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Autoimmunity Reviews 5 (2006) 132–135
AUTOIMMUNITY REVIEWS
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A short review of the pathogenesis of Sjögren's syndrome

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Available online 28 September 2005

Abstract

Sjögren's syndrome can present in a heterogeneous manner with symptoms varying from systemic features such as unexplained fever, weight loss and neurological manifestations to the more typical symptoms of dry mucus membranes. There is discussion of the wide differential diagnosis, followed by a brief overview of the diagnosis, extraglandular manifestations and pathogenesis of primary Sjögren's syndrome.

Keywords: Primary Sjögren's syndrome; T and B cell activation; Epithelial cells; Apoptosis retroviruses

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1. Background

In order to discuss the multitude of diagnostic possibilities, a case of a 26 year old Caucasian woman is described. The patient was originally from Australia, had been in the UK for 6 months following an overland trip through south-east Asia, and worked in the administration department of a hospital. She lived in a house with 14 other people, was a non-smoker and drank about 24 units of alcohol per week. She did not participate in illegal drug-taking.

Her presenting complaint was one of a 2 month history of a 'flu-like illness characterised by pharyngitis, rhinorrhoea, cough, sputum, wheeze, fevers and mouth ulcers; followed by a symmetrical polyarthritis affecting mainly her hands. Her arthritic symptoms were intermittent, always following a febrile illness each of which lasted for about 1 week. There was no other significant history relating to the presenting complaint. She had a past medical history of asthma and eczema, and her mother was taking methotrexate for rheumatoid arthritis.

Clinical examination revealed synovitis of her right 2nd and 3rd metacarpo-phalangeal joints (MCPJs) and her left 2nd MCPJ, a small aphthous ulcer on the lateral side of her tongue and a scattered polyphonic wheeze. She had no lymphadenopathy or hepatosplenomegaly, and the clinical examination was otherwise normal.

Investigations revealed a raised inflammatory response with an ESR of 58 mm/hr, CRP of 46g/dl,

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doi:10.1016/j.autrev.2005.08.005

normal lymphocytes and eosinophils, an anti-streptolysinO titre (ASOT) mildly elevated, negative parvovirus serology, and a weakly positive ANA but negative rheumatoid factor. In addition she had normal hand, feet and chest radiographs. Sputum culture revealed normal respiratory flora, and blood cultures were sterile.

On review 2 weeks later, she had deteriorated dramatically with a widespread active synovitis, ongoing fevers, pharyngitis and haemoptysis. Furthermore, she had lost nearly 5 kgs in weight. Once again, there was no evidence of lymphadenopathy or organomegaly on clinical examination. The differential diagnosis at this stage ranged from rheumatoid arthritis and other inflammatory arthritides, parvovirus-associated arthritis, post-streptococcal arthritis, to Churg-Strauss syndrome, Wegener's granulomatosis, tuberculosis and HIV. Investigations aimed at narrowing the differential included:

Investigation	Result
Sputum ZN stain and culture for mycobacterium	Negative ZN stain and culture after 12 weeks
HIV1 and 2	Negative
cANCA, anti-GBM	Negative
AntiCCP antibodies	Negative
High-resolution CT chest	Moderate left sided pleural effusion and right sided bronchiectasis (Fig. 1A)
Pulmonary function tests	Mild restrictive defect with reduced transfer factor (KCO)
Bronchoscopy and broncho-alveolar lavage	Non-contributory
Anti-Ro and La antibodies	Positive
Lower lip biopsy	See Fig. 1B
Schirmer's test	4 mm in 5 min

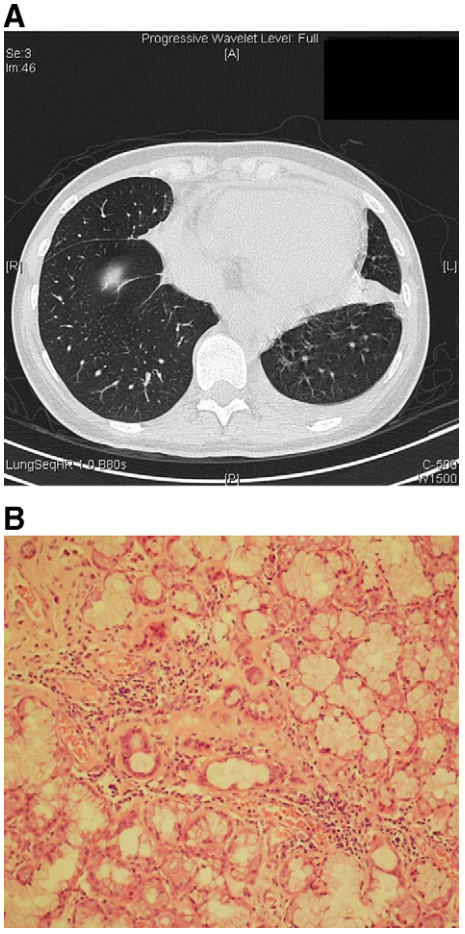

Fig. 1. A) CT scan of chest showing right sided pleural effusion and bronchiectatic changes in the left lung. B) Histology of lower lip salivary gland biopsy showing focal lymphocytic aggregates.

2. Discussion

This case highlighted a diagnostic conundrum with many potential diagnoses. The definitive diagnosis of primary Sjögren's syndrome (pSS) was reached through concordance with the American–European consensus group diagnostic criteria [1]: the patient had symptoms of dry eyes and a dry mouth daily for >3months with a positive Schirmer's test; positive Ro and La autoantibodies; and a minor salivary gland biopsy showing a focus score of >1.

Pulmonary involvement in Sjögren's syndrome is well documented with xerotrachea causing cough, lymphocytic interstitial pneumonitis (LIP) and pleural effusions due to serositis the most commonly reported [2,3]. Bronchiectasis is rarely associated with pSS. Other systemic manifestations of pSS include arthritis, renal tubular acidosis, haematological involvement (such as auto-immune haemolytic anaemia), cryoglobulinaemia, cutaneous vasculitis and neurological involvement.

The pathology of pSS is not fully understood. There is an infiltration of both T and B lymphocytes in to the exocrine glands [4]. T cells are characterised by CD4+CD45RO+ve cells, which secrete IFNγ and IL10 and are poorly proliferative [5,6]. In a mouse model of SS, the disease can be induced by adoptively transferring fodrin (a putative auto-antigen, involved in apoptosis)-stimulated CD4+ cells into normal syngeneic recipients [7]. A more recent study has determined the role of Id3 in the development of SS. Id3 is an early response gene involved in T cell receptor-mediated cell selection. Id3 knockout mice develop SS and adoptive transfer of Id3 knockout T cells caused SS in non-susceptible mice [8]. Cytotoxic CD8+ CD103+ve T cells have been described to localise around epithelial cells and may contribute to the destruction or activation

of these cells [9]. Indeed, epithelial cell activation has been proposed by some to be the major pathological process in Sjogren's syndrome with increased expression of Class II antigens, and Fas on epithelial cells in this disease [10]. That apoptosis is involved in the pathogenesis of Sjogren's syndrome is supported by Ro and La antibodies expressed on the surface of apoptotic cells which are found in the inflamed salivary glands [11] and this association of Ro and La antibodies with apoptotic cells may play a role in the pathogenesis of neonatal lupus and congenital heart block in children of mothers with pSS [12,13]. B lymphocytes account for up to 20% of the cells found in the salivary tissue. B cell activation leads to the production of autoantibodies and polyclonal hyper-gammaglobulinaemia characteristic of SS, and the B cell activation may account for the increased propensity of these patients to developing lymphomas [14]. BLyS (or BAFF) is a member of the TNF superfamily, and is involved in B cell maturation and survival. It is found at increased levels in serum, salivary tissue and synovial fluid of patients with pSS, and is expressed by T cells [15]. Moreover, BLyS transgenic mice display a phenotype similar to pSS or SLE [16]. These data together imply a role for T and B cell interaction in the pathogenesis of pSS.

A viral aetiology is suggested by several pieces of evidence: there is persistence of both CMV and EBV viral particles in the salivary glands of patients with Sjögren's syndrome [17]; retroviruses such as HIV and HTLVI can cause syndromes very similar to Sjögren's [18], and a transgenic mouse overexpressing the HTLV1 tax gene suffers from sialadenitis, suggesting that a single viral gene product can generate inflammation [19]. More recently, an association between SS and a human endogenous retrovirus (HERV-K113) allele has been described [20]. Furthermore in a small study of 7 patients with Sjögren's syndrome, treatment with zidovudine resulted in significant clinical improvement [21]. Molecular mimicry may also play a role: the La antibody shows sequence homology with the retroviral gag protein [22], while there is sequence homology with Ro and La and feline retroviruses [23].

Take-home messages

- pSS is autoimmune disorder characterised clinically by salivary and lacrimal gland destruction and hypofunction; and a multitude of extraglandular manifestations including renal; pulmonary; neurological and haematological abnormalities; and an increased propensity to develop B cell lymphoma.
- The pathogenesis may involve the persistence of viral antigens in the salivary tissue; particularly the retroviruses.
- Pathological findings involve infiltration of T and B cells of an activated memory phenotype, and destruction of the epithelial cells.
- Abnormal regulation of apoptosis may play a role in the activation of the infiltrating cells and of the epithelium.
- Anti-Ro and -La antibodies are useful in the diagnosis, and may be pathogenic.

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Clinical HLA, and small bowel immunohistochemical features of children with positive serum antiendomysium antibodies and architecturally normal small intestinal mucosa.

Antiendomysium antibodies have a high sensitivity and specificity for celiac disease. A small percentage of subjects positive for these antibodies have a small intestinal mucosa hitherto considered normal. Paparo F. et al. (Am J Gastroenterol 2005;100:2294–8) conducted this study in order to characterize the clinical, serological, immunogenetic, and immunohistological features of these subjects. From 409 patients who were positive for celiac-related antibodies, the authors selected 24 (5.9%) patients who had normal small intestinal mucosa. One hundred age-matched celiac patients with a "flat" small intestinal mucosa, and 50 age-matched nonceliac children were also studied. Eleven (45.8%) of the 24 patients had a distinct infiltrate pattern, i.e., an increase in CD3+ intraepithelial lymphocytes (>2SD of the nonceliac group), whereas 17 (70.8%) had a higher density of intraepithelial gammadelta+ cells. In 17 (70.8%) patients, the number of lamina propria CD25+ cells was increased and/or the expression of ICAM-1 and crypt HLA-DR was enhanced. The authors conclude that most of the patients with serum antiendomysium antibodies and normal jejunal histology showed immunohistochemical signs of immune activation in the epithelium, lamina propria, and crypts. They recommend that such patients be monitored to assess their progress and to determine whether they need a gluten-free diet.

Neuropsychologic functioning and health status in systemic lupus erythematosus: Does ethnicity matter?

Despite increased severity of lupus in blacks, including more frequent neuropsychiatric manifestations, there is sparse data on neuropsychlogic function in black patients with lupus. Doninger NA. et al. (J Clin Rheumatol 2005;11:250–56)examined neuropsychologic functioning and health-related variables among blacks (n = 34) and whites (n = 14) fulfilling ACR criteria for SLE. Blacks and whites performed comparably on measures of verbal and visual memory, working memory, and motor speed after controlling for estimates of premorbid cognitive ability. Black trended towards poorer performance on specific attention/processing speed measures. Pain, fatigue, depression, anxiety, physical and emotional well-being were unrelated to ethnicity. Ethnicity-related differences in overall damage, noncognitive neuropsychiatric manifestations, and prevalence of nephritis revealed greater severity among blacks. Blacks evidencing lower premorbid ability may be at greater vulnerability for poorer functional outcomes (e.g., coping skills, medical compliance and employment) if they experience disease-related cognitive dysfunction.