Infantile Pulmonary Hemosiderosis

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Abstract

Pulmonary hemosiderosis in infants (< 1 year of age) is a syndrome characterized by pulmonary hemorrhage and hemosiderin-laden macrophages. As there are multiple incompletely understood etiologies regarding this syndrome, this paper discusses the etiologic and pathophysiologic mechanisms, with particular attention to Heiner’s syndrome, Wegener’s granulomatosis, and the toxigenic mold Stachybotrys. It also provides diagnostic guidelines to assist in the investigation of infantile hemoptysis and the institution of a treatment approach to the infant with IPH.

Introduction

Hemoptysis is defined as bleeding observed in expectorated secretions originating from the lung parenchyma or the related tracheobronchial structures. The most common causes of hemoptysis in the general population include neoplasms, foreign body aspiration, infection (bronchitis, cystic fibrosis, pneumonia), localized lower airway bleeding (arteriovenous malformations), pulmonary venous hypertension, and pulmonary embolism (figure 1).(1) Hemoptysis in the infant is rare, with the most common cause being pulmonary venous hypertension linked to congenital heart disease followed by infection.(2) Pulmonary hemosiderosis of any cause in an infant is even rarer, with etiologies exemplified by Heiner’s syndrome, Wegener’s granulomatosis, toxigenic mold exposure, Lane-Hamilton syndrome (pulmonary hemosiderosis associated with celiac disease with correlation between dietary gluten and pulmonary hemorrhage)(3), and idiopathic pulmonary hemosiderosis (IPH).

Review

HEINER’S SYNDROME

Heiner’s syndrome is defined as rhinitis, chronic cough, wheezing, or respiratory distress with demonstrable pulmonary infiltrates on radiography, positive milk precipitins, and resolution of symptoms upon removal of cow’s milk products.(4) Heiner in 1962 first characterized an ill-defined syndrome comprising seven children with a myriad of respiratory findings (hemoptysis, pulmonary hemosiderosis, rhinitis, cough, wheeze, tachypnea, and dyspnea) and positive cow’s milk precipitins in serum, with improvement in respiratory symptoms upon removal of cow’s milk from the diet.(5) Heiner revisited this syndrome in 1978,(6) where two infants with “milk-related pulmonary hemosiderosis” underwent lung biopsy. Staining of lung tissue showed deposition of IgG and bovine serum albumin by immunofluorescence. This histological finding led to speculation that Heiner’s syndrome might be a type III hypersensitivity reaction. However, these findings have not been definitively corroborated in the literature. In addition, the cases reported were noted to have positive skin prick testing to cow’s milk in addition to positive precipitins, which brings to question whether or not part of the clinical presentation may have been IgE-mediated.

Whether or not food adverse reactions can be mediated solely by specific IgG has long been a controversial issue. More than 30 years ago it was demonstrated that IgG4 participated in anaphylactic reactions in animal models(7) and it was shown to be present incrementally in individuals undergoing immunotherapy.(8) These two findings led some to believe that IgG4 played an important role in human atopic disease, and supporting these thoughts are more recent reports indicating an association between IgG4 and atopic diseases, especially eczema,(9-10) but there is no clear evidence for this specific antibody in the pathogenesis of allergy-related symptomatology. For example, in a controlled study of 47 children with a history of cow’s milk protein allergy (verified by oral milk challenge) there was no relationship between specific IgG4 levels and positive food challenge.(11) Furthermore, another study of 44 children aged four months to five years with clinically proven cow’s milk allergy showed no relationship between symptoms and levels of IgG to cow’s milk when compared to matched healthy controls.(12) Additionally, a study by Dannaeus failed to demonstrate a relationship between food-specific IgG titers and symptoms in 69 children.(13) Moreover, in a controlled study of 40 children with egg allergy, no relationship was made between egg-specific IgG4 levels and their symptoms.(14) Finally, and trying to settle this controversy, two studies found that almost all infants who were fed cow’s milk formula had an IgG response to cow’s milk protein by six months, regardless of atopic symptoms.(15-16) Adding evidence to the
studies just mentioned, there is a significant amount of research suggesting that IgG4 may be protective against atopy; T-regulatory cells, through production of IL-10 and TGF-β, may play a role in the production of IgG4 and deviation of the immune system towards a nonallergic pathway.(17) The literature also provides scattered documentation of Heiner’s syndrome through several case reports with some undergoing food challenges in clinical settings. Moissidis et al. reported a series of eight cases of “milk-induced pulmonary disease” in which elimination of milk resulted in symptomatic improvement, with three of the children undergoing challenges to cow’s milk reported as positive.(18) However, the cases seem not to present symptoms up until weeks or even months on the suggested offending agent and have absent IgE titers against milk as opposed to the cases reported by Heiner. Some of them were treated with systemic steroids after limited evaluations.

**WEGENER’S GRANULOMATOSIS**

Wegener’s granulomatosis (WG) is a small-vessel vasculitis that has been associated with pulmonary hemorrhage in young children. Most adult patients generally first seek medical attention for upper or lower airway involvement, and 75-80% of patients with WG will develop glomerulonephritis.(19) Antibodies directed against proteinase-3 (c-ANCA) are the most common antibody seen in WG in up to 80-85% of patients.(20) WG is classically seen in adults (25 to 50 years), but it is becoming increasingly recognized in children. In a retrospective study of 17 children with WG the age of diagnosis varied from 2 weeks to 14 years.(21) Four of the cases ranged from two weeks to three months in age (all female), and three of these cases presented with respiratory involvement. However, none of these infants had respiratory involvement alone. Three of the infants had upper airway involvement, and two had renal involvement. Akikusa et al. studied the clinical features and outcome of 25 children in whom the average age of diagnosis was 14.5 years (range 8 to 17 years) with a female predominance.(22) The overwhelming majority of patients were also positive for c-ANCA (95%) and pulmonary involvement was the dominant clinical feature, but 88% of the patients also had renal involvement at presentation.

**TOXIGENIC MOLD**

Further diagnostic consideration in infantile hemoptysis includes potential toxic exposures. In experimental animal models, intranasal exposure to Stachybotrys spores resulted in severe alveolar and interstitial inflammation with hemorrhage; and in infant rats, S. chartarum placed directly into the trachea led to fatal pulmonary hemorrhage.(23) A possible link between Stachybotrys and idiopathic pulmonary hemorrhage in children was first entertained during the 1990s in Cleveland, where in a seven year span, 30 infants were hospitalized for pulmonary hemorrhage.(24) The hemorrhagic episodes were often heralded by a prodrome of cough, congestion, irritability, and occasional epistaxis, with nearly three quarters of them requiring mechanical ventilation. The most effective treatment reported was systemic corticosteroids, along with removal from the home environmental and environmental tobacco smoke exposure. Several of the patients were found to have hemoglobinuria, and every patient with a peripheral blood smear evaluated showed at least 1+ fragmented or damaged red cells. These findings may have prompted further evaluation for vasculitis, but it is unknown whether those evaluations were undertaken in that direction. On environmental survey of the patients’ homes, it was found that 25 patients had exposure to environmental tobacco smoke (ETS), 26 of the patients lived in water-damaged homes, and 25 of the infants were found to live in homes where Stachybotrys chartarum was detected. It was speculated that ETS in these households caused pulmonary vasoconstriction, enhancing the effects of the mold’s toxins. An earlier case-control study of the Cleveland outbreak initially revealed that infants with pulmonary hemorrhage were 16 times more likely to live in water-damaged homes, and exposure to ETS increased the odds of pulmonary hemorrhage by eightfold.(25) However, it was later reported that the epidemiologic association between fungi and the above cases was not substantiated adequately.(26) The odds ratio between cases and controls was thought to be initially inaccurately reported, and the real ratio was re-calculated to be 1.5. However, it is notable that Stachybotrys has been isolated from the BAL fluid of a seven year-old boy that had pulmonary hemosiderosis, preceded by a prodrome of fatigue, chronic cough, and recurrent pneumonia.(27) Prior to the initiation of his symptoms, the family had recently moved into a 25 year-old farmhouse which had severe flood damage. Upon cleaning the farmhouse according to the Centers for Disease Control and Prevention Guidelines, the symptoms resolved.

**IDIOPATHIC PULMONARY HEMOSIDEROSIS**

Idiopathic pulmonary hemosiderosis (IPH) presents as recurrent hemoptysis with HLM in BAL samples, often with a varying degree of microcytic, hypochromic anemia (rarely requiring blood transfusion). Work-up for other causes of pulmonary hemorrhage, such as infection, neoplasm, structural abnormalities, pulmonary venous hypertension, pulmonary-renal
syndromes, and Heiner’s syndrome is negative.\(^{(1)}\) The incidence of IPH is unknown, with estimates varying vary between 0.24\(^{(28)}\) to 1.23\(^{(29)}\) cases per million with a balanced sex distribution classically presenting during the first ten years of life.\(^{(30)}\) The majority of patients with IPH tend to respond to treatment with long-term oral corticosteroids with a 5-year projected survival of 86%.\(^{(30)}\) Other steroid-sparing therapies have been tried with varying degrees of success.

### Discussion

There is considerable diagnostic complexity inherent in cases of infantile hemoptysis without a readily apparent cause or pre-existing and predisposing conditions. IPH is a diagnosis of exclusion, thus it is important to rule-out all other potential etiologies of pulmonary hemosiderosis, such as pulmonary-renal syndromes, Heiner’s syndrome, or toxigenic mold exposure, many of which may require tissue diagnosis. Based on the diagnostic complexity associated with a potentially grave prognosis if not aggressively treated, we advocate a comprehensive history and physical exam (focusing on abuse, suffocation, and mold exposure/presence at home) and initial basic evaluations including a complete blood count with differential, erythrocyte sedimentation rate, renal function tests and urinalysis, coagulation studies, stool guaiac, and chest radiography. Some of the cases will reveal trauma, infection, foreign body, or a bleeding diathesis. Additional investigation should be based on the results of these previous evaluations, and may include an echocardiogram to rule out congenital heart disease with pulmonary venous hypertension. More advanced serologic evaluations may include specific IgE and IgG to cow’s milk protein as well as a cow’s milk precipitins panel drawn for Heiner’s syndrome, immunoglobulin titers against Stachybotrys, and FANA, c-ANCA, and glomerular basement membrane antibody titers to investigate the possibility of pulmonary-renal syndromes. It should be noted, however, that infants may not develop sufficient antibody titers against Stachybotrys to aid in diagnosis. Additional imaging modalities should be considered such as a high resolution CT scan in search for subtle congenital malformations; and finally endoscopic visualizations (nasolaryngobronchoscopy and esophagogastroduodenoscopy) ought to be strongly entertained to search for localized upper or lower airway or gastroesophageal lesions as a source of bleeding. BAL should be obtained during bronchoscopy and sent for cell count and differential, lipid- and hemosiderin-laden macrophages, and microbiological analysis, including different stains and cultures for bacteria, fungi (to include Stachybotrys), acid fast mycobacteria, pneumocystis, and viruses. If possible, quantitative PCR for Stachybotrys should also be sent. If a systemic (versus localized) pulmonary disorder is found, then tissue analysis should follow and should include hematoxylin and eosin stains, immunofluorescence for IgG, IgA, IgM, C3 and fibrinogen, and electron microscopy for ultrastructural analysis. We advocate a very extensive analysis of cases of hemoptysis, especially in light of the calculated mortality if certain conditions are left untreated (14% mortality in 5 years).\(^{(30)}\) If after all these investigations a concrete cause of pulmonary hemosiderosis cannot be identified, then the diagnosis of IPH should be entertained (Figure 2).

It has been previously published that macrophages take 2–3 days to become hemosiderin-laden,\(^{(1)}\) peaking at 14 days, and mostly clearing by three weeks after an acute bleed.\(^{(31)}\) However, detection of HLM may be quite variable depending on the timing and severity of bleeding, and sampling technique. It has been our experience that HLM have failed to show four days after an episode of hemoptysis—either indicating that those cells were not present yet, that the level of bleeding was not enough, or that IPH may have a heterogenous presentation and the affected segments were not targeted for investigation during the bronchoscopy. It has also been our experience that lung biopsies reveal a large number of HLM per high powered field (over 25) with only a few of them detected in BAL, suggesting that there needs to be substantial tissue bleeding in order to be detected by bronchoscopic BAL, as the disease could be heterogeneous and heavily affected areas may randomly not be targeted for BAL.

Even though it has not been reported in the literature it is theoretically possible that passively transferred maternal antibodies may cause disease in the infant with hemoptysis, therefore we suggest that if the child is less than four months of age and has positive ANCA titers then evaluating the mother’s antibodies may provide a source of those antibodies. If the child has started on any gluten-containing products in the diet, a celiac panel should also be considered. We also advocate that a careful environmental survey of the patient’s home be undertaken to look for any mold-ridden areas, especially around the child’s main living area.

While there have been several reports on the treatment of IPH to date, there is no consensus on what the best approach is. If a diagnosis of IPH is
made during the acute phase, treatment with systemic steroids (either prednisolone or methylprednisolone) should be initiated with a dose of 2 milligrams per kilogram (mg/kg) per day for 2 weeks.(32) If the child responds well to this therapy, we recommend beginning azathioprine (AZA) at a dose of 3-5 mg/kg per day, with the steroids gradually tapered over a period of 4-6 weeks. Azathioprine (AZA) achieves safe and effective symptom control while minimizing or eliminating the dose of systemic steroids.(33-35) The addition of inhaled corticosteroids (ICS) started during steroid tapering as systemic corticosteroid-sparing agents is limited to single case reports(36-37) that suggest a decreased need for oral prednisolone with the use of ICS. This approach should be considered in patients on AZA. If symptoms recur following the steroid taper, oral prednisolone should be given for an additional 1-2 weeks; if symptoms develop during the steroid taper, the dose of oral prednisolone should be increased to 2 milligrams per kilogram per day for 2-4 weeks, followed by a re-attempt to taper (Figure 3).(33) The use of elemental iron at a dose of 3 milligrams per kilogram per day(33) should only be instituted in anemic patients following the resolution of acute bleeding episodes, as enhanced deposition of iron in the lung may predispose to pulmonary fibrosis.(28, 34) The practitioner should also be aware of other treatment modalities including hydroxychloroquine (HCQ) at a dose of 3-5 milligrams per kilogram per day started simultaneously with steroids,(32) cyclophosphamide (CTX) dosed at 1-2 milligrams per kilogram per day,(38) which has been used as immunosuppressive agents in patients with an unfavorable response to oral corticosteroids alone.(32, 34)

We recommend following the infants with a full clinical evaluation, CBC and guaiac every month (for follow-up of persistent bleeding and AZA toxicity), chest radiography every two-three months, and a repeated bronchoscopy after a couple of months if the previous studies have normalized. At that time, if there are no or very few HLM present in the BAL, then therapy can be slowly withdrawn. Close follow-up needs to be performed to assure that the patient remains well and a bronchoscopy should be considered several months later to confirm that the disease has subsided. Presence of HLM in the BAL, especially along with increased sleeping respiratory rate, positive stool guaiac, or changes on the chest roentgenogram may indicate the need for continuing or re-starting therapy. It is still unclear how long therapy should be prolonged and what a “safe” index of HLM in these patient is, so frequent monitoring and the establishment of an excellent patient-physician understanding is needed based on the complexities of this disorder and the potentially grave prognosis.

This paper demonstrates the difficulties when investigating hemoptysis and pulmonary hemosiderosis in an infant. Given the limited studies performed in previously reported cases, our experience with multiple false positive tests, and data from the literature in other conditions, it is possible that some previous cases were not fully investigated and therefore not precisely diagnosed. We understand that it is difficult to have a unified diagnostic and therapeutic approach to infantile pulmonary hemosiderosis, but based on the current knowledge we provide our recommendations. Further research into the disease is needed to explore its unknown etiologic and pathophysiologic mechanisms. In doing so, we may be able to strip the diagnosis of its “idiopathic” label and provide more effective treatment to those affected.

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Illustrations

Illustration 1

Differential Diagnosis of Hemoptysis in an Infant

**Differential Diagnosis of Infantile Hemoptysis**

*Most common*
- Trauma
- Suffocation
- Foreign body
- Infection
- Cystic fibrosis
- Pulmonary hypertension / congenital heart disease
- Arteriovenous malformation
- Spurious (upper airway bleeding, gastrointestinal bleeding)

*Rare*
- Pulmonary-renal syndromes
  - Wegener's granulomatosis
  - Scleroderma
- Goodpasture's disease
- Diffuse capillaritis
- Henoch-Schönlein purpura
- Toxigenic mold exposure
- Larte-Hamilton syndrome
- Idiopathic pulmonary hemosiderosis

Illustration 2

Diagnostic flowchart for an infant with hemoptysis.
Illustration 3

Treatment algorithm for idiopathic Pulmonary Hemosiderosis
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