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CLINICAL VIGNETTE

Hemoptysis in a 16-month-old Child with Trisomy 21

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Case Report

A 16-month-old female infant with trisomy 21 presents with hemoptysis. She was initially seen with four-days of cough, nasal congestion, and non-bloody diarrhea. She also had five to six episodes of blood streaked, brownish sputum. She had no fevers, epistaxis, petechiae or other rashes. Mild fatigue was reported, without signs of respiratory distress or increased work of breathing. There was no known foreign body ingestion/ aspiration.

Patient had mild gross motor and speech delay, as well as an atrial septal defect which is monitored clinically. She does not take any medications, except for an over the counter multivitamin. Recent medical history was notable for five episodes of recurrent viral upper respiratory infections (URIs) during the prior respiratory season, one episode of acute otitis media, and one episode of respiratory syncytial virus (RSV) bronchiolitis. She received a dose of dexamethasone during one of the URI episodes.

Family history was significant for hypertension, seasonal allergies, and asthma in the immediate family. However, there was no significant history of chronic lung disease, cystic fibrosis, sudden death, or autoimmune disorders other than a maternal grandmother with autoimmune thyroiditis. She attends daycare regularly, and lives at home with her mother, father, and three older siblings. No one smokes in the household, there are no pets at home, which has hardwood flooring and area rugs, with some indoor plants.

On a physical exam, the patient had friable mucosa of her nares, however no active bleeding. Her respiratory exam included clear breath sounds with no crackles or wheezes. SpO_2 was as 98% on room air. A chest x-ray (CXR) was only notable for a right upper lobe (RUL) opacity. White blood cell (WBC) was 9.21 x 10E3/uL. hemoglobin (Hgb) was 9.1 g/dL and hematocrit (HCT) was 32.3%.

Given concern for a presumed bacterial pneumonia, the patient was started on amoxicillin-clavulanate. However, two days later she woke up with bright red blood-filled mucus on her face, without fevers or dyspnea. She continued to have eight or nine witnessed episodes of blood in mucus with no associated epistaxis or vomiting. She had normal stools without blood, and no bruising. Her cough was described as persistent, however, it was not worsening. Repeat CXR showed persistent RUL opacity and slight worsening perihilar patchy opacities. Her hemoglobin was unchanged. Given persistent symptoms of hemoptysis and worsening opacities on CXR, she was admitted to the hospital.

During the admission, an upper airway evaluation was performed by otolaryngology, which was negative for any active bleeding. Complete blood count showed a WBC of 5.58 x 10E3/uL, Hgb 9.2 g/dL, HCT 31.1%, and platelets 251 x 10E3/uL. Peripheral smear demonstrated normocytic normochromic anemia. WBC differential showed 48.6% neutrophils, 40.9% lymphocytes, 3.0% eosinophils, 6.5% monocytes, 0.5% basophils. Reticulocyte count 4.13%, which was elevated with an absolute retic number of 0.15, immature retic fraction 26.5%, and retic Hgb content 33.8. C-reactive protein was elevated to 1.9 mg/dL, and mild transaminitis with aspartate aminotransferase 73 U/L, alanine aminotransferase 54 U/L and normal alkaline phosphatase of 161 U/L and total bilirubin of 0.4 mg/dL. Iron studies were within normal limits.

The patient was discharged home to complete a full course of amoxicillin-clavulanate and was scheduled to follow up with the pediatric pulmonary. She continued to have persistent episodes of bright red blood per sputum following completion of antibiotics. Additional evaluation for atypical pneumonia, fungal pneumonia as well as the hypersensitivity pneumonitis panel were negative. Repeat CXR showed worsening patchy infiltrates and she was started on high dose prednisone 30 mg daily. Over the following 2 weeks she showed improvement of infiltrates and resolution of blood in her sputum and was continued on steroid taper.

The patient had return of symptoms when the steroid was weaned down to 1 mg daily, and required urgent admission to the pediatric ICU given hypoxia and worsening hemoptysis. Her Hgb dropped to 5.8 mg/dL on presentation in the ICU. Computed tomography (CT) of the chest showed ground glass opacities in both lungs with no evidence of diffuse interstitial lung disease. She received blood transfusions as well as high dose steroids and antibiotics. After stabilization she underwent bronchoscopy with bronchoalveolar lavage (BAL). This revealed diffuse alveolar hemorrhage with mild bronchomalacia. She also underwent an upper gastrointestinal endoscopy, which had no abnormal findings. CT angiography of the chest showed no vascular anomalies. BAL showed iron- and lipid-laden macrophages. As a result, a presumed diagnosis of intrapulmonary hemorrhage secondary to idiopathic pulmonary

hemosiderosis (IPH) was made. Lung biopsy performed one month later, after her symptoms stabilized, confirmed the diagnosis.

Discussion

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease primarily diagnosed in pediatric patients characterized by persistent diffuse alveolar hemorrhage.[1] The pathophysiology of IPH is not entirely understood, however it is known that the deposition of hemosiderin in alveolar macrophages likely results in alveolar injury. Consequences of hemosiderin accumulation and pulmonary tissue damage include iron deficiency anemia, radiographic lung findings, and hemoptysis which are hallmarks of IPH.[2]

Although existing literature is primarily limited to case reports, a growing body of evidence supports the role of autoimmune dysfunction in the development of IPH. A recently published review by Saha et al. of 10 observational studies comprised of 288 pediatric patients with IPH, found 26.4% positive for at least one autoantibody. These included antinuclear antibodies, anti-neutrophil cytoplasm antibodies, and anti-smooth muscle antibodies.[3] Notable associations have also been made between IPH and celiac disease (Lane-Hamilton syndrome), as well as cow's milk protein allergy (Heiner syndrome).[2] A multicenter study examining risk factors for recurrent IPH identified antinuclear antibody positivity as a significant predictor for disease resistant to steroid therapy.[4] Although there is no definitive evidence to suggest autoimmunity plays a role in the direct pathogenesis of IPH, recognizing this association is critical for evaluation of alveolar hemorrhage and will inform future studies.

This case highlights the unique diagnostic challenge associated with IPH and brings attention to notable aspects of clinical presentations which may favor evaluation for IPH. Suspected IPH evaluation is undertaken after exclusion of alternative explanation of alveolar hemorrhage, as the classical presentation of IPH is non-specific. Patients commonly undergo a prolonged period of uncertainty before a diagnosis has been made. Due to exclusion of more common causes of pediatric pulmonary hemorrhage such as cystic fibrosis, congenital heart disease, or malignancy.[5,6] One survey study reported more than 60% IPH patients were initially misdiagnosed.[7] Our patient was empirically treated for presumed bacterial pneumonia, and only after recurrent, persistent symptoms and otherwise negative evaluation that lung biopsy established her diagnosis.

Although non-specific, our patient's medical history of trisomy 21 is a useful diagnostic clue in the setting of her overall presentation consistent with IPH. An analysis by Alimi et al. identified 34 pediatric patients with IPH, among which nine (26%) presented with Down syndrome.[8] In this study, Down syndrome patients presented at a younger age and had increased disease severity with higher rates of relapse. Down syndrome patients had significantly higher rates of pulmonary arterial hypertension and were more likely to succumb to their illness. Existing hypotheses regarding the observed risk for IPH in the setting of Down syndrome include congenital cardio-pulmonary abnormalities, pulmonary arterial hypertension, infection or aspiration, as well as immune dysregulation.[9]

The relationship between IPH and immunologic dysfunction is supported by the therapeutic response to high dose systemic steroids which remains the treatment of choice. Systemic steroids are commonly used for acute exacerbation, as well as for long term maintenance therapy.[1,10] In this case the patient initially responded to high dose prednisone before precipitously worsening upon steroid taper. Although not yet standardized, immunosuppressive agents such as hydroxychloroquine, azathioprine, cyclophosphamide, 6-mercaptopurine, rituximab, and mycophenolate have been utilized for maintenance therapy.[2,7,11]

Recent advancements beyond the traditional management of IPH with systemic corticosteroids and immunomodulators represents an exciting avenue for future research. Liposteroids are a novel formulation of dexamethasone palmitate contained within a hydrophobic liposome. Limited studies examined use of liposteroids as an alternative treatment for IPH with minimal side effects compared to systemic corticosteroids.[11-13] Despite ongoing work on treatment strategies for IPH, long-term outcomes remain poor. Persistent alveolar hemorrhage leading to end-stage lung disease have resulted in lung transplantation for IPH. Post-transplant disease recurrence is common. However, among four lung transplants described in the literature, one living donor transplant demonstrated no recurrence at five years.[14] Moreover, post-transplant disease recurrence appears to be treatable with additional immunosuppression.

This vignette documents a unique infant with IPH, a rare cause of diffuse alveolar hemorrhage manifesting with unexplained hemoptysis. Continued efforts are necessary to minimize delayed diagnosis as well as examine the efficacy of both existing and novel treatment strategies.

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