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Case Report
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Idiopathic Pulmonary Hemosiderosis in a 25-Year-Old Female: A Case Report

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Abstract

Background: Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of diffuse alveolar haemorrhage (DAH) associated with a significant delay in diagnosis. This condition is more commonly described in the paediatric cohort, although there has been an increasing number of adult reported cases with a male predominance. Given the rarity of this entity, the incidence, optimal immunosuppressive treatment, and prognosis largely remains unknown in the adult population.

Case presentation: We present a rare case of IPH in a 25-year-old female who presented with recurrent episodes of haemoptysis and associated iron deficiency anaemia. Her initial presentation was presumed to be secondary to a bronchopneumonia. However, she experienced ongoing relapsing-remitting haemoptysis episodes across a three-year period. After extensive investigations that were negative for pulmonary infection, anti-glomerular basement membrane disease (anti-GBM), anti-neutrophil cytoplasmic associated (ANCA) vasculitis, and other rheumatologic conditions, a diagnosis of IPH was made via a surgical lung biopsy demonstrating intra-alveolar haemosiderin-laden macrophages. Her symptoms improved on prednisolone and azathioprine.

Conclusion: Timely recognition of the clinical and radiological features of this condition are important to facilitate early diagnosis and initiation of treatment. This has significant implications given the risks of respiratory failure and disease progression resulting in pulmonary fibrosis and end-stage lung disease.

Keywords: Idiopathic pulmonary hemosiderosis; Cannabinoids; Melatonin; Neuro-immunotherapy; Opioids; Pineal gland

Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of DAH of unknown aetiology. Patients with IPH typically present with recurrent episodes of DAH, resulting in a variable degree of respiratory symptoms. The classical triad in IPH is characterised by haemoptysis, radiological chest infiltrates, and iron deficiency anaemia. IPH predominantly affects children and is rare in adults. IPH is considered a diagnosis of exclusion, and all competing diagnoses therefore need to be carefully evaluated and excluded. To our knowledge, there has only been 84 adult reported cases since 1950. The aetiology of IPH still largely remains unknown with immunologic dysfunction, genetic, and environmental influences being hypothesised as contributing factors. In adults, the course is protracted with a more favourable prognosis in contrast to children. Steroid therapy remains the mainstay of treatment. Our report demonstrates the rare case of IPH in an adult female managed with combination therapy prednisolone and azathioprine with improvement in symptoms.

Case Report

A 25-year-old female presented to a rural hospital with a two-week history of haemoptysis, cough, New York Heart Association (NYHA) class II dyspnoea, and unintentional weight loss 10 kg over 4 months, and night sweats. This occurred on a background of childhood asthma on no inhaler therapy and previous post-partum haemorrhage. She was an active smoker of 5 pack years but denied exposure to other toxic chemicals and recreational drug use. She was not on any regular medications. On arrival, she was found to be anaemic with associated iron deficiency (Hb 69, ferritin 31, transferrin saturation 3%) requiring packed red blood cell transfusion. She was not in respiratory distress.

Chest X-ray (CXR) demonstrated patchy diffuse air space disease, more prominent in the left lower lobe (Figure 1).

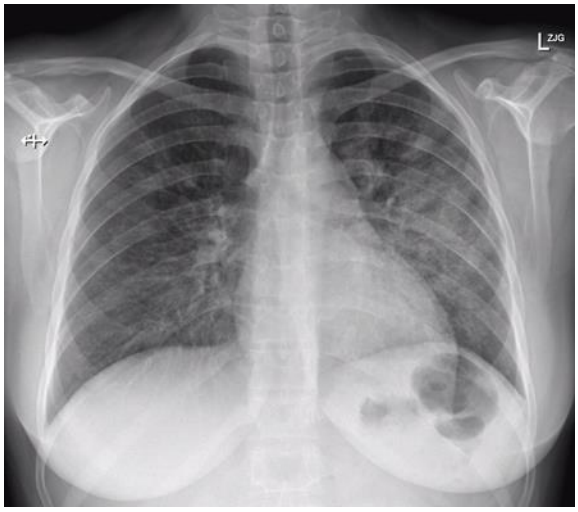

Figure 1: *CXR, Diffuse bilateral ground-glass opacification appears slightly more prominent on the left than the right.*

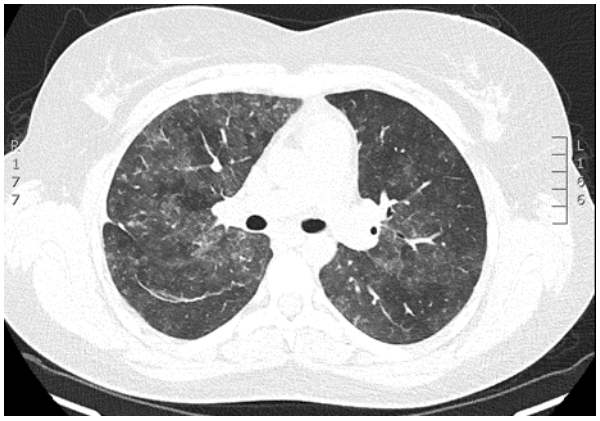

Figure 2: *HRCT Chest, Extensive centrilobular ground-glass opacities scattered in all lobes of both lungs.*

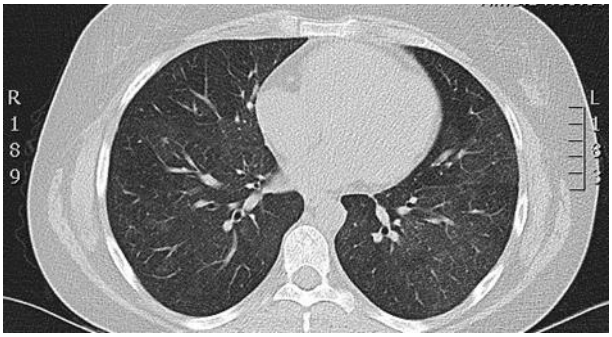

Figure 3: *HRCT chest, Bilateral centrilobular ground glass opacities, further decreased in conspicuity.*

Computed tomography (CT) chest/abdomen/pelvis demonstrated extensive bilateral pulmonary parenchymal abnormalities comprising of poorly defined centrilobular ground-glass opacities. These were further demonstrated on high-resolution computed tomography (HRCT) (Figure 2). There were no CT features to suggest intra-thoracic or intra-abdominal neoplasia. Other investigations included: positive ANA 40 with negative results for ENA, anti-glomerular basement membrane, c-ANCA/p-ANCA, anti-MPO/PR3, anti-cardiolipin, anti-b2 glycoprotein, hepatitis A/B/C/HIV, anti-cyclic citrullinated peptide, respiratory viruses, and avian precipitins. She had preserved renal function without proteinuria or haematuria. Coagulation studies and von Willebrand factor were normal. Sputum microbiology demonstrated normal respiratory flora. She received antibiotic treatment to empirically cover for a community-acquired pneumonia. The patient was initially referred for consideration for lung biopsy for definitive diagnosis however her symptoms and radiological appearances improved. Her presentation was therefore initially presumed secondary to a resolving bronchopneumonia.

She continued to experience remitting-relapsing episodes of haemoptysis with associated symptomatic iron deficiency anaemia across a three-year period. Serial HRCTs demonstrated persisting ground glass opacification throughout the lungs. These episodes were usually managed with tranexamic acid, packed red blood cell transfusion, iron infusion, and antibiotic treatment. Bronchoalveolar lavage (BAL) demonstrated a predominance of macrophages (87%%), diffuse alveolar haemorrhage, no malignant cells, and the absence of bacterial, viral, and fungal pathogens. Transbronchial biopsies demonstrated prominent intra-alveolar and interstitial haemosiderin deposition indicative of remote intra-alveolar haemorrhage. Her haemoptysis worsened in volume over this period, coughing up to 1-2 cups daily. Autoimmune screening and anti-GBM remained negative, however her ANA titres increased to 640. Coeliac antibodies were negative.

The case was discussed at the interstitial lung disease multi-disciplinary meeting, and she was referred to a tertiary centre for video-assisted thoracoscopic surgery (VATS) lung wedge resection. Biopsies demonstrated evidence of intra-alveolar haemorrhage, type II pneumocyte hyperplasia, and intra-alveolar haemosiderin-laden macrophages. There was no evidence of vasculitis or capillaritis. Based on the histopathological findings, a diagnosis of idiopathic pulmonary hemosiderosis was made. She was initially commenced on non-aggressive treatment with hydroxychloroquine 200 mg daily however she presented with another recurrent episode of haemoptysis post initiation of treatment. She was later trialled on a tapering prednisolone course and azathioprine with associated clinical and radiological improvement (Figure 3). Ongoing smoking cessation advice was provided.

Discussion

IPH is a rare cause of DAH resulting in deposition and accumulation of haemosiderin in the lungs [1,2]. Knowledge of

this entity is limited, and the diagnosis is often delayed by 2-3 years [1-4]. The diagnostic challenge of this condition poses a significant issue as some patients may present in acute respiratory failure, and disease progression can result in pulmonary fibrosis and end-stage lung disease [1]. This condition is more commonly reported in the paediatric population which accounts for more than 80% of reported cases [1-5]. The estimated incidence ranges from 0.24 to 1.23 cases per million [6,7], whilst the prevalence in a single hospital retrospective study in the United States is estimated to be 6.71 cases per million patients in the paediatric cohort [8]. The incidence and prevalence of this condition is largely unknown in the adult population. In a recent retrospective review of literature, there has been a total of 84 reported adult cases from 1950 to 2021 [3]. Of these patients, the majority were males (64.3%), and the median age was 27 years [3,9]. In adults, the course is often prolonged, symptoms less pronounced, and the prognosis may be more favourable compared to children, although data remains limited [1,3,5,12].

The pathogenesis of IPH still largely remains unknown, although an autoimmune mechanism has gained momentum from the identification of autoantibodies and response to corticosteroid therapy [1,2,4,5]. Saha et al. reported approximately one in five patients in an adult cohort population testing positive for an autoantibody, with antibodies specific for coeliac disease (CD) being the most common [3]. The co-existence of IPH and CD has been described as Lane-Hamilton syndrome (LHS) [1-,4,11]. Interestingly, most patients with LHS do not suffer from gastrointestinal symptoms, and many studies have recommended testing for coeliac antibodies when diagnosed with IPH [3,11]. A gluten-free diet has been associated with improved respiratory symptoms and long-term outcomes in these patients [2,11]. Other commonly reported autoantibodies in adults include rheumatoid factor and anti-thyroid antibodies. Previous studies have also suggested a complex interplay involving genetic, allergic, and environmental factors. No specific genetic markers have been identified yet, however the possibility of a genetic predisposition is suggested by several reports describing familial clustering of cases [9]. A retrospective database review has shown that Down Syndrome has been associated with pulmonary hypertension and worse prognosis [2,5,10]. The allergic hypothesis stems from the isolation of plasma antibodies against cow's milk protein (IgE and IgG) in children diagnosed with IPH [1,2,5] however no prospective studies have validated this association and testing against cow's milk protein is controversial. Environmental exposure to second-hand smoking, highly potent fungal toxin (particularly *Stachybotrys chartarum*), and pesticides have been associated with pulmonary haemorrhage [1,2,5]. The mechanism for lung injury involves excessive iron deposition, possibly inefficient handling of the iron load by the alveolar macrophages, oxidative damage, inflammation, and eventual fibrosis [1,2,9].

The clinical presentation of IPH in the adult population is highly variable [1,4]. Patients often present with intermittent episodes of haemoptysis interspersed between periods of relative normalcy [1,2]. Haemoptysis ranges from intermittent, scanty, to daily frank bleeding and occasionally, massive haemorrhage resulting in acute respiratory failure [1,2]. Most patients develop iron deficiency anaemia from blood loss in the lung. In the recent largest retrospective review to date, there appeared to be a higher reported incidence of symptoms compared to previous reviews. Signs and symptoms include anaemia (91.6%), dyspnoea (85.5%), haemoptysis (26.2%), and chest pain (10.7%) [3]. The classical triad comprising of haemoptysis, anaemia, and radiologic chest abnormalities was present in almost 80% of patients [3-5]. Systemic symptoms, such as fever, night sweats, weight loss, or loss of appetite was seen in nearly half of the patients (45%). This is a significant finding given that the presence of fever and other non-specific systemic symptoms may incorrectly dissuade clinicians from considering the diagnosis IPH and lean towards an infectious aetiology for the respiratory symptoms, resulting in a delay in diagnosis [3].

Given the absence of a defining serological marker, IPH remains a diagnosis of exclusion from other more common aetiologies of DAH [1]. This includes the exclusion of infection, coagulopathies, anti-GBM disease, ANCA- associated vasculitis (AAV), and other rheumatologic conditions. Toxin and drug exposure also require exclusion [1,2,5]. The imaging features of IPH are non-specific and no radiological features are pathognomonic for IPH. CXR findings depend on the acuity and severity of alveolar haemorrhage. During the acute episode, CXR usually demonstrate diffuse alveolar opacification involving the peri-hilar and lower lung zones, although it may also encompass all lung lobes in more severe cases of haemorrhage [1,2,3,9]. HRCT is more sensitive and demonstrates ground-glass opacification within the same distribution [1,3,9]. With repeated episodes of alveolar haemorrhage, fibrotic changes may develop in the form of reticulation, subpleural honeycombing, traction bronchiectasis, and bronchiolectasis in the postero-basilar areas [1]. Bronchoscopic evaluation is generally performed to identify DAH and exclude infection and structural airway abnormalities [1]. A diagnosis of DAH is made via observation of progressively more bloody return on serial aliquots on BAL [1,2]. The cell count demonstrates the predominance of haemosiderin-laden macrophages which is suggestive but not diagnostic [1,2,5]. A lung biopsy is often required to provide a definitive histopathologic diagnosis [1,5]. During an acute episode of alveolar haemorrhage, histopathologic analysis of the lung tissue reveals intra-alveolar haemorrhage, free and intra-cytoplasmic haemosiderin within the macrophages, hyperplasia of type II pneumocytes, and thickening of inter-alveolar septa from deposition of haemosiderin [1,2]. A key finding is the absence of

capillaritis that is seen in AAV, connective tissue, and anti-GBM disease [1,2,9].

Data regarding the optimal dosing and duration of therapy is limited with the absence of prospective and randomised controlled data. Treatment of IPH is based on anecdotal case reports or small case series [2]. Corticosteroids alone or in combination with other immunosuppressive regimens represent the primary modality of treatment, however a recent systemic review did not show corticosteroids to be statistically associated with improved survival [1,3,5,9]. During the acute phase of alveolar haemorrhage, the initial dosing ranges between 0.5 and 0.75 mg/kg/day of prednisone with a maximum of 60 mg/day. Induction treatment should continue until pulmonary haemorrhage has stopped and chest radiograph shows partial or complete regression of newly acquired opacifications, which usually requires 4-8 weeks [1,5,9]. At this point, a taper of 2.5 mg or 5 mg every other week is continued until a daily dose of 10-15 mg is reached [1,5]. The optimal duration of therapy with corticosteroid still largely remains unknown [5]. In adults, the recurrence rate is generally lower than in children and if the patient remains well-controlled for 12-18 months, slow tapering is reasonable until discontinuation. Unfortunately, recurrent bleeding during maintenance therapy is not uncommon and is usually treated with an escalation of the steroid dose [1-3]. Several reports have detailed the addition of immunosuppressive medications in conjunction with initial steroid therapy in patients who have recurrent episodes of haemorrhage that limit tapering, including hydroxychloroquine, azathioprine, cyclophosphamide, methotrexate, 6- mercaptopurine, and inhaled corticosteroid. Evidence for this approach remains limited. In addition, several reports describe the successful use of azathioprine in combination with oral steroids for maintenance therapy [1,4,5,9]. Patients with evidence of concomitant coeliac disease should follow a gluten-free diet [4].

The lack of prospective studies or large registries makes the evaluation of prognosis of IPH in the adult population difficult to assess [9]. Children typically have a more severe symptomatic presentation than adults and can present acutely with respiratory failure [3,10]. Adults generally have a longer disease course with milder symptoms and more favourable prognosis. Patients usually die from acute respiratory failure in the setting of acute haemorrhage or chronic respiratory failure due to pulmonary fibrosis. The risk factors that contribute to poor outcomes in the adult population are uncertain [2,12].

Conclusion

IPH is a rare disorder associated with DAH and a significant temporal delay in diagnosis. Diagnosis is established by demonstrating intra-alveolar deposition of haemosiderin-laden macrophages on lung biopsy and excluding other causes of DAH. This case illustrates IPH in an adult female who experienced an improvement in her symptoms after maintenance treatment with combination prednisolone and azathioprine. Further prospective studies are required to evaluate the efficacy of corticosteroid and other immunosuppressive therapy.

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