Childhood-Onset Sjögren Syndrome Presenting as Pulmonary Hemorrhage

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abstract

Primary Sjögren syndrome is an autoimmune disease characterized by inflammation of the salivary and lacrimal exocrine glands but can also present with systemic extraglandular manifestations, including pulmonary disease. Commonly described pulmonary manifestations of Sjögren syndrome include airway disease, interstitial lung disease, pulmonary arterial hypertension, and lymphoproliferative disorders. However, diffuse alveolar hemorrhage as a sequela of Sjögren syndrome has rarely been described in the adult literature and has never been described in a child. Here we report the case of an 11-year-old girl who presented with diffuse alveolar hemorrhage and was diagnosed with childhood-onset Sjögren syndrome who otherwise lacked typical clinical features, such as sicca symptoms, at the time of presentation. She was successfully treated with corticosteroids and rituximab, with sustained pulmonary remission 1 year post diagnosis. Our case highlights the heterogenous presentation of Sjögren syndrome in the pediatric population and the need for increased awareness among pediatric providers to recognize potential systemic manifestations of this disease to avoid delayed diagnosis.

Primary Sjögren syndrome is a chronic autoimmune disease classically characterized by exocrine gland dysfunction but can also present with systemic organ involvement. Diagnosis of childhood-onset Sjögren syndrome is particularly challenging because sicca symptoms (sensation of dry eye and/or dry mouth) are less common at diagnosis in children compared with adult patients.[1] Children are more likely to present with recurrent parotitis, lymphadenopathy, and systemic symptoms.[1]

Pulmonary involvement has been well described as a potential sequela of Sjögren syndrome and occurs in ~9% to 20% of patients.[2] Interstitial lung disease is a recognized pulmonary manifestation. On the basis of histologic studies, nonspecific interstitial pneumonia is the most commonly reported, followed by usual interstitial pneumonia, lymphoid interstitial pneumonia (LIP), and organizing pneumonia.[3–5] Diffuse alveolar hemorrhage (DAH), a rare and life-threatening manifestation, has rarely been reported with Sjögren syndrome and only in patients diagnosed with Sjögren syndrome in adulthood.[6–8] We present the first reported case of a pediatric patient whose initial presentation of Sjögren syndrome was pulmonary hemorrhage, which was successfully treated with immunosuppression.

CASE REPORT

A previously healthy 11-year-old girl presented in August 2019 to a local

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emergency department for evaluation of acute-onset chest pain and fever in the setting of a 1-week history of fatigue and myalgias. She was initially diagnosed with a viral illness. With ongoing symptoms and new-onset respiratory distress, she presented to our hospital's emergency department for reevaluation 3 days later. Vital signs at presentation included tachycardia to 140 beats per minute, tachypnea of 30 breaths per minute, and oxygen saturation of 94% on room air. Laboratory work revealed a hemoglobin level of 4.6 g/dL. The patient also had an elevated erythrocyte sedimentation rate of 53 mm/hour and a C-reactive protein level of 2.7 mg/dL, consistent with systemic inflammation. A chest computed tomography scan revealed extensive bilateral airspace opacities (Fig 1A), most concerning for pulmonary hemorrhage or infectious process. She was admitted to the PICU for noninvasive positive pressure ventilation, antibiotic treatment, and packed red blood cell transfusion.

After initial stabilization, pulmonary function testing was performed and revealed significantly elevated diffusion lung capacity of carbon monoxide of 169% predicted and restrictive physiology, with a total lung capacity of 67% predicted. The elevation in diffusion lung capacity of carbon monoxide was concerning for pulmonary hemorrhage because blood in the lining of the alveoli can bind carbon monoxide. Flexible bronchoscopy was pursued and revealed diffuse mucosal pitting and bloody return on bronchoalveolar lavage, with >130 000 red blood cells per mm^3, confirming pulmonary hemorrhage. No organisms grew from the bronchoalveolar lavage fluid, and broad infectious testing results were negative, so antibiotics were discontinued. A lung biopsy via video-assisted thoracoscopic surgery was performed, and the pathology revealed marked alveolar hemorrhage with hemosiderin laden macrophages, LIP, and extensive vascular remodeling (Fig 1B). Because of extensive vascular remodeling, an echocardiogram was obtained and revealed normal segmental cardiac anatomy, normal biventricular function, and no evidence of pulmonary hypertension. The N-terminal pro–B-type natriuretic peptide level was also normal.

Given systemic inflammation and evidence of interstitial lung disease with negative results on infectious testing, a rheumatologic workup was pursued because of high suspicion of a connective tissue disorder. Results revealed a positive antinuclear antibody level, with a titer of 1:1280 in a speckled pattern, and positive anti-SSA/Ro and anti-SSB/La antibody levels. Additional findings included a positive rheumatoid factor of 72.7 IU/mL and a total immunoglobulin G level of 1552 mg/dL, which is near the upper limit of normal. Pertinent negative findings included negative anti-double stranded DNA, anti-Smith, and anti-phospholipid antibody levels. Although LIP has rarely been reported in patients with systemic lupus erythematosus and juvenile idiopathic arthritis, our patient did not meet American College of Rheumatology or Systemic Lupus Erythematosus International Collaborating Clinics classification criteria for systemic lupus erythematosus, nor did she have any arthritis to suggest juvenile idiopathic arthritis. The result of an enzyme-linked assay for myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibodies was negative, as was that for anti-glomerular basement membrane antibodies, making anti-neutrophil cytoplasmic antibody–associated vasculitis and Goodpasture syndrome, respectively, unlikely causes for this patient's pulmonary hemorrhage. Urine studies revealed no evidence of nephritis, which can be seen in lupus or renal tubular acidosis, which can be seen in Sjögren syndrome.

In the setting of positive anti-SSA/Ro and anti-SSB/La antibody levels

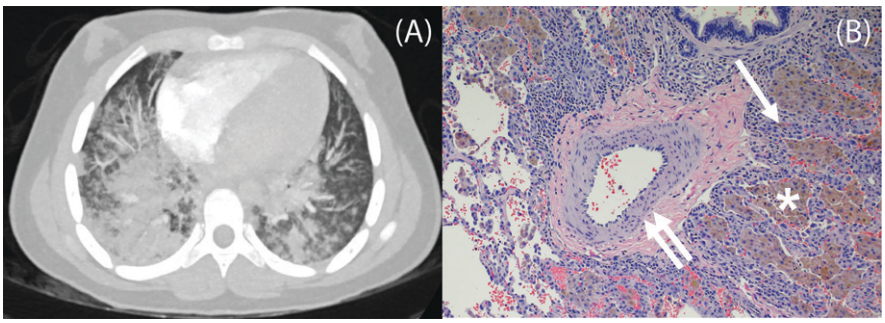

FIGURE 1

A, Chest computed tomography scan revealing bilateral airspace disease with ground-glass nodules. B, Lung biopsy specimen revealing vascular remodeling (double arrows), hemosiderin laden macrophages (star), and LIP (arrow).

and LIP on the lung biopsy specimen, there was concern for Sjögren syndrome as the etiology of her presentation. A Schirmer's test by using filter paper to evaluate for dry eyes was performed, and the results were normal bilaterally. The patient also denied any subjective sicca symptoms and had no significant history of dental caries. Salivary gland ultrasound (SGUS) imaging was obtained of her bilateral parotid and submandibular glands. In contrast to a normal submandibular gland from a healthy control (Fig 2B), the patient's imaging revealed global inhomogeneity of the tissue, multiple hypoechoic lesions, and hyperechogenic reflections in her submandibular glands (Fig 2A), consistent with subclinical salivary gland involvement.

On the basis of her evaluation, the patient was diagnosed with childhood-onset Sjögren syndrome. Because of life-threatening pulmonary hemorrhage, the patient was treated with high-dose intravenous methylprednisolone at 1000 mg daily for 3 days, followed by daily oral prednisone. Rituximab, an anti-CD20 monoclonal antibody, was also given as part of induction therapy at a dose of 375 mg/m^2 once a week for 4 weeks. Rituximab is increasingly used to treat patients with systemic manifestations of Sjögren syndrome[9,10] and has also revealed efficacy for treatment of DAH in other diseases, such as granulomatosis with polyangiitis.[11] In addition, the patient was also started on hydroxychloroquine.

The patient responded well to induction therapy, with normalization of hemoglobin and inflammatory marker levels. She was able to wean off prednisone 4 months after her initial diagnosis. One year after disease onset, she undergoes maintenance rituximab infusions every 6 months and continues hydroxychloroquine and has shown no signs of recurrent hemorrhage.

DISCUSSION

We report a case of childhood-onset Sjögren syndrome, presenting with DAH and LIP, that was successfully treated with immunosuppression. Pulmonary manifestations have been well described in Sjögren syndrome, but DAH remains a rare manifestation that has only been described a handful of times in the literature and has never been reported as the presenting symptom in childhood-onset Sjögren syndrome.

A review of available literature revealed a previous report of DAH in an adult patient with Sjögren syndrome but in the setting of cryoglobulinemia and thrombotic microangiopathy.[7] Although we did not test our patient for the presence of cryoglobulins, she did not have physical examination findings typical of cryoglobulinemia, such as skin purpura or ulceration. She also had normal complement levels and a negative testing result for acute hepatitis.

DAH with concurrent nonspecific interstitial pneumonia has also been reported post mortem in an adult patient found to have Sjögren syndrome.[6] This patient received warfarin therapy for a history of atrial fibrillation, and it is unclear what role anticoagulation may have played in his presentation. He did not respond to immunosuppressive treatment and ultimately died.

There are reports of patients with a previous diagnosis of recurrent idiopathic pulmonary hemosiderosis (IPH) in childhood who were diagnosed with Sjögren syndrome in adulthood.[8,12] IPH is a rare disease, commonly presenting in childhood, characterized by recurrent episodes of DAH without a clear identifiable cause, although it is possible that the diagnosis could be missed. Certainly, there is a role of progressive autoimmunity in IPH. In one study of long-term outcomes of IPH in children, researchers found that ~25% of patients over time developed an identifiable systemic autoimmune disease,[13] but it is also

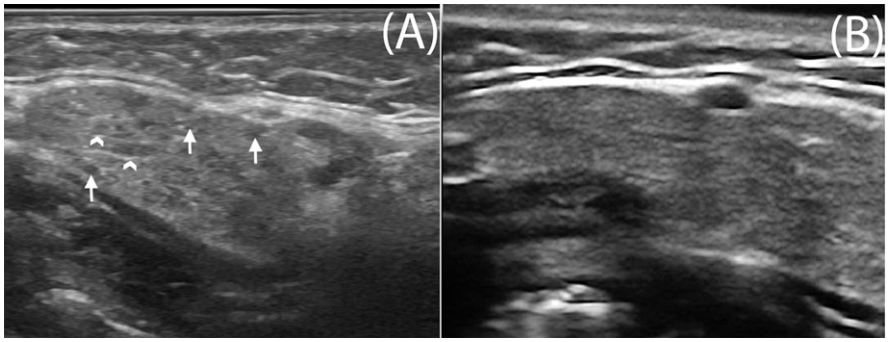

FIGURE 2
A, Ultrasound of the submandibular gland from the patient reveals global heterogeneity of the gland, presence of multiple hypoechoic areas (arrows), and hyperechogenic reflections (arrowheads). B, Ultrasound image of a normal submandibular gland from a healthy control.

possible that Sjögren syndrome was overlooked as the cause of alveolar hemorrhage. Increased awareness of Sjögren syndrome as a potential etiology could lead to earlier diagnosis, appropriate treatment, and possible prevention of sequelae, such as pulmonary fibrosis.

Our case illustrates the inherent variability in the presentation of childhood-onset Sjögren syndrome. For the pediatric primary care provider, it may be misleading to focus primarily on the presence of sicca symptoms alone to guide index of suspicion. Subjective sicca symptoms are often late findings of the disease and therefore less common in children compared with adults. Recurrent parotitis, in contrast to sicca symptoms, is the most common presenting feature in the pediatric population. Primary care providers should consider Sjögren syndrome in children with recurrent episodes of parotid swelling without infectious cause.[1,14]

Further complicating the diagnosis of Sjögren syndrome for pediatricians, guidance, such as the 2016 American College of Rheumatology and European League Against Rheumatism classification criteria,[15] developed for adult patients has low sensitivity when applied to pediatric populations.[16] To improve diagnostic accuracy of pediatric Sjögren syndrome, Bartůnková eta al[17] proposed a set of pediatric-specific criteria, which is not yet validated and not routinely used in clinical practice.

SGUS is a potential noninvasive method to aid in diagnosis, especially in the setting of subclinical manifestations.[18,19] Studies have revealed adequate sensitivity and specificity regarding SGUS abnormalities in Sjögren syndrome.[19,20] Mossel et al[21] also demonstrated good correlation in patients with Sjögren syndrome between SGUS and the current gold standard of salivary gland biopsy. Because SGUS has become increasingly used in clinical practice, Takagi et al[22] have suggested a classification criterion that integrates the 2016 American College of Rheumatology and European League Against Rheumatism criteria with salivary ultrasound scoring. This method revealed improved diagnostic accuracy of Sjögren syndrome that more closely reflects the clinical diagnosis of Sjögren syndrome compared to classification criteria.[22] However, this set of classification criteria is not yet validated.

Lack of pediatric-specific diagnostic criteria makes Sjögren syndrome a challenging diagnosis in children. Pediatric providers must remain vigilant for unusual manifestations of Sjögren syndrome in the pediatric population. Pulmonary conditions, such as DAH and interstitial lung disease, can be the initial presenting symptom of pediatric inflammatory connective tissue disease, such as Sjögren syndrome. A high index of suspicion and broad differential diagnosis with comprehensive laboratory evaluation and imaging is important to prevent incorrect or delayed diagnosis.

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ABBREVIATIONS

DAH: diffuse alveolar hemorrhage
IPH: idiopathic pulmonary hemosiderosis
LIP: lymphoid interstitial pneumonia
SGUS: salivary gland ultrasound

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