Idiopathic Pulmonary Hemosiderosis

enyi it A.[1], Ayy ld zO.[2], Babayi it C.[1],Y ld r m M.[2], Büyükbayram H.[3]

Departments of Chest Diseases[1], Internal Medicine[2] and Pathology[3], School of Medicine, Dicle University, Diyarbak r, Turkey

Key words: *Idiopathic pulmonary hemosiderosis, fluticasone propionate*

Idiopathic pulmonary hemosiderosis (IPH) is an exceptionally rare cause of alveolar haemorrhage that occurs primarily in infants and children (1-9). It was first described by Virchow in 1864 (8).The clinical manifestations of diffuse alveolar haemorrhage typically include hemoptysis, infiltrated areas on the chest radiograms, dyspnea, and iron deficiency anemia (10,11). Familial inheritance has also been reported (2,5). Although the pathogenesis remains unclear, available evidence suggests an immune disorder (12,13). An association between IPH and coeliac disease has also been reported, (10,12,13).

IPH is predominantly a disease of childhood (11,13); however, adults, usually over 30 years old, constitutes 20% of reported cases (13). There is a 2:1 male predominance in adults (3). The clinical picture is characterised by either recurrent episodes of life-threatening hemoptysis or intermittent blood-streaked sputum (13). In addition, fever, cough, substernal chest pain and fatigue, secondary to iron deficiency anemia are also reported (8,13). Sequelae of recurrent episodes of alveolar haemorrhage include pulmonary fibrosis, progressive respiratory failure and cor pulmonale (6).

We present an IPH case that was diagnosed by demonstration of hemosiderin-containing macrophages in bronchoalveolar lavage specimen.

Case report

A 17-year-old man was admitted to the hospital for evaluation of shortness of breath and hemoptysis. His history had actually begun 1.5 years prior to this hospital admission, when hemoptysis developed spontaneously. The patient had received non-specific antibiotic and symptomatic therapy because of hemoptysis then and been hospitalised for further investigation and treatment since he had had progressive hemoptysis during the last one month. His family history revealed that his two brothers had died when they were 4 and 5 months old. The family reported no exposure to toxic chemicals.

The pulse rate was 88/min, the blood pressure was 125/70 mmHg, and respiration rate 19/min. The examination of the head, neck and gastrointestinal tract was normal. The physical examination revealed bilateral basilar crackles on the chest and pallor of the skin.

Laboratory evaluation revealed an iron deficiency anemia (hematocrit: 31.8 %, serum iron:65 mg/dl, total iron-binding capacity:400 mg/dl), normal urinalysis and normal serum urea nitrogen. The smear of the peripheral blood demonstrated marked hypochromia and microcytosis. The bone marrow examination revealed a marked erythroid hyperplasia without other abnormality. Complement C3 and C4 levels and liver function tests were normal. The platelet count, prothrombin time and partial thromboplastin time were normal. Other laboratory tests included the followings: normal sedimentation rate; and negative antinuclear antibody, rheumatoid factor, anti-glomerular basement membran (anti-GBM) antibodies and anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA). Biochemical parameters were found within normal limits. Repeated stool examinations for occult blood were negative.

The chest roentgenogram obtained during the acute hemoptysis episode demonstrated bilateral diffuse patchy infiltrations while it was entirely normal at remission (Figure 1-2).

Pulmonary function test revealed FEV_1 and FVC that were 43 percent and 63 percent of predicted value, respectively. Room air arterial blood gas analysis revealed pH of 7.40, $PaCO_2$ of 32 mm Hg and PaO_2 of 75mm Hg. High-resolution computed tomography (HRCT) scan of thorax revealed bilateral patchy, ground-glass appearance (Figure 3).

Ventilation-perfusion scintigraphy showed bilateral non-segmental hypoperfused areas, especially in the superior and posterobasal segments of the lower lob of the left lung. Parotid scintigraphy was normal. A barium study of the upper and lower gastrointestinal tract was normal.

Fiberoptic bronchoscopy (FOB) was performed during remission period. FOB demonstrated normal tracheobronchial mucosa and anatomy. Bronchoalveolar lavage (BAL) was performed in the right middle lobe. Hemosiderin-laden macrophages were present in bronchial washings (Figure 4). Bronchial washings and cultures were negative for pathogenic bacteria, acid fast bacilli and fungi.

The patient was diagnosed to have IPH and was started on a regimen of 120 mg/day steroid that was slowly tapered over a four-week period. Therapy continued with 1000 mg/day inhaled fluticasone propionate.

Accepted for Publication: 19 September 2000

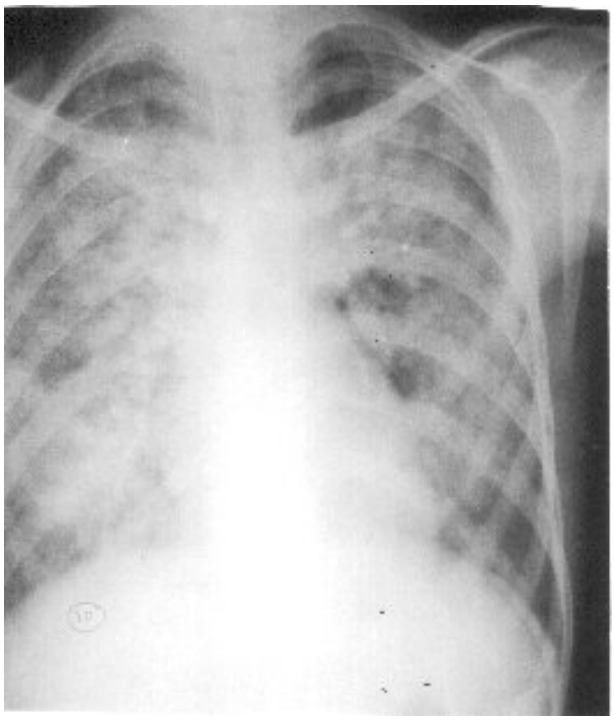

Figure 1. Bilateral diffuse infiltrations in the chest radiograph performed during an acute episode of hemoptysis.

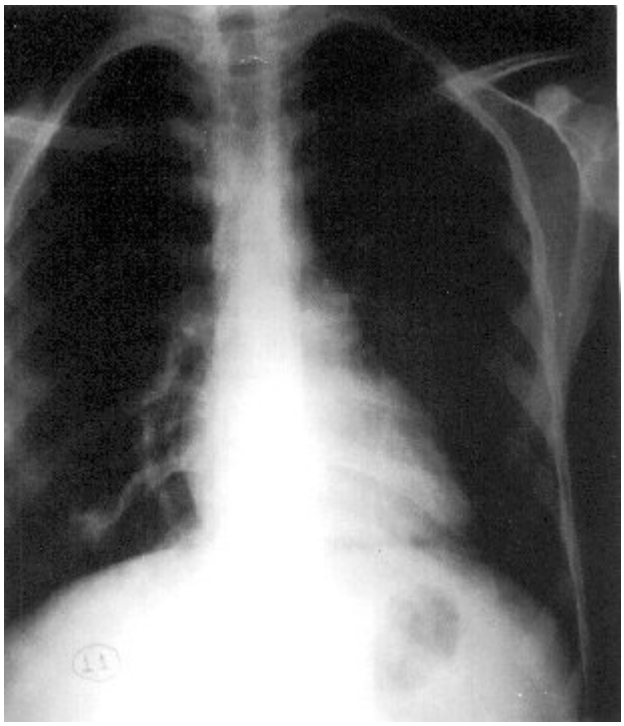

Figure 2. Chest X-ray normal in remission period.

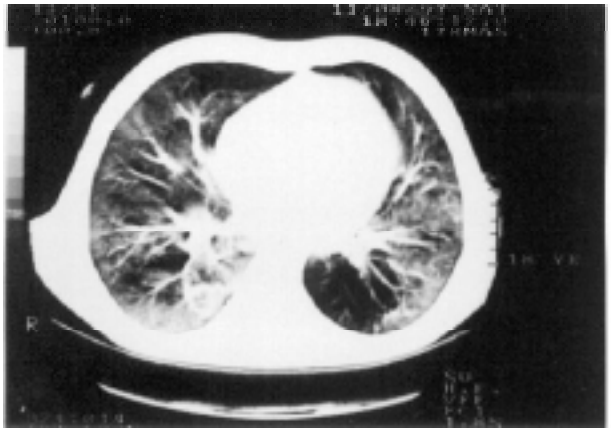

Figure 3. High resolution computed tomography scan shows patchy ground-glass appearence in both lungs.

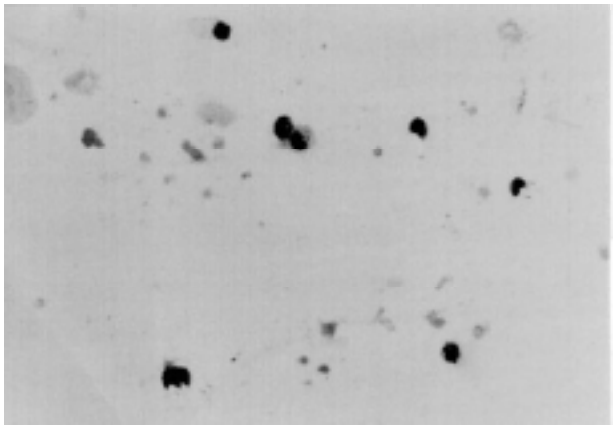

Figure 4. Blue stained hemosiderin pigments present in macrophages (x 200 Pearls Iron Stain)

Discussion

IPH is diagnosed by the clinical triad of hemoptysis, pulmonary infiltrates, and anemia in the absence of renal disease and other disorders that might be considered in the differential diagnosis (7). Diagnosis of IPH can be made only when other specific causes of diffuse alveolar haemorrhage have been excluded (12,13). Efforts to rule out other causes of diffuse alveolar haemorrhage such as mitral valve disease, systemic vasculitis, or the connective tissue diseases are essential (13). In our case, mitral valve disease was ruled out by echocardiography. Other possible reasons that may cause diffuse alveolar haemorrhage were eliminated by measurement of the serum antibody levels. However, in some adult cases, lung tissue specimen is needed to confirm the diagnosis and to exclude those entities associated with pulmonary capillaritis (13). Our patient had no evidence of systemic vasculitis or collagen vascular disease and other conditions associated with diffuse alveolar haemorrhage. He had also no known exposure to exogenous triggers such as D-penicillamine or trimellitic anhydrate.

The pathogenesis of this condition remains unknown, and there are no associated antibodies or other serum markers in the idiopathic cases (6). The histologic examination of the lung reveals bland alveolar haemorrhage with hemosiderin accumulation (13). Siderophages may be found in sputum, BAL fluid, or tracheal or gastric aspirates in patients with recent episodes of alveolar haemorrhage (6). Sputum stained for hemosiderin shows iron-laden macrophages, a finding of considerable diagnostic value in those patients without gross hemoptysis (4). Our case was not subjected to biopsy

but he was diagnosed as IPH by demonstration of hemosiderin-laden macrophages in bronchoalveolar lavage specimen and by elimination of all other possible reasons that may cause diffuse alveolar haemorrhage.

In approximately 20% of pediatric cases, lymphadenopathy and hepatosplenomegaly are found (13). Hepatomegaly 4 cm exceeding the costal margin in the midclavicular line was detected in our case and all other reasons of hepatomegaly were ruled out.

Many children with IPH have a history of milk or gluten sensitivity (6). In this case medical history revealed no milk or gluten sensitivity.

Exacerbations of IPH may occur with symptoms of infection. Leaker et al. speculated that, against the background of predisposing capillaritis, local inflammatory cell traffic triggered by infection results in an amplification of the capillaritis, further endothelial cell damage, and haemorrhage (12).

Most patients are febrile at some time during the course of the illness. The degree of temperature elevation is quite variable. Whether the temperature elevation in some cases is related to the development of bacterial pneumonia is unclear (8). We detected that hemoptysis attacks occurred during exacerbations.

Iron deficiency anemia is characteristic and can be profound (6). Iron deficiency may persist despite normal total body iron stores, because hemosiderin within alveolar macrophages is not available to develop erythrocytes. The clinical course of IPH is variable, but recurrent episodes of alveolar haemorrhage over several years are characteristic (2,6,7,13). The disease is characterised by remissions and relapses (8). In 75% of cases, the mean survival is 3 to 5 years. However, adults have a better prognosis (13). Our patient had hemoptysis twice during the last 1.5 years. The quantity of hemoptysis can be variable and is not a reliable index of the degree of pulmonary haemorrhage because alveolar bleeding does not readily reach the central airways (2).

Chest radiographs have reportedly varied from patchy/ diffuse alveolar infiltrates during acute haemorrhage to persistent interstitial infiltrates after prolonged courses (4,6,11). Following cessation of bleeding, chest radiographs may be normalised within 1-2 weeks (6). Progression of the disease is accompanied by miliary stippling of the lung and perihilar fibrosis (4). CT reveals areas of ground glass opacification, representing foci of alveolar hemorrhage (6). Our case was hospitalised during an episode of hemoptysis and his chest radiograph revealed diffuse infiltrations. After 14 days' steroid therapy, however, chest radiograph showed no pathological appearance.

Optimal therapy for IPH is not clear. Controlled studies evaluating therapeutic regimens have not been done (6). Systemic corticosteroids and immunosupressive agents are commonly used in the treatment of the disease (1). Corticosteroids are considered the mainstay of therapy, but the long-term effectiveness of these drugs in preventing recurrence or progression of this disease is unknown (2-4,6). Despite continued corticosteroid therapy, complete clinical remission can not be achieved and malaise, mild anemia, fatigue, and polyartralgias may persist (7). Recurrent pulmonary haemorrhage may cause iron overload within the lung and predispose generation of tissue-damaging reactive oxygen species, such as hydroxyl radical. Present evidence, though suggestive, does not rigorously prove that reactive oxygen species are involved in IPH. However, the use of an iron chelating agent like deferoxamine may be an area for clinical investigation in this rare disease (2). No form of treatment seemed to influence survival (4). Long term remission was achieved by inhaled corticosteroid therapy (1,4,14). We applied inhaled fluticasone propionate therapy after prednisolone treatment. The patient has been in remission for four months and no hemoptysis has been detected during this time.

References

1. Öztürk A, Sezer M, Evrenkaya R, Ba ak M, Üskent N: diopatik pulmoner hemosiderozis: Vaka takdimi.Türk Hematoloji-Onkoloji Dergisi 7: 111-113, 1997.
2. Louic S, Russell LA, Richeson RB, Cross CE: Circulating immune complexes with pulmonary hemorrhage during pregnancy in idiopathic pulmonary hemosiderosis. Chest 104: 1907-1909, 1993.
3. Turino GM: Respiratory diseases. In:Cecil Textbook of Medicine. Respiratory Diseases. (Eds. Plum F, Bennett JC) W.B. Saunders Company. Philadelphia, 20th ed. 1996, pp: 368-463.
4. Fairbanks VF, Beutler E: Hereditary atransferrinemia and idiopathic pulmonary hemosiderosis. In:Williams hematology. (Eds. Beutler E, Lichtman MA, Coller BS, Kipps TJ) McGraw-Hill Health Professions Division. New York. Fifth ed. 1995, pp: 524-528.
5. Breckenridge RL, Ross JS: Idiopathic pulmonary hemosiderosis. A report of familial occurrence. Chest 75: 638, 1979.
6. Lynch III JP, Leatherman JW: Alveolar hemorrhage syndromes. In: Fishman's pulmonary diseases and disorders. (Eds. Fishman AP, Elias JA, Fishman JA, Grippi MA, Kaiser LR, Senior RM) McGraw-Hill Health Professions Division. New York. Third ed. 1998, pp: 1193-1210.
7. O'donohue WJ: Idiopathic pulmonary hemosiderosis with manifestations of multiple connective tissue and immune disorders. Treatment with Cyclophosphamide. Am Rev Respir Dis 109: 473-479, 1974.
8. Ognibene AJ, Johnson DE: Idiopathic pulmonary hemosiderosis in adults. Report of case and review of literature. Arch Int Med. 111: 503-510, 1963.
9. Yeager H, Powell D, Weinberg RM, Bauer H, Bellanti JA, Katz S. Idiopathic pulmonary hemosiderosis. Ultrastructural studies and response to azathioprine. Arch Intern Med. 136: 1145-1149, 1976.
10. Pacheco A, Casanova C, Fogue L, Sueiro A: Long-term clinical follow-up of adult idiopathic pulmonary hemosiderosis and celiac disease. Chest 99: 15 25-26, 1991.

11. Buschman DL, Ballard R: Progressive massive fibrosis associated with idiopathic pulmonary hemosiderosis. Chest 104: 293-295, 1993.

12. Leaker B, Cambridge G, du Bois RM, Neild GH: Idiopathic pulmonary hemosiderosis: a form of microscopic polyarteritis? Thorax 47: 988-990, 1992.

13. Schwarz MI, Cherniack RM, King TE: Diffuse alveolar hemorrhage and other rare infiltrative disorders. In:Textbook of respiratory medicine. (Eds. Murray JF, Nadel JA) Vol 2. W. B. Saunders Comp. Philadelphia, pp: 1889-1912, 1994.

14. Tutor JD, Eid NS: Treatment of idiopathic pulmonary hemosiderosis with inhaled flunisolide. South-Med-J 88: 984-986, 1995.

Correspondence:
Yrd. Doç. Dr. Abdurrahman enyi it
Dicle Üniversitesi T p Fakültesi
Gö üs Hastal klar Anabilim Dal
Diyarbak r, TURKEY