Case Report

Primary Sjögren's Syndrome in Dizygotic Adolescent Twins: One Case with Lymphocytic Interstitial Pneumonia

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ABSTRACT. Primary Sjögren's syndrome (pSS) is uncommonly recognized in childhood, and familial cases are rare. Pulmonary involvement in pediatric pSS is infrequently reported. In adults, asymptomatic pulmonary involvement is increasingly recognized, manifest by pulmonary function test abnormalities and changes on high resolution computerized tomographic scan. We describe a case of pSS in a 14-year-old Vietnamese-Canadian girl who presented with pulmonary symptoms, radiologic changes, and biopsy confirmation of lymphocytic interstitial pneumonia. Her dizygotic twin sister has primary SS without extraglandular manifestations. To our knowledge this is the first report of pediatric pSS with lymphocytic interstitial pneumonia and multiple pulmonary nodules on chest radiograph. We review the literature on pulmonary involvement and familial cases of pSS in childhood. (J Rheumatol 2005;32:1603–6)

Key Indexing Terms:
CHILD SJÖGREN'S SYNDROME LYMPHOCYTIC INTERSTITIAL PNEUMONIA TWINS

Childhood onset of primary Sjögren's syndrome (pSS) is uncommon, and has a lower frequency of sicca symptoms and a higher frequency of parotitis than adult onset disease[1]. Although extraglandular manifestations may be present, they are seldom severe[2]. Familial occurrence of pSS is uncommon at any age[2-4]. We describe dizygotic twins with adolescent onset of pSS, one of whom had lymphocytic interstitial pneumonia.

CASE REPORTS

Patient 1. A 14-year-old previously healthy Vietnamese-Canadian girl presented to her primary physician with a one month history of cough and mild shortness of breath on exertion. She denied orthopnea, chest pain, hemoptysis, fever, weight loss, or night sweats. There was no history of travel, tuberculosis exposure, or animal exposure. She had dry mouth, occasional epistaxis, and fatigue, but no ocular sicca symptoms, alopecia, rash, photosensitivity, oral or nasal ulcers, or gastrointestinal, genitourinary or musculoskeletal symptoms. She had not missed any school due to her illness and had received no treatment.

Her history included 4 transient episodes of right-side parotitis that resolved over 7 to 10 days with oral antibiotic therapy alone. The first of these episodes was at age 3 and they were not otherwise investigated and pSS was not diagnosed; the last episode was at age 10. She had frequent dental caries and a dental abscess. She has a dizygotic twin sister with pSS.

When seen at British Columbia's Children's Hospital examination revealed a well looking adolescent girl with temperature 37.4°C, heart rate 90/min, respiratory rate 22/min, and oxygen saturation 96% in room air. She was not dyspneic but had an occasional nonproductive cough. The conjunctivae were clear and eyes moist. The mouth was dry with poor salivary pool and poor dentition. There was no facial rash, and no nasal or oral ulcer. She had small mobile anterior and posterior cervical lymph nodes but no generalized lymphadenopathy and no parotid enlargement or tenderness. She had mild clubbing, diminished breath sounds at both bases, and diffuse crackles throughout both lung fields. Cardiac, abdominal, musculoskeletal, neurologic, and dermatologic examinations were normal.

Ophthalmologic evaluation revealed mild right keratitis. Schirmer's test and Rose-Bengal stain were not done. Investigations shown in Table 1 were in addition to tests to exclude infection and malignancy. Diagnostic imaging and histopathology are shown in Figure 1. A biopsy of a right lower lobe lesion was consistent with lymphocytic interstitial pneumonia (LIP).

She was treated with 3 daily pulses of intravenous methylprednisolone (1 g/day) and then with prednisone (1 mg/kg/day) and hydroxychloroquine. Her prednisone was tapered, with clinical and radiographic improvement.

Patient 2. The dizygotic twin sister of the first patient was diagnosed with pSS one year previously on the basis of recurrent parotitis (annually since age 7) and the laboratory abnormalities listed in Table 1. Previous episodes of parotitis were treated with oral antibiotic, typically resolved over 5 to 7 days, and were not investigated. At age 13 she presented with bilateral parotitis unresponsive to intravenous antibiotic and was treated with prednisone and hydroxychloroquine, had complete resolution of her parotid swelling, and has had no further recurrences. She has no oral or ocular sicca symptoms and no clinical features suggestive of lupus. She has not had any respiratory symptoms and chest radiography is normal. She continues to have persistent hypergammaglobulinemia and elevated erythrocyte sedimentation rate and is currently being treated with hydroxychloroquine and low dose prednisone.

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Table 1. Clinical and laboratory features in our 2 cases.

	Reference Values	Patient 1	Patient 2
Clinical features		PS, X	PS
Extraglandular features		LIP	None
Pulmonary function	FEV1/FVC	100	Not done
	FVC%	60	
	FEV1%	66	
	DLCO	80% predicted	
Ro/SSA (U/ml)	0–46	1166	1165
La/SSB (U/ml)	0–14	879	749
ANA	< 1:40	1:1280	1:1280
RF Latex titer	< 1:2	1:512	1:32
IgG (g/l)	7.16–17.11	44.9	24.8
IgA (g/l)	0.47–2.49	5.89	2.33
IgM (g/l)	0.15–1.88	19.1	3.64
Anti-dsDNA by RIA	Neg	Neg	Neg
Anti-Smith (U/ml)	0–40	45	35
Vesmatic ESR (mm/h)	< 31	100	70
White blood cell ($\times 10^9$/l)	3.9–10.2	6.28	3.72
Hemoglobin (g/l)	117–149	102	100

PS: history of parotid swelling; X: history of xerostomia; LIP: lymphocytic interstitial pneumonia; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: lung diffusion capacity of carbon monoxide; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate.

DISCUSSION

These 2 sisters illustrate 2 unusual features of juvenile pSS: familiality and pulmonary involvement. There are only 3 previous reports of pulmonary involvement in pSS[5-7] and 3 reports of affected siblings[2-4].

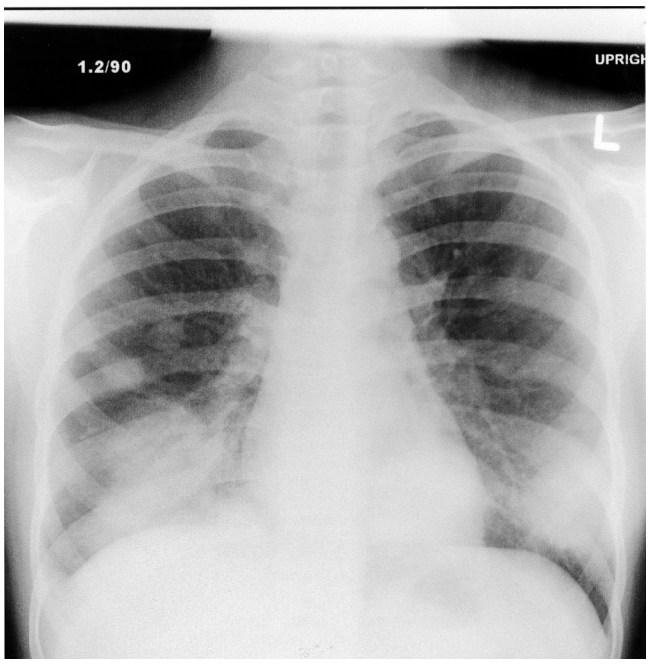
One report described a 2-year-old girl with recurrent upper respiratory tract infection and diffuse interstitial infiltrations on chest radiograph, and with lymphocytic infiltrate on parotid biopsy. Clinically she responded to corticosteroid therapy; radiographic abnormalities persisted for an unstated period[6]. The other reports provide minimal clinical information: a 24-year-old woman with a 14 year history of episodic fever, arthralgia, adenopathy, and parotitis had no respiratory symptoms and normal chest radiograph, but low DLCO associated with normal lung volumes[5]. The last report describes one of 42 children with pSS as having interstitial pneumonia but provides no other clinical details[5,7].

Reports of pulmonary involvement in adult patients with pSS vary from 9% to 60% depending on the variables measured[8,9]. Interstitial lung disease and small airways disease are most frequent, are associated with Ro/SSA, and often present early in the disease course. A review of high resolution computerized tomography (CT) abnormalities in 60 adults with pSS and pulmonary symptoms showed ground-glass attenuation (92%), small subpleural nodules (78%), non-septal linear opacity (75%), interlobular septal thickening (55%), bronchiectasis (38%), and cysts (30%)[10]. Airspace consolidation was recognized in 25%. Large nodules, as were found in our patient, are infrequently reported in the absence of another disease process such as amyloidosis or sarcoidosis[11,12]. LIP occurs in 0.9% of pSS patients, and is characterized by interstitial reticulonodular infiltrates with or without consolidation on diagnostic imaging, restricted lung volumes, low diffusion on pulmonary function test, and diffuse interstitial lymphoid infiltrate on biopsy[13]. Thus our Patient 1 is unique in that LIP has not been recognized in pediatric pSS, and multiple parenchymal nodular densities are unusual radiographic and CT findings for LIP.

The only other sibling pairs with probable childhood pSS reported in the English literature are summarized in Table 2[2-4]. Familial cases of pSS are also infrequently reported in the adult population[14,15]. Clinical manifestations are remarkably similar between siblings. Genetic studies of pSS reveal strong associations with HLA-DR3; homozygosity may be associated with younger age of onset[16]. pSS is probably a polygenic disorder resulting from several genes interacting with environmental factors. Future studies comparing the clinical, serological, and genetic features of familial pSS are needed to gain further understanding of the phenotypic-genotypic relationship of pSS.

It is important to note that in both our patients recurrent parotitis was the initial clinical manifestation of pSS. Recurrent parotitis is common in childhood and the differential diagnosis is broad, including idiopathic (non-autoimmune), mechanical (stone, stricture), infectious (bacterial, viral), and malignant and inflammatory (SS) etiologies. Recurrent parotitis in childhood is a well described condition of unknown etiology. It likely represents recurrent attacks of ascending infection due to a congenital abnormality of the salivary gland ducts. The peak incidence is in boys aged 3 to 6 years, and symptoms tend to resolve near puberty. The initial presentation is usually unilateral parotid swelling of gradual or sudden onset, in the absence of sicca complex or systemic symptoms[17]. Treatment is conservative, and most cases resolve with expectant management. Infectious parotitis and malignant infiltration of the parotid gland tend to have a distinct clinical presentation. Clues that recurrence of parotitis may indicate SS are onset in late childhood or early adolescence, with the presence of sicca symptoms, rash, arthralgia, systemic symptoms, and positive autoantibodies to nuclear antigens Ro/SSA and La/SSB. A recent review of our clinic population and of reports from the literature found parotitis to be present in 54% (72/133) of cases of childhood onset pSS[1]. Thus, recurrent parotitis in a child or adolescent should alert the clinician to possible pSS.

Our case reports are limited by the absence of objective evidence of ocular or salivary gland involvement. Neither case fulfills either the validated American-European Consensus Group classification criteria for adults[18] or proposed diagnostic criteria for children[19]. Tests to document objective evidence of salivary gland involvement (salivary scintigraphy, parotid sialography, unstimulated salivary



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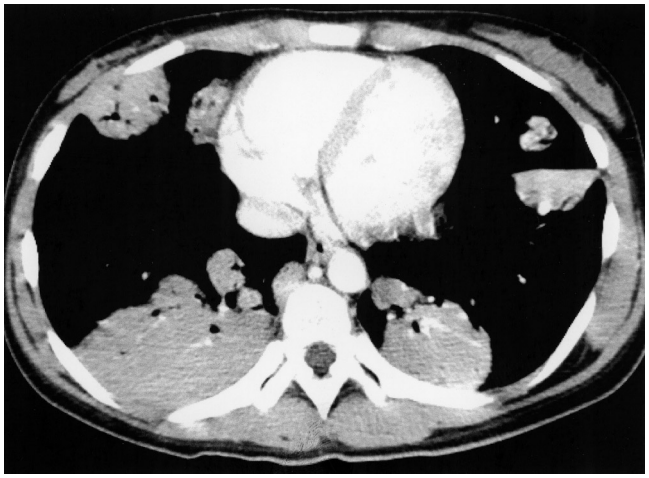

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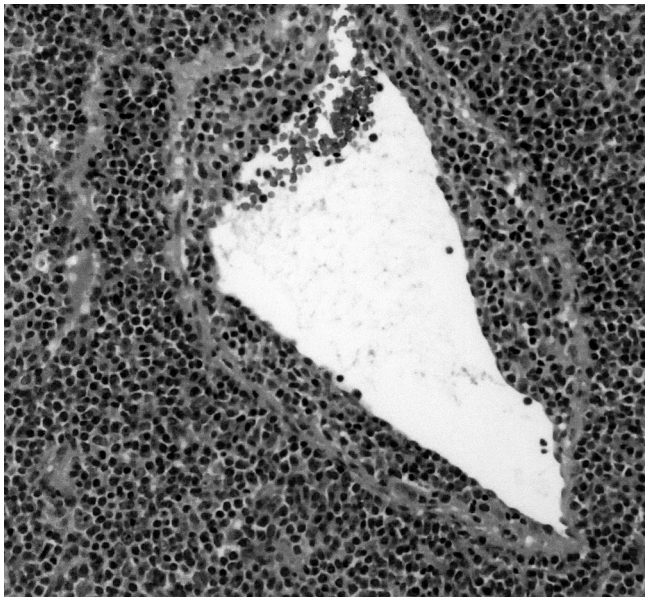

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Figure 1. Patient 1. Diagnostic imaging and histopathology. A. Chest radiograph (AP) on initial presentation shows multiple bilateral areas of abnormal pulmonary consolidation with the largest in the lower lobes. B. CT scan (enhanced) through the lower lung fields showing multiple parenchymal densities with air bronchograms in both lungs ranging from 1 to 8 cm diameter. There is no mediastinal lymphadenopathy. C. Lung biopsy showing bronchiole with predominant lymphocytic infiltrate (right) and germinal center (lower left). Higher resolution shows sheets of lymphoid cells with predominant plasmacytoid features. No Hodgkin's cells are seen. Immunohistochemistry: mixed B and T cell lineage. Flow cytometry: reactive population of cells without kappa or lambda restriction. There is no clonality. Epstein-Barr virus; negative. (Figure 1C courtesy of Dr. G. Jevon. Original magnification × 100.)

Table 2. Siblings with pediatric pSS reported in the literature.

Age at Onset	Sex	Relationship	Clinical Features	Laboratory Features	Reference
4^1, 8^2	F	Siblings	KS[1,2], X[1,2], achalasia[1,2], gastric hyposecretion[1,2]	Not recorded	3
9^1, 10^2	F	Identical twins	Bilateral dacryoadenitis; KS	ANA: negative[1]/1 in 40[2] anti ds DNA, ENA, RF negative[1,2] biopsy*	4
12^1, 13^2	M	Identical twins	PS[1,2], KS[1]	RF–[1], RF+[2] ANA+[1,2], SSA/SSB+[1,2], Hypergammaglobulinemia[1,2]	2

KS: keratoconjunctivitis sicca; X: xerostomia, PS: parotid swelling; * non-granulomatous interstitial lymphoid infiltrate in lacrimal gland (Twin 1); lymphoid infiltration minor salivary gland (Twin 2). [1] Sibling 1; [2] sibling 2.

flow), objective evidence of ocular involvement (Schirmer test, Rose-Bengal score), and minor salivary gland biopsy to characterize histopathological features would undoubtedly aid in confirming the diagnosis. However, on review of risks and benefits of the above ancillary tests, consultants' consensus opinion unanimously favored a diagnosis of pSS, and tests were deferred. Noninvasive investigations including ultrasound, magnetic resolution imaging (MRI), and MRI sialography are promising alternatives to conventional invasive tests to detect salivary exocrine gland structural change[20]. Increased availability and widespread use of noninvasive investigations may aid in the development of validated diagnostic criteria for childhood pSS. Until such time, clinical acumen will prevail as the gold standard.

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