Case Report

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Autoimmune Features of Wiskott-Aldrich Syndrome: A Case Report

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Abstract

Diffuse alveolar hemorrhage in a pediatric patient requires urgent and aggressive therapy. Here we report a young child with Wiskott-Aldrich syndrome and anti-platelet antibody manifesting as recurrent pulmonary hemorrhage due to pauci-immune capillaritis that was successfully treated with rituximab.

Keywords: Capillaritis; Autoimmune thrombocytopenia; Wiskott-Aldrich syndrome

Introduction

Wiskott-Aldrich Syndrome (WAS), was first described in 1937 by Wiskott and its inheritance pattern was substantiated as an X-linked disorder by Aldrich et al. in 1954 [1,2]. The disorder is a result of a mutation of the WAS protein (WASp) which belongs to family of a cytoskeleton regulatory proteins and is encoded on Xp11.22.3 The typical clinical presentation includes thrombocytopenia, eczema, and recurrent infections [1-3]. However, disease manifestation and severity of WAS may be highly variable and atypical, and is often associated with autoimmune features [4-6].

Case Report

Here we present a 2-year-old African American male with a chief complaint of recurrent tachypnea of 6 months duration. The tachypnea was associated with cough but there was no reported wheeze, dyspnea, choking, gagging, or dysphagia. There was no reported associated fever or other symptoms of viral upper respiratory infection during this time (no rhinorrhea, sneezing, or nasal congestion). The patient's past medical history was notable for infections requiring hospitalizations including grade 2 necrotizing enterocolitis (that was medically treated) and osteomyelitis of the right femur, fever of unknown origin (daily to monthly), idiopathic hemosiderosis, pericardial effusion, mild atopic dermatitis, milk protein allergy, chronic anemia, and fluctuating thrombocytopenia. For his presumed idiopathic hemosiderosis, he had been on daily steroids, but was transitioned to monthly intravenous pulse steroids (30 mg/kg daily for 3 days each month). The patient's work up to that point had included an unremarkable bone marrow biopsy and a peripheral blood smear that was noted to have normal platelet morphology.

His exam at presentation was noted for tachypnea (78/min), tachycardia (121/min), hypoxemia (SaO_2 of 80), and mild hypotension (103/58 mmHg). He was noted to be fussy though consolable, and to have dysmorphic facies that appeared cushingoid with hypertelorism, a flattened nasal bridge, high-arched palate, and large lips. He had coarse breath sounds throughout all lung fields without wheeze, and had mild subcostal retractions but no other signs of distress. His abdominal exam showed no hepatosplenomegaly or masses but there were a few birthmarks of linear vitiligo. He did not have any current eczematous lesions. He had no clubbing or cyanosis but did have hand and pedal edema. His exam was otherwise unremarkable.

Chest X-ray and CT showed worsening interstitial changes. He had been responsive to high-dose steroids for exacerbations up to this point. Extensive infection workup including Mycoplasma pneumoniae, Chlaymdia pneumoniae, legionella, CMV, parvovirus B19, RSV, parainfluenza, adenovirus, and influenza screens and blood culture were negative. A lung wedge biopsy of right middle lobe showed increase in interstitial stromal cells, type II pneumocyte hyperplasia, mixed acute and chronic inflammation (with lymphocytes, plasma cells, and eosinophils), intra-alveolar hemorrhage, pleural hemorrhage and fibrosis, and numerous hemosiderin-laden macrophages. Pathology report, both in-house and from an outside expert, indicated capillaritis as diagnosis. Even though serology showed anti-platelet antibodies, the markers of vasculitis were negative (Table 1). Immune deficiency workup showed lymphocytes without WAS protein expression and sequencing of WAS gene revealed pathogenic mutation (Table 1).

Table1: Laboratory and diagnostic testing.

Laboratory Test	Value	Normal Range

Complete Blood Count		
White blood cell count	16.3 thou/dcL	5-15 thou/dcL
Hemoglobin	8 g/dL	10-15 g/dL
Hematocrit	25.4%	32-43%
Platelets	49 thou/mcL	200-470 thou/mcL
Eosinophils	1.7 thou/mcL	0-1.2 thou/mcL
(Differential normal otherwise)		
Reticulocyte	2%	0.5-1.5%
ESR	87 mm/hr	0-13 mm/hr
CRP	337.7 mg/L	5-9 mg/L
Immunoglobulins		
IgG	2683 mg/dL	175-600 mg/dL
IgA	963 mg/dL	4.4-46 mg/dL
IgM	64.7 mg/dL	20-80 mg/dL
IgE	1416 kunits/L	≤ 30 kunits/L
IgD	3 mg/L	<179 mg/L
Lymphocyte mitogen screen		
PHA stimulation	101,245 cpm	>93,000 cpm
CON A stimulation	154,571 cpm	>76,000 cpm
PWM stimulation	93,829 cpm	>85,000 cpm
FOXP3		
% positive	99%	87-100%
Absolute FOXP3	55 cells/mcL	78-468 cells/mcL
STAT3 Mutation	Negative	Negative
WASp flow cytometry	None expressed	
WAS gene analysis	Pathogenic hemizygous deletion-frameshift (c.106_107delTT; p.F36*)	No mutation
Total complement (CH50)	60 units/mL	30-60 units/mL
Vaccine Titers:		
Tetanus antitoxoid	0.3 IntUnits/mL	>0.15 IntUnits/mL
Haemophilus influenza	>9 mcg/mL	>1 mcg/mL
Streptococcal pneumonia		
Serotype 1	0.9 mcg/mL	>2 mcg/ml
Serotype 3	4.4 mcg/mL	>2 mcg/ml
Serotype 14	9.6 mcg/mL	>2 mcg/ml
Serotype 19	3.1 mcg/mL	>2 mcg/ml
Serotype 23	18.5 mcg/mL	>2 mcg/ml
Serotype 51	4 mcg/mL	>2 mcg/ml
Anti-platelet antibody		
GP IIb/IIIa	Positive	Negative
GP Ia/Iia	Positive	Negative
GP Ib/IX	Positive	Negative
GP HLA Class I	Positive	Negative
Coombs	Negative	Negative
C4	23.8 mg/dL	10-47 mg/dL
ANA	Negative	Negative
Rheumatoid factor	<15 IntUnits/mL	0-15 IntUnits/mL
cANCA	0.47	0-0.79
Myeloperoxidase autoantibody	0.26	0-0.79
HIV-1,2 Antibody	Non-reactive	Non-reactive
Lymphocyte subset panel		
% CD3	73%	62-87%
Absolute CD3	797/uL	570-2400/uL
% CD4	59%	32-64%
Absolute CD4	642/uL	430-1800/uL
% CD8	9%	15-46%
Absolute CD8	97/uL	210-1200/uL
CD4:CD8 ratio	6.56	0.80-3.90
% natural killer cells	10%	4-26%
Absolute NK cells	111/uL	78-470/uL
% CD19	12%	6-23%
Absolute CD19	130/uL	91-610/uL
% CD45RA	16%	5-37%
Absolute CD45RA	530/uL	130-1100/uL
%CD45RO	14%	12-38%
Absolute CD45RO	163/uL	220-1000/uL

Clinical Course

He was admitted to the hospital and placed on broad-spectrum antibiotics but blood, urine, and respiratory cultures remained negative. He underwent echocardiogram to assess for vegetation, and full body MRI to assess for osteomyelitis, both of which were negative. Bronchoscopy was negative for infection. He received pulse intravenous steroids (30 mg/kg, IV, daily for 3 days) without improvement in his respiratory status despite previously favourable response. A trial of IVIG at anti-inflammatory doses (2 gram/kg) was administered without significant benefit.

He continued to be anaemic and thrombocytopenic throughout his hospital admission, and received multiple

transfusions of packed red blood cells, as well as a platelet transfusion. Due to his worsening respiratory status and pulmonary hypertension, he was placed on the lung transplant list.

Given concern for pauci-immune small vessel vasculitis, he was started on rituximab. This was deemed the safer choice over cyclophosphamide, with a concern for hemorrhagic cystitis as a potential life-threatening complication given his bleeding history. He received four weekly doses of rituximab (375 mg/m^2, IV) with resolution of pulmonary hemorrhage and improvement in his respiratory status. Lymphocyte subset panel after rituximab revealed nearly absent B cells. CRP trended down to the low 30's, which is his baseline. Subsequently, he was hospitalized once more due to a CNS bleeding associated with rotaviral gastroenteritis. He is currently undergoing evaluation for unrelated matching donor hematopoietic stem cell transplantation (HSCT); a compatible cord blood unit has been identified.

Discussion

Diffuse alveolar hemorrhage is a medical emergency, most often associated with pulmonary capillaritis. The causes of diffuse alveolar hemorrhage can be divided into cases associated with capillaritis and those without (Table 2) [7-9]. The patient's initial diagnosis prior to this admission was idiopathic pulmonary hemosiderosis, a diagnosis of exclusion, based on initial biopsy where no vessel damage seen. The lung biopsy during this hospitalization, however, was consistent with pauci-immune capillaritis [10,11] and changed the patient's treatment course with rituximab. Treatment for autoimmune disease in WAS may include steroids, cyclophosphamide, azathioprine, IVIG and rituximab [5,12]. Our patient received multiple pulses of high dose methylprednisolone in addition to monthly infusions. Initially, the pulmonary capillaritis responded to methylprednisolone but over time the therapy became less effective. Following rituximab, pulmonary symptoms improved with no further lung hemorrhage once he was treated with rituximab. Neither steroids nor rituximab improved his autoimmune thrombocytopenia. Therefore, the patient is currently waiting on compatible cord blood HSCT.

Table 2: Causes of diffuse alveolar haemorrhage.

With capillaritis	Without capillaritis
Antiphospholipid antibody syndrome	Acute idiopathic pulmonary hemorrhage of infancy
Behcet's disease	Acute respiratory distress syndrome
Churg-Strauss syndrome	Arteriovenous malformations
Cryoglobulinemia	Bone marrow transplantation
Drug-induced capillaritis (retinoic acid, phenytoin, propylthiouracil)	Celiac disease
Goodpasture's syndrome	Chronic heart failure
Henoch-Schonlein purpura	Coagulopathies
Idiopathic pulmonary-renal syndrome	Drug or toxin associated disease
IgA nephropathy	Heiner syndrome
Lung transplant rejection	Idiopathic pulmonary hemosiderosis
Microscopic polyangiitis	Mitral valve stenosis
Mixed connective tissue disease	Pulmonary capillary hemangiomatosis
Pauci-immune pulmonary capillaritis	Pulmonary hypertension
Polyarteritis nodosa	Pulmonary lymphagnioleiomyomatosis
Polymyositis/dermatomyositis	Pulmonary veno-occlusive disease
Systemic lupus erythematosus	Vascular thrombosis
Systemic rheumatoid arthritis	
Wegener's granulomatosis	

Capillaritis is generally associated with systemic autoimmune disease, and capillaritis as an isolated entity is relatively rare [7-9]. However, autoimmune diseases are common in WAS (22% to 77%) [5,6] and vasculitis is a known complication of WAS occurring in approximately 20% of patients [7]. The types of vasculitis found in WAS include cerebral vasculitis, cardiac vasculitis and Henoch-Schonlein purpura [12,13]. The vasculitis of WAS can affect the small and

medium vessels of the stomach, gastrointestinal tract, gallbladder, liver, kidneys, aorta and cerebral vessels. In addition, a necrotizing vasculitis affecting the skin has been described in these patients [12,14,15]. Capillaritis in children is rare and only half of the largest series of 8 children reported had evidence of autoimmune disease [11]. In our case, platelet counts fluctuated between 40-90 thou/mcL and positive anti-platelet antibodies were the only serologic finding of note to suggest autoimmune diseases. Therefore we are left with the conclusion that the pauci-immune capillaritis is a complication of the underlying WAS. Previous reports in patients with WAS with pulmonary involvement occurred in the setting of respiratory infections [6,13,16]. We found no clear evidence of a precipitating infection in our patient.

The etiology behind autoimmunity in WAS is unclear. Structurally disturbed platelets in WAS are predicted to undergo peripheral destruction in spleen to some degree. Studies have shown that dysregulated T-lymphocytes from WAS patients have decreased ability to produce interleukin-2 (IL-2). IL-2 plays a pivotal role in maintaining peripheral tolerance through activation Fas- induced cell death. Without sufficient IL-2 self-reactive T-cells are unable to undergo apoptosis leading to autoimmunity [14]. IL-2 also plays a role in maintaining balance between suppressive and effector cells. IL-2 regulates CD4+CD25+ T-cells which allow for the immunosuppressive effects of IL-4 and IL-10. It also induces interferon-gamma and tumor necrosis factor production [14]. Defective natural killer (NK) cytolytic activity may also contribute to autoimmune disease in WAS. Patients with WAS have an increased frequency of herpesvirus where their NK cells are unable to clear the infection leading to continued inflammation [14,17].

This case highlights the spectrum of clinical presentation of WAS including a rare condition of capillaritis in young children. Expeditious risk/benefit analyses of treatment options must be exercised. Pulse steroid therapy appears to be most effective in pulmonary capillaritis [13] however, it was no longer effective in our case. Severe infection, growth retardation, hypertension, gastrointestinal bleeding, or osteopenia/osteonecrosis can occur as a side effect of steroids. Other anti-inflammatory agents such as IVIG, hydroxychloroquine, azathioprine, or cyclophosphamide can be used as adjunctive immunosuppressants [13]. We opted against cyclophosphamide, due to potential for hemorrhagic cystitis, which could further aggravate our already critically ill patient. Finally, use of rituximab has allowed prevention of further lung hemorrhage and emergent intervention in our case. However, this therapy was ineffective in improving autoimmune thrombocytopenia. The only curative treatment for all aspects of WAS is HSCT, which currently has a survival rate of approximately 90%. Optimum results are obtained from matching sibling donors, but improved outcomes are being seen with alternative donors. A compatible cord blood HSCT is planned along with genetic counseling and female carrier detection. Rituximab should be considered in WAS patients with capillaritis, especially if acute complications occur while evaluating for transplant.

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