# Cutaneous Vasculitis in Primary Sjögren Syndrome

## *Classification and Clinical Significance of 52 Patients*

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**Abstract:** To analyze the different clinical and histologic types of cutaneous vasculitis in patients with primary Sjögren syndrome (SS), we investigated the clinical and immunologic characteristics of 558 consecutive patients with primary SS from our units and selected those with clinical evidence of cutaneous lesions, excluding drug reactions and xeroderma. All patients fulfilled 4 or more of the diagnostic criteria for SS proposed by the European Community Study Group in 1993. A total of 89 (16%) patients presented with cutaneous involvement (88 female patients and 1 male; mean age, 51.8 yr).

The main cutaneous involvement was cutaneous vasculitis, present in 52 (58%) patients. There were 51 (98%) female patients and 1 (2%) male, with a mean age at diagnosis of cutaneous vasculitis of 51 years (range, 20–80 yr). Fourteen presented with cryoglobulinemic vasculitis, 11 with urticarial vasculitis, and the remaining 26, with cutaneous purpura not associated with cryoglobulins. A skin biopsy specimen was obtained in 38 patients (73%). Involvement of small-sized vessels was observed in 36 (95%) patients (leukocytoclastic vasculitis), while the remaining 2 (5%) presented with medium-sized vessel vasculitis (necrotizing vasculitis). Patients with cutaneous vasculitis had a higher prevalence of articular involvement (50% vs 29%, $p = 0.044$), peripheral neuropathy (31% vs 4%, $p < 0.001$), Raynaud phenomenon (40% vs 15%, $p = 0.008$), renal involvement (10% vs 0%, $p = 0.028$), antinuclear antibodies (88% vs 60%, $p = 0.002$), rheumatoid factor (78% vs 48%, $p = 0.004$), anti-Ro/SS-A antibodies (70% vs 43%, $p = 0.011$), and hospitalization (25% vs 4%, $p = 0.005$) compared with SS patients without vasculitis. Six (12%) patients died, all of whom had multisystemic cryoglobulinemia.

In conclusion, cutaneous involvement was detected in 16% of patients with primary SS, with cutaneous vasculitis being the most frequent process. The main characteristics of SS-associated cutaneous vasculitis were the overwhelming predominance of small versus medium vessel vasculitis and leukocytoclastic versus mononuclear vasculitis, with a higher prevalence of extraglandular and immunologic SS features. Small vessel vasculitis manifested as palpable purpura, urticarial lesions, or erythematosus maculopapules, with systemic involvement in 44% of patients in association with cryoglobulins in 30%. Life-threatening vasculitis was closely related to cryoglobulinemia.

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## INTRODUCTION

Sjögren syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands[13]. In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary SS. The histologic hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy)[74] to a systemic process with diverse extraglandular manifestations[21,64].

There is a wide spectrum of cutaneous involvement in primary SS, but it has been little studied. Vasculitis is one of the most characteristic extraglandular SS manifestations, and, although it has many clinical forms, affecting arteries of different sizes, veins and/or capillaries of various organs, usually appears as skin lesions. In recent years, progress has been made in identifying the characteristics of specific types of vasculitis, thus facilitating a more accurate diagnosis[39]. Even so, the clinical characteristics and diversity of vasculitis associated with primary SS have been little studied[1,54]. The aims of this study were to determine the specific

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characteristics of cutaneous involvement in patients with primary SS, with emphasis on the different clinical and histologic types of SS-associated vasculitis.

## METHODS

### Patients

Between 1994 and 2002, we investigated the clinical and immunologic characteristics of 380 consecutive patients with primary SS from the Department of Autoimmune Diseases of Hospital Clinic of Barcelona (Spain), 83 patients from the Rheumatology Unit of Hospital de Vilajoyosa (Spain) and 95 patients from the Rheumatology Unit at the Clinica Universitaria Bolivariana (Colombia). All patients fulfilled 4 or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993[81] and underwent a complete history and physical examination. Diagnostic tests for SS (rose bengal staining, Schirmer test, parotid scintigraphy, and salivary gland biopsy) were performed according to the recommendations of the European Community Study Group[81]. We considered as exclusion criteria for the diagnosis of primary SS preexisting autoimmune or hematologic diseases, and hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV) infections. Clinical and serologic characteristics of all patients were collected in a protocol form. To minimize possible interobserver bias, the inclusion criteria and variables of the protocol were agreed to by all participating physicians. Information collected by protocol forms was transferred to a computerized database program (SPSS for Windows, Chicago, IL).

Patients were included in the study when there was clinical evidence of cutaneous lesions, excluding drug reactions and xeroderma. Vasculitis was defined as a clinicopathologic process characterized either pathologically, by evidence of vascular damage (inflammation on blood vessel wall), or clinically, when cutaneous lesions, evaluated by a consultant dermatologist (CH), were considered characteristic of vasculitis. Cutaneous vasculitis was classified according to the approach of Stegeman and Kallenberg[70]. Polyarteritis nodosa was diagnosed according to the 1990 American College of Rheumatology (ACR) criteria[47]. Cryoglobulinemic vasculitis was diagnosed when positive serum cryoglobulins were accompanied by clinical features characteristic of vasculitis. Urticarial vasculitis was diagnosed when long-lasting (more than 24 hours) indurated weals, which may be itchy, painful, or tender, or accompanied purpura, occurred spontaneously or at minor trauma sites. Other cutaneous processes were clinically diagnosed by a consultant dermatologist (CH). To compare clinical and immunologic characteristics of patients with vasculitis we selected a control group of SS patients without cutaneous vasculitis matched for age, gender, and ethnicity.

### Immunologic Studies

Immunologic tests included antinuclear antibodies (ANA) (indirect immunofluorescence using mouse liver/kidney/stomach as substrates); antimitochondrial antibodies (AMA); antiparietal cell antibodies; antismooth muscle antibodies and antiliver-kidney microsome antibodies type-1 (indirect immunofluorescence); precipitating antibodies to the extractable nuclear antigens Sm, RNP, Ro/SS-A, and La/SS-B (ELISA); ANCA (indirect immunofluorescence); and rheumatoid factor (RF) (latex fixation and Waaler-Rose tests). Complement factors (C3 and C4) were measured by nephelometry (Behring BNA nephelometer). Serum cryoglobulins were measured after centrifugation.

### Statistical Analysis

Chi-square and Fisher exact tests were applied to analyze qualitative differences. For comparison of quantitative parameters, the Student t-test was used in large samples of similar variance, and the nonparametric Mann-Whitney U-test was used for small samples. Values of quantitative variables are expressed as mean standard error of the mean (SEM). Statistical significance was established at $p < 0.05$. Statistical analysis was performed with the SPSS program.

## RESULTS

A total of 89/558 (16%) patients with primary SS and cutaneous involvement were included in the study. There were 88 (99%) female patients and 1 (1%) male, with a mean age at diagnosis of cutaneous involvement of 51.8 years (range, 23–80 yr), and a mean age at SS diagnosis of 56.6 years (range, 18–83 yr). Cutaneous vasculitis was observed in 52 (9%) patients. Non-vasculitic cutaneous processes included annular erythema (n = 9), erythema nodosum (n = 7), livedo reticularis (n = 7), thrombocytopenic purpura (n = 3), psoriasis (n = 3), vitiligo (n = 2), lichen planus (n = 2), nodular vasculitis (n = 1), cutaneous amyloidosis (n = 1), Laugier-Hunziker disease (n = 1), annular granuloma (n = 1), and other lesions in 3. In 4 patients, more than 1 cutaneous process was described.

### Cutaneous Vasculitis

The main cutaneous involvement was cutaneous vasculitis, present in 52 (58%) patients (Table 1). There were 51 female patients and 1 male, with a mean age at diagnosis of cutaneous vasculitis of 51 years (range, 20–80 yr). Cutaneous lesions included palpable purpura in 38 (73%) patients, erythematous macules in 17 (33%), erythematous papules in 2 (4%), and ulcers/ischemia in 2 (4%). Cutaneous lesions were located in the lower limbs in 48 (92%), the upper limbs in 13 (25%), the trunk in 5 (10%), and the face in 3 (6%). The main extraglandular features observed in

 

**TABLE 1.** Main Features of 52 Patients With Primary Sjögren Syndrome and Cutaneous Vasculitis

| | Patients with Primary SS With Cutaneous Vasculitis (n = 52) No. (%) |
|---|---|
| Epidemiologic data | |
| Female | 51 (98) |
| Mean age at diagnosis of vasculitis (yr) | 51.13 ± 2.23 |
| Cutaneous lesions | |
| Palpable purpura | 38 (73) |
| Erythematous macules | 17 (33) |
| Erythematous papules | 2 (4) |
| Ulcers/ischemia | 2 (4) |
| Extraglandular features | |
| Articular involvement | 26 (50) |
| Raynaud phenomenon | 21 (40) |
| Peripheral neuropathy | 16 (31) |
| Fever | 9 (17) |
| Pulmonary involvement | 7 (14) |
| Glomerulonephritis | 5 (10) |
| Non-Hodgkin lymphoma | 2 (4) |
| Hematologic data | |
| Anemia (Hb <11 g/dL) | 25/49 (51) |
| Leukopenia | 11/49 (22) |
| Thrombocytopenia | 3/48 (6) |
| ESR>50 mm/h | 25/47 (53) |
| Hypergammaglobulinemia >25% | 20/34 (59) |
| Immunologic data | |
| ANA | 45/51 (88) |
| RF | 38/49 (78) |
| Anti-Ro/SS-A | 35/50 (70) |
| Hypocomplementemia | 17/35 (49) |
| Cryoglobulinemia | 15/34 (44) |
| Anti-La/SS-B | 19/49 (39) |
| Histologic data | |
| Leukocytoclastic vasculitis | 36/38 (95) |
| Lymphocytic vasculitis | 1/38 (3) |
| Necrotizing vasculitis | 2/38* (5) |

*One of these patients showed coexisting leukocytoclastic vasculitis.

these patients were articular involvement in 26 (50%), Raynaud phenomenon in 21 (40%), peripheral neuropathy in 16 (31%), fever in 9 (17%), pulmonary involvement in 7 (14%), and glomerulonephritis in 5 (10%). At the onset of the vasculitis, hematologic data showed anemia (hemoglobin <11 g/dL) in 25/49 patients (51%), leukopenia in 11/49 (22%), and thrombocytopenia in 3/48 (6%). Erythrocyte sedimentation rate (ESR) was >50 mm/h in 25/47 (53%) patients, and hypergammaglobulinemia (>25%) was present in 20/34 (59%). ANA were detected in 45/51 (88%) patients, RF in 38/49 (78%), anti-Ro/SS-A antibodies in 35/50 (70%), hypocomplementemia in 17/35 (49%), cryoglobulins in 15/34 (44%), and anti-La/SS-B antibodies in 19/49 (39%). A biopsy specimen from the skin was obtained in 38 patients (73%). The main histologic diagnosis was leukocytoclastic vasculitis in 36, lymphocytic vasculitis in 1, and necrotizing vasculitis in 2. In 1 patient, leukocytoclastic and necrotizing vasculitis were found to coexist. Involvement of medium-sized vessels was observed in 2 (5%) patients (both with necrotizing vasculitis), while the remaining 36 (95%) had small vessel vasculitis.

Cutaneous vasculitis was treated with oral corticosteroids in 38 (73%) cases, 7 of which required doses >30 mg/day. Seven (13%) patients received immunosuppressive agents (4 cyclophosphamide and 3 azathioprine), and 2 received plasmapheresis. Other treatments included nonsteroidal antiinflammatory drugs (NSAIDs) in 10 cases, antihistamines in 5, chloroquine in 4, and dapsone in 1 patient. Nine patients received no treatment. Twenty-five (48%) patients had a single episode of cutaneous vasculitis; the remaining 27 suffered relapsing vasculitis. Thirteen (25%) patients were hospitalized due to vasculitic symptomatology. Two (4%) patients with cutaneous vasculitis developed non-Hodgkin lymphoma.

Twenty-three of 52 (44%) patients presented clinical evidence of systemic vasculitis, with peripheral neuropathy in 16 patients, pulmonary involvement in 7, glomerulonephritis in 5, mesenteric vasculitis in 2, and pancreatic vasculitis in 1. In addition, 2 patients presented severe cutaneous involvement, with ulcers, ischemia, and digital necrosis. Of these patients, 9/16 (56%) had cryoglobulins. Six (12%) patients died 1–11 years after the diagnosis of vasculitis, all of whom had severe, multisystemic cryoglobulinemia with neuropathic (n = 5), renal (n = 4), pulmonary (n = 3), mesenteric (n = 2), and pancreatic (n = 1) vasculitic involvement. The cause of death was mesenteric ischemia in 2 patients, sepsis in 2, refractory glomerulonephritis with terminal renal failure in 1, and non-Hodgkin lymphoma progression in 1.

Patients with cutaneous vasculitis had a higher prevalence of articular involvement (50% vs 29%, $p = 0.044$), peripheral neuropathy (31% vs 4%, $p < 0.001$), Raynaud phenomenon (40% vs 15%, $p = 0.008$), renal involvement (10% vs 0%, $p = 0.028$), ANA (88% vs 60%, $p = 0.002$), RF (78% vs 48%, $p = 0.004$), anti-Ro/SS-A antibodies (70% vs 43%, $p = 0.011$), and hospitalization (25% vs 4%, $p = 0.005$) compared with the control group of SS patients without vasculitis (Table 2). When patients were compared according to ethnicity, Spanish patients with cutaneous vasculitis had a higher prevalence of fever (27% vs 0%, $p = 0.018$), ESR >50 mm/h (65% vs 31%, $p = 0.037$), and hospitalization (36% vs 5%, $p = 0.018$) compared with Colombian patients.

**TABLE 2.** Clinical and Immunologic Characteristics of Patients with Primary Sjögren Syndrome, According to the Presence or Absence of Cutaneous Vasculitis

| | Vasculitis (n = 52) No. (%) | No Vasculitis (n = 52) No. (%) | p Value |
|---|---|---|---|
| Articular involvement | 26 (50) | 15 (29) | 0.044 |
| Peripheral neuropathy | 16 (31) | 2 (4) | <0.001 |
| Raynaud phenomenon | 21 (40) | 8 (15) | 0.008 |
| Renal involvement | 5 (10) | 0 (0) | 0.028 |
| Pulmonary fibrosis | 7 (14) | 5 (10) | - |
| Hospitalization | 13 (25) | 2 (4) | 0.005 |
| Antinuclear antibodies | 45/51 (88) | 30/50 (60) | 0.002 |
| Rheumatoid factor | 38/49 (78) | 24/50 (48) | 0.004 |
| Anti-Ro/SS-A antibodies | 35/50 (70) | 22/51 (43) | 0.011 |
| Anti-La/SS-B antibodies | 19/49 (39) | 14/51 (27) | - |

### SS-Associated Small Vessel Vasculitis

A possible approach to classifying SS-associated small vessel vasculitis (SVV) could be the differentiation of cryoglobulinemic vasculitis, urticarial vasculitis, and non-cryoglobulinemic, non-urticarial leukocytoclastic vasculitis (Table 3). Cryoglobulinemic SVV was diagnosed in 14 (27%) of the 52 SS patients with cutaneous vasculitis. All were women, with a mean age of 56 years at the time of vasculitis diagnosis. All patients presented palpable purpura in the lower extremities, with involvement of the upper extremities in 5 patients with ulcers/digital ischemia in 2. Urticarial SVV was diagnosed in 11 (21%) of the 52 SS patients with cutaneous vasculitis. All were women, with a mean age of 46 years at the time of vasculitis diagnosis. The predominant cutaneous lesions were erythematosus urticariform macules in lower (9 cases) and upper (5 cases) extremities. Finally, non-cryoglobulinemic, non-urticarial SVV was diagnosed in the remaining 26 (50%) patients, of whom 25 were women, with a mean age of 51 years at the time of vasculitis diagnosis. The predominant cutaneous lesion was palpable purpura in the lower extremities in 23 patients.

### SS-Associated Medium Vessel Vasculitis

Two SS patients had medium vessel vasculitis (MVV). The first was a 73-year-old woman diagnosed with polyarteritis nodosa after presenting with fever, arthritis, livedo reticularis, polyneuropathy, and papulonecrotic cutaneous lesions. Histologic analysis of the skin and muscle disclosed necrotizing vasculitis of medium-sized arteries. The patient was treated with prednisone and intravenous cyclophosphamide, with improvement of vasculitic symptomatology. One year later, the patient was diagnosed with SS.

The second patient was diagnosed with SS at 45 years of age. One year later, she presented with cutaneous purpura in lower extremities with positive cryoglobulins, and a cutaneous biopsy showing leukocytoclastic vasculitis. At 60 years of age, she was hospitalized for acute abdominal pain, fever, cutaneous purpura, and paresthesia, with elevated pancreatic enzymes. After an exploratory laparotomy, a partial pancreatectomy was performed. Five days later, the patient's condition worsened and a second laparotomy disclosed mesenteric ischemia, and a partial colectomy was performed. The patient died 5 days later from sepsis. The postmortem examination showed necrotizing vasculitis involving pancreatic and mesenteric arteries.

## Non-Vasculitic Cutaneous Lesions

### Annular Erythema

Nine patients had annular, polycyclic, photosensitive, erythematosus maculopapular lesions. All were women, with a mean age of 52 years. The main sites affected were the face in 7, the upper extremities in 3, and the trunk in 2. Other extraglandular SS features were Raynaud phenomenon in

**TABLE 3.** Cutaneous Vasculitis in 52 Patients with Primary SS: Prevalence, Epidemiologic Profile, Histologic Confirmation, and Mortality

| | No. (%) | Female No. (%) | Mean Age at Diagnosis of Vasculitis (yr) | Histologic Confirmation No. (%) | Death No. (%) |
|---|---|---|---|---|---|
| SS-associated SVV | | | | | |
| Cryoglobulinemic vasculitis | 14 (27) | 14 (100) | 56 | 11 (79) | 5 (36) |
| Urticarial vasculitis | 11 (21) | 11 (100) | 46 | 9 (82) | 0 (0) |
| Other leukocytoclastic vasculitis (noncryoglobulinemic, nonurticarial) | 26 (50) | 25 (96) | 51 | 16 (62) | 1 (4) |
| SS-associated MVV | | | | | |
| Necrotizing vasculitis of medium-sized arteries | 2* (4) | 2 (100) | 59 | 2 (100) | 1 (50) |

Abbreviations: SVV = small vessel vasculitis; MVV = medium vessel vasculitis.
*Includes 1 patient with coexisting SVV.

2 and articular involvement in 2. All 9 patients were positive for ANA and anti-Ro/SS-A antibodies, 5 were positive for anti-La/SS-B antibodies, and 4 for RF. No patient fulfilled classification criteria for systemic lupus erythematosus[31].

### Livedo Reticularis

Seven patients had livedo reticularis. All were women, with a mean age of 61 years. The main extraglandular SS features were articular involvement in 5, peripheral neuropathy in 2, and Raynaud phenomenon in 2. The main immunologic data were positive ANA in 6, anti-Ro/SS-A antibodies in 4, anti-La/SS-B antibodies in 2, RF in 4, and hypocomplementemia in 2. Vasculitis was diagnosed in 3 of the 7 patients with livedo reticularis (leukocytoclastic vasculitis in 2 and polyarteritis nodosa in 1). No patient suffered repeated thrombotic events or abortions. Antiphospholipid antibodies, tested in 5/7 patients, were repeatedly negative.

### Erythema Nodosum

Seven patients had erythema nodosum. All were women, with a mean age of 49 years. The main extraglandular SS features were articular involvement in 6, fever in 2, Raynaud phenomenon in 2, and pulmonary involvement in 2. The main immunologic data were positive ANA in 6, anti-Ro/SS-A antibodies in 1, RF in 1, and hypocomplementemia in 1.

In 2 patients, sarcoidosis coexisting with primary SS was diagnosed. The first was a 62-year-old woman admitted to our department due to arthritis, erythema nodosum, and chest pain. She had a 12-year history of recurrent uveitis, and primary SS had been diagnosed 4 years previously based on the existence of xerostomia, xerophthalmia, positive ocular tests, and a salivary gland biopsy demonstrating lymphocytic infiltrates (grade IV of Chisholm-Mason classification) without noncaseating granulomas. Chest X-ray and lung computed tomography (CT) revealed mediastinal lymph node enlargement. Ga scintigraphy showed high uptake in the mediastinum. A mediastinoscopy was performed with a biopsy of 1 of these nodes. Histopathologic examination revealed a nonnecrotizing granulomatous inflammatory process compatible with sarcoidosis.

The second patient was a 39-year-old previously healthy woman referred to our department due to anterior uveitis in the left eye. Chest X-ray and lung CT disclosed bilateral hilar adenopathies. The bronchoalveolar lavage revealed a predominantly lymphocytic inflammatory process, although the transbronchial lung biopsy was normal. Seven years later, the patient presented with xerostomia and xerophthalmia. Physical examination revealed cutaneous maculopapular lesions on the back, with similar lesions adjacent to an old scar on the knee. Histopathologic examination showed noncaseating granulomas compatible with sarcoidosis. Salivary gland biopsy showed lymphocytic infiltrates (grade IV of the Chisholm-Mason classification) without noncaseating granulomas. The remaining 5 SS patients with erythema nodosum presented no other autoimmune or infectious processes.

### Other Cutaneous Lesions

Of the remaining patients, 3 had purpura in lower extremities in association with low platelet counts (thrombocytopenic purpura). Three patients had psoriasis, 2 vitiligo, 2 lichen planus, 1 nodular vasculitis, 1 cutaneous amyloidosis, 1 Laugier-Hunziker disease, and 1 annular granuloma. Finally, nonspecific cutaneous rash was observed in 3 patients.

## DISCUSSION

In the current study, we found a wide spectrum of cutaneous involvement in patients with primary SS, with vasculitis being the most frequent cutaneous process. We found cutaneous vasculitis in 10% of patients, a prevalence similar to those of the main series, which range from 9% to 32%[21]. Although the names and definitions proposed by the Chapel Hill Consensus Conference[38] are increasingly used for the diagnosis of primary vasculitis[39], this classification does not address the diagnosis of vasculitis in patients with a well-defined systemic autoimmune disease. In primary SS, Alexander et al proposed the term cutaneous ''inflammatory vascular disease'' (IVD) in 1983, describing 2 distinct types of IVD, neutrophilic (NIVD) and mononuclear (MIVD)[1,54]. Since then, SS-associated vasculitis has not been specifically studied using currently accepted vasculitis classification.

Several characteristics of SS-associated cutaneous vasculitis stand out in the present study. The first is the overwhelming predominance of leukocytoclastic as opposed to mononuclear vasculitis, unlike the results described by Molina and Alexander and colleagues[1,54]. These differences may be partly explained by the substantial association with cryoglobulinemia in our patients. In addition, most of our patients were biopsied 24–48 hours after the onset of cutaneous vasculitis which also contributed to the predominance of NIVD, as it has been suggested that MIVD might represent a later stage of a preexisting NIVD[24]. A second point of interest was the analytical profile of our patients with cutaneous vasculitis, which showed a higher prevalence of anemia, elevated ESR, and hypergammaglobulinemia, according to previous studies[76]. Our patients also had a higher frequency of immunologic markers, with ANA, RF, and anti-Ro/SS-A antibodies being present in more than 70%. This analytical and immunologic profile has been described in smaller series of patients, whose authors also described a close correlation between positive anti-Ro/La antibodies and cutaneous vasculitis[1,2,27,55,76]. Of the 28 patients described by Alexander et al[1], 24 had positive anti-Ro/SS-A, 11 anti-La/SS-B antibodies, and 7 cryoglobulins, and the

9 patients described by Tsokos et al[76] had positive ANA and RF, and 7 cryoglobulins and hypocomplementemia.

The current study showed a wide variety of vasculitic involvement in primary SS, with the clinical expression depending on the size (small vs medium vessel vasculitis) and site (cutaneous vs internal organs) of the vessels involved.

## Small Vessel Vasculitis

Ninety-four percent of our SS patients with histologically confirmed cutaneous vasculitis had SVV. Although cutaneous vasculitis is generally thought of as being palpable purpura, other types of lesions can occur, such as vesicles, pustules, bullae, urticaria, necrotic lesions, ulceration, and livedo reticularis. In our patients, although palpable purpura was the predominant cutaneous lesion in 73%, some other lesions were frequent (erythematosus macules/papules in 35% and urticaria in 21%), while other lesions, such as nodules, ulcers, or ischemic lesions, were infrequent. A similar diversity was described by Molina et al[54] in 45 SS patients with cutaneous vasculitis, with purpura found in 40%, urticaria in 27%, erythematous lesions in 27%, and nodules in 7%. All the 9 patients described by Tsokos et al[76] had cutaneous purpura, and 3 had cutaneous ulcers.

SVV is a point where the classification schema for vasculitis shows the greatest degree of confusion in relation to terminology and distinguishing 1 entity from another[31]. Our preliminary approach to these patients was to classify them according to the presence or absence of cryoglobulins. Cryoglobulinemia was the cause of cutaneous SVV in 30% of our patients. In recent series, cryoglobulins were present in 16%–19% of patients with SS[63,78]. The clinical significance of cryoglobulinemia in primary SS is threefold. First, cryoglobulins have been associated with a higher prevalence of extraglandular disease[78,79], as occurred in most of our patients who had fever, arthritis, glomerulonephritis, and neuropathy. This suggests that cryoglobulins are a sensitive marker of systemic extraglandular involvement in patients with SS. Second, cryoglobulinemia in SS is associated with the development of non-Hodgkin lymphoma. In 1996, Tzioufas et al[78] prospectively demonstrated that mixed monoclonal cryoglobulinemia is a predictive factor for lymphoma development in primary SS. Voulgarelis et al[82] found skin vasculitis in 11 (33%) of 33 European SS patients with non-Hodgkin lymphoma. Third, our study showed a close association between cryoglobulinemia and life-threatening vasculitic involvement, since all the SVV patients who died had multisystemic cryoglobulinemic vasculitis. In a 2002 study by Ioannidis et al[37], palpable purpura was associated with increased mortality (hazard ratio of 3.0) in a cohort of 723 patients with primary SS, and 17/32 deaths occurred in patients with either lymphoproliferation or cryoglobulinemia. In summary, SS-associated cryoglobulinemia should be considered as a potential life-threatening situation, with a high risk of developing systemic vasculitis and lymphoproliferative disorders, or death.

Seventy percent of our SS patients with SVV had non-cryoglobulinemic leukocytoclastic vasculitis, of whom 15 (20%) had urticarial lesions (mainly maculopapular lesions) predominantly in the upper extremities, face, and trunk. It is unclear whether these lesions should be classified specifically as urticarial vasculitis or as a clinical variant of SS-associated leukocytoclastic vasculitis[28,42,65]. It has been suggested that urticarial vasculitis is not a separate entity in patients with systemic autoimmune diseases, because in some patients with immune complex-mediated vasculitis and extensive complement activation, cutaneous SVV may cause local edema resulting in urticaria[87]. Urticaria associated with vasculitis persists longer than typical non-vasculitic urticaria (>24 h) and often evolves to purpuric lesions. Urticarial lesions should be considered as a specific clinical expression of leukocytoclastic vasculitis in some SS patients, as suggested by Alexander et al in 1983[1].

Fifty percent of our patients with vasculitis had cutaneous purpura not associated with cryoglobulinemia, with a higher frequency of serologic features such as elevated ESR, hypergammaglobulinemia, and positive RF and autoantibodies. Most (if not all) of these patients could be considered to have Waldenstrom benign hypergammaglobulinemic purpura, first described in 1943 in female patients with recurrent purpura in lower extremities, hypergammaglobulinemia, increased ESR, and mild anemia[84]. Later studies demonstrated that SS is found in about 50% of secondary cases[16]. Thus, SS-associated SVV may be accepted as a well-characterized extraglandular manifestation of SS with different patterns of clinical expression, mainly palpable purpura but also urticarial or maculopapular lesions, in association with cryoglobulins in 30%.

## Medium Vessel Vasculitis

Two of our patients had SS-associated MVV. The first had systemic necrotizing vasculitis coexisting with cryoglobulinemia. Acute necrotizing vasculitis in patients with primary SS manifesting as polyarteritis nodosa-like vasculitis was first described by Tsokos et al in 1987[76]. We have identified 19 reports of additional SS patients with systemic necrotizing vasculitis (Table 4)[2,6,7,10,15,17,22,29,35,36,40,45,46,54,59,67,76,91], involving muscle (10 cases), gastrointestinal tract (7 cases), peripheral nerve (4 cases), kidney (3 cases), central nervous system (CNS) (2 cases) and pancreas, gallbladder, spleen, parotid gland, and spinal cord (1 case each). However, the coexistence of small and medium size vasculitis in the same SS patient (as occurred in our patient) was also first described by Tsokos et al[76]. Of the 19 cases referred to above, 5 had coexisting cryoglobulinemia.

The second patient fulfilled the ACR criteria for polyarteritis nodosa, leading to a final diagnosis of coexisting polyarteritis nodosa and primary SS. The coexistence of

 

primary SS with other primary systemic vasculitis is exceptional; only 2 patients with coexisting Horton disease and 1 with microscopic polyangiitis have been reported[9,53,61]. Although some authors have reported the existence of polyarteritis nodosa or polyarteritis nodosa-like vasculitis in patients with primary SS, these patients had no aneurisms or other typical features of polyarteritis nodosa. Thus, it may be considered that necrotizing vasculitis of the medium arteries is a very infrequent SS-associated vasculitic process, occurring in less than 5% of SS patients with vasculitis, and the coexistence of SS with a true primary vasculitis is an exceptional situation.

## Life-Threatening Vasculitis

Clinically, vasculitis can range from a benign, restricted process (for example, cutaneous leukocytoclastic angiitis) to a life-threatening systemic vasculitis. All types of vessels from any organ may be affected, with a wide variety of signs and symptoms. Tsokos et al[76] pointed out that the severity of vasculitis in SS depends on the histologic type (necrotizing vasculitis being more severe than leukocytoclastic) and the site (internal more severe than external) of the vasculitic lesions. In our SS patients, we differentiated between vasculitis confined to the skin, observed in 56% of patients, and systemic vasculitis, observed in the remaining 44%. This suggests that cutaneous vasculitis expresses systemically in almost half of patients. The main systemic vasculitic involvement was neuropathic, pulmonary, and renal, associated with cryoglobulinemia in more than half the cases, with severe cutaneous involvement, intestinal, and pancreatic vasculitis being infrequent. Although most of the severe cases of vasculitis reported in SS patients were due to necrotizing vasculitis (see Table 4), there are some reports of life-threatening leukocytoclastic vasculitis, with intestinal involvement in 4 patients and cutaneous involvement in 2[6,15,22,54,76,91].

Although infrequent, systemic vasculitis may be considered the main autoimmune cause of death in patients with primary SS. In our patients with cutaneous vasculitis, 6/52 (12%) died due to multisystemic vasculitic involvement; Molina et al[54] described a similar percentage (10%) in 50 patients with cutaneous vasculitis. Of the 19 reported deaths of SS patients with vasculitis (including our cases), the main causes were CNS involvement in 6, gastrointestinal perforation in 5, hematologic neoplasia in 3, sepsis in 2, renal failure in 1, and hemolytic anemia in 1. Cryoglobulins were determined in 12 of these patients, and were positive in 10 (83%) cases.

## Non-Vasculitic Cutaneous Involvement

Nine patients (all with positive anti-Ro/SS-A antibodies) had polycyclic, photosensitive, erythematosus maculopapular lesions, clinically similar to annular erythema or subacute cutaneous lupus erythematosus. Although SS-associated annular erythema has been considered as the Asian counterpart of subacute cutaneous lupus erythematosus in white patients, recent cases have been reported in non-Asian SS patients[86]. It thus seems that SS-annular erythema and subacute cutaneous lupus erythematosus are difficult to differentiate clinically. McCauliffe et al[51] could not identify disease-specific Ro autoantibodies in sera from patients with SS-annular erythema and subacute cutaneous lupus erythematosus, and suggested that the 2 diseases might have a similar pathogenic origin. Our results suggest that polycyclic, photosensitive cutaneous lesions (clinically identical to Asian annular erythema or Caucasian subacute cutaneous lupus erythematosus) may occur in a specific subset of patients with primary SS and positive anti-Ro/SS-A antibodies. This cutaneous manifestation of primary SS may be considered the counterpart of the subacute cutaneous lupus erythematosus lesions observed in systemic lupus erythematosus patients with positive anti-Ro/SS-A antibodies. Some patients diagnosed with isolated subacute cutaneous lupus erythematosus (without additional clinical or immunologic data of systemic lupus) may have underlying primary SS. Nevertheless, SS patients with these photosensitive lesions should always be followed up to rule out possible evolution to systemic lupus erythematosus.

Seven of our SS patients had livedo reticularis. Vasculitis was diagnosed in 3, with no other autoimmune diseases being detected. In 1987, Ingram et al[35] reported 2 SS patients with livedo reticularis and a devastating aPL-related noninflammatory vasculopathy (probably, a catastrophic APS). Thus, in patients with primary SS, livedo reticularis should be considered as an exceptional cutaneous manifestation in the absence of underlying vasculitic or thrombotic disease.

Erythema nodosum was found in 7 of our patients with primary SS, a rarely reported association. In 1984, Gouet et al[23] reported a patient with erythema nodosum, SS, and Vogt-Koyanagi disease, and Yamamoto et al[89] described 4 patients with primary SS and erythema nodosum not associated with other autoimmune or infectious diseases. Of our 7 patients, 2 had coexisting sarcoidosis. We found 5 additional reports of patients with erythema nodosum, sarcoidosis, and SS[12,18,19,69,80]. Salivary gland biopsy was performed in 3, showing focal sialadenitis in 2 (coexisting SS and sarcoidosis) and noncaseating granulomas in 1 (sarcoidosis mimicking SS). This suggests that in patients with primary SS, the appearance of erythema nodosum may be indicative of coexisting sarcoidosis.

We describe 1 patient with nodular vasculitis not associated with other autoimmune or infectious processes. Nodular vasculitis is a lobular panniculitis associated with vasculitis of the septal blood vessels and characterized by a chronic eruption of nodular, erythematous, painful lesions

**TABLE 4.** Life-Threatening Vasculitis in Patients with Primary Sjögren Syndrome, Previous Reports

| Author (Reference) | Histology | Site of Vasculitic Involvement | Cryog. | Death |
|---|---|---|---|---|
| *Tsokos*[76] | Necrotizing | Ileum | + | GI |
| *Tsokos*[76] | Necrotizing | Kidney | + | - |
| *Peyronnard*[59] | Necrotizing | Gallbladder, spleen | ND | |
| *Sato*[67] | Necrotizing | CNS, GI, kidney, pancreas | ND | Sepsis |
| *Lahoz Rallo*[45] | Necrotizing | Muscle | - | - |
| *Alexander*[2] | Necrotizing | Spinal cord | + | CNS |
| *Lie*[46] | Necrotizing | Bowel | ND | - |
| *Inoh*[36] | Necrotizing | Colonic ulcers | ND | - |
| *Herreman*[29] | Necrotizing | Muscle | ND | - |
| *Gottenberg*[22] | Necrotizing | Muscle, nerve | ND | - |
| *Gottenberg*[22] | Necrotizing | Muscle, nerve | ND | - |
| *Gottenberg*[22] | Necrotizing | Muscle, nerve | ND | - |
| *Gottenberg*[22] | Necrotizing | Muscle, nerve | ND | - |
| *Kaltreider*[40] | Necrotizing | Muscle, kidney, CNS, GI | + | CNS |
| *Kaltreider*[40] | Necrotizing | Muscle | - | AlHA |
| *Kaltreider*[40] | Necrotizing | Muscle | - | Sarcoma |
| *Kaltreider*[40] | Necrotizing | Muscle | - | - |
| *Bloch*[6] | Necrotizing | Muscle, parotid, bowel | ND | Sarcoma |
| *Anonymous*[10] | Necrotizing | Colon ulcers | + | GI |
| *Tsokos*[76] | Leukocytoclastic | Rectum | + | - |
| *Tsokos*[76] | Leuko/EO | Digital gangrene | + | - |
| *Bloch*[6] | Leukocytoclastic | Bowel | ND | - |
| *Durez*[15] | Leukocytoclastic | Cutaneous ulcers | + | - |
| *Gottenberg*[22] | Leukocytoclastic | Ileum | ND | - |
| *Zuniga-Montes*[91] | Leukocytoclastic | Cutaneous ulcers | ND | - |
| *Molina*[54] | Leukocytoclastic | CNS | ND | CNS |
| *Molina*[54] | Leukocytoclastic | Bowel | ND | GI |
| *Molina*[54] | Leukocytoclastic | Gallbladder, appendix, mesentery | ND | - |
| *Molina*[54] | Mononuclear | CNS | ND | CNS |
| *Molina*[54] | Mononuclear | CNS | ND | CNS |
| *Ferreiro*[17] | ND | CNS | ND | CNS |
| *Canhao*[7] | ND | CNS | ND | - |

Abbreviations: ND = not done; Cryog. = cryoglobulinemia; CNS = central nervous system; GI = gastrointestinal; AIHA = autoimmune hemolytic anemia; EO = endarteritis obliterans.

occurring predominantly on the posterior and lateral surfaces of the legs[14]. To our knowledge, idiopathic nodular vasculitis has not been described in patients with primary SS. In 2000, Cardinali et al[8] reported an SS-HCV patient with nodular vasculitis, in whom cultures for fungi and mycobacteria were negative. Other types of panniculitis have been reported occasionally in patients with primary SS, including septal[77], Weber-Christian[57], plasma cell[52], and granulomatous panniculitis[73].

Other cutaneous lesions infrequently reported in primary SS were found in the current study, including lichen planus, thrombocytopenic purpura, vitiligo, and cutaneous amyloidosis. A possible association between lichen planus and primary SS has been suggested by Lundstrom et al[48], who analyzed SS features in 39 patients with oral lichen planus and found that a third of them had clinical and histologic SS features. Eleven cases (including the 2 from the current study) of association between lichen planus and SS have been described[5,11,75].

Idiopathic thrombocytopenic purpura in patients with primary SS, described in 3 of our patients, is rare, as severe thrombocytopenia in primary SS is exceptional[64]. Only 14 other cases have been reported[4,20,30,44,49,56,62,66,68,72,83,85,88,90]. Four cases of vitiligo associated with SS have been reported[43,50]. Vitiligo and sicca syndrome are often seen in patients with graft-versus-host disease. Martin et al[50] described a woman with posttransfusion microchimerism who developed SS and vitiligo. Six cases of cutaneous

 

amyloidosis in SS patients have been reported[3,26,33,34,41,58,60]. Finally, we found in some patients other cutaneous processes not previously reported in patients with primary SS, such as Laugier-Hunziker disease and annular granuloma.

The wide diversity of cutaneous processes, both vasculitic and non-vasculitic, observed in our patients with primary SS suggests that skin involvement in primary SS manifests in different clinical and histologic forms. The range of skin lesions includes specific cutaneous disorders, such as Waldenstrom purpura, annular erythema, idiopathic thrombocytopenic purpura, urticarial vasculitis, polyarteritis nodosa-like vasculitis, and essential cryoglobulinemia, which have sometimes been considered as separate processes occurring concurrently with primary SS. The current study shows that these processes may be considered an intrinsic part of the spectrum of cutaneous involvement in primary SS, either associated with SS-related analytical features (that is, hypergammaglobulinemia, anti-Ro/SS-A antibodies, or thrombocytopenia), or forming part of the spectrum of SS-associated vasculitis (including urticarial, necrotizing, and cryoglobulinemic vasculitis).

In conclusion, cutaneous involvement was detected in 16% of our patients with primary SS, with cutaneous vasculitis being the most frequent process (involving 10% of our SS patients). The main characteristics of SS-associated cutaneous vasculitis were the overwhelming predominance of small versus medium vessel vasculitis, and leukocytoclastic versus mononuclear vasculitis. SS patients with cutaneous vasculitis had a higher prevalence of extraglandular, analytical (anemia, elevated ESR, and hypergammaglobulinemia), and immunologic (ANA, RF, anti-Ro/SS-A, and cryoglobulins) features. SS-associated SVV may manifest as palpable purpura, urticarial lesions, or erythematosus maculopapules. It was associated with cryoglobulins in 30% of patients, with systemic involvement in 44%. Life-threatening vasculitis was closely related to cryoglobulinemia: in all our patients with cutaneous vasculitis who died, death was due to multisystemic cryoglobulinemic vasculitis. Due to its frequency and prognostic significance, we suggest that cryoglobulinemia plays a central role in the vasculitis associated with primary SS.

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## REFERENCES

1. Alexander EL, Arnett FC, Provost TT, Stevens MB. Sjogren's syndrome: Association of anti-Ro (SS-A) antibodies with vasculitis, hematologic abnormalities and serologic hyperreactivity. *Ann Intern Med.* 1983;98:155–159.
2. Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjogren's syndrome. *Medicine (Baltimore).* 1982;61:247–257.
3. Aoki A, Ono S, Ueda A, Hagiwara E, Takashi T, Ideguchi H, Misumi M, Sasaki T, Ikezawa Y, Inayama Y, Inoue Y, Ishigatsubo Y. [Two cases of limited cutaneous nodular amyloidosis with primary Sjogren's syndrome.] *Nihon Rinsho Meneki Gakkai Kaishi.* 2002;25:205–211.
4. Balquet MH, Hatron PY, Gosset D, Savinel P, Devulder B. [Autoimmune thrombopenic purpura revealing primary Sjogren's syndrome. 2 cases.] *Rev Med Interne.* 1989;10:253–255.
5. Bermejo Fenoll A, Lopez Jornet MP. [Oral lichen planus and Sjogren's syndrome. 2 cases of association.] *Av Odontoestomatol.* 1991;7:29–33.
6. Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ. Sjogren's syndrome: A clinical, pathological, and serological study of sixty-two cases. *Medicine (Baltimore).* 1965;44:187–231.
7. Canhao H, Fonseca JE, Rosa A. Intravenous gammaglobulin in the treatment of central nervous system vasculitis associated with Sjogren's syndrome. *J Rheumatol.* 2000;27:1102–1103.
8. Cardinali C, Gerlini G, Caproni M, Pimpinelli N, Fabbri P. Hepatitis C virus: A common triggering factor for both nodular vasculitis and Sjogren's syndrome [letter]? *Br J Dermatol.* 2000;142:187–189.
9. Chagnon JP, Brion N, Yeni P, Barge J, Isoul R, Carbon C. [Late recurrence of Horton's disease with sicca syndrome.] *Sem Hop.* 1983; 59:189–191.
10. Clinicopathologic conference. Sjogren's syndrome. *Am J Med.* 1964;37: 578–591.
11. Collet E, Dalac S, Brichon P, Lorcerie B, Besancenot JF, Lambert D. [The association of lichen planus and primary Gougerot-Sjogren syndrome.] *Ann Dermatol Venereol.* 1989;116:483–486.
12. Cox NH, McCrea JD. A case of Sjogren's syndrome, sarcoidosis, previous ulcerative colitis and gastric autoantibodies. *Br J Dermatol.* 1996;134:1138–1140.
13. Daniels T, Fox PC. Salivary and oral components of Sjogren's syndrome. *Rheum Clin Dis North Am.* 1992;18:571–589.
14. Distler O, Palitzsch KD, Hoheneutner U, Muller-Ladner U, Lang B. A 30 year history of panniculitis. *J Rheumatol.* 2000;27:507–509.
15. Durez P, Tourne L, Feremans W, Mascart-Lemone F, Heenen M, Appelboom T. Dramatic response to intravenous high dose gammaglobulin in refractory vasculitis of the skin associated with Sjogren's syndrome. *J Rheumatol.* 1998;25:1032–1033.
16. Ferreiro JE, Pasarin G, Quesada R, Gould E. Benign hypergammaglobulinemic purpura of Waldenstrom associated with Sjogren's syndrome. Case report and review of immunologic aspects. *Am J Med.* 1986;81: 734–740.
17. Ferreiro JE, Robalino BD, Saldana MJ. Primary Sjogren's syndrome with diffuse cerebral vasculitis and lymphocytic interstitial pneumonitis. *Am J Med.* 1987;82:1227–1232.
18. Ferrer J, Bosch X, Cervera R, Font J, Ingelmo M. Sarcoidosis or primary Sjogren's syndrome? *Ann Rheum Dis.* 1988;47:965–966.
19. Folwaczny M, Sommer A, Sander CA, Kellner H. Parotid sarcoidosis mimicking Sjogren's syndrome: Report of a case. *J Oral Maxillofac Surg.* 2002;60:117–120.
20. Fukuda K, Iwanaga T, Horiuchi A. [A case of overlapping syndrome with Sjogren's syndrome, ITP and Hashimoto's disease.] *Rinsho Ketsueki.* 1979;20:1675–1680.
21. Garcia-Carrasco M, Ramos-Casals M, Rosas J, Pallares L, Calvo-Alen J, Cervera R, Font J, Ingelmo M. Primary Sjogren syndrome: Clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine (Baltimore).* 2002;81:270–280.
22. Gottenberg JE, Sibilia J, Lacroix C, Godmer P, Andre MH, Guillevin L, Mariette X. Primary Sjogren's syndrome associated with life-threatening vasculitis. *Arthritis Rheum.* 2002;46(Suppl):S369.
23. Gouet D, Anquez M, Risse JF, Becq-Giraudon B. [Association of Vogt-Koyanagi disease, Gougerot-Sjogren syndrome and erythema nodosum.] *Presse Med.* 1984;13:624.
24. Gower RG, Sams WM Jr, Thorne EG, Kohler PF, Claman HN. Leukocytoclastic vasculitis: Sequential appearance of immunoreactants and cellular changes in serial biopsies. *J Invest Dermatol.* 1977;69: 477–484.
25. Haimowitz JE, McCauliffe DP, Seykora J, Werth VP. Annular erythema of Sjogren's syndrome in a white woman. *J Am Acad Dermatol.* 2000; 42:1069–1072.
26. Haraguchi H, Ohashi K, Yamada M, Hasegawa M, Maeda S,

 

Komatsuzaki A. Primary localized nodular tongue amyloidosis associated with Sjogren's syndrome. *ORL J Otorhinolaryngol Relat Spec.* 1997;59:60–63.
27. Harley JB, Alexander EL, Bias WB, Fox OF, Provost TT, Reichlin M, Yamagata H, Arnett FC. Anti-Ro(SS-A) and anti-La(SS-B) in patients with Sjogren's syndrome. *Arthritis Rheum.* 1986;29:196–206.
28. Hassan ML, Perez Cejudo JA, Yachi del Pino E, Schroh RG. [Vasculitic urticaria: Study of 12 cases.] *Med Cutan Ibero Lat Am.* 1990;18: 179–184.
29. Herreman G, Ferme I, Diebold J, Baviera E, Audouin J, Bazin C, Godeau P. [Gougerot-Sjogren syndrome, periarteritis nodosa, non-Hodgkin's lymphoplasmocytic lymphoma and acquired C4 deficiency.] *Ann Med Interne (Paris).* 1983;134:19–25.
30. Higashi K, Matsuki Y, Hidaka T, Aida S, Suzuki K, Nakamura H. Primary Sjogren's syndrome associated with hyaline-vascular type of Castleman's disease and autoimmune idiopathic thrombocytopenia. *Scand J Rheumatol.* 1997;26:482–484.
31. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40:1725.
32. Hunder G. Vasculitis: Diagnosis and therapy. *Am J Med.* 1996;100: 37S–45S.
33. Ideura H, Tsukada Y, Maezawa A, Ueki K, Nojima Y, Naruse T. Sjogren's syndrome and multiple amyloidomas. *J Rheumatol.* 2000;27: 1325–1326.
34. Inazumi T, Hakuno M, Yamada H, Tanaka M, Naka W, Tajima S, Harada T, Nishikawa T. Characterization of the amyloid fibril from primary localized cutaneous nodular amyloidosis associated with Sjogren's syndrome. *Dermatology.* 1994;189:125–128.
35. Ingram SB, Goodnight SH Jr, Bennett RM. An unusual syndrome of a devastating noninflammatory vasculopathy associated with anticardiolipin antibodies: Report of two cases. *Arthritis Rheum.* 1987;30: 1167–1172.
36. Inoh M, Tokuda M, Maruoka T, Kinashi M, Kurata N, Okawa M, Takahara J. [Multiple colonic ulcers in a patient with Sjogren's syndrome.] *Ryumachi.* 1995;35:585–588.
37. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. *Arthritis Rheum.* 2002;46:741–747.
38. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG, McCluskey RT, Sinico RA, Rees AJ, van Es LA, Waldherr R, Wiik A. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994;37:187–194.
39. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med.* 1997; 337:1512–1523.
40. Kaltreider HB, Talal N. The neuropathy of Sjogren's syndrome. Trigeminal nerve involvement. *Ann Intern Med.* 1969;70:751–762.
41. Kanoh T, Suzuki K, Kawaguchi S. [Multifocal nodular AL amyloidosis in primary Sjogren's syndrome.] *Rinsho Ketsueki.* 1998;39:1157–1162.
42. Kawana S, Nishioka K, Nishiyama S. [Urticarial erythema with neutrophilic infiltration—correlation of cutaneous vascular changes with clinical severity.] *Nippon Hifuka Gakkai Zasshi.* 1991;101: 951–957.
43. Klisnick A, Schmidt J, Dupond JL, Bouchou K, Rousset H, Thieblot P, Humbert P, Vidal E, Aumaitre O. [Vitiligo in multiple autoimmune syndrome: A retrospective study of 11 cases and a review of the literature.] *Rev Med Interne.* 1998;19:348–352.
44. Kondo H, Sakai S, Sakai Y. Autoimmune haemolytic anaemia, Sjogren's syndrome and idiopathic thrombocytopenic purpura in a patient with sarcoidosis. *Acta Haematol.* 1993;89:209–212.
45. Lahoz Rallo C, Arribas Lopez JR, Arnalich Fernandez F, Monereo Alonso A, Llanos Chavarri MC, Camacho Siles J. [Necrotizing vasculitis of the panarteritis nodosa type in a long-course primary Sjogren's syndrome.] *An Med Interna.* 1990;7:528–530.
46. Lie JT. Isolated necrotizing and granulomatous vasculitis causing ischemic bowel disease in primary Sjogren's syndrome. *J Rheumatol.* 1995;22:2375–2377.
47. Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, Arend WP, Calabrese LH, Leavitt RY, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum.* 1990;33:1088–1093.
48. Lundstrom IM, Anneroth KG, Bergstedt HF. Salivary gland function and changes in patients with oral lichen planus. *Scand J Dent Res.* 1982;90:443–458.
49. Mallet H. [Association of thrombocytopenic purpura, Hashimoto's thyroiditis and Gougerot-Sjogren syndrome.] *Rev Med Interne.* 1989; 10:576.
50. Martin L, Watier H, Vaillant L, Aractingi S. Sjogren's syndrome and vitiligo in a woman with posttransfusion microchimerism. *Am J Med.* 2001;111:419–421.
51. McCauliffe DP, Faircloth E, Wang L, Hashimoto T, Hoshino Y, Nishikawa T. Similar Ro/SS-A autoantibody epitope and titer responses in annular erythema of Sjogren's syndrome and subacute cutaneous lupus erythematosus. *Arch Dermatol.* 1996;132:528–531.
52. McGovern TW, Erickson AR, Fitzpatrick JE. Sjogren's syndrome plasma cell panniculitis and hidradenitis. *J Cutan Pathol.* 1996;23: 170–174.
53. Meloni F, Nigro D, Transi MG, Belli S, Arcieri A, Bottazzi M, Bernardi A. Horton's disease and Sjogren's syndrome. A case report. *Clin Exp Rheumatol.* 1989;7:660–661.
54. Molina R, Provost TT, Alexander EL. Two histopathologic prototypes of inflammatory vascular disease in Sjogren's syndrome: Differential association with seroactivity to rheumatoid factor and antibodies to Ro (SS-A) and with hypocomplementemia. *Arthritis Rheum.* 1985;28: 1251–1258.
55. Moutsopoulos HM, Zerva LV. Anti-Ro (SS-A)/La (SS-B) antibodies and Sjogren's syndrome. *Clin Rheumatol.* 1990;9(Suppl 1):123–130.
56. Nichols C, Brightman VJ. Parotid calcifications and cementomas in a patient with Sjogren's syndrome and idiopathic thrombocytopenic purpura. *J Oral Pathol.* 1977;6:51–60.
57. Osato M, Yamaguchi K, Tamiya S, Yamasaki H, Okubo T, Suzushima H, Asou N, Sakata K, Kawakita M, Takatsuki K. A human T-cell lymphotropic virus type-I carrier with chronic renal failure, aplastic anemia, myelopathy, uveitis, Sjogren's syndrome and panniculitis. *Intern Med.* 1996;35:742–745.
58. Pablos JL, Cogolludo V, Pinedo F, Carreira PE. Subcutaneous nodular amyloidosis in Sjogren's syndrome. *Scand J Rheumatol.* 1993;22: 250–251.
59. Peyronnard JM, Charron L, Beaudet F, Couture F. Vasculitic neuropathy in rheumatoid disease and Sjogren syndrome. *Neurology.* 1982;32:839–845.
60. Praprotnik S, Tomsic M, Perkovic T, Vizjak A. Is Sjogren's syndrome involved in the formation of localised nodular amyloidosis? *Clin Exp Rheumatol.* 2001;19:735–737.
61. Radaelli F, Meucci G, Spinzi G, Terruzzi V, Imperiali G, Lenoci N, Strocchi E, Sangiovanni A, Terreni N, Quarenghi M, Minoli G. Acute self-limiting jejunitis as the first manifestation of microscopic polyangiitis associated with Sjogren's disease: Report of one case and review of the literature. *Eur J Gastroenterol Hepatol.* 1999;11:931–934.
62. Ramakrishna R, Kchaudhuri, Sturges A, Manoharan A. Haematological manifestations of primary Sjogren's syndrome: A clinicopathological study. *Q J Med.* 1992;84:547–554.
63. Ramos-Casals M, Cervera R, Yague J, Garcia-Carrasco M, Trejo O, Jimenez S, Morla RM, Font J, Ingelmo M. Cryoglobulinemia in primary Sjogren's syndrome: Prevalence and clinical characteristics in a series of 115 patients. *Semin Arthritis Rheum.* 1998;28:200–205.
64. Ramos-Casals M, Font J, Garcia-Carrasco M, Brito M-P, Rosas J, Calvo-Alen J, Pallares L, Cervera R, Ingelmo M. Primary Sjogren syndrome: Hematologic patterns of disease expression. *Medicine (Baltimore).* 2002;81:281–292.
65. Rostoker G, Uzzan B, Epardeau B, Chapman A. [Urticarial vasculitis associated with apparently primary Gougerot-Sjogren syndrome.] *Ann Dermatol Venereol.* 1986;113:59–62.
66. Sanal O, Ersoy F, Metin A, Tezcan I, Berkel AI, Yel L. Selective IgA deficiency with unusual features: Development of common variable immunodeficiency, Sjogren's syndrome, autoimmune hemolytic anemia and immune thrombocytopenic purpura. *Acta Paediatr Jpn.* 1995;37: 526–529.
67. Sato K, Miyasaka N, Nishioka K, Yamaoka K, Okuda M, Nishido T,

 

Uchima H. Primary Sjogren's syndrome associated with systemic necrotizing vasculitis: A fatal case. *Arthritis Rheum.* 1987;30:717–718.
68. Schattner A, Friedman J, Klepfish A, Berrebi A. Immune cytopenias as the presenting finding in primary Sjogren's syndrome. *Q J Med.* 2000; 93:825–829.
69. Seinfeld ED, Sharma OP. TASS syndrome: Unusual association of thyroiditis, Addison's disease, Sjogren's syndrome and sarcoidosis. *J R Soc Med.* 1983;76:883–885.
70. Stegeman CA, Kallenberg CG. Clinical aspects of primary vasculitis. *Springer Semin Immunopathol.* 2001;23:231–251.
71. Stone JH, Nousari HC. "Essential" cutaneous vasculitis: What every rheumatologist should know about vasculitis of the skin. *Curr Opin Rheumatol.* 2001;13:23–34.
72. Sugai S, Shimizu S, Tachibana J, Sawada M, Hirose Y, Takiguchi T, Konda S. Monoclonal gammopathies in patients with Sjogren's syndrome. *Jpn J Med.* 1988;27:2–9.
73. Tait CP, Yu LL, Rohr J. Sjogren's syndrome and granulomatous panniculitis. *Australas J Dermatol.* 2000;41:187–189.
74. Talal N. Clinical and pathogenetic aspects of Sjogren's syndrome. *Semin Clin Immunol.* 1993;6:11–20.
75. Tanei R, Katayama I, Katou I, Ota Y, Nishiyama S. [Six cases of Sjogren's syndrome with lichen mucosae—studies on the histopathology of salivary gland and clinical manifestation of sicca features in the patients with lichen mucosae.] *Nippon Hifuka Gakkai Zasshi.* 1990; 100:1241–1249.
76. Tsokos M, Lazarou SA, Moutsopoulos HM. Vasculitis in primary Sjogren's syndrome: Histologic classification and clinical presentation. *Am J Clin Pathol.* 1987;88:26–31.
77. Tsukahara T, Fujioka A, Horiuchi Y, Eto H, Nishiyama S, Akaboshi T, Kokubo T. A case of cytophagic histiocytic panniculitis with sicca symptoms and lupus nephritis. *J Dermatol.* 1992;19: 563–569.
78. Tzioufas AG, Boumba DS, Skopouli FN, Moutsopoulos HM. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjogren's syndrome. *Arthritis Rheum.* 1996;39: 767–772.
79. Tzioufas AG, Manoussakis MN, Costello R, Silis M, Papadopoulos NM, Moutsopoulos HM. Cryoglobulinemia in autoimmune rheumatic diseases. Evidence of circulating monoclonal cryoglobulins in patients with primary Sjogren's syndrome. *Arthritis Rheum.* 1986;29: 1098–1104.
80. van de Loosdrecht A, Kalk W, Bootsma H, Henselmans JM, Kraan J, Kallenberg CG. Simultaneous presentation of sarcoidosis and Sjogren's syndrome. *Rheumatology (Oxford).* 2001;40:113–115.
81. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, Bjerrum KB, Braga S, Coll J, de Vita S, Drosos AA, Ehrenfeld M, Hatron PY, Hay EM, Isenberg DA, Janin A, Kalden JR, Kater L, Kontinnen YT, Maddison PJ, Maini RN, Manthorpe R, Meyer O, Ostuni P, Pennec Y, Prause JU, Richards A, Sauvezie B, Shiodt M, Sciuto M, Scully C, Shoenfeld Y, Skopouli FN, Smolen JS, Snaith ML, Tishler M, Todesco S, Valesini G, Venables PJW, Wattiaux MJ, Youinou P. Preliminary criteria for the classification of Sjogren's syndrome. *Arthritis Rheum.* 1993;36:340–347.
82. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome: A multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. *Arthritis Rheum.* 1999;42:1765–1772.
83. Wada M, Kamimoto H, Park SY, Shintani S, Nakasho K. Autoimmune hepatitis concomitant with hypergammaglobulinemic purpura, immune thrombocytopenia, and Sjogren's syndrome. *Intern Med.* 2001;40: 308–311.
84. Waldenstrom J. Kliniska metoder for pavisanda av hyperproteinami arch deras praktiska varde for diagnostiken. *Nord Med.* 1943;20: 2288–2295.
85. Watanabe M, Fujimoto T, Iwano M, Shiiki H, Nakamura S. [Report of a patient of primary Sjogren syndrome, IgA nephropathy and chronic idiopathic thrombocytopenic purpura.] *Nihon Rinsho Meneki Gakkai Kaishi.* 2002;25:191–198.
86. Watanabe T, Tsuchida T, Ito Y, Kanda N, Ueda Y, Tamaki K. Annular erythema associated with lupus erythematosus/Sjogren's syndrome. *J Am Acad Dermatol.* 1997;36(2 Pt 1):214–218.
87. Wisnieski JJ. Urticarial vasculitis. *Curr Opin Rheumatol.* 2000;12: 24–31.
88. Yamaike N, Saigo K, Imoto S, Miyachi H, Morita S, Maeda Y, Tomofuji Y, Chinzei T. Autoimmune hepatitis accompanied by idiopathic thrombocytopenic purpura and Sjogren's syndrome. *Intern Med.* 2002;41:72.
89. Yamamoto T, Yokoyama A, Yamamoto Y, Mamada A. Erythema nodosum associated with Sjogren's syndrome. *Br J Rheumatol.* 1997; 36:707–708.
90. Zittoun R, Debain P, James JM, Bilski-Pasquier G. [Hematological manifestations and complications in Sjogren's syndrome.] *Sem Hop.* 1978;54:1011–1020.
91. Zuniga-Montes LR, Gonzalez-Buritica H. Leg ulcers in a patient with primary Sjogren's syndrome. *Arthritis Rheum.* 1994;37:1335–1337.

 