

A Rare Case of Idiopathic Pulmonary Hemosiderosis in an Adult

Naveen Raj^{1*}, Jillian Cepeda² and Seth Gottlieb²

¹Larkin Hospital/ Nova Southeastern University, 3100 Coral Hills Drive #302, Coral Springs, Florida 33065, USA

²Department of Internal Medicine and Pulmonary/Critical Care, Mount Sinai Medical Center, Miami Beach Florida, USA

*Corresponding author: Naveen Raj, Larkin Hospital/ Nova Southeastern University, 3100 Coral Hills Drive #302, Coral Springs, Florida 33065, USA, Tel: 954-895-3062; Fax: 954-433-8112; E-mail: ntr203@gmail.com; nraj81@yahoo.com

Received date: Feb 28, 2014, Accepted date: Jul 11, 2014, Published date: Jul 15, 2014

Copyright: © 2014 Raj N, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Idiopathic Pulmonary Hemosiderosis is a rare condition, primarily affecting the pediatric population. IPH is characterized by the triad of hemoptysis, iron deficiency anemia, and diffuse pulmonary infiltrates, though not all the symptoms may be seen. Due to the myriad of diseases that present as such, IPH is often a diagnosis of exclusion. Treatment with corticosteroids prevents further episodes of hemoptysis, and improves the anemia. We report on a rare case of IPH in an adult who presented with chronic anemia and shortness of breath.

Introduction

Alveolar hemorrhage encompasses a group of disorders that is characterized by destruction of the pulmonary microvasculature and resulting blood extravasation into the alveolar space [1]. Many disease states are implicated in alveolar hemorrhage, of which Idiopathic Pulmonary Hemosiderosis (IPH) is a rare cause. IPH is classically characterized by a triad of hemoptysis, anemia and pulmonary infiltrates on chest X-rays; and usually occurs before the age of 10 years. An estimated incidence of 0.24 to 1.23 cases per million children per year has been reported in selected populations [2,3]. Approximately 20% of IPH cases occur during adulthood [4]. The diagnosis of IPH requires elimination of all other causes. As such, it is often a diagnosis of exclusion and requires lung biopsy or bronchoscopy with bronchoalveolar lavage (BAL) showing hemosiderin-laden macrophages called siderophages. First line treatment is systemic corticosteroid therapy. In cases of corticosteroid resistance or dependence and/or unfavorable outcome, immunosuppressants are utilized. We report a case of an adult woman who presented with a two year history of intermittent shortness of breath, and a chronic anemia, but without significant hemoptysis or underlying lung disease. A thorough workup failed to reveal any alternative diagnosis. A lung biopsy confirmed hemosiderin laden macrophages and IPH was diagnosed. She responded well to corticosteroid treatment.

Case Presentation

A 47 year old obese Caucasian female presented to our hospital complaining of worsening shortness of breath over the previous three months. This was her second hospitalization at our institution for shortness of breath. Her first hospitalization was two years ago. At that time, her chest xray showed diffuse alveolar infiltrates and a bronchoscopy revealed non-specific bloody secretions. A thorough infectious disease and rheumatology workup was negative (Table 1) and she was started on an empiric trial of steroids that improved her condition. She was discharged home pending a more extensive outpatient workup including a lung biopsy, but was lost to follow-up until her recent admission.

Test	Result
Anti-gliadin IGA, Anti-gliadin IGG	not detected
Sm Ab	Negative
Sm-RNP-Ab	Negative
Hep C ab	Non-reactive
HBV surface Ag	Non-reactive
GBM	<1.0
Cryoglobulin	Negative
C3	131.0
C4	22.9
SSA/SSB	<1.0
Beta 2 Glycoprotein IgG/IgM/IgA	<9
Lupus anticoagulant	not detected
Centromere ab	not detected
Tissue Transglutaminase	no ab detected
Anti-ds DNA	Negative
RF	Negative
SCL70 (scleroderma)	Negative
ESR 42	not detected
ANA	Negative
Anti-cardiolipin igG/IgM	Negative
ANCA Screen	Negative
Myeloperoxidase Ab	Negative
Proteinase 3-Ab	no Ab detected

Chlamydia pneumonia ab	Negative
Mycoplasma IgM	Negative
Strep Pneumonia/Legionella urinary antigen	Negative
Influenza A and B antigen	Negative
Cd4/cd8 ratio	2.89
HIV ab (2011)	Negative

Table 1: Labwork from first admission in 2011

Her past medical history included type II diabetes, hypertension, hyperlipidemia and depression. Her surgical history included a cholecystectomy. Medications were hydrochlorothiazide, metformin, subcutaneous insulin, ketorolac, simvastatin, and duloxetine. Family history was noncontributory. She was married with no children, and was unemployed. Social history was significant for half a pack/day cigarette smoking for twenty years. On review of systems, she admitted to fatigue and shortness of breath, but denied hemoptysis, fever, chills or gastro-intestinal and genitourinary symptoms.

On physical exam, she was afebrile with a pulse rate of 109, and otherwise stable vital signs. Her oxygen saturation was 90%, increasing to 94% on two liters of oxygen by nasal cannula. She was in no acute distress and was alert and oriented. Her skin was warm and dry with no rash. Neck exam revealed no jugular venous distention or thyromegaly. Her thorax revealed symmetrical chest excursion and no accessory muscle use. Pulmonary exam revealed diffuse pulmonary crackles, with no wheezing. Cardiac exam revealed a slight tachycardia but no murmurs.

Abdomen was soft and non-tender, with normal bowel sounds. Pulses were present and normal in all extremities and there was no peripheral edema or lymphadenopathy. Neurological and musculoskeletal exam were normal. Pertinent laboratory findings included a microcytic iron deficiency anemia (Hgb 7 g/dl, MCV: 75.1, Hct: 25.1%) and a glucose level of 336. The rest of her labs, including white blood cell count, platelet count, lactic acid, erythrocyte sedimentation rate and basic metabolic profile were within normal range. Gross and microscopic urinary analysis was negative for hematuria, proteinuria or casts. Chest xray showed scattered infiltrates (Figure 1).

A computerized tomography pulmonary angiogram (CTPA) revealed increased bilateral diffuse groundglass opacities and mosaic pattern suggesting an evolving infectious process, alveolar edema or hemorrhage (Figure 2). Her current symptoms were thought to be a continuation of her initial disease presentation two years prior.

Increased bilateral diffuse groundglass opacities and mosaic attenuation. Findings were suggestive of evolving infectious process, alveolar edema or hemorrhage.

As she had a previously negative infectious and rheumatology workup, a lung biopsy was planned. A video-assisted thoracoscopic surgery (VATS) with wedge resection biopsy of the lateral segment of the right middle lobe, basilar segment right lower lobe and posterior segment right upper lobe was performed (Figure 3, Figure 4). On histopathology, hemosiderin laden macrophages within alveolar spaces were found throughout the biopsied specimens. There was absence of vasculitis, capillaritis, and granulomas. Immunofluorescence antibody (IFA) testing did not reveal any

immune complexes. Considering the above data, a diagnosis of IPH was made.

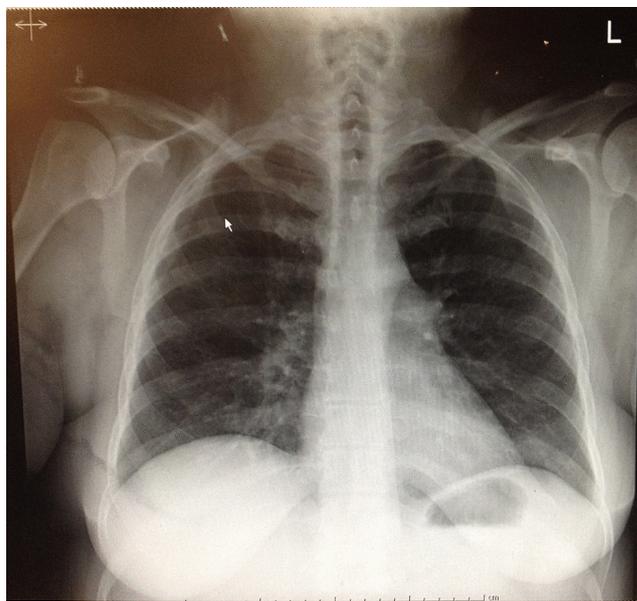


Figure 1: Scattered infiltrates on chest xray at admission

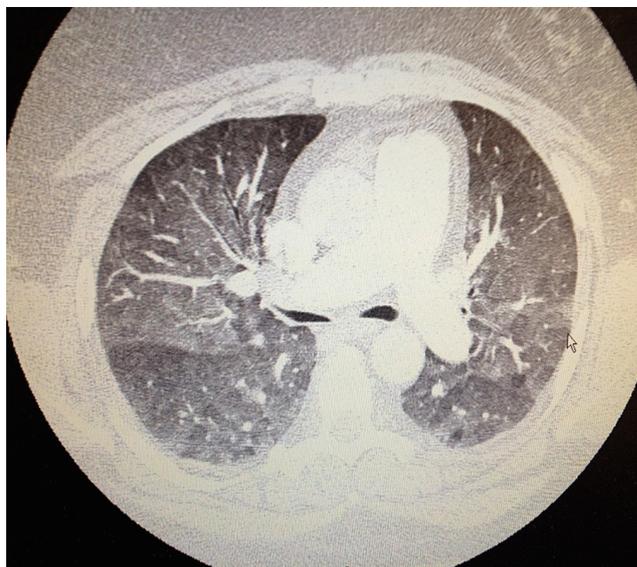


Figure 2: CTA Pulmonary Angiogram, Initial imaging

She was started on oral prednisone 80 mg daily (1 mg/kg of bodyweight) and was also transfused two units of packed red blood cells. On her discharge home eleven days after admission, her shortness of breath had improved, and her hemoglobin level had stabilized at 10 g/dl.

She was discharged home on prednisone 40 mg twice daily for 6 weeks with a taper of 0.5 mg/kg for another 6 weeks thereafter. On 9 month follow-up, she was in good clinical condition and repeat chest

CT scan showed resolution of ground glass opacities (Figure 5). She is currently on prednisone 15 mg daily.

Discussion

Idiopathic pulmonary hemosiderosis is a rare cause of pulmonary hemorrhage. It is categorized as a “bland hemorrhage” due to absence of vasculitis or capillaritis (Table 2). Due to its rarity, there is no discernable clinical presentation pathognomonic for IPH in adults exclusively.

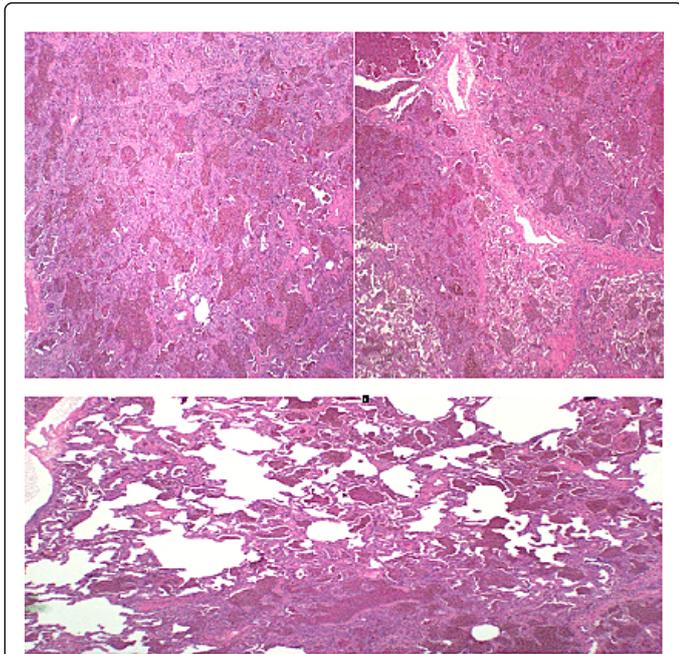


Figure 3: All three photos show alveolar hemorrhage with hemosiderin laden macrophages located within expanded alveolar spaces (low power)

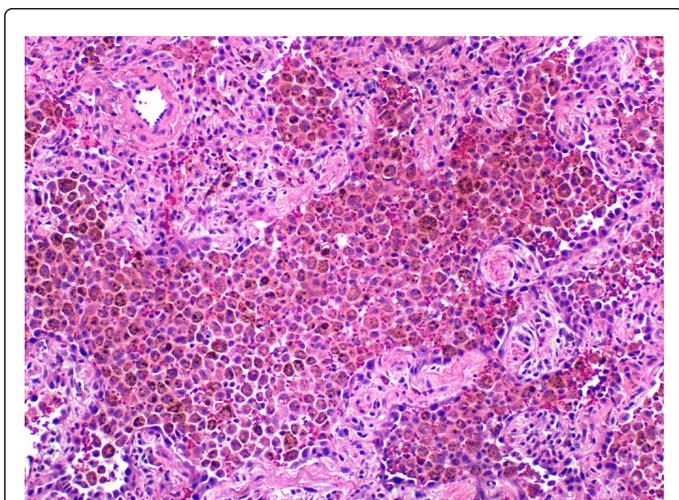


Figure 4: Expanded alveolar spaces containing hemosiderin laden macrophages (high power view)

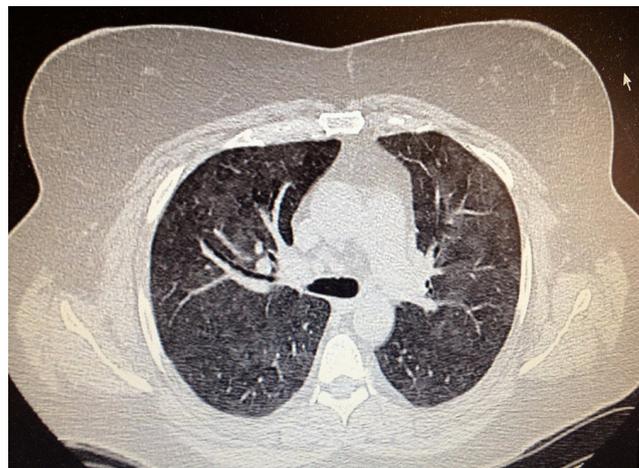


Figure 5: CT Chest without contrast- 9 months after treatment initiation

Interval improvement in bilateral lung aeration with decrease in diffuse groundglass opacities and mosaic attenuation.

IPH commonly presents with the triad of dyspnea, hemoptysis, and iron deficiency anemia in both children and adults. Our patient did not exhibit hemoptysis. While it is unclear how atypical this presentation is, Gencer et al. has previously reported on two adult patients presenting with IPH, without hemoptysis as a symptom [5]. The diagnosis of IPH requires elimination of other causes, and lung biopsy confirmation.

Pulmonary capillaritis	Diffuse alveolar damage
Systemic lupus erythematosus	Systemic lupus erythematosus
Goodpasture syndrome	Radiation therapy
Antiphospholipid syndrome	Crack cocaine inhalation
Wegener granulomatosis	Cytotoxic drugs
Microscopic polyangiitis	Acute respiratory distress syndrome
Mixed cryoglobulinemia	Bland pulmonary hemorrhage
Behçet syndrome	Multiple myeloma
Polymyositis	Subacute bacterial endocarditis
Scleroderma	Systemic lupus erythematosus
Rheumatoid arthritis	Goodpasture syndrome
Henoch-Schönlein purpura	Negative pressure pulmonary edema
Pauci-immune glomerulonephritis	Mitral stenosis
Mixed connective tissue disorder	Coagulation disorders
Idiopathic pulmonary fibrosis	Idiopathic pulmonary hemosiderosis
IgA nephropathy	Drugs
Ulcerative colitis	Unclassified
Myasthenia gravis	Pulmonary capillary hemangiomatosis

Acute lung allograft rejection	Lymphangioleiomyomatosis
Autologous bone marrow transplant	Pulmonary veno-occlusive disease

Table 2: Causes of alveolar hemorrhage

The pathogenesis remains controversial, with various theories suggesting an autoimmune, allergic, genetic or environmental basis [6]. The allergic hypothesis is based on an association between IPH and cow's milk allergy (Heiner syndrome) though this remains controversial [7,8]. The environmental theory was suggested after the occurrence of IPH in a cluster of infants possibly exposed to the black mold *Stachybotris chartarum* in Cleveland, Ohio in the mid 1990's, but was not further confirmed on subsequent investigations [9,10]. An autoimmune etiology seems the most logical as a positive response to immunosuppressive therapies in reducing the severity of pulmonary hemorrhage and fibrosis is seen [1]. Other studies also show that one of four children who survive IPH develop immune disorders as adults [1,11] and three out of four children with IPH have circulating C1q-binding immune complexes [12]. A French pediatric cohort study of 25 children with IPH showed five of the patients also had familial cases of autoimmune diseases: 2 patients with ankylosing polyarthritis, one with celiac disease, one with telangiectasis, one with type 1 diabetes, and one with hereditary spherocytosis. In addition, most of the patients (17 out of 25) had auto-immune antibodies at diagnosis. The most frequent auto-immune antibodies found in the cohort were: SMA (50% of the tested patients); ANA (45%) and ANCA (40%). These antibodies are usually associated with vasculitis and systemic diseases [8]. Rheumatoid arthritis is the most frequent auto-immune systemic disease in the general population (0.5 to 1%) and can be associated with respiratory symptoms, typically with a diffuse parenchymal lung condition [8,13]. We thus suggest screening IPH patients for rheumatoid arthritis, Lupus, and ANCA-associated vasculitis. Our patient had a negative workup for any systemic autoimmune disease.

Another interesting association is seen between IPH and celiac disease. This association was first described in 1971 by Lane and Hamilton studying a few isolated cases. Subsequent studies have documented a number of cases comprising IPH concurrent with celiac disease and the condition is now known as Lane-Hamilton syndrome (LHS). Singhal et al. conducted a comprehensive review of the literature. A total of 35 patients with Lane Hamilton syndrome have been reported in 29 case reports so far. Out of these thirty five patients, thirteen (37.1%) were adults, and 18 (51.4%) had gastrointestinal symptoms [14]. Interestingly, more than half (54.2%) of the 35 patients had an improvement in pulmonary symptoms through a gluten free diet (GFD). Previous studies have suggested LHS is two manifestations of a single disease. It is already known that there is a high prevalence of celiac disease (1.8%-14.6%) in patients with iron deficiency anemia (IDA) of obscure origin [8,15] The prevalence is as high as 20% in IDA resistant to treatment with iron. In addition, IDA can be the only abnormality in up to 40% of patients with celiac disease [16]. Thus, there is strong evidence showing association between celiac disease and IDA of obscure origin especially anemia not responding to iron therapy [8]. In IPH, recurrent alveolar hemorrhage leads to pulmonary interstitial hemosiderin deposition. This can occur even in the absence of overt hemoptysis. The result is IDA despite normal total iron body stores. The proposed pathophysiology in LHS is that hemosiderosis in celiac disease occurs due to deposition of immune complexes involving an autoantigen like

gluten on alveolar basement membrane, or to a direct reaction between the antigen of alveolar basement membrane and an antibody like antireticulin [8]. We therefore propose screening for IPH in celiac disease patients that have a disproportionately severe anemia. Likewise, we also recommend screening IPH patients for celiac disease, even if they do not have gastrointestinal symptoms. This could be achieved through either antibody testing, esophagoduodenoscopy (EGD) with duodenal biopsy or even an empiric trial of a gluten free diet, together with steroid treatment, to assess whether the anemia and dyspnea improve. In our patient, antibody testing for celiac disease was negative, and she did not have any gastrointestinal symptoms. She was encouraged to adopt a gluten free diet and an outpatient EGD was discussed. She discontinued the diet shortly after discharge and the EGD has yet to be performed.

Though there is strong evidence for an autoimmune basis for IPH, interestingly there is no accumulation of immune complexes on lung biopsy. Lung biopsy is diagnostic for IPH, and reveals hemosiderin laden macrophages (siderophages) characteristic of alveolar hemorrhage. This is coupled with the histopathological absence of immune complexes, vascular malformation, malignancy, granuloma, and capillaritis ("bland hemorrhage") [2,17]. IPH is thus diagnosed upon exclusion of other causes of alveolar hemorrhage [1]. During IPH, chest CT can reveal diffuse lung infiltrates, and pulmonary function tests (PFT's) show an increase in diffusing capacity for carbon monoxide (DLCO), indicative of alveolar hemorrhage [1].

Regarding IPH treatment, corticosteroids represent the cornerstone of treatment. Prior case studies report remission of pulmonary bleeding, and an improvement in anemia and dyspnea. A slower progression to pulmonary fibrosis is also noted. Different regimens, ranging from 0.5 mg/kg/day to 2 mg/kg/day during acute symptoms, have been used. A tapering regimen is employed after the acute symptoms have resolved [1]. Other treatment options have been utilized in steroid refractory cases or in an effort to reduce long term corticosteroid side effects, though studies are limited to a few case reports. Azathioprine and Cyclophosphamide has been used in a small number of patients with success either in combination with oral corticosteroids or as second line treatment [18-21]. In a study by Kabra et al., 17 pediatric patients with IPH were successfully treated in the acute phase with a combination of prednisolone and Hydroxychloroquine [21]. In another study, 6-mercaptopurine maintenance therapy was used with some success to achieve steroid-free long term survival in children with IPH [22]. In two cases of refractory IPH, lung transplantation was performed but bleeding within the allograft has discouraged future attempts [1,23,24]. A challenge in IPH is the highly variable clinical course. Most of the patients continue to have episodes of pulmonary hemorrhage despite therapy. Death usually occurs from acute pulmonary hemorrhage or chronic respiratory failure. An estimated 14-29% of IPH patients die from respiratory failure and one study showed a five-year survival of 86% in patients who received long-term immunosuppressive therapy [25]. Adults seem to have a more prolonged survival compared to children. Patients that survive long term may develop pulmonary fibrosis due to recurrent intrapulmonary bleeding.

Conclusion

In our case, the patient did not exhibit the typical triad of IHP. She did not have hemoptysis. The clinical suspicion of IPH was raised when a thorough infectious, oncologic and rheumatology workup failed to reveal the cause of her chronic dyspnea, anemia, and findings

on the chest HRCT. Lung biopsy confirmed the diagnosis of IPH, revealing a bland alveolar hemorrhage with siderophages. There was no evidence of concomitant celiac disease. Therapeutic approach with corticosteroids was initiated, with successful improvement in her symptoms. IPH should be considered in any patient presenting with unexplained hemoptysis, anemia, and shortness of breath. Once tissue diagnosis is confirmed, treatment with corticosteroids and/or immunosuppressants should be initiated, and a screening for celiac disease, vasculitis, and other autoimmune conditions be performed.

References

1. Tzouveleakis A, Ntolios P, Oikonomou A, Koutsopoulos A, Sivridis E, et al. (2012) Idiopathic pulmonary hemosiderosis in adults: a case report and review of the literature. *Case Rep Med* 2012: 267857.
2. Kjellman B, Elinder G, Garwicz S, Svan H (1984) Idiopathic pulmonary haemosiderosis in Swedish children. *Acta Paediatr Scand* 73: 584-588.
3. Ohga S, Takahashi K, Miyazaki S, Kato H, Ueda K (1995) Idiopathic pulmonary haemosiderosis in Japan: 39 possible cases from a survey questionnaire. *Eur J Pediatr* 154: 994-995.
4. Kahraman H, Köksal N, Ozkan F (2012) Eight Years Follow-up of a Case with Idiopathic Pulmonary Hemosiderosis After Corticosteroid Therapy. *N Am J Med Sci* 4: 49-51.
5. Gencer M, Ceylan E, Bitiren M, Koc A (2007) Two sisters with idiopathic pulmonary hemosiderosis. *Can Respir J* 14: 490-493.
6. Agata H, Kondo N, Fukutomi O, Takemura M, Tashita H, et al. (1997) Pulmonary hemosiderosis with hypersensitivity to buckwheat. *Ann Allergy Asthma Immunol* 78: 233-237.
7. Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL (2005) Milk-induced pulmonary disease in infants (Heiner syndrome). *Pediatr Allergy Immunol* 16: 545-552.
8. Taytard J, Nathan N, de Blic J, Fayon M, Epaud R, et al. (2013) New insights into pediatric idiopathic pulmonary hemosiderosis: the French RespiRare(*) cohort French RespiRare® group. *Orphanet J Rare Dis* 8: 161. doi: 10.1186/1750-1172-8-161.
9. Centers for Disease Control and Prevention (CDC) (2000) Update: Pulmonary hemorrhage/hemosiderosis among infants--Cleveland, Ohio, 1993-1996. *MMWR Morb Mortal Wkly Rep* 49: 180-184.
10. Dearborn DG, Smith PG, Dahms BB, Allan TM, Sorenson WG, et al. (2002) Clinical profile of 30 infants with acute pulmonary hemorrhage in Cleveland. *Pediatrics* 110: 627-637.
11. Le Clainche L, Le Bourgeois M, Fauroux B, Forenza N, Dommergues JP, et al. (2000) Long-term outcome of idiopathic pulmonary hemosiderosis in children. *Medicine (Baltimore)* 79: 318-326.
12. Blanco A, Solís P, Gómez S, Linares P, Sánchez Villares (1984) C1q-binding immune complexes and other immunological studies in children with pulmonary hemosiderosis. *Allergol Immunopathol (Madr)* 12: 37-44.
13. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H (2010) Interstitial lung diseases in children. *Orphanet J Rare Dis* 5: 22.
14. Singhal KK, Janmeja AK, Sodhi R, Punia RS (2013) Hemoptysis in patients of celiac disease with disproportionately severe anemia: tip of the iceberg? *Multidiscip Respir Med* 8: 25.
15. Zamani F, Mohamadnejad M, Shakeri R, Amiri A, Najafi S, et al. (2008) Gluten sensitive enteropathy in patients with iron deficiency anemia of unknown origin. *World J Gastroenterol* 14: 7381-7385.
16. Unsworth DJ, Lock RJ, Harvey RF (2000) Improving the diagnosis of coeliac disease in anaemic women. *Br J Haematol* 111: 898-901.
17. Green RJ, Ruoss SJ, Kraft SA, Duncan SR, Berry GJ, et al. (1996) Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. *Chest* 110: 1305-1316.
18. Kamienska E, Urasinski T, Gawlikowska-Sroka A, Glura B, Pogorzelski A (2009) Idiopathic pulmonary hemosiderosis in a 9-year-old girl. *Eur J Med Res* 14 Suppl 4: 112-115.
19. Krumsiek A, Poggemann V, Wertzel H, Achenbach HJ (2010) [Recurrent hemoptysis in a 29-year old woman]. *Internist (Berl)* 51: 1561-1566.
20. Sant'Anna CC, Horta AA, Tura MT, March Mde F, Ferreira S, et al. (2007) [Idiopathic pulmonary hemosiderosis treated with azathioprine in a child]. *J Bras Pneumol* 33: 743-746.
21. Colombo JL, Stolz SM (1992) Treatment of life-threatening primary pulmonary hemosiderosis with cyclophosphamide. *Chest* 102: 959-960.
22. Kabra SK, Bhargava S, Lodha R, Satyavani A, Walia M (2007) Idiopathic pulmonary hemosiderosis: clinical profile and follow up of 26 children. *Indian Pediatr* 44: 333-338.
23. Luo XQ, Ke ZY, Huang LB, Guan XQ, Zhang XL, et al. (2008) Maintenance therapy with dose-adjusted 6-mercaptopurine in idiopathic pulmonary hemosiderosis. *Pediatr Pulmonol* 43: 1067-1071.
24. Calabrese F, Giacometti C, Rea F, Loy M, Sartori F, et al. (2002) Recurrence of idiopathic pulmonary hemosiderosis in a young adult patient after bilateral single-lung transplantation. *Transplantation* 74: 1643-1645.
25. Saeed MM, Woo MS, MacLaughlin EF, Margetis MF, Keens TG (1999) Prognosis in pediatric idiopathic pulmonary hemosiderosis. *Chest* 116: 721-725.