A Case of Idiopathic Pulmonary Hemosiderosis in a 30-Year-Old Man

Vitalii Poberezhets, MD and Oksana Poberezhets, MD, PhD†*

Abstract: Idiopathic pulmonary hemosiderosis is a rare interstitial lung disease that occurs mostly in childhood. Usually, it presents with diffuse alveolar hemorrhage with no identified etiology. This report describes a young male patient who presented a clinical pattern of fatigue, dyspnea, and hemoptysis with iron-deficiency anemia. The iron-deficiency anemia in this patient was resistant to oral elemental iron therapy. This patient had typical findings on chest computed tomography (diffuse ground-glass opacities of the lungs) and bronchoalveolar lavage (detected siderophages). The patient obtained corticosteroid therapy after confirmation of idiopathic pulmonary hemosiderosis diagnosis, which led to improvement of symptoms in one week. This case report shows that early diagnosis and quick initiation of corticosteroid therapy is an effective approach, which reveals the symptoms and prevents complications.

Key Words: idiopathic pulmonary hemosiderosis (IPH), case report, young man

(*Clin Pulm Med* 2020;27:64–66)

Idiopathic pulmonary hemosiderosis (IPH) is a rare interstitial lung disease that presents with diffuse alveolar hemorrhage. The etiology of IPH is not identified. Usually, IPH occurs in childhood with several cases of intra-alveolar bleeding.[1] If these episodes of alveolar bleeding repeat, it leads to the increased deposition of hemosiderin in the alveolar macrophages and to the progression of iron-deficiency anemia.[2] There are some other types of primary pulmonary hemosiderosis apart from IPH. They are Heiner syndrome—which is associated with hypersensitivity to proteins of cow's milk—and Goodpasture syndrome—which is associated with antibody to the lung's and kidney's basement membrane.[3,4] According to Chin et al,[5] 12.8% of all patients have milk protein allergy as comorbidity, and 4.7% have celiac disease. According to Alimi et al,[6] biologically confirmed cow's milk allergy appears in 8% of such patients.

Clinically IPH usually presents with iron-deficiency anemia that does not respond to oral elemental iron therapy and with signs of respiratory failure. Patients complain of cough, dyspnea, and hemoptysis as well.[7]

CASE REPORT

A 30-year-old male patient was admitted to the Regional Centre for Diagnostics and Treatment of Lung Diseases with the symptoms of unknown anemia and infiltrations in both lungs. At admission, the patient complained of dyspnea, cough, and fatigue. Objectively, his physical examination was as follows: the skin was slightly pale, he had tachycardia (heart rate was 95 beats/min), normal blood oxygen saturation level (98%), and normal blood pressure (125/85 mm Hg). The respiratory rate was 19 breaths per minute, and body temperature was 36.7°C. Lymphadenopathy was absent. Auscultation of the lungs showed bilateral crepitation.

During the last 4 months, the patient had been treated by his general practitioner (GP) because of the iron-deficiency anemia using oral elemental iron drug therapy, which had no positive result. One week ago, the patient noticed the appearance of dyspnea and dry cough. The GP recommended performing a chest x-ray, which revealed infiltrates of both lungs. The GP examined the patient and excluded community-acquired pneumonia, as there were no other clinical signs, but suspected interstitial lung injury. Thereby, he redirected the patient to the Regional Centre for Diagnostics and Treatment of Lung Diseases for further determination of the diagnosis and treatment.

The patient's laboratory results showed mild anemia (hemoglobin was 11.2 g/dL, erythrocytes were 3.79×10^{9}/L) with signs of microcytosis and hypochromia, normal platelet count, and other parameters of the complete blood count. The results revealed decreased levels of mean cell hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin. The erythrocyte sedimentation rate was 33 mm/h, and serum C-reactive protein and blood glucose levels were normal. We found an accelerated number of erythrocytes, leukocytes, and changed macrophage cells in the sputum analysis. The coagulation tests, and liver and renal function tests were normal. HIV antibody test was negative. Serologic tests (antinuclear antibodies, rheumatoid factor, anti-glomerular basement membrane, anti-smooth muscle antibodies, IgE for cow's milk, anti-neutrophilic cytoplasmic antibodies) were negative, thereby excluding autoimmune diseases. However, it should be noted that Chin et al[5] presented that more than a third of the patients with diffuse alveolar hemorrhage and positive lung biopsies for capillaritis could have negative autoimmune serologies.

Instrumental investigations of the patient: electrocardiogram was normal except for the presence of tachycardia (92 beats/min), and ultrasound investigation of the internal organs of the abdomen was normal. Spirometry examination showed a mild restrictive pattern [forced expiratory volume in the first second (FEV_1) was 71%, forced vital capacity (FVC) was 73%, and FEV_1/FVC ratio was 83%]. Lung volume determination of diffusing capacity measurements was not assessed.

It was decided to perform computed tomography (CT) of the chest. This examination revealed ground-glass opacities of both lungs with the focus on the right one (Figs. 1, 2).

Bronchoscopy was performed to obtain bronchoalveolar lavage (BAL) fluid. BAL fluid investigation discovered many erythrocytes, hemosiderin-laden macrophages (alveolar macrophages filled with hemosiderin), and several neutrophils and eosinophils. Sequential lavage specimens were not collected.

Diagnosis of IPH was confirmed, because we found a combination of the treatment-resistant anemia, specific CT features of the lungs, and discovered siderophages in BAL fluid.

First-line treatment for this patient included corticosteroids in the form of prednisolone (1 mg/kg/d) orally during 1 month. In 1 week, the patient felt a gradual improvement of his symptoms, and, in 10 days, he was discharged from the hospital.

DISCUSSION

In this case, we described an example of IPH in an adult male patient. It is an unusual case taking into account low

From the Departments of *Propedeutics of Internal Medicine; and †Internal Medicine №1, National Pirogov Memorial Medical University, Vinnytsya, Ukraine.

Disclosure: The authors declare that they have no conflicts of interest.

Address correspondence to: Vitalii Poberezhets, MD, Department of Propedeutic of Internal Medicine, National Pirogov Memorial Medical University, Pirogov Street, 56, Vinnytsia 21018, Ukraine. E-mail: poberezhets_vitalii@vnmu.edu.ua.

ISSN: 1068-0640/20/2703-0064
DOI: 10.1097/CPM.0000000000000357

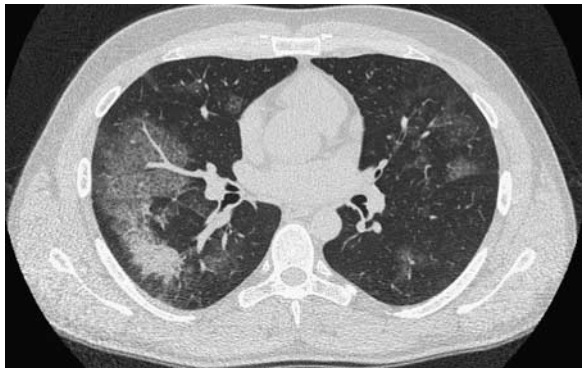

FIGURE 1. Computed tomography of the chest shows diffuse ground-glass opacities, predominant in the right lung.

prevalence of IPH (0.24 to 1.23 cases per million) and the average age of patients usually being under 10 years.[3,6] Moreover, it is quite problematic to assess the prognosis for adult patients with IPH because most of the large patients' series included children and adolescents. Miwa et al[8] presented a 0% mortality rate and mean survival duration of 45.2 ± 6.2 months among 9 adult patients with IPH. Le Clainche et al[9] highlighted a mean survival period of 2.5 years after diagnosis in the group of 15 children. Liu et al[10] found residual morbidity of nearly half of children with IPH. This diagnosis usually is determined by exclusion of any other causes for recurrent episodes of alveolar hemorrhage, such as systemic vasculitis, coagulopathy (anticoagulants), toxin injury (acid, crack cocaine), systemic disorders of the connective tissue, drug-associated (amiodarone, nitrofurantoin, cytotoxic drug therapy) causes, bone marrow transplantation, malignancy, and embolism. To cope with this task, it is crucial to examine carefully the patient's medical and life history, perform precision examination, and carry out several specific laboratory investigations and instrumental methods.[11]

IPH is characterized by the typical combination of respiratory failure with hemoptysis and is resistant to treatment of iron-deficiency anemia. These symptoms are combined with diffuse lung infiltration. Continuous intra-alveolar bleeding leads to the development of iron-deficiency anemia. Such anemia has a microcytic hypochromic pattern, and it is resistant to oral iron therapy.[2] Even if there are no respiratory symptoms present, but the patient presents with anemia refractory to iron therapy, IPH must be considered as a possible diagnosis.

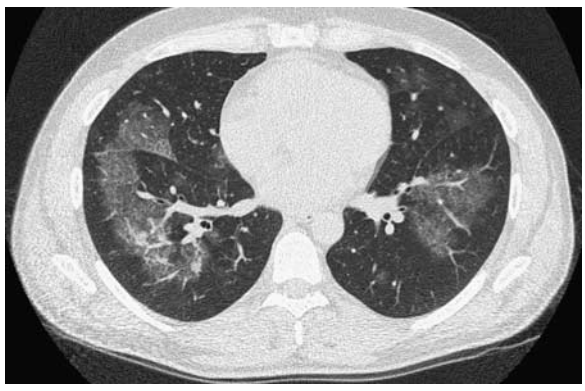

FIGURE 2. Computed tomography of the chest shows diffuse ground-glass opacities of both lungs.

However, in a case, when respiratory symptoms are absent, other diseases that could lead to iron-deficiency anemia (such as gastrointestinal pathology, tumors, congenital heart disease, and granulomatosis) should be excluded.[12]

Hemoptysis is quite a rare symptom among children, who usually swallow sputum.[7] In adult patients, it occurs almost in 100% of all the patients with alveolar hemorrhage, because they can expectorate sputum more effectively than children. Hemoptysis could be present during a few hours or could persist for several days. However, some adult patients do not have hemoptysis.

Our patient also presented another common sign of alveolar bleeding—respiratory failure manifesting in progressive exertional dyspnea and tachypnea. The presentation of these symptoms depends on the intensity of the diffuse alveolar hemorrhage.

X-ray of the chest and high-resolution computed tomography (HR-CT) helped to determine typical lung infiltrates in the form of diffuse ground-glass opacities. In case of several repeated episodes of diffuse alveolar hemorrhage, it induces the development of pulmonary fibrosis that could be detected radiologically in the form of variable fibrosis.[13]

Moreover, diagnostics of IPH could be performed by detecting signs of diffuse alveolar hemorrhage using lung biopsy. Lung biopsy is critical in performing differential diagnosis with interstitial lung diseases and vasculitis.[2] Another option is using bronchoscopy to detect hemosiderin-laden macrophages (siderophages) and to obtain the BAL fluid for further calculating Golde score. Golde score is a specific method used to estimate the quantity of hemosiderin in alveolar macrophages after using Prussian blue stain.[3] However, it should be noted that siderophages may appear in BAL fluid in small amounts in healthy individuals who smoke or in those with pneumonia. Usually, it takes 50 hours after pulmonary hemorrhages for hemosiderin-laden macrophages to become visible in BAL fluid.[13]

In our case, we did not use lung biopsy to confirm the diagnosis because there was a clear clinical pattern, chest CT features, and typical siderophages detected in the BAL fluid.[14] Previously, the only option to perform biopsy was an open lung biopsy or traditional transbronchial lung biopsy, but now a new method could be used for this purpose—transbronchial lung cryobiopsy.[2] Transbronchial lung cryobiopsy is extremely useful for the quick and safe diagnosis of intra-alveolar hemorrhages.[14]

In our case, we used monotherapy with corticosteroids in high dose, and it led to prompt regression of the symptoms in seven days. First-line treatment of IPH usually contains corticosteroids in the form of methylprednisolone in doses of 2 to 4 mg/kg/d or prednisolone 0.5 to 1 mg/kg/d with further dose decrease. Duration of such treatment depends on the dynamics of clinical symptoms, radiologic signs, and anemia evolution.[3]

However, methylprednisolone pulse therapy is another option that could be used especially in cases of IPH among children with massive pulmonary hemorrhage and hypoxemic respiratory failure. This approach includes high-dose methylprednisolone (10 mg/kg/d) for the first 3 days with the following systemic corticosteroid maintenance therapy with a standard dose of corticosteroids.[15]

In case of very severe symptoms, and instrumental and laboratory life-threatening findings, other immunosuppressive therapies could be added (hydroxychloroquine, azathioprine, and cyclophosphamide). According to Chin and colleagues 98.7% of all patients with IPH obtained corticosteroids as initial therapy and 84.0% as chronic therapy, respectively. Other medications included hydroxychloroquine (33.3% and 64.0%),

azathioprine (8.0% and 37.3%), and cyclophosphamide (4.0% and 16.0%).[5]

While obtaining such long-term immunosuppressive maintenance therapy, we should focus our attention on the adverse effects of steroids and other drugs. Fewer side effects were reported by liposteroid therapy compared with other corticosteroids, but, still, patients showed low bone mineral density.[16] Long-term use of cyclophosphamide in low dose is effective in treating childhood IPH, but it leads to the development of thrombocytopenia.[17] Sant'Anna et al[18] showed that azathioprine did not lead to side effects among children with IPH, which shows that it is well tolerated in this age group during 6-month usage. Side-effect profile of hydroxychloroquine in children usually includes gastrointestinal symptoms.[19]

Duration of long-term corticosteroid therapy depends on each clinical situation, and therefore there is no unique approach to determine its duration. Ioachimescu et al[20] highlight that, initial treatment of the acute stage by prednisolone in standard dose until the new lung infiltrates resolve, and then the dose of corticosteroid must be decreased if symptoms do not recur. According to Alimi et al,[6] 30% of the patients need to receive maintenance therapy even after 1 year and 25% after 5 years' of follow-up, while Le Clainche et al[9] report that 93% of patients need to receive corticosteroid therapy for a duration varying from 4 to 24 years. Ioachimescu and colleagues present treatment with prednisolone for 24 years. Duration of other immunosuppressors' usage also varies greatly. For azathioprine, it could last from 6 months[18] to 11 years,[20] long-term treatment using cyclophosphamide in low dose for childhood IPH lasts even for >3 years,[17] and, for hydroxychloroquine usage in children, it could last for many years as well.[19] Some studies also report other probable management options such as methotrexate, immunoglobulin, N-acetylcysteine, and mycophenolate. However, these medications have a great toxicity profile and should be used carefully.[5]

CONCLUSIONS

The present case emphasizes that IPH may occur not only in children but also in adults. Early diagnosis is crucial for patients' survival and should be based on detecting special symptoms of progressive respiratory failure, hemoptysis, and iron-deficiency anemia with the combination of diffuse alveolar hemorrhage signs on chest x-ray and HR-CT. Prompt start of treatment with corticosteroids in high dose is an effective approach, which prevents complications of intra-alveolar hemorrhage and improves survival.

REFERENCES

1. Zhang Y, Luo F, Wang N, et al. Clinical characteristics and prognosis of idiopathic pulmonary hemosiderosis in pediatric patients. *J Int Med Res*. 2019;47:293–302.
2. Bakalli I, Kota L, Sala D, et al. Idiopathic pulmonary hemosiderosis—a diagnostic challenge. *Ital J Pediatr*. 2014;40:35.
3. Taytard J, Nathan N, de Blic J, et al. New insights into pediatric idiopathic pulmonary hemosiderosis: the French RespiRare(®) cohort. *Orphanet J Rare Dis*. 2013;8:161.
4. Ward ND, Cosner DE, Lamb CA, et al. Top differential diagnosis should be microscopic polyangiitis in ANCA-positive patient with diffuse pulmonary hemorrhage and hemosiderosis. *Case Rep Pathol*. 2014;2014:286030.
5. Chin CI, Kohn SL, Keens TG, et al. A physician survey reveals differences in management of idiopathic pulmonary hemosiderosis. *Orphanet J Rare Dis*. 2015;10:98.
6. Alimi A, Taytard J, Abou Taam R, et al. Pulmonary hemosiderosis in children with Down syndrome: a national experience. *Orphanet J Rare Dis*. 2018;13:60.
7. Castellazzi L, Patria MF, Frati G, et al. Idiopathic pulmonary haemosiderosis in paediatric patients: how to make an early diagnosis. *Ital J Pediatr*. 2016;42:86.
8. Miwa S, Imokawa S, Kato M, et al. Prognosis in adult patients with idiopathic pulmonary hemosiderosis. *Intern Med*. 2011;50:1803–1808.
9. Le Clainche L, Le Bourgeois M, Fauroux B, et al. Long-term outcome of idiopathic pulmonary hemosiderosis in children. *Medicine (Baltimore)*. 2000;79:318–326.
10. Liu AC, Segaren N, Cox TS, et al. Is there a role for magnetic resonance imaging in the evaluation of non-traumatic intraparenchymal haemorrhage in children. *Pediatr Radiol*. 2006;36:940–946.
11. Park MS. Diffuse alveolar hemorrhage. *Tuberc Respir Dis (Seoul)*. 2013;74:151–162.
12. Koker SA, Gözmen S, Oymak Y, et al. Idiopathic pulmonary hemosiderosis mimicking iron deficiency anemia: a delayed diagnosis. *Hematol Rep*. 2017;9:55–61.
13. Mukai Y, Agatsuma T, Ideura G. Early diagnosis of idiopathic pulmonary haemosiderosis: increased haemosiderin-laden macrophages in repeat bronchoscopy. *Respirol Case Rep*. 2018;6:e00304.
14. Kania A, Misiaszek M, Vašáková M, et al. Cryobiopsy in the diagnosis of idiopathic pulmonary hemosiderosis: a case report. *J Thorac Dis*. 2019;11:3195–3201.
15. Li YT, Guo YX, Cai LM, et al. Methylprednisolone pulse therapy rescued life-threatening pulmonary hemorrhage due to idiopathic pulmonary hemosiderosis. *Am J Emerg Med*. 2017;35:1786.e3–1786.e7.
16. Doi T, Ohga S, Ishimura M, et al. Long-term liposteroid therapy for idiopathic pulmonary hemosiderosis. *Eur J Pediatr*. 2013;172:1475–1481.
17. Huang SH, Lee PY, Niu CK. Treatment of pediatric idiopathic pulmonary hemosiderosis with low-dose cyclophosphamide. *Ann Pharmacother*. 2003;37:1618–1621.
18. Sant'Anna CC, Horta AA, Tura MT, et al. Idiopathic pulmonary hemosiderosis treated with azathioprine in a child. *J Bras Pneumol*. 2007;33:743–746.
19. Braun S, Ferner M, Kronfeld K, et al. Hydroxychloroquine in children with interstitial (diffuse parenchymal) lung diseases. *Pediatr Pulmonol*. 2015;50:410–419.
20. Ioachimescu OC, Sieber S, Kotch A. Idiopathic pulmonary haemosiderosis revisited. *Eur Respir J*. 2004;24:162–170.