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Vasculitis in Sjögren's Syndrome

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Abstract

Sjögren's syndrome is a chronic autoimmune disease that is commonly manifested by immune attack on the exocrine glands with resultant dry eyes and dry mouth. Sjögren's syndrome patients also have disease in other organs. One of the most common extraglandular manifestations is vasculitis. Skin vasculitis, with palpable purpura clinically and leukocytoclastic vasculitis on pathological examination, is common. Although half of those individuals with subcutaneous vasculitis have only a single episode, skin vasculitic involvement is associated with more severe disease. Necrotizing vasculitis of medium-sized vessels resembling polyarteritis nodosa can occur in Sjögren's syndrome patients. Experience in therapy for vasculitis is limited, but intravenous IgG may be effective. Recent data support a relationship between neuromyelitis optica (Devic disease) and Sjögren's syndrome. Sjögren's syndrome patients with optic neuritis or transverse myelitis have anti–aquaporin-4, which are characteristic of Devic disease. Devic disease patients have salivary lymphocytic infiltration similar to that found among Sjögren's syndrome patients.

Keywords

Sjögren's syndrome; Vasculitis; Purpura; Devic disease; Neuromyelitis optica

Introduction

Sjögren's syndrome is a common, chronic autoimmune disorder that characteristically affects the salivary and lacrimal glands [1]. Immune injury to these exocrine glands leads to the common symptoms of dry eye and dry mouth. Criteria for classification for research purposes have been agreed upon for primary Sjögren's syndrome [2]. These include persistent and severe dry eyes and dry mouth, as well as objective measures of eye and mouth dryness. Along with these four, there are two additional criteria, one of which must be satisfied for a patient to be classified as having Sjögren's syndrome. These two criteria are the presence of anti-Ro (or SSA) in the serum and the presence of focal lymphocytic infiltrates of the salivary glands. The latter are usually demonstrated by pathological examination of minor salivary glands acquired from a lip biopsy [3].

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Secondary Sjögren's syndrome occurs in the setting of another autoimmune disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma, or primary biliary cirrhosis. About 20% of those with these diseases have secondary Sjögren's syndrome. Primary Sjögren's syndrome occurs without another systemic autoimmune disease and is most commonly found among women in middle- to late-adulthood, with men only constituting about 10% of patients [1]. Primary Sjögren's syndrome may be one of the most common rheumatic autoimmune diseases, second only to rheumatoid arthritis in incidence and prevalence [4].

Sjögren's syndrome is considered autoimmune based on two findings. First, there is a characteristic infiltration of lymphocytes found in the salivary and lacrimal glands of patients. The lymphocytes are found in clusters of greater than 50 cells and can be graded according to a focus score, which counts the number of clusters per mm3 of tissue [3]. The second finding that defines the disease as autoimmune is the presence of antibodies binding self in the blood of patients. Anti-Ro (or SSA), which is part of the classification criteria, is found in the serum of up to 90% of patients with Sjögren's syndrome, while anti-La (or SSB) is found in a smaller number. Several other autoantibodies are found in the serum of Sjögren's patients [5], including anticentromere [6], antimuscarinic receptor [7], and anti-aquaporin [8•]. Some of these autoantibodies may be functional in that binding of the antigen leads to glandular dysfunction [6, 9].

There are other manifestations of the disease beyond involvement of the exocrine glands. These manifestations demonstrate the systemic nature of Sjögren's syndrome and can include pulmonary fibrosis as well as kidney disease, usually in the form of interstitial nephritis with renal tubular acidosis. Some patients may have central nervous system disease that mimics multiple sclerosis, while others have peripheral neuropathy [10•]. Vasculitis is another common manifestation of Sjögren's syndrome that can take many forms. Most of these extraglandular (that is, problems elsewhere, besides the salivary and lacrimal glands) forms are more common among patients with anti-Ro and/or anti-La. The present review considers the latest developments in vasculitis associated with primary Sjögren's syndrome.

Rash as a Manifestation of Vasculitis

Classical Description

Sjögren's syndrome is not an ancient disease. Although it was described in part in the latter stages of the 19th century, including a report by Osler [11], Henrik Sjögren today receives credit for description of the illness in his 1933 dissertation (see [12] for English translation). Thus, we cannot look to ancient writings of the Greeks, or to medieval physicians, or to the dawn of scientific medicine in the 1700 s for a description of vasculitis in Sjögren's syndrome. Instead, vasculitis manifested as a rash in Sjögren's syndrome patients was described much later.

In a series of papers in the early-1980s, Alexander, Provost, and co-workers described the clinical and pathological features, as well as the associations of vasculitic rash among patients with Sjögren's syndrome [13–15]. In one report, they studied 22 primary Sjögren's patients with documented skin rash [13]. These patients all had dry eyes and dry mouth

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along with an abnormal Schirmer's test and a minor salivary gland biopsy with a focus score greater than 1 [3]. Thus, these patients definitely meet the present classification criteria [2]. Ten of the 22 had purpura, while 7 had chronic urticaria. The remaining five had other skin lesions such as erythema nodosum, erythema multiforme, macules, or subcutaneous nodules. All patients underwent a skin biopsy, and cutaneous vasculitis was found in 19 of the 22. Leukocytoclastic vasculitis was seen in 14 of the patients, and a perivascular mononuclear infiltrate was found in 8, while 2 patients had both pathologies. A total of 80% of those with purpura had leukocytoclastic vasculitis, and the other two patients with purpura had both leukocytoclastic vasculitis and a mononuclear infiltrate. In addition, six of the seven with urticaria also had leukocytoclastic lesions. Hypocomplementemia was associated with leukocytoclastic vasculitis, while the presence of anti-Ro and anti-La was associated with skin vasculitis in general. All 16 patients with skin vasculitis had anti-Ro, and 9 also had anti-La. The three patients without vasculitis were anti-Ro and anti-La negative. The same group emphasized the association of neutrophilic vasculitis with serologic markers such as hypocomplementemia and hypergammaglobulinemia, along with the association with anti-Ro and anti-La [15].

More recently, a much larger cohort of patients with primary Sjögren's syndrome was examined for the significance and correlates of cutaneous vasculitis [16], as well as described completely [17]. Among 558 primary Sjögren's syndrome patients, 89 had cutaneous involvement, 52 of whom (58%) had cutaneous vasculitis [16]. Among these, 14 had cutaneous vasculitis associated with cryoglobulinemia, 11 had urticarial vasculitis, and 26 had purpura without evidence of cryoglobulins. It is worth noting that serologic evidence of hepatitis C infection was an exclusion criterion in this study [16]. Thus, those patients with cryoglobulinemia did not have concomitant hepatitis C. In general, patients with cutaneous vasculitis had more severe disease with more extraglandular involvement than those without cutaneous vasculitis (Table 1).

The association of cutaneous vasculitis with the serologic abnormalities found among patients with Sjögren's syndrome is of interest. Antinuclear antibodies were determined by indirect immunofluorescence, while anti-Ro and anti-La were determined by immunoprecipitation, and rheumatoid factor was determined by latex fixation [16]. If determined by other means, the associations are unlikely to be reproduced. This is especially relevant for highly sensitive enzyme-linked immunosorbent assay methods that detect low-titer, low affinity antibodies, the significance of which is unknown.

The clinical aspects of cutaneous vasculitis are also addressed in this paper [16]. About half of the patients had a single episode of cutaneous vasculitis, with recurrent problems in the remaining half. The lower extremities were the most common site of the rash. The majority (73%) of patients were treated with glucocorticoids. A few required high doses or other immunosuppressant drugs. Nine patients received no treatment.

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Recent Developments in Sjögren's Syndrome–Associated Cutaneous Vasculitis

Investigators continue to study novel autoantibodies in the serum of patients with Sjögren's syndrome associated with vasculitis. Anticentromere antibodies are present in a small subset of Sjögren's syndrome patients. Some case reports suggest that cutaneous vasculitis is more common in patients with this specificity [18]. Such patients may be initially inappropriately diagnosed as having scleroderma [18]. However, in a retrospective study of 535 Sjögren's syndrome patients, the 20 with anticentromere autoantibodies did not have an increased incidence of purpura [6]. Another study examined 40 consecutive patients with leukocytoclastic vasculitis, 2 of whom had Sjögren's syndrome, for IgG antineutrophil cytoplasmic antibodies (ANCA). One of the two Sjögren's syndrome patients was positive [19]. To the author's knowledge, IgA ANCA has not been studied further in Sjögren's syndrome.

As has been previously described [20], palpable purpura with leukocytoclastic vasculitis is occasionally the presenting problem in Sjögren's syndrome [21]. Nail fold capillaroscopic findings had nonspecific abnormalities in about one third of 61 Sjögren's syndrome patients. The presence of abnormal capillaroscopic findings was associated with Raynaud's phenomenon, but not vasculitis [22]. Jaccoud's arthritis (defined as reducible or fixed deviation of the fingers from the metacarpal axes) was found in 5 of 161 Sjögren's syndrome patients, 4 of whom had cutaneous vasculitis. In addition, three were men [23]. Of course, none of these clinical or serologic associations of vasculitis among Sjögren's syndrome patients have been confirmed in studies of other cohorts.

Systemic Vasculitis in Sjögren's Syndrome

Classical Description

In a study of 75 Sjögren's syndrome patients, 49 underwent biopsy for suspected vasculitis. Of these 49, 41 had vasculitis identified pathologically [14]. There were 11 specimens with vasculitis in a muscle biopsy, 5 in a nerve biopsy, 3 in a lung biopsy, and 2 in a kidney biopsy. Unfortunately, this paper includes primary and secondary Sjögren's syndrome, and it is not possible to separate the results of each group. Three patients had visceral—that is, something other than skin—nerve or muscle involvement. All three had pulmonary vasculitis, two of whom had renal vasculitis and one of whom had central nervous system disease. The latter, who had primary Sjögren's syndrome, died of vasculitis involving the spinal cord and was reported separately [24]. The association of Sjögren's syndrome with myelitis and Devic disease is considered separately below. The presence of peripheral or visceral vasculitis was strongly associated with the presence of antiRo and anti-La in these 75 patients [14].

Another older study found that 9 of 70 Sjögren's syndrome patients had vasculitis [25]. Some patients had an acute necrotizing arteritis of medium-sized vessels that resembled polyarteritis nodosa, except there were no aneurysms. Similarly, in a 2004 study, another group found that 2 of 52 primary Sjögren's syndrome patients had vasculitis of medium-

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sized arteries [16]. One was diagnosed with both Sjögren's syndrome and polyarteritis nodosum, and one had necrotizing vasculitis of the pancreatic and mesenteric arteries [16]. Of note, while hepatitis C, much less its association with a Sjögren's syndrome–like illness, was unknown at the time these earlier studies [14, 25] were conducted, hepatitis C was an exclusion criterion in the last study [25].

In perhaps the largest study of Sjögren's syndrome ever conducted, investigators from Spain in the GEMESS Study Group examined clinical features in 1,010 Spanish primary Sjögren's syndrome patients [17]. Ninety-one had vasculitis, which was more common in those with onset before 35 years of age, but vasculitis was not independently associated with respect to age at onset in a multivariate analysis. In addition to age at onset, other subsets were examined, including long-term (>10-year) duration, as well as positive antinuclear antibody, rheumatoid factor, or anti-Ro/La. Vasculitis was only increased among those with a long duration of disease. In this study, vasculitis was considered as a single variable without division according to pathology or location. In another large study of 400 Sjögren's syndrome patients, 29 (7%) had peripheral neuropathy, 37 (9%) had pulmonary involvement, 25 (6%) had renal disease, 5 (1%) had myositis, 4 (1%) had central nervous system involvement, and 4 (1%) had acute pancreatitis [26], but it is not clear in this report who among these patients had vasculitis as the underlying pathophysiologic mechanism of extraglandular involvement.

Recent Developments in Sjögren's Syndrome–Associated Systemic Vasculitis

As noted previously, some Sjögren's syndrome patients develop a necrotizing vasculitis of medium-sized arteries that resembles that found in polyarteritis. Patients such as these continue to be reported as case reports or small case series. A recent case report showed an excellent response to oral cyclophosphamide [27]. ANCA associated granulomatous vasculitis (formerly known as Wegener's granulomatosis) with concomitant Sjögren's syndrome is also reported occasionally, including a recent patient with limited ANCA-associated granulomatous vasculitis [28]. The reported patients generally have convincing evidence of both diseases with characteristic pathology, as well as ANCA and anti-Ro/La positivity [28–30]. It is not clear whether such patients have Sjögren's syndrome with granulomatous vasculitis, ANCA-associated granulomatous vasculitis with salivary involvement, or both diseases independently. Because of the rarity of such patients, determining how the conditions are interrelated will be difficult.

Several studies have examined therapy in patients with extraglandular involvement. Several case reports and case series describe the efficacy of intravenous (IV) IgG in patients with peripheral neuropathy [31, 32•, 33– 36]. Both ataxic and painful forms of Sjögren's-related peripheral neuropathy have benefited. The largest of these reports included five patients with painful sensory neuropathy who were treated with 0.4 g of IgG/kg per day for 5 days [33]. The patients were assessed with visual analogue pain scales. There was an average reduction in the score of about 75%, with duration of improvement of 2 to 6 months. One patient was examined by quantitative sensory testing and improved. There are no randomized, blinded

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trials of IgG in Sjögren's syndrome; such trials are unlikely to be conducted, and there is likely a publication bias in that success is reported more easily and often than failure. Nevertheless, IV IgG is a viable treatment option for neuropathy in Sjögren's syndrome. Cyclophosphamide therapy has reversed cardiomyopathy from vasculitis in a Sjögren's syndrome patient [37]. Finally, a phase 2 trial of leflunomide in Sjögren's syndrome showed resolution of leukocytoclastic vasculitis in the three patients in the trial with this finding, but the results of this trial were otherwise disappointing [38].

Other Recent Findings in Sjögren's Vasculitis

In a study of 60 men with Sjögren's syndrome compared with 432 women with the disease, vasculitis was not found to be more common among the men, while several other extraglandular complications were more common among men [39]. The investigators in Barcelona have studied an incident cohort of Sjögren's syndrome that numbers 263 consecutively diagnosed patients [40]. This is one of the few (and the largest) incident cohorts ever developed. In an average follow-up time of 58 months, 25 patients (9.5%) developed vasculitis. Seventeen of these 25 involved the peripheral nerves, while 13 were cutaneous. In addition, three had kidney, two had bowel, and one had pancreas involvement. Of the 20 undergoing biopsy, 4 had medium sized vessel necrotic vasculitis. The only clinical correlate at diagnosis for the development of vasculitis was more severe grade parotid scintigraphy abnormalities. Vasculitis was also studied as an independent variable associated with survival. Nine patients died in follow-up. The correlates of death in a multivariate analysis were vasculitis, scintigraphy scores of grade III or IV, low serum complement, and cryoglobulinemia [40]. The adjusted hazard ratio for vasculitis was 4.48.

Devic Disease (Neuromyelitis Optica) and Sjögren's Syndrome

Devic disease, or neuromyelitis optica, is considered a rare variant of multiple sclerosis that is manifested by optic neuritis and transverse myelitis, especially longitudinally extensive transverse myelitis [41]. An autoantibody characteristic and perhaps highly specific for this syndrome is designated NMO-IgG [42], and the antigen for this autoantibody is aquaporin-4 [43]. Aquaporin-4 is expressed in all the salivary glands [44] as well in perivascular astrocytes [43]. Diagnostic criteria for this disease are available and were recently revised [45].

Patients with Sjögren's syndrome having neurological disease consisting of transverse myelitis have been reported for many years [46]. Recent data suggest an association of Devic disease with Sjögren's syndrome. This association appears to be than more the coexistence of two unrelated conditions. One report studied American and French cohorts, including 153 American patients with neuromyelitis optica spectrum disorders [47]. About 16% were positive for anti-Ro or anti-La, but only 2% met criteria for Sjögren's syndrome, while another 2% met the American College of Rheumatology criteria for SLE. All patients with Sjögren's syndrome or SLE had anti–aquaporin-4. Anti– aquaporin-4 and anti-Ro were associated in both the American and French cohorts. None of the 49 patients with Sjögren's syndrome or SLE but without optic neuritis or transverse myelitis had anti–aquaporin-4. Disappointingly for our purposes herein, the authors publishing this paper did not

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distinguish between Sjögren's syndrome and SLE, which were considered together as a single entity [47].

Another recent study examined Sjögren's syndrome and SLE separately for antibodies directed against aquaporin-4, including an assay using recombinant aquaporin-4 [48••]. Of 22 patients with Sjögren's syndrome and neurological involvement, 3 had transverse myelitis extending over fewer than 3 vertebral segments, 2 had longitudinally extensive transverse myelitis (extending over ≥3 vertebral segments), 2 had a single episode of optic neuritis, and 20 had peripheral polyneuropathy. One of the two patients with longitudinally extensive transverse myelitis had NMO-IgG and anti-aquaporin. Among 20 SLE patients with neurological manifestations, 6 of 6 with longitudinally extensive transverse myelitis and 2 of 2 with recurrent optic neuritis had these antibodies. No SLE or Sjögren's syndrome patient without one of these two neurological findings had these antibodies.

Kahlenberg [49••] very recently and comprehensively reviewed the literature concerning the association of neuromyelitis optica spectrum disorders with Sjögren's syndrome. The author will not attempt to repeat this effort, but several points can be made. Kahlenberg [49••] found 63 reported patients with myelitis in the setting of Sjögren's syndrome, 21 of whom (of 57 evaluated) also had optic neuritis, most of which was recurrent. Eighteen of 21 in whom testing was performed had NMO-IgG in their serum. All but 10 of the 63 patients had anti-Ro. However, a surprising number did not have sicca symptoms. On the other hand, another study of 16 patients with neuromyelitis optica (Devic disease) undergoing minor salivary gland biopsy found that all had inflammation consistent with Sjögren's syndrome, with focus score greater than 3 in 9 [50]. Only two of the nine met the classification criteria for Sjögren's syndrome [2]. Seven of eight patients with isolated longitudinally extensive transverse myelitis had a focus score greater than 3, and, again, only two met classification criteria for Sjögren's syndrome [50].

Thus, the relationship of Sjögren's syndrome and neuromyelitis optica spectrum diseases is not worked out. However, one can say that the evidence is strong that NMO-IgG and anti-aquaporin in Sjögren's syndrome or SLE are markers of recurrent optical neuritis and longitudinally extensive transverse myelitis. Treatment directed at neuromyelitis optica is probably the best choice in Sjögren's syndrome patients with these manifestations. A small percentage (1%–5%) of all acute myelitis is associated with Sjögren's syndrome [51].

The pathophysiology also has not been investigated thoroughly. Perhaps there is immunologic cross-reaction between aquaporin-4 and aquaporin-5, which is expressed at high levels in the salivary gland. A functional role has been proposed, but not proven for NMO-IgG in Devic disease [52]. Whether a similar functional role is operative in Sjögren's syndrome awaits further investigation.

Conclusions

Vasculitis is a common manifestation of Sjögren's syndrome that is usually manifested as a rash or as peripheral neuropathy. Vasculitis is associated with the presence of anti-Ro and anti-La, as least when measured by precipitation, as well as other extra-exocrine gland

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involvement. Some patients have a systemic vasculitis that shows involvement of medium-sized arteries and can mimic polyarteritis nodosa. Devic disease (neuromyelitis optica) can be found simultaneously with Sjögren's syndrome. This combination is strongly associated with antibodies binding aquaporin-4, which is expressed in astrocytes and the salivary gland. The pathophysiologic relationship of these two diseases and this autoantibody marker is not elucidated.

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Table 1

Association of cutaneous vasculitis among 670 Sjögren's syndrome patients

	Cutaneous Vasculitis	
Entity	**Present, %**	**Absent, %**
Arthritis	50	29
Peripheral neuropathy	31	4
Raynaud's phenomenon	40	15
Renal disease	10	0
Positive antinuclear antibodies test	88	60
Positive rheumatoid factor	78	48
Positive anti-Ro/SSA	70	43
Positive anti-La/SSB	39	27

Cutaneous vasculitis was present in 52 patients and absent in 618 (Data from Ramos-Casals et al. [16])