

Case Report

Recurrence of Idiopathic Pulmonary Hemosiderosis Associated with Rising Plasma IgE Levels and Antibody Titers to Specific Inhalants during a 10-Year Follow-Up

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ABSTRACT

We report 10-year follow-up of a boy diagnosed with idiopathic pulmonary hemosiderosis (IPH). In early childhood, the primary etiology appeared viral, and frequent exacerbations occurred with respiratory infection. Progressive elevation of total IgE and graminaceous grass pollen-specific antibodies gradually become more evident. Furthermore, the flowering period of these plants had coincided with exacerbations in the previous couple of years. The most recent admission to our hospital followed relapse of IPH after an excursion to a nature park during the flowering period. Since the last hospitalization, relapse has not occurred for over a year during treatment with inhaled beclomethasone and leukotriene antagonist, with intravenous liposteroid initially administered on alternate days, tapering to every 6 days. Although these findings were observed from a single case, they suggest that exposure to plant allergens can trigger exacerbation of IPH. Pediatricians should be aware that relapse of IPH may be caused by inhalants and that the underlying mechanism of relapse may vary during the disease course. (*Pediatr Asthma Allergy Immunol* 2005; 18[3]:161–166.)

INTRODUCTION

IDIOPATHIC PULMONARY HEMOSIDEROSIS (IPH) is a rare, sporadic, and fatal disease of unknown etiology characterized by episodes of hemoptysis that result from bleeding into the lung, and by pulmonary infiltration and secondary iron-deficiency anemia. Although IPH appears to be a phenomenon with numerous possible pathophysiologies, immunological disorder^{1–6} and genetic factors⁷ may have some role in the pathogenesis. However, the etiology of the repeated intraalveolar hemorrhage is poorly understood. We report a pediatric case of IPH in which relapse appears to have been associated with allergy to inhalants.

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CASE REPORT

A 10-year-old boy was admitted to our hospital after developing dyspnea. He had a 10-year history of IPH. Initially, he was referred to our hospital for evaluation of anemia at the age of 6 months. Laboratory findings at that time were as follows: decreased red blood cell count of $1.64 \times 10^6/\mu\text{L}$; hemoglobin 3.1 g/dL; serum iron 9 $\mu\text{g/dL}$; increased serum LDH (1,333 IU/L); specific IgE antibody to cow's milk positive. Severe iron deficiency anemia, respiratory distress with increased density of the lung fields on chest computed tomography (CT) (Fig. 1), and hemosiderin-laden macrophages in gastric aspirate (Fig. 2) confirmed the diagnosis of IPH. During this first hospitalization, the patient was successfully treated with methyl prednisolone pulse therapy in the acute phase and with liposteroid (dexamethasone palmitate, Limethasone[®], Mitsubishi Pharma, Osaka, Japan) as maintenance therapy in the chronic phase.⁸

The patient had been hospitalized 15 times with recurrent IPH by the time of the most recent admission. Liposteroid was administered throughout this period to maintain remission, while oral prednisolone or methyl prednisolone pulse therapy was used during relapse. Frequent exacerbations of IPH occurred with symptoms of respiratory infection in early childhood. During the child's development, symptom-free intervals gradually became more prolonged, although complete cure was never evident.

Allergies to foods such as milk and egg albumen resolved early in the course of the disease; however, allergy to inhalants such as timothy grass (*Phleum pratense*, ooawagaeri) and sweet vernal grass (*Anthoxanthum odoratum*, harugaya) emerged with concomitant elevation of total IgE levels (Table 1). Multiple antigen simultaneous test (MAST) was strongly positive for these two grasses as early as 3 years of age. During the child's development, total IgE titer also rose: to 395.6 (IU/ mL) at age 6, 1,042 at age 9, and 1,933 at age 10. In addition, a recent MAST was strongly positive for ragweed (*Ambrosia artemisiifolia*) and Japanese cedar (*Cryptomeria japonica*) and weakly positive for mugwort (*Artemisia vulgaris*). In recent years, exacerbations of IPH appeared to occur during visits to the countryside in the flowering season of these plants, although no symptoms consistent with bronchial asthma or allergic rhinitis occurred. No eosinophilia was observed on repeated peripheral blood examinations during the follow-up period, probably due to long-term steroid treatment. Multiple perinuclear antineutrophil cytoplasmic antibody (P-ANCA) tests were negative. Pulmonary function tests were first performed at the age of 7 years, revealing mild restrictive ventilatory impairment, in accordance with chronic IPH. Pulmonary function has been examined subsequently once or twice every year, and the extent of restrictive ventilatory impairment has remained unchanged.

Two weeks prior to the most recent recurrence, the patient developed a mild relapse of IPH for the first time in almost 2 years; however, this resolved during 1 week of hospitalization, and he was able to reattend school.



FIG. 1 Chest computed tomography (CT) scan on the first admission shows increased lung field density, especially in the dorsal zone (September 1993).

IDIOPATHIC PULMONARY HEMOSIDEROSIS WITH RISING IgE

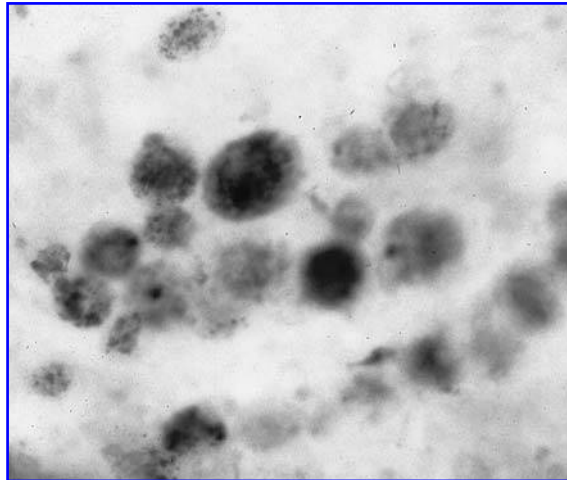


FIG. 2 Hemosiderin-laden macrophages (siderophages) from gastric juice. A Prussian blue iron stain demonstrates dark hemosiderin granules in macrophages. (Original magnification, $\times 600$.)

In June, during the flowering period of grasses such as timothy grass and sweet vernal grass, 2 days prior to the most recent admission, the patient joined a school excursion to a nature park. After 2 h of walking on a mountain trail, he suddenly developed fever and dyspnea. As the dyspnea subjectively improved on the way home, he consulted his family doctor after a night's rest and was prescribed antibiotics. However, progressive dyspnea recurred that evening, and the patient was hospitalized as an emergency admission.

On physical examination, the patient appeared cyanotic and short of breath. Temperature was 37.6°C , pulse 160/min, respiratory rate 42/min, and blood pressure 112/68 mm Hg. Examination of the chest revealed bilateral coarse rales without wheezing. Auscultation of the heart and abdominal examination were unremarkable.

Initial laboratory studies revealed the following: Hb, 14.2 g/dL; WBC, $23.7 \times 10^3/\mu\text{L}$ with 84% polymorphs, 7% bands, 9% lymphocytes and no monocytes or eosinophils; and platelet count, $370 \times 10^3/\mu\text{L}$.

TABLE 1. CHANGES IN IgE TITER AND RAST/MAST SCORE FOR SPECIFIC ANTIGENS

Date	1993.9	1993.10	1993.11	1996.8	1997.3	1999.3	2002.3	2003.6
Total IgE (IU/mL)	3.8					395.6	1042	1933
Method	RAST	RAST	RAST	MAST	RAST	MAST	MAST	MAST
Egg albumen		2	1	0	0	0	0	1/0
Cow's milk	1	1	0	0	0	0	0	0
Timothy grass (<i>Phleum pratense</i>)				3		3	3	3
Sweet vernal grass (<i>Anthoxanthum odoratum</i>)				3	3	3	3	3
Ragweed (<i>Ambrosia artemisiifolia</i>)				0		1/0	2	3
Mugwort (<i>Artemisia vulgaris</i>)				0		0	1	1
Japanese cedar (<i>Cryptomeria japonica</i>)				0	0	3	3	3
House dust		0	0	0	0	0	1/0	1
Tick (<i>Dermatophagoides</i>)		0	0	0	0	0	1/0	1/0
Cat dander				0		0	1/0	2
Dog dander				0		1/0	1	3

RAST, radioallergosorbent test; MAST, multiple antigen simultaneous test; RAST score positive; ≥ 2 ; MAST score positive, ≥ 1 .

A general biochemical screen revealed marked elevation of CRP (14.9 mg/dL) and mildly raised LDH (358 IU/L). Cultures of blood and pharyngeal swabs were both negative. Anti-mycoplasma titer was also negative. Arterial blood gas analysis revealed a pH of 7.392, $p\text{CO}_2$ of 31.1 mm Hg, and $p\text{O}_2$ of 58.4 mm Hg on room air. On 100% oxygen by face mask, SaO_2 measured by pulse oximetry increased from ~70% to 90%. Chest x-ray demonstrated bilateral diffuse reticulo-nodular interstitial changes, preserved lung volumes, and no focal alveolar infiltration (Fig. 3), suggesting massive alveolar hemorrhage. He was diagnosed as having recurrence of IPH with concomitant severe bacterial infection and was promptly treated with pulsed methyl prednisolone for 3 days and empirical intravenous ceftazidime (CAZ) and immunoglobulins (single infusion). On day 3, LDH increased further to 745 IU/L, and Hb fell to 9.7 g/dL. Dyspnea and pyrexia resolved, and CRP was negative on day 5. Inhaled beclomethasone was started on day 12. Following the methyl prednisolone pulse therapy, oral prednisolone was administered at 30 mg/day for a week, before tapering to 10 mg/day, and this was discontinued on day 20, when intravenous liposteroid (dexamethasone 2.5 mg) was begun as maintenance therapy on alternate days. After discharge, the administration interval of liposteroid was gradually extended to every 6 days. He has continued beclomethasone inhalation. Pranlukast (Onon®, Ono Pharmaceutical, Osaka, Japan), a selective, competitive cysteinyl leukotriene antagonist, was used during the flowering period of the above-mentioned grasses (generally May–August). The patient has had no recurrence of IPH for over 1 year.

DISCUSSION

Ten-year follow up of the present case suggested a close association between immune response to inhaled allergens and IPH recurrence. Characterized by the triad of pulmonary infiltrates, iron deficiency anemia, and hemoptysis, IPH is diagnosed only when all known causes of pulmonary hemorrhage have been excluded. Pulmonary hemorrhage in IPH can occur in association with immunological changes.

Pulmonary hemorrhage with immune complex disease has been reported as a manifestation of connective tissue disorders such as systemic lupus erythematosus, Henoch-Schönlein purpura, mixed connective tissue disease, and Wegener granulomatosis. Pulmonary hemorrhage related to hypersensitivity may occur, such as that associated with delayed hypersensitivity to proteins from cow's milk (Heiner syndrome).¹ Pulmonary hemorrhage is also a possible complication associated with a delayed-type hypersensitivity to gluten proteins and buckwheat protein.^{2,3} In addition, pulmonary hemorrhage has been associated with microscopic polyarteritis and segmental, necrotizing crescent glomerulonephritis,^{4,5} and with positive antineutrophil cytoplasmic antibodies directed against myeloperoxidase.^{4,6} These previous reports strongly suggest that pul-



FIG. 3 Chest radiograph obtained on admission shows bilateral, diffuse reticulonodular shadows (June 2004).

monary alveolar hemorrhage results from alveolar or alveolocapillary membrane destruction due to alveolar membrane-antibody reaction or autoimmune microvasculitis. Immunological changes are accordingly implicated as a cause of pulmonary hemorrhage, and in some forms of IPH this mechanism appears highly likely.

In contrast, the mechanism by which recurrence or exacerbation of IPH occurs is poorly understood. The causes of recurrent pulmonary hemorrhage in children, whose lungs are still growing and differentiating, are likely to be multifactorial and synergistic, and the mechanisms must accordingly be complex and various. During the growth process, the mechanism by which exacerbations of IPH occur may vary from the underlying mechanism of onset.

A considerable number of cases of pulmonary hemosiderosis appear to be correlated with food allergy, but few have been reported to be related to inhalants. Le Clainche et al. have described patients with high levels of IgE and asthma that developed after the diagnosis of IPH, and noted that no similar cases were reported in other studies.⁹ It is unclear as yet whether the relationship between high IgE titer and IPH was incidental or causal. In the present case, we believe that recent exacerbations were not associated with a known mechanism but with an allergic reaction, whereas relapses appeared to occur with every respiratory infection before the patient reached school age. Although there was no evidence of common allergic diseases such as pediatric asthma and atopic dermatitis over the 10-year period, total IgE titer rose gradually, and graminaceous grass pollen-specific antibodies became more evident. Furthermore, the flowering period of these plants, to which specific antibody titers had been rising, had coincided with the patient's exacerbations in the preceding couple of years. This strongly suggests that exposure to gramineous grass allergen can trigger an exacerbation of IPH. Moreover, while we note that these findings should be interpreted with caution as they represent those of a single case with a relatively short period of observation, absence of relapse during treatment with beclomethasone inhalation and leukotriene antagonist for over a year support this hypothesis.

It was difficult to determine the cause of elevated CRP and WBC counts, as negative blood and pharyngeal swab culture suggested that obvious infection was not evident. High CRP levels often herald the onset or exacerbation of autoimmune or connective tissue disease, and indeed the association of IPH with connective tissue disease has been reported.¹⁰ Although no connective tissue disease has occurred in the present patient, it is necessary to perform careful follow-up to detect the development of autoantibody, which might herald autoimmune disease, as well as to monitor any exacerbation of allergic reaction.

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