IPH is based on exclusion, requiring thorough review and elimination of other causes of intrapulmonary hemorrhage or other extrapulmonary diseases.[4] In a study reported by Saeed et al., each of 17 patients with IPH had anemia and cough as initial clinical presentation.[5] Pallor as the sole presenting symptom without cough in the patients with IPH was unusual and such patients might have been erroneously diagnosed.[6-7] The clinical course of IPH has been extremely variable, and some of the patients continue to have pulmonary hemorrhage despite aggressive therapy. The therapeutic regimens in IPH are controversial, and corticosteroids have been thought to be effective in decreasing the frequency of hemorrhage. However, some authors suggested that corticosteroid therapy did not alter the long-term course or prognosis of IPH.[8] We presented 2 young children, both of them were diagnosed to have severe anemia initially without underlying causes even after thorough investigations by experienced hematologists. We reviewed literatures and discussed the clinical course, possible etiologies, diagnosis, treatment, and prognosis.

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CASE REPORT

Case 1

A 4-year-old previously healthy boy suffered from progressive pale-looking and yellowish discoloration for one month. Physical examination revealed pallor and weakness. Auscultation of chest revealed normal air entry and breath sounds. There was no hepatomegaly or splenomegaly. He had no history of bleeding or trauma either. Hemogram on admission showed a hemoglobin (Hb) level of 4.0 g/dL, mean corpuscular hemoglobin (MCH) of 17.2 pg/cell, and mean corpuscular volume (MCV) of 63.1 fL. The initial workup included Coomb's test, peripheral blood (PB) smear, reticulocyte count, bilirubin, glucose-6-phosphate dehydrogenase deficiency, and Hb electrophoresis. He was diagnosed to have microcytic and hypochromic anemia after extensive hematological investigations. Other studies screening for immunologic disorders included C3 and C4 complements, antinuclear antibody (ANA), antiglomerular basement membrane antibodies (Anti-BM Abs) and antineutrophil cytoplasmic antibody (ANCA) were unremarkable. Chest roentgenography (CXR) on admission revealed diffuse perihilar infiltrates (Fig. 1A). This finding, associated with the diagnosis of anemia, led to the suspicion of IPH. Bronchoscopy was promptly arranged which revealed diffuse fresh blood coating on trachea, carina, and segmental bronchi. In addition, bronchoalveolar lavage (BAL) fluid was obtained for cytologic analysis. Microscopic examination of BAL fluid revealed many hemosiderin-laden macrophages using Berlin stain (Fig 1B). In order to exclude other possibilities, chest computed tomography (CT), and echocardiography were performed. Only chest CT showed focal patchy ground-grass opacities and consolidation in bilateral lungs (Fig. 1C). He was discharged with oral prednisolone therapy (2 mg/kg/day) and received regular follow-up at our outpatient department for the following 6 months. The follow-up Hb levels were within normal limits and he was free of pulmonary symptoms.

Case 2

This 3-year-old girl was admitted to our hospital because of pale appearance and exertional dyspnea 10 days before admission. Her physical examination

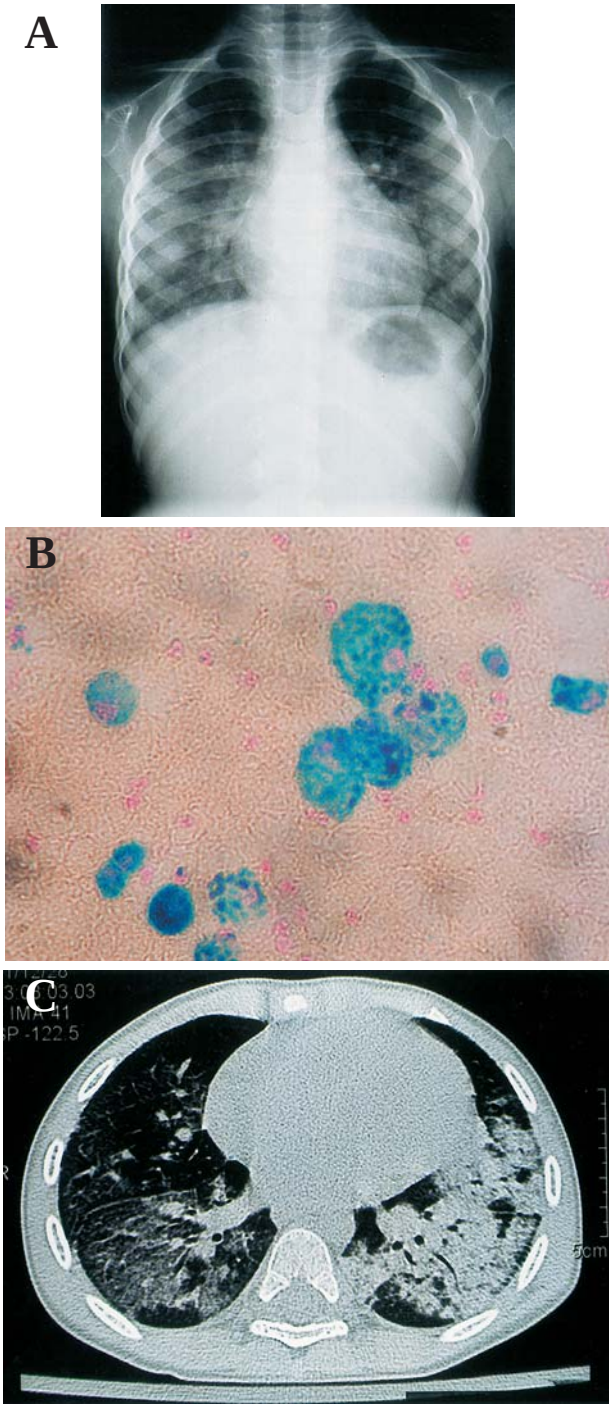

Fig. 1 (A) Case 1. Plain chest radiograph demonstrating bilateral perihilar infiltrations. (B) Berlin stain of BAL fluid showing hemosiderin pigments in macrophages (original magnifications, ×400). (C) Chest CT revealing ground glass opacities in the right lower lobe and consolidation in the lingular segment and left lower lobe

revealed respiratory distress but auscultation of chest was normal. There were no decreased air entry or abnormal breath sounds. Neither hepatosplenomegaly nor bruises were found. Hemogram on admission showed Hb of 4.9 g/dL, MCV of 60.4 fL, and MCH of 15.0 pg/cell. Microcytic and hypochromic anemia was impressed. According to her history, there were no reasons to explain her anemia. She had been admitted previously to other hospital with a similar episode 9 months prior to this admission. At that time, Hb was 6.6 g/dL, and she required ventilator support and high-fraction oxygen because of respiratory failure. She was hospitalized for 32 days, with a diagnosis of pneumonia, acute respiratory distress syndrome (ARDS), and anemia. This event had been attributed to pneumonia and pneumonia-associated ARDS.

After discharge, her condition remained uneventful without medications until 10 days prior to this admission. She received multiple transfusions and oxygen therapy in the intensive care unit. Initial laboratory data, including PB smear, Coomb's test, bilirubin, prothrombin time/activated partial thromboplastin time, and Hb electrophoresis were all within normal limits. Screening studies for immunologic disorders such as C3 and C4 complements, ANA, Anti-BM Abs, and ANCA were obtained too; nonetheless, none of the results were remarkable. Iron deficiency anemia (IDA) was the only diagnosis without reasonable causes. CXR on admission showed consolidation over bilateral lung fields and perihilar areas (Fig. 2). It led to the suspicion of pulmonary hemorrhage. BAL fluid was acquired by bronchoscopy, and abundant hemosiderin-laden macrophages were discovered in it using Prussian stain. Immunologic and cardiogenic disorders predisposing to pulmonary hemorrhage were excluded by echocardiography and immunologic examinations. With the diagnosis of IPH, intravenously administered hydrocortisone was instituted. Respiratory distress improved after transfusions and oxygen supplement.

She was sent home with oral prednisolone (1.5 mg/kg per day) after 6 days of hospitalization. She has been well for the following 8 months and received regular follow-up at the outpatient department. She only had mild unproductive cough but no hemoptysis, exertional dyspnea, or other respiratory symptoms. No anemia has been found during this period of follow-up, and the sequential CXR revealed only perihilar infiltrations.

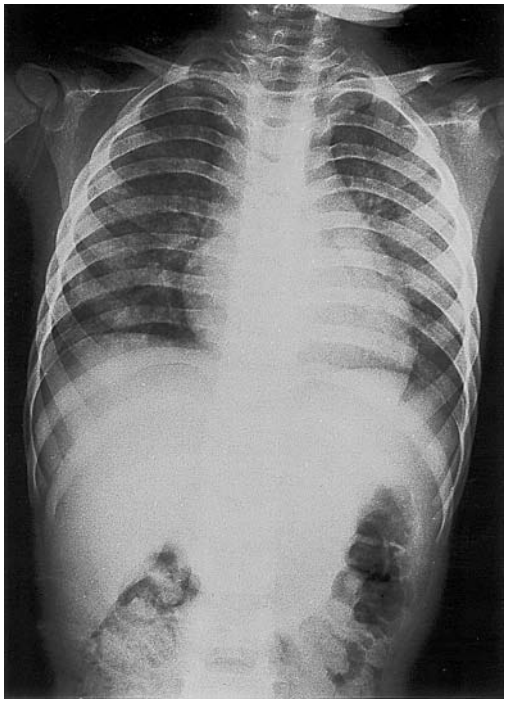

Fig. 2 Case 2. Plain chest radiograph showing consolidation over bilateral lung fields and perihilar area.

DISCUSSION

IPH, a rare disease in children with unknown etiology, is characterized by IDA, and chronic or recurrent pulmonary symptoms such as cough, hemoptysis, and dyspnea.[4,9] In this report, the sole presenting feature of these two patients with IPH was anemia. Exertional dyspnea had been attributed to anemia initially and no further investigations perused. The first approach was directed toward IDA in our cases but did not have a definite diagnosis even after a series of studies. Compatible changes on CXR in combination with anemia led to the suspicion of IPH. Confirmatory diagnosis was based on exclusion of other possibilities.

Environmental factors may participate in the pathogenesis of IPH. Etzel et al. proposed that some fungus may play an important role in the development of infant IPH.[10] Stachybotrys atra (or chartarum) was isolated in almost all of the case homes. The spores from such fungus are not infectious but

produce several kinds of toxins, mainly trichothecenes, which are potent protein synthesis inhibitors.[11] These toxins may cause capillaries to become fragile when rapid endothelial basement membrane formation occurs. Thus these infants are at risk of stress hemorrhage. Vesper SJ et al. also verified that haemolysin stachylysin produced by Stachybotrys chartarum had a particular role in the pathogenesis of IPH.[12]

With the widespread availability of flexible fiberoptic bronchoscopy in children, this procedure has become a useful tool in establishing diagnosis of IPH and in the exclusion of other possibilities.[9] Lung biopsy should initially be obtained by fiberoptic bronchoscopy with transbronchial forceps, which is a minor invasive procedure. The biopsy specimens should be sent for both immunofluorescence and electron microscopy studies in addition to light microscopy. Biopsies should also have no specific pathological findings in order to exclude other diseases such as Wegener's granulomatosis, vasculitis or pulmonary embolism.

Various therapeutic regimens have been tried in IPH, but their efficacy is difficult to evaluate.[1] Treatment with corticosteroids is commonly employed and is based on the possible immunological pathogenesis of IPH. The use of corticosteroids in treating acute or long-term course is dependent on empiricism.[13] While high-dose corticosteroids may reduce the morbidity and mortality of an acute episode, but the effectiveness of long-term treatment remains uncertain.[13] Inhaled corticosteroids have been tried in some cases when systemic treatment failed.[14] A variety of immunosuppressive agents, such as azathioprine, cyclophosphamide, and hydroxychloroquine, have been used in the treatment of IPH by either solely or in combination with oral corticosteroids.[4,15-18] Because of the lack of large and comparable patient series as well as inadequate follow-up in previous studies, the prognosis of IPH remains unclear. However, the use of corticosteroids and immunosuppressive agents may be beneficial in treating IPH and also influence prognosis.[5,19]

The long-term prognosis of IPH is extremely variable, and most patients suffer from multiple episodes regardless of aggressive therapy. Respiratory failure caused by pulmonary hemorrhage or progressive pulmonary insufficiency may lead to death even in the first episode. Case 2 suffered from respiratory failure 9 months prior to this admission. Although the final diagnosis was pneumonia and ARDS, we highly suspected that could be the first episode of IPH even without confirmatory evidences. The more alert we become with IPH, the earlier we can diagnose and treat it correctly. Chryssanthopoulos et al. reported a survival time of 2.8 years in 30 patients.[8] Saeed et al. reported a five-year survival for IPH patients treated with long-term immunosuppressive therapy was 86%.[5] It showed that aggressive treatment in IPH will have a longer survival and a better prognosis.

In conclusion, anemia without any pulmonary symptoms may be the sole presenting feature of IPH, especially in young children. Hemoptysis, which was considered as a prerequisite event of pulmonary hemorrhage, may not be present in young children with IPH. We recommend that when a given case with unexplainable anemia and bilateral perihilar infiltrations on CXR should be suspected to have the possibility of pulmonary hemorrhage even without any respiratory symptoms.

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以貧血爲唯一表現的原發性肺血鐵沉積症：兩病例報告

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原發性肺血鐵沉積症於兒童是一個罕見且未知原因的疾病。它的特色有三個：咳血、肺部X光浸潤、及缺鐵性貧血。我們報告2個皆是因爲臉色蒼白，但無咳血或任何呼吸道症狀而住院的3歲及4歲病童。單以貧血爲唯一表現的原發性肺血鐵沉積症是不尋常的。入院當時所照的胸部X光片使我們懷疑肺出血。經由軟式支氣管鏡檢查所取得的氣管肺泡灌洗液中出現許多的血鐵質載滿的巨噬細胞，因而確定原發性肺血鐵沉積症的診斷。之後即以類固醇治療，2個病人皆反應良好，定期於門診追蹤至今未再發病。我們認爲因爲確立診斷困難的緣故，原發性肺血鐵沉積症可能沒有被診斷出。正如這兩個例子給我們的啓示：隱性的出血，特別是在幼童身上，可能是原發性肺血鐵沉積症的唯一表現。此兩病童分別以類固醇治療6及8個月，到目前爲止是成功的。(長庚醫誌2004;27:824-9)

關鍵字：原發性肺血鐵沉積症，血鐵質載滿的巨噬細胞，貧血，氣管肺泡灌洗液。

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