



Prognostic value of Sjögren's syndrome autoantibodies

R. Hal Scofield^{1,2,3}, Anum Fayyaz^{1,2,3}, Biji T. Kurien^{1,2,3}, Kristi A. Koelsch^{1,2,3}

¹Arthritis & Clinical Immunol Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; ²Department of Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; ³Medical and Research Services, US Department of Veterans Affairs Hospital, Oklahoma City, OK, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: RH Scofield, A Fayyaz; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: R. Hal Scofield, MD. Arthritis & Clin Immunol Program, Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104, USA. Email: Hal-Scofield@omrf.ouhsc.edu.

Abstract: Sjögren's syndrome is in part considered an autoimmune disease because patient sera contain antibodies binding self-structures. In fact, in addition to anti-Ro (or SSA) and anti-La (or SSB), which are included in the classification criteria, there are a wide variety of autoantibodies found among these patients. We reviewed English-language MEDLINE sources. Anti-Ro and anti-La found among healthy individuals, including mothers giving birth to infants with neonatal lupus, predicts future connective tissue disease. Those with Sjögren's syndrome can be divided into two groups; patients with only exocrine gland involvement and those with systemic disease. The presence of anti-Ro/La is associated with systemic, extraglandular disease. Rheumatoid factor is also associated with extraglandular disease while anti-cyclic citrullinated peptide (CCP) is likely associated with inflammatory arthritis and progression to rheumatoid arthritis. Anti-mitochondrial antibodies are uncommon but predict progression to primary biliary cirrhosis. Cryoglobulinemia is found in excess among those with non-Hodgkin's lymphoma. Determination of autoantibodies on the sera of Sjögren's syndrome patients has prognostic implications for Sjögren's syndrome itself as well as associated diseases.

Keywords: Sjögren's syndrome; autoantibodies; prognosis; congenital heart block

Received: 18 June 2018; Accepted: 15 August 2018; Published: 30 October 2018.

doi: 10.21037/jlpm.2018.08.05

View this article at: <http://dx.doi.org/10.21037/jlpm.2018.08.05>

Introduction

Sjögren's syndrome is characterized by the presence autoantibodies in the sera of patients. The common specificities, which are included in various classification criteria (1-3) as well as diagnostic schema, are anti-Ro (or SSA) and anti-La (or SSB). However, a large number of autoantibodies have been identified in the sera of these patients. There are data suggesting autoantibodies are produced within the disease salivary gland (4,5), and data suggesting that some autoantibodies in Sjögren's may be pathogenic (6). We herein review data concerning the prognostic significance of Sjögren's syndrome autoantibodies.

Autoantibodies predict disease

A substantial, but not the only (7), reason to consider a disease autoimmune is the presence of serum antibodies directed against self; that is, autoantibodies. In almost every autoimmune disease for which there are data, autoantibodies are present years before the clinical illness (8). Thus, Sjögren's syndrome is among a large group of autoimmune diseases where autoantibodies are known to precede disease, but the risk of disease in a given antibody-positive individual is not well characterized. However, there are data that bear directly on the prognostic value of anti-Ro or anti-La in healthy individuals.

Neonatal lupus, consisting of congenital heart block as

well as neonatal lupus dermatitis, hepatitis and hematologic abnormalities results from passively acquired autoantibody from mother to fetus (9,10). Complete congenital heart block as a manifestation of neonatal lupus is a serious medical condition, which commonly requires cardiac pacemaker implantation and occasionally results in death (11). The pathogenicity of anti-Ro and anti-La in neonatal lupus has been studied extensively [reviewed in (12,13)].

Neonatal lupus, including complete congenital heart block, complicates 1–2% of pregnancies of anti-Ro positive mothers with up to 20% of subsequent pregnancies also affected (14–22). However, many of the mothers of infants with neonatal lupus are well at the time of the birth of the affected child. Several smaller, early studies demonstrate the prognostic value of anti-Ro and anti-La in this situation. One study followed 11 anti-Ro/La positive women after the birth of a child with neonatal lupus. Eight of the 11 developed dry eyes during the follow-up period of almost 5 years (23). Another study found 23 of 52 mothers were asymptomatic at the time of birth, with 11 of the 23 developing a rheumatic disease in median follow-up of 3.7 years (11). A larger study of mothers enrolled in the US National Registry of Neonatal Lupus examined the fate of 229 mothers with at least 6 months of follow-up, of whom 51 were asymptomatic at the time of the birth of an affected child (24). Of these 51, 7 developed Sjögren's syndrome, 4 systemic lupus erythematosus (SLE) and 1 a lupus-Sjögren's overlap with a median time to progression of 3.15 years. Thirty-seven other mothers had some symptoms at the time of the birth and were designated as having pauci-undifferentiated autoimmune syndrome. These women also progressed over time. Six developed Sjögren's syndrome, while 4 developed SLE. The 10-year risk of developing Sjögren's syndrome was estimated to be about 28% (24).

Studies have now been carried out among 117 primary Sjögren's syndrome patients who were enrolled in population-based studies of healthy individuals, prior to the onset of Sjögren's syndrome (25,26). The 117 Sjögren's syndrome subjects were matched to 117 healthy control subjects. Of 88 seropositive Sjögren's syndrome subjects, 84 had at least one autoantibody present prior to the diagnosis of Sjögren's syndrome with autoantibody present up to 20 years prior to disease (26). The predictive values of anti-La and anti-Ro for the development of pSS were 34 and 30, respectively (26).

Thus, there have been studies of mothers giving birth to children with neonatal lupus, as well as sera from persons destined to go on to develop primary Sjögren's syndrome.

Taken together, these studies indicate that the presence of anti-Ro or anti-La in the sera of healthy individuals predicts the future onset of Sjögren's syndrome.

Autoantibodies in Sjögren's syndrome

Anti-Ro and anti-La

Autoantibodies binding the ribonuclear proteins Ro and La are the most common specificities found in the sera of Sjögren's syndrome patients (27–30). The Ro particle consists of Ro60 plus several small cytoplasmic RNAs (hyRNA) (31). Generally, the Ro-ribonuclear particle is located in the nucleus, the cytoplasm, or apoptotic blebs, depending upon the conditions (32–35). Ro52 (also known as TRIM21) is unrelated to Ro60 in terms of amino acid sequence. Nonetheless, anti-Ro52 is frequently found in conjunction with anti-Ro60 in pSS. The La protein functions as an RNA III polymerase, and is at times physically associated with the Ro60-hyRNA complex (36).

A variety of methods can be used to detect these antibodies. Originally, double immunodiffusion was employed (37), and is still used in a few specialty laboratories. RNA precipitation is likely the most sensitive and specific method but similar to double immunodiffusion is not commonly performed in a clinical setting. Counter-immunoelectrophoresis, enzyme linked immunosorbent assay (ELISA) and simultaneous bead assays are more frequently employed (38). Method of detection may be a critical point as most of the clinical associations of anti-Ro and anti-La were determined using older assays. Meanwhile, high-throughput, easily automated techniques such as ELISA or multiplex bead assay are now commercially available. Such assays generally have low specificity compared to the traditional ones because of measurement of lower avidity, lower concentration antibody (39). Thus, clinical correlations found with one assay may not hold true with another assay that has different sensitivity and specificity characteristics. As an example, a study of small fiber peripheral neuropathy found no association with anti-Ro using ELISA or a multiplex bead assay, while there was an association with the presence of both anti-Ro and anti-La determined by Ouchterlony double immunodiffusion (40).

The occurrence of both anti-Ro and anti-La antibodies has interesting predictive value. Both of these antibodies are commonly found among primary Sjögren's patients—up to about 50%—as above, depending on the method (41). In fact, the presence of both anti-Ro and anti-La tends to

Table 1 Prognostic autoantibodies in Sjögren's syndrome

| Autoantibodies | Prevalence, % | Properties | Clinical association |
|-------------------|---------------|--|-----------------------------|
| Anti-Ro/SSA | 50–70 | Disease marker in healthy Lymphoma predictive model | Younger age, extraglandular |
| Anti-La/SSB | 25–40 | Disease marker in healthy Lymphoma predictive model | Extraglandular |
| Rheumatoid factor | 36–74 | Phenotype marker Lymphoma predictive model | Anti-Ro/La, extraglandular |
| Anti-CCP | 3–10 | Phenotype marker | Arthritis |
| AMA | 3–10 | Phenotype marker | Elevated liver enzymes, PBC |
| ACA | 3–27 | Phenotype marker | Raynaud's phenomenon |
| Cryoglobulins | 3–12 | Phenotype marker Lymphoma predictive model | lymphoma, extraglandular |

Anti-Ro/SSA and anti-La/SSB are associated with systemic disease with anti-Ro part of the most recent classification criteria. Other autoantibodies are important for neither diagnosis nor research classification but identify Sjögren's syndrome patients with certain clinical features. CCP, citrullinated cyclic peptide; AMA, anti-mitochondrial antibody; ACA, anti-centromere antibody; PBC, primary biliary cholangitis.

identify pSS patients as opposed to SLE patients. A British study found 29 of 35 patients with both anti-Ro and anti-La had Sjögren's. Meanwhile, only 23 of 53 with only anti-Ro had Sjögren's, while 25 had SLE and 13 had another disease (42). Thus, anti-La occurred in a subset of patients with anti-Ro, but the combination of anti-Ro and anti-La was more specific for Sjögren's syndrome than anti-Ro alone. Furthermore, the presence of both anti-Ro and anti-La in Sjögren's syndrome is associated with more severe disease, while the presence of both among SLE patients is associated with less severe disease

As above, in the original and many subsequent descriptions, anti-La was always found with concomitant anti-Ro (37,43), but a few subjects are encountered with anti-La alone with the detection techniques commonly used now. Recent data from 2 independent Sjögren's cohorts (Oklahoma Sjögren's Cohort and Sjögren's Syndrome International Clinical Alliance) suggest that patients with only anti-La do not have a Sjögren's-like illness, although the anti-La is not a false positive (44,45). Thus, the new ACR/EULAR research classification criteria do not include anti-La (1,2).

Some patients with Sjögren's syndrome have a disease limited to the exocrine glands while other patients have a systemic disease. The presence of anti-Ro and anti-La has prognostic implications in that these autoantibodies

may identify patients with the potential for systemic manifestations. Data from a large cohort in Barcelona showed that 292 (29%) of 1,010 primary Sjögren's syndrome patients had disease limited to the exocrine salivary and lacrimal glands. This limited, sicca-only disease was associated with an absence of anti-Ro (46). Anti-Ro/La positive patients from this same cohort had a number of statistically significant correlations, including parotid enlargement, Raynaud's, arthritis, vasculitis, renal tubular acidosis, peripheral neuropathy, cytopenias, and rheumatoid factor (46). Other large studies of primary Sjögren's syndrome have had similar results with higher prevalences of extraglandular manifestations such as splenomegaly, lymphadenopathy, vasculitis and Raynaud's phenomenon among those patients with anti-Ro/La (47). Thus, there are a number of correlations of anti-Ro and anti-La antibodies in Sjögren's syndrome (*Table 1*). In addition, the presence of anti-Ro also is associated with more severe salivary gland involvement as demonstrated by worse dysfunction, greater enlargement and more intense lymphocytic infiltration (48,49). Finally, there has been a long term prospective study of 100 primary Sjögren's syndrome patients that found only those with anti-Ro developed extraglandular disease (50).

Of interest, there may be an exception to the idea that anti-Ro/La imparts risk of extraglandular complications; namely, pulmonary involvement. In a study of 507 primary

Sjögren's syndrome subjects, all of whom had chest CT scan, 50 were found to have bronchiectasis. Of the 50 with bronchiectasis, only 27% had anti-Ro, while 54% of the 457 with bronchiectasis had anti-Ro (51). Neither restrictive nor obstructive lung disease, both more common manifestations of Sjögren's lung disease (52,53), were investigated in this study. Thus, bronchiectasis may not be associated with anti-Ro, but confirmation of this finding will be needed.

Sjögren's patients are at increased risk for lymphoma, perhaps as high as 50-fold above the population risk. Mucosal associated lymphoid tissue (MALT) lymphoma is the most common malignancy seen but other types of lymphoma also occur more frequently than expected (54). The evidence concerning anti-Ro and an association with lymphoma is not clear. Long term follow-up studies have had opposite results. One study from England found a higher risk for non-Hodgkin's lymphoma among patients with both anti-Ro and anti-La (50), while another study with about the same duration of follow-up failed to find such an association (55). Papageorgiou and colleagues recently concluded that anti-Ro/La is not a risk factor for lymphoma in Sjögren's syndrome (54). However, in a case-control study of 381 primary Sjögren's syndrome patients without non-Hodgkin's lymphoma and 92 with, Fragkioudaki and colleagues (56) found several independent risk factors, including the presence of anti-Ro and/or anti-La. In a multivariate analysis, anti-Ro and/or anti-La remained in the model and became part of a predictive tool that included not only anti-Ro/La but also Raynaud's, lymphadenopathy, monoclonal gammopathy, rheumatoid factor, and hypocomplementemia (56). With 92 patients, this is, we believe, the largest study of Sjögren's-associated non-Hodgkin's lymphoma ever conducted. Overall, a safe conclusion seems to be that anti-Ro/La is associated with an increased risk of lymphoma in Sjögren's syndrome.

There are associations of anti-Ro/La that are not clinical in nature but are of interest. In gene expression studies performed on peripheral blood mononuclear cells, elevated expression of interferon-regulated genes is found almost exclusively among primary Sjögren's syndrome patients that have anti-Ro (57). Sophisticated proteomic studies of anti-Ro60 circulating in the peripheral blood demonstrate turnover of antibody at approximately 3-month intervals, notwithstanding long-term high titer anti-Ro60. Thus, indicating that anti-Ro60 is produced by short-lived B cells with rapid turnover, instead of long lived plasma cells (58). Furthermore, other studies from this same group show that anti-Ro antibodies are produced by public clonotypes (59,60).

However, with newer methods of detection, anti-La is occasionally found without anti-Ro. Two recent independent analyses have concluded that patients with only anti-La and no anti-Ro do not have Sjögren's syndrome (44,45).

Despite the lack of association of anti-La alone with the disease, anti-La found in conjunction with anti-Ro imparts prognostic information.

Rheumatoid factor

Rheumatoid factor is of prognostic value in Sjögren's syndrome because of its association with systemic disease (61), a relationship that holds in all racial and ethnic groups thus far studied (62). Rheumatoid factor is found in up to 50% of those with Sjögren's syndrome, and is also strongly associated with the simultaneous presence of both anti-Ro and anti-La (63). In a retrospective study of 212 Sjögren's patients, rheumatoid factor was associated with not only systemic disease but also use of glucocorticoid (64). Both pulmonary and renal disease have been found in excess among primary Sjögren's syndrome patients with rheumatoid factor (65,66). The latter finding with renal disease was with IgA rheumatoid factor. As mentioned above, rheumatoid factor makes a contribution to a predictive model for non-Hodgkin's lymphoma (56). Similar to anti-Ro and anti-La, rheumatoid factor is a marker of more severe lacrimal and salivary gland dysfunction (67). Thus, we conclude that rheumatoid factor is an important prognostic factor in Sjögren's syndrome.

Anti-centromere antibody (ACA)

While ACA are commonly found in those with limited scleroderma (CREST), these autoantibodies are also found in a small subset of primary Sjögren's syndrome. In fact, Raynaud's phenomenon was the most common association of ACA in a large study of more than 1,000 connective disease patients (68). However, sicca is also a common finding among those with ACA in their sera with Renier and colleagues finding 40 of 67 (76%) ACA-positive patients had sicca symptoms (69). Thus, ACA occurs in a variety of clinical settings. In primary Sjögren's syndrome the prevalence is 3.7% to 27% when detected by indirect immunofluorescence, but probably higher (20% to 25%) when detected by other methods such as Western blot (70,71). In a prospective study of 2,627 subjects with an inflammatory rheumatic illness, there were 41 ACA positive patients, of whom 7 had primary Sjögren's syndrome (72). Thus, ACA is found in a small percentage of those with

primary Sjögren's syndrome.

ACA recognize three major species, known as CENP-A, CENP-B, CENP-C (73). However, the binding of these autoantigens varies between patients with Sjögren's syndrome and CREST. In the latter, patient sera generally bind both CENP-B and CENP-C, while sera from primary Sjögren's syndrome patients commonly bind only CENP-C (74,75). Recent epitope mapping of the binding of the CENP proteins also saw a different pattern of antibody binding when comparing sera from primary Sjögren's syndrome and systemic sclerosis (76). Thus, the origin, pathogenesis, and clinical associations of ACA may differ between scleroderma and primary Sjögren's syndrome.

Several investigations have studied the clinical manifestations of Sjögren's syndrome in regards to ACA, and studies have come to different conclusions about these associations as well as the significance of these autoantibodies in the disease. One group has suggested that ACA should be incorporated into the diagnostic and classification criterion (65), while another group interprets its findings oppositely (77). In the latter study, only 3 of 87 anti-Ro/La negative subjects would have avoided a salivary gland biopsy because of ACA positivity (77). In the first study, ACA was associated with more abnormal Schirmer test values as well as increased corneal damage as assessed by corneal staining (65). The Barcelona group, Ramos-Casals and colleagues, studied ACA among 402 Sjögren's patients and found only 8 of 402 (2%) primary Sjögren's syndrome sera had ACA when detected by ELISA. Six of the 8 had Raynaud's phenomenon while 3 had pulmonary disease, but anti-Ro was found in only 1 of the 8. In long term follow-up, 3 of these 8 developed sclerodactyly (78). A recent study of articular involvement by ultrasound found no correlation with ACA in 48 primary Sjögren's syndrome patients of whom 10 had ACA (79). We conclude that while ACA are found in a subset of patients, there is no compelling evidence that such patients make up a clinically important subset of Sjögren's syndrome.

Cryoglobulinemia

Immunoglobulins that precipitate *in vitro* at temperatures less than 37 °C are termed cryoglobulins. Cryoglobulinemia is found in association with infectious disease, malignancy or autoimmune disease with the most common cause chronic Hepatitis C infection. Immune-mediated tissue damage in the form of vasculitis is the common manifestation of cryoglobulinemia, and usually takes the form of skin, kidney or peripheral nerve involvement (80).

A small (3–4%) but definite percentage of subjects with primary Sjögren's syndrome have cryoglobulinemia along with evidence of clinical disease related to the cryoglobulinemia with up to a third of patients having cryoglobulins in their sera without clinical disease (81,82). Commonly Sjögren's syndrome patients have a type II mixed cryoglobulinemia with a monoclonal immunoglobulin component, which has rheumatoid factor activity (81,83). Consequently, cryoglobulinemia is associated with non-Hodgkin's lymphoma in Sjögren's syndrome (82,84-89). For example, in a retrospective study, risk of development of lymphoma among 266 patients followed over 18 years was increased more than 4-fold among those with cryoglobulinemia (89). A multicenter study of 661 patients found the presence of cryoglobulins had a relative risk of 6.8 for non-Hodgkin's lymphoma (90). Worsened mortality is associated with cryoglobulinemia (89). In a study of 515 primary Sjögren's syndrome patients studied over a mean follow-up of 110 months, 33 patients died. In a multivariate analysis, those who met criteria for cryoglobulinemic vasculitis were more likely to die with an odds ratio of about 4.5 (82). A monoclonal gammopathy is also associated with poorer survival (91).

Other manifestations of the disease are associated with cryoglobulinemia including cutaneous vasculitis, skin ulceration, peripheral neurological disease, as well as pulmonary and renal involvement (86,92-97). However, some primary Sjögren's syndrome patients develop a hypergammaglobulinemic cutaneous vasculitis that is not associated with lymphoma, which should be distinguished from cryoglobulinemic vasculitis (84). A recent long-term follow-up study found cryoglobulinemia was the most predictive factor for development of new extraglandular manifestations (86). Disease activity is also greater among those patients with cryoglobulinemia, which are associated with high activity in specific domains of the EESDIA; namely, constitutional, lymphadenopathy, glandular, cutaneous, peripheral nervous system, hematological and biological (98,99).

Thus, cryoglobulinemia is an important prognostic factor in primary Sjögren's syndrome. Finding of a cryoglobulin in the serum of a patient impacts risk of progression of extraglandular manifestations, development of lymphoma, and even mortality.

Other autoantibodies

Autoantibodies against cyclic citrullinated peptides (anti-

CCP) are most commonly associated with rheumatoid arthritis. Citrullination is a post-translational modification resulting from the deimination of arginine. A number of proteins can undergo this process and become the targets of these antibodies, including filaggrin, vimentin, fibronectin, fibrinogen and collagen (100). There are large number of commercially available assay, which use a variety of techniques for determining the presence of anti-CCP. Despite the differences, the performance of the different assays is similar (101).

From 3% to 10% of Sjögren's syndrome patients have anti-CCP in their sera (102-104). The presence of anti-CCP in the sera of Sjögren's syndrome patients has been associated with inflammatory arthritis in multiple studies (105-107). One study found a strong association of anti-CCP and arthritis with an odds ratio of 7.6 but no association with other extraglandular manifestations (108). In contrast, other studies find no association of anti-CCP with arthritis as a manifestation of Sjögren's syndrome (102,103). After an initial diagnosis of primary Sjögren's syndrome, progression to rheumatoid arthritis has been studied. Among 405 primary Sjögren's syndrome patients in an average of 60 months follow-up, 23 progressed to rheumatoid arthritis. In multivariate analysis anti-CCP was associated with progression with an odds ratio of 2.5 (109). The preponderance of the evidence suggests that anti-CCP identifies primary Sjögren's syndrome patients with an increased risk of inflammatory arthritis as well as an increased risk of developing rheumatoid arthritis.

Sjögren's patients occasionally have anti-mitochondrial antibodies, with prevalence ranging from 1.7–13% (110). Primary biliary cholangitis patients characteristically have anti-mitochondrial antibodies found in their sera. Based on similarities in the 2 diseases, especially in regards to both manifesting as an autoimmune epithelitis, one group proposes that primary biliary cholangitis is Sjögren's of the liver and Sjögren's is primary biliary cholangitis of the salivary glands (110). In one study, anti-mitochondrial antibodies were found 3 of 180 primary Sjögren's syndrome patients. Two of the 3 developed primary biliary cholangitis in follow-up of 5 years (111). In an older study, among 45 primary Sjögren's syndrome patients, 12 had abnormal liver enzymes and 5 of these had anti-mitochondrial antibodies (3 by indirect immunofluorescence and 2 by molecular testing). Further, 4 of these 5 were found to have primary biliary cholangitis. One patient with anti-mitochondrial antibodies had no biochemical evidence of liver disease (112). Thus, analogous to the findings

for rheumatoid factor and rheumatoid arthritis, anti-mitochondrial antibodies may identify primary Sjögren's syndrome patients with a risk of liver disease and a risk of development of primary biliary cholangitis.

Other antibodies may be found in up to 20% of those with primary Sjögren's syndrome, including anti-DNA, anti-RNP, anti-Sm, anti-SCL70, anti-Jo-1, anti-neutrophil cytoplasmic, and anti-cardiolipin (78). Thirteen of the 82 (16%) patients with one of these autoantibodies developed some other another autoimmune disease in addition to Sjögren's syndrome (78). No patient without one of these Sjögren's-atypical antibodies developed another autoimmune disease. So for at least a minority, these antibodies predicted future progression. These data indicate that 'secondary' Sjögren's syndrome can be manifest prior to the supposed 'primary' autoimmune disease. As discussed above, this is also the case with rheumatoid arthritis and primary biliary cirrhosis and their respective autoantibodies. While imparting prognosis information, these data raise the question of the relevance of primary and secondary Sjögren's syndrome.

Research has found a number of other autoantibodies in the sera of Sjögren's syndrome patients, including anti- α -fodrin, NA-14, TRIM38, anti-proteasome activator and anti-muscarinic 3 receptor, among others [reviewed in (12)]. However, determination of these autoantibodies is not routinely performed clinically.

Novel antibodies

Antibodies binding salivary gland protein 1 (SP-1), carbonic anhydrase 6 (CA6) and parotid secretory protein (PSP) were found in murine Sjögren's-like illness as well as humans with Sjögren's syndrome and non-Sjögren's sicca (113). Furthermore, commercial testing for these antibodies is now available. Among those with primary Sjögren's syndrome, about half with a focus score >1.0 on salivary gland histopathology and negative anti-Ro/La, had anti-SP-1 (113). However, the prognostic value of these autoantibodies is yet to be determined.

Conclusions

In addition to the canonical anti-Ro and anti-La, many autoantibodies are present in the sera of patients with primary Sjögren's syndrome. The presence of anti-Ro/La distinguishes patients with exocrine gland involvement from those with systemic involvement. In addition, several pathogenic features of disease, including excess expression

of interferon-regulated genes, are associated with anti-Ro/La. Rheumatoid factor, anti-mitochondrial antibodies and anti-CCP also confer prognostic data in the setting of primary Sjögren's syndrome. The presence of cryoglobulins is associated with systemic and more active disease along with increased risk of lymphoma. Several novel autoantibodies have recently been described but prognostic value is as yet unknown. Anti-Ro/La in the sera of healthy individuals prognosticates the development of connective tissue disease, especially Sjögren's syndrome.

Acknowledgements

Funding: This work was supported in part by NIH grants AR053483, AI082714, and GM104938 as well as US Department of Veterans Affairs Merit Review grant BX001451.

Footnote

Conflicts of Interest: RH Scofield has accepted honorarium and travel expenses from Abbvie Korea. Other authors have no conflicts of interest to declare.

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doi: 10.21037/jlpm.2018.08.05

Cite this article as: Scofield RH, Fayyaz A, Kurien BT, Koelsch KA. Prognostic value of Sjögren's syndrome autoantibodies. *J Lab Precis Med* 2018;3:92.