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Fatal Invasive Aspergillosis in a Child with Idiopathic Pulmonary Hemosiderosis

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Idiopathic pulmonary hemosiderosis (IPH) is primarily a significant life-threatening situation in childhood, and that is an uncommon disease identified mainly in children and adolescents. It is defined by recurrent diffuse alveolar hemorrhage that causes the accumulation of hemosiderin-laden macrophages. The predictive incidence of IPH in children and adolescents is 0.24-1.23 cases per million. Besides, the IPH mortality rate as high as 50%.[1]

A 16-year-old boy was accepted to our pediatric intensive care unit (PICU) with complaints of dyspnea and fever. The patient was investigated due to hemoptysis, clubbing, and anemia 2 years ago, and he has complained about it for 3 years. At admission, the boy presented dyspnea, tachypnea, unable to maintain oxygen saturation in the air room (Sat O_2 = 55%), and he looked very pale. The result corresponded to iron-deficiency anemia except for serum ferritin levels. At admission to our clinic, radiographically, chest x-ray demonstrated widespread opacification of bilateral lungs, and computed tomography (CT) revealed widespread bilateral ground-glass opacities, interlobular septal thickening, and indicated interstitial lung disease (Figure 1). Laboratory examination detected a negative rheumatological workup except for antineutrophil cytoplasmic antibodies (ANCA +1/32). Inborn metabolic diseases, primary immune deficiency, and a bone marrow aspiration revealed normal. Serological tests were not suggestive of an acute infection. Galactomannan antigen blood level was detected as 0.71 (normal range, 0-0.5). But the endotracheal aspiration specimen level was 0.41 (normal range, 0-0.5). Also, the patient's endotracheal aspiration culture showed *Aspergillus fumigatus* 10 000 CFU/mL, and both blood culture and urine culture were also negative. On the 15th day of PICU admission, despite all efforts, the patient died due to severe recurrent pulmonary hemorrhage. Pathology specimen showed *Aspergillus fumigatus* (Figure 2).

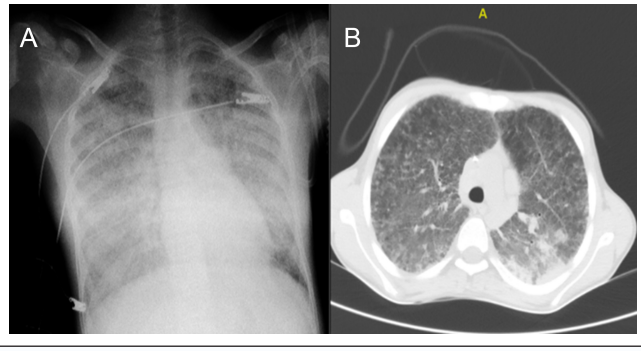

Figure 1. Radiologic evaluation: (A) Posteroanterior chest x-ray demonstrating bilateral pulmonary infiltrations. (B) Computerized tomography scan of the chest showed ground-glass opacities and interlobular septal thickening in both lung fields.

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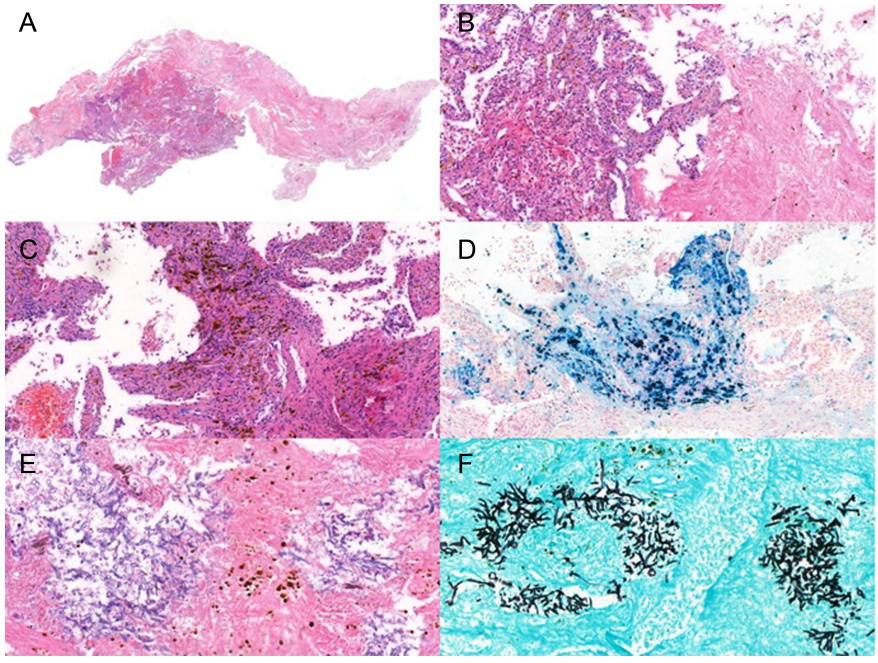

Figure 2. Microscopic evaluation: Pulmonary parenchymal necrosis (A, B), pulmonary hemosiderosis (C, D – Prussian blue), and fungal hyphae (E, F – Grocott methenamine silver). Slides were scanned with digital scanner (Pannoramic 250 Flash III, 3DHISTECH Ltd., Hungary) in 40× objective and photographed with CaseViewer 1.4 (3DHISTECH Ltd., Hungary) in 0.7× (A), 10× (B, C, D), and 20× (E, F) magnifications.

Aspergillus can cause a broad spectrum of diseases, including invasive disease in patients with immune deficiency, saprophytic disease in immunocompetent individuals, and allergic disease in atopic individuals. Aspergillus does not cause disease in most immunocompetent people. However, under certain conditions, different forms of infections may occur in immunocompetent people. Case reports and case series of invasive pulmonary aspergillosis (IPA) are increasingly reported in immunocompetent patients, especially in critically ill patients. In the literature, it is reported that 5% to 7% of IPA cases occurred in critically ill nonimmunocompromised hosts.[2,3] The risk factors for positive *Aspergillus* spp. samples for the nonneutropenic immunocompetent ICU patients included age, ARDS, steroids, bacterial infection, COPD, and organ failures.[4,5] Our patient did not have any risk factors that may cause a propensity to develop IPA such as asthma, steroid usage, or immunosuppressant treatment. Considering both IPA and IPH's pathophysiology, we may speculate that the main problem may be macrophage dysfunction or increasing activity of *Aspergillus* due to elevated iron levels in the alveoli. In the literature, a relationship was reported between the amount of iron in alveolar macrophages and the activity of invasive fungal agents. Changes in iron metabolism in macrophages also affected the signal pathways, making the host susceptible to a fungal infection somewhere. Reducing the amount of iron in macrophages reduces the risk of fungal infections.[5] In this study that provided a pathogenetic model of mucormycosis, it is shown that the change of iron metabolism disorder in macrophages was essential in antifungal immunity in the lung and led to the development of immune deficiency.[6] Because our patient was diagnosed with IPH, we can say that the alveoli were filled with iron, and macrophage functions were thus impaired. Therefore, he became vulnerable to aspergillosis.

Idiopathic pulmonary hemosiderosis is a rare disease, and pediatricians must doubt IPH even if not hemoptysis with iron deficiency anemia, which no signs of improvement with iron supplementation together with respiratory distress. To date, a few cases of IPH were ANCA positive, and there was no report IPH-related invasive aspergillosis and mortality in a child. It has not been previously described in the literature that recurrent pulmonary bleeding is a risk factor for invasive aspergillosis.

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