A Rare Case of Idiopathic Pulmonary Hemosiderosis in an Adult

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

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.
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, lactate, 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.

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)

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 |
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, esophagogastroduodenoscopy (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 [1,2,3,24]. 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.

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