Sjögren's syndrome: A retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology

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Abstract

Objective

Various cutaneous manifestations have been described (xerosis, eyelid dermatitis, angular cheilitis, cutaneous vasculitis and annular erythema) in Sjögren's syndrome (SS), but so far only three studies on large numbers of SS patients have been carried out. The frequency of cutaneous manifestations and their association with specific clinical or immunological parameters have never been studied. The aim of the Italian Group of Immunodermatology was to evaluate these associations in a large number of SS patients.

Methods

A retrospective review was performed on 93 patients with SS followed over a ten-year period (1990-2000) at 6 Italian dermatological centers. They were subdivided into two groups, 62 with primary SS and 31 with secondary SS, and the frequency of cutaneous manifestations and specific antibodies was determined and compared between them.

Results

We found significantly higher levels of xerosis (p=0.009) (56.4% versus 25.8%) and angular cheilitis (p=0.017) (38.7% versus 16.1%) in primary SS patients than in those with secondary SS. A significant association of xerosis with anti-SSA+SSB (p=0.033) antibodies was also demonstrated. Eyelid dermatitis and pruritus were common but less specific cutaneous symptoms. Annular erythema was found more often in primary (6.45%) than in secondary (3.2%) SS and was associated with SSA+SSB antibodies in 75% of the cases. Cutaneous vasculitis was present in 30.6% of primary SS (manifesting as palpable purpura in 84%) and in 29.3% of secondary SS cases.

Conclusion

Xerosis is the most frequent and characteristic cutaneous manifestation of primary SS. It is not linked to decreased sebaceous or sweat gland secretion, but more probably to a specific alteration of the protective function of the stratum corneum. Angular cheilitis is a common but less specific skin lesion in SS and is associated with xerosis and xerostomia.

Key words

Xerosis, angular cheilitis, eyelid dermatitis, annular erythema, cutaneous vasculitis.

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Introduction

Various cutaneous alterations may appear during the course of Sjögren's syndrome (SS), the main ones being: xerosis, eyelid dermatitis, angular cheilitis, annular erythema and cutaneous vasculitis. Other lesions are less typical and have been described only anecdotically or as characteristic of a specific country (1-5). So far three studies on large numbers of patients have been published – two American studies investigating 171 (4) and 62 patients (5) respectively, and a third reporting on 30 Japanese cases (1). Each of these studies has some limitations, however, resulting in a bias in their results. In 1973 the diagnostic criteria for SS had not yet been defined and the clinical features in the Ueki *et al*.'s series, such as the high prevalence of annular erythema (13%), erythema multiforme (13%), erythema pernio (20%) and amyloidosis cutis nodularis atrophicans (3%), seem to be peculiar to Japan (1). In addition, the frequency of cutaneous manifestations and their association with specific clinical and/or immunological subsets of the syndrome were not studied. To this end, the Italian Group of Immunodermatology of the Italian Society of Dermatology and Venereology conducted a retrospective evaluation of 93 cases of SS seen over a ten-year period (1990-2000), focusing on the main cutaneous lesions of this syndrome.

Materials and methods

All patients with a diagnosis of SS seen at six dermatological centres (Florence, Genoa, Sassari, Siena, Rome and Terni) over the last ten years (1990-2000) were retrospectively studied. The series comprised 93 patients with either primary or secondary Sjögren's syndrome. The diagnosis was made on the basis of clinical, histopathological, immunopathological and serological evaluations, according to the European Community Study Group criteria (6). When any four of the six diagnostic items was found primary SS was diagnosed, while the presence of an associated disease indicated secondary SS. Exclusion criteria were pre-existing lymphoma, acquired immunodeficiency disease (AIDS), sarcoidosis, graft vs host disease and sialoadenitis.

Xerophthalmia was detected by an abnormal Schirmer's test (< 5 mm in 5 min.) (7) and the Rose Bengal score (> 4 according to Van Bijsterveld' s scoring system) (7, 8). In biopsied patients xerostomia was confirmed by the detection of at least one focus (50 lymphomonocytic cells) in a 4 mm^2 sample of glandular tissue from a minor salivary gland (9).

The presence of xerosis, eyelid dermatitis, angular cheilitis, annular erythema and cutaneous vasculitis was evaluated and their correlation with Ro(SSA) and La(SSB) antibodies in the two disease groups was determined. Our evaluation focused on the frequency of these features independently of the treatments being given to the patients.

Cutaneous xerosis was diagnosed on the basis of both subjective symptoms (pruritus, dryness, a "pin prick-like" sensation) and objective signs such as rough, anelastic, hypotrophic or fine scaling skin.

Eyelid dermatitis was defined as erythematous, infiltrated and lichenificated lesions of the upper and/or lower eyelids associated with itching or a foreign body sensation, and was classified by type: type I – lichenified erythema; type II – moderate lichenified lesion with papular eruption; and type III – oedema with slight lichenification (11).

Annular erythema was also evaluated and classified by type: (1) annular lesions with an elevated border; (2) multiple erythematous papules; and (3) erythematous and figurated infiltrated plaques.

Because the study was retrospective, our purpose was to evaluate the frequency of the various cutaneous lesions in primary and secondary SS independently of their histopathological features. Biopsies had been conducted in only a few patients who exhibited xerosis, because of its persistent clinical course. The remaining cutaneous signs in SS are characterized by an intermittent clinical course, so at the time of any given examination only a few patients would have shown active lesions. Histopathological examination

was also performed in 3 primary SS patients – 2 with cutaneous vasculitis and 1 with annular erythema – and only to confirm the diagnosis.

All 93 patients had undergone routine laboratory examinations and serology. In particular, antinuclear antibodies (ANA) were detected by indirect immunofluorescence (IIF) on rat liver sections or Hep-2 cells (12). Anti-extractable nuclear antigens antibodies (anti-SSA and anti-SSB antibodies) were determined by counterimmuno-electrophoresis (13) or ELISA. Anti-thyroglobulin-microsomal and gastric parietal cell autoantibodies were detected by either IIF or ELISA. Circulating immune complexes (C1q and C3 binding IgG) were determined by ELISA(14) while C3 and C4 were assayed by the radial immunodiffusion technique (15). Rheumatoid factor was determined by the microslide latex test (Behringwerk, Madsburg, Germany). Five primary SS patients with and 5 patients without eyelid dermatitis were patch-tested using the GIRDCA(Gruppo Italiano Ricerca Dermatiti Contatto e Ambientali) standard series (16).

Fisher's exact test was used to compare the frequency of the various cutaneous features and immuno-serological findings between the primary and secondary SS patients. Statistical parameters were considered significant when $p < 0.05$. All calculations were performed using Stata 7.0 statistical software (Stata Corporation, College Station, Texas).

Results

Patients

Of the 93 patients 62 had primary SS and 31 had secondary SS. Secondary SS was associated with systemic lupus erythematosis (SLE) in 11/31 patients: 6 had systemic SLE, 3 subacute SLE, and 2 discoid SLE. Another 11 presented systemic sclerosis and in the remaining 9 SS was associated with various connective tissue diseases (3 rheumatoid arthritis, 3 undifferentiated connective tissue disease, 2 mixed connective tissue disease, 1 polyendocrinopathy). Most of the patients were female (81/93) with a mean age of 57.4 years (range 27 to 92 years). There were only 4 men in the series, with a mean age of 47 years (range 33 to 55 years), all of whom had primary SS.

Autoantibodies

Anti-SSA antibodies were detected in 36/62 primary SS and in 8/31 secondary SS patients. Anti-SSA+SSB antibodies were found in 19/62 primary SS and in 4/31 secondary SS patients. The difference in the presence of SSA+SSB autoantibodies between primary and secondary SS was highly significant ($p = 0.0077$). ANA were positive in 37/62 primary SS and 21/31 secondary SS patients. Finally, anti-thyroglobulin, anti-microsomial and anti-gastric parietal cell autoantibodies were detected in 8/62 primary SS and 3/31 secondary SS patients.

Cutaneous manifestations

The presence of cutaneous lesions including xerosis, angular cheilitis, eyelid dermatitis, annular erythema and vasculitis were evaluated in the two disease subgroups (Fig. 1).

Xerosis was observed in 34/62 primary SS and in 8/31 secondary SS patients ($p = 0.009$). An association of xerosis with anti-SSA+SSB antibodies was observed in 15/34 primary SS patients but this correlation could reflect the underlying SS rather than a real correlation with xerosis (Table I). The average age of the primary SS patients with xerosis was 65 years and of those without xerosis 50 years. Primary SS patients with xerosis and anti-SSA+ SSB

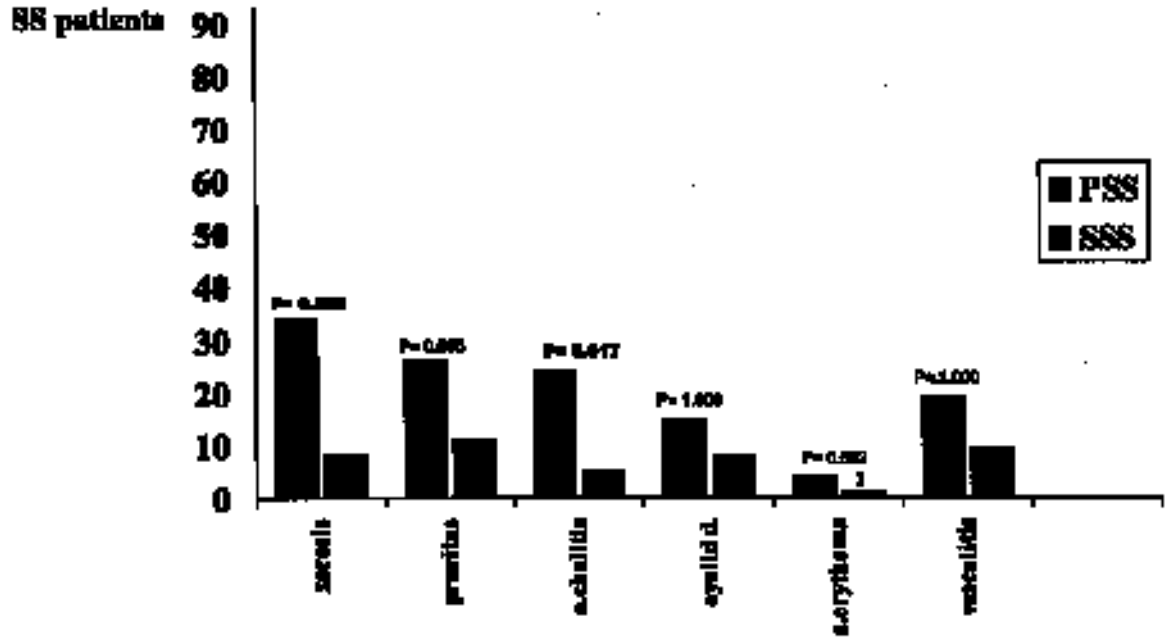

Fig. 1. Incidence of various cutaneous manifestions in 62 primary (PSS) and 31 secondary (SSS) Sjögren's syndrome patients. Among these xerosis and angular cheilitis showed a significant statistical association with PSS ($p < 0.05$).

Table I. Cutaneous involvement (xerosis, pruritus, eyelid dermatitis and annular erythema) in 62 primary SS patients and 31 secondary SS patients: clinical and immunological findings.

	Xerosis	Pruritus	Eyelid dermatitis	Angular cheilitis	Annular erythema		Xerosis	Pruritus	Eyelid dermatitis	Angular cheilitis	Annular erythema
Primary SS (n = 62)						Secondary SS (n = 31)					
Patients	34/62 (54.8%)	26/62 (41.9%)	15/62 (24%)	24/62 (38.7%)	4/62 (6.45%)	Patients	8/31 (25.8%)	11/31 (38.3%)	8/31 (25.8%)	5/31 (16.1%)	1/31 (3.2%)
SSA+ SSB	15/34 (44.1%) p = 0.033	7/26 (26.9%)	7/15 (46.6%)	9/24 (37.5%)	3/4 (75%)	SSA+ SSB	3/8 (37.5%)	1/11 (9%)	1/8 (12.5%)	1/5 (4%)	0
SSA	6/34 (17.6%)	8/26 (30.7%)	3/15 (20%)	8/24 (33.3%)	0 0	SSA	0	2/11 (18.1%)	2/8 (25%)	1/5 (4%)	0

Table II. Presence of cutaneous vasculitis in 19/62 patients with primary Sjögren's syndrome: clinical and immunological findings.

	Clinical features							Autoantibodies		
	Patients	Palpable purpura°	Other cutaneous lesions	Raynaud's phenomenon	Rheumatoid factor	Hyper-γ globulins	Cryoglobulins	SSA/SSB	SSA	ANA
	8	-	Finger ulcers	+	-	+	-	+	-	+
	9	+		+	+	+	-	+	-	+
	11	+		+	+	+	-	-	-	+
	19	+	L. reticularis*	-	+	-	-	-	+	+
	29	-	L. reticularis	-	+	-	+	+	-	+
	30	+		-	-	-	-	-	+	-
	39	+	Acrocyanosis	+	-	-	-	-	-	+
	40	+		+	-	+	-	+	-	+
	69	+		+	-	-	-	-	-	-
	78	-	Leg ulcers	-	-	+	+	-	+	+
	79	+		-	+	-	-	-	-	+
	80	+		+	-	-	-	-	+	+
	81	+		-	+	+	-	-	-	+
	83	+		+	+	-	+	-	-	-
	85	+		+	+	+	-	+	-	+
	86	+		-	+	+	-	+	-	-
	87	+		+	+	+	-	+	-	+
	88	+		-	+	+	-	+	-	+
	91	+		-	-	-	-	-	-	+
Total no.	19/62	16/19	5/19	11/19	11/19	10/19	3/19	8/19	4/19	15/19
%	30.6	84.2	26.3	57.6	57.6	52.6	16.7	42.1	21	78.9

*L. reticularis: livedo reticularis..

were younger (53.7 years) than those without the antibodies (61 years). Pruritus was found in 26/62 primary SS and in 11/31 secondary SS cases. In 19/26 of the primary SS patients, pruritus co-existed with xerosis. There was no significant correlation between pruritus and autoantibodies (Table I).

The frequency of eyelid dermatitis was not statistically significant, being observed in 15/62 primary SS and in 8/31 secondary SS patients (all female) (Fig. 1). Severity ranged from slight erythema and infiltration of the upper eyelid to lichenification and/or brown hyperpigmentation. Eyelid dermatitis was associated with xerosis in 13/15 and with xerophthalmia in 14/15 primary SS cases. Anti-SSA+SSB antibodies were present in 7/15 primary SS patients with eyelid dermatitis (Table I). Ten primary SS patients (5 with and 5 without eyelid dermatitis) were selected for patch-test examination at one of the dermatological centers (Florence); 4 patients with eyelid dermatitis and 3 without tested positive. Timerosal (4 cases) and nickel sulphate (3 cases) were the most frequent sensitizers, but we did not find a significant correlation between these sensitizing haptens and the eyewash used for the treatment of ocular dryness.

Annular erythema was more frequent in primary SS (4/62) than in secondary SS (1/31) (Fig. 1). In 2 primary SS patients recurrent annular lesions were observed. In one case they were small in number and size (0.5 cm) with ele-

vated borders, symmetrically distributed on the forehead and temples. In the other case they took the form of multiple erythematous papules on the lateral surface of the thighs, ranging from 0.5 to 1.5 cm in diameter and distributed in a ring configuration. In this case biopsy revealed only hyperorthokeratosis and a perivascular and perifollicular lymphohistiocytic infiltrate. In the remaining cases (2 with primary SS and one with secondary SS), annular lesions were not observed during examination but were reported by the patients. They were described as recurrent, persistent (8-25 days) and as either erythematous and figurated or as slightly infiltrated plaques on the neck. Anti-SSA+SSB antibodies were present in 3/4 primary SS cases with annular erythema (Table I), but due to the small number of patients this finding was not statistically significant.

The frequency of angular cheilitis (i.e. recurrent, symmetrical erythematosquamous infiltrated lesions, often itching and fissuring) either observed by the clinician or reported by the patient, was significant ($p = 0.017$) in primary SS (24/62). Instead it was found in only 5/31 secondary SS cases (Fig. 1). In 17/24 of the primary SS and in 3/5 of the secondary SS cases angular cheilitis was associated with the presence of xerosis. These findings were not statistically significant, but there is clearly a clinical link between xerosis and cheilitis.

Finally, cutaneous vasculitis was present in 19/62 primary SS cases and in 9/31 secondary SS cases (Fig. 1). Palpable purpura was the most common clinical feature, being present in 16/19 primary SS patients with vasculitis (Table II). In the 2 cases for which a biopsy was available, the purpura was associated with leukocytoclastic vasculitis. Moreover, primary SS vasculitis was associated with Raynaud's phenomenon in 57.6%, with hypergammaglobulinemia in 52.6%, and with FR in 57.6% of the cases. ANA were the predominant serological markers and anti-SSA+SSB autoantibodies were also frequent, being present in 78.9% and 42.1% of the primary SS cases respectively (Table II). The extrapolation of cases with palpable purpura among the primary SS cases with vasculitis revealed a decreased incidence of SSA + SSB autoantibodies (6/16 pts.) and ANA (11/16 pts.), while the presence of FR (10/16 pt.) was higher and hypergammaglobulinemia was about the same (8/16 pts.). Cryoglobulins were detected in 3/62 of the primary SS patients overall, and in 3/19 of those primary SS cases with cutaneous vasulitis (Table II). Cryoglobulins did not show a significant correlation with palpable purpura.

Extra-cutaneous manifestations

Keratoconjunctivitis sicca predominated, being present in 90/93 SS patients. Xerostomia was present in 88/93 SS patients and was often associated with dental caries (37/88). Moreover, 29/93 SS patients complained of mucosal dryness especially of the respiratory tract (crusting nose, cough and thirst) and 3/29 of them also complained of vaginal dryness and dyspareunia. Arthralgias were present in 72/93 SS patients, myalgias in 17/93, Raynaud's phenomenon in 41/93, subclinical thyroid disease in 25/93 and hepatic involvement (cirrhosis, primitive biliary cirrhosis, chronic active hepatitis) in 14/93. None had pulmonary or renal involvement.

Three female SS patients were HCV+, 2 with primary SS and one with secondary SS. Xerosis was present in all 3 cases. One primary SS patient (age 42 yrs.) was SSA+SSB positive, but did not show any other cutaneous features. The other primary SS patient (age 69 years) also had anamnestic nodular vasculitic lesions (confirmed by a previous histological examination), pruritus and was FAN+. The secondary SS (SS/AR) patient (age 60 years) showed considerable cutaneous involvement (xerosis, pruritus, eyelid dermatitis, angular cheilitis) and was FAN+ and HBV+. None of the 3 patients had circulating cryoglobulins in their serum.

Discussion

SS is a chronic, slowly progressive autoimmune exocrinopathy of unknown etiology characterized by a reduction in lachrymal and salivary gland secretion and, as a consequence, by keratoconjunctivitis sicca and xerostomia (4, 8). From an organ-specific disorder, SS may evolve into a systemic (extraglandular) disease affecting the internal organs (lungs, kidney, muscles, blood vessels) and can in a few cases eventually develop into a B cell lymphoproliferative disorder (17). Sjögren's syndrome may be either primary or secondary, i.e. associated with other connective tissue diseases. ANA are positive in about 90% of patients (18), anti-SSB antibodies in 40%, anti-SSA antibodies in 70%, (19), rheumatoid factor in 60% and polyclonal hypergammaglobulinemia in 80% (8).

Cutaneous manifestations are not uncommon (1-5) and our study confirmed that the prevalence of xerosis, angular cheilitis and annular erythema was higher in primary SS than in secondary SS, while the frequency of pruritus and eyelid dermatitis was similar in the two forms of SS.

According to the literature, dry skin is a common feature (23% to 67%) in SS patients (4,5). Our study confirmed that xerosis in well defined cutaneous areas is a frequent manifestation of primary SS (43%) and is less common in secondary SS (25.8%). Moreover in our study xerosis was clearly age-related (the mean age of primary SS patients with xerosis was 15 years higher than the patients without xerosis) and was significantly associated with SSA+SSB antibodies.

Xerosis is associated with various cutaneous diseases (such as atopic and contact dermatitis) and with topical (e.g. retinoid acid, benzyl-benzoate) and systemic (e.g. aromatic retinoids, psoralens) treatments (20). Moreover, xerosis may be present as a paraphysiologic condition in elderly patients (> 70 years), especially during the winter, and also as an "idiopathic" condition presenting without any apparent cause (21).

The pathogenetic mechanism of xerosis in SS is not yet clearly understood, although decreased activity of the sebaceous or eccrine sweat glands has been suggested. Bloch *et al.* reported that 67% of 62 patients complained of dry skin and 27% of them presented notice-

ably decreased sweating (5). In his report of a single SS patient, Feurman (22) found decreased cholinergic-stimulated sweating, while histological examination revealed a reduction in the number and size of the eccrine glands. Other studies of cholinergic stimulated sweating in SS patients have shown either a decrease or no difference from normal subjects (4,23,24). These, however, were conducted on small numbers of patients, did not take in account that the sweating rate differs between the two sexes, and involved patients with both primary SS and secondary SS. Rees & Pal studied the ionthophoresis pilocarpine stimulated sweat secretion in 22 primary SS patients and 22 age- and sex-matched normal controls and found no significant difference (25). Recent immunohistochemical studies in idiopathic xerosis documented damage to the integrity of the epidermis, with significant changes in the epidermal expression of basal and differentiation-related keratins, and the premature expression of involucrine. A very slight and age-independent decrease in Trans-Epidermal Water Loss (TEWL) has also been observed (21). Furthermore, Fabbri *et al*. (personal comunication) reported no significant difference in the number, size, histological or histochemical characteristics of the sebaceous and eccrine sweat glands in punch-biopsies of xerotic skin from the deltoid area of 5 patients with primary SS versus 5 age- and sex-matched normal control subjects; moreover, in the primary SS cases cutaneous xerosis appeared to be related to alterations in the basal and differentiation related keratins. In SS xerosis is probably also linked to specific alterations in the stratum corneum's barrier function, as in idiopathic xerosis.

Pruritus was a common (73%) although less specific symptom, being present with equal frequency in primary SS (41.9%) and secondary SS (38%); it therefore could be a simple consequence of skin dryness.

In Japanese SS patients annular erythema is often present (26-29), but in our experience this lesion is rare. It is more frequently associated with primary SS (6.45%) than secondary SS (3.5%), but this difference is not statistically significant. A correlation with anti-SSA + SSB antibodies has been reported in as many as 78 - 100% of primary SS cases (29). We detected anti-SSA+SSB antibodies in 75% (3/4) of primary SS patients with annular erythema, but this finding was not significant due to the small number of patients.

Annular erythema lesions have been described as recurrent, often developing on the face and trunk, clearing without pigmentation, and not photosensitive (26-31). Our study confirms this description; we found annular lesions of all three clinical types affecting the face, back and upper extremities; they were recurrent and cleared without atrophy or pigmentation. Only in one case (type 3, involving multiple erythematous papules located on the lateral surface of the thighs) a histological examination was performed and it showed a slight monuclear infiltrate in the upper dermis without epidermal involvement. Anti-SSA+SSB antibodies were not detected. Thus, Asian patients appear to have lesions that might be considered analogous to SCLE in Caucasians, although the latter are not photosensitive. Finally, annular erythema may occur in SLE patients, in SS patients without any histological evidence of SLE, or in patients with both diseases (29).

Eyelid dermatitis can be found in various connective tissue diseases, particularly SS, and especially in the elderly (mean age 61 years) (11). Our patients were relatively young (mean age 57 years) and had lesions only on the upper eyelids, which could be ascribed to type I and type II eyelid dermatitis. It was present in 25% of our primary SS and in 24% of our secondary SS patients. Timerosal (4 cases) and nickel sulphate (3 cases) were the most frequent sensitizers. Although our sensitization rate (70.5%) was higher than that reported by Koiano & Nishioka (58%) (32), we found no correlation between sensitizing haptens and eyelid dermatitis, because there was a high incidence of contact sensitization in primary SS both with (4/5) and without eyelid dermatitis (3/5). The Schirmer test was positive in 93.3% of the primary SS patients with eyelid dermatitis and in 100% of the secondary SS patients with eyelid dermatitis. In addition, all the patients complained of ocular dryness and foreign body sensation. Therefore ocular dermatosis may not be merely a simple consequence of contact sensitisation, but also the result of continuous rubbing of the periorbital area due to ocular dryness (32). We can postulate that ocular dryness is enhanced in xerosis, because eyelid dermatitis was associated with xerosis in 86% of primary SS and in 77% of secondary SS cases.

Angular cheilitis is another recognized mucocutaneous manifestation in SS. It was found in 38.7% in our primary SS, but in only 16% of our secondary SS patients. It is well known that xerostomia plays a role in oral candidosis signs such as angular cheilitis, which has been reported in 24% of SS patients with oral candidosis (33). In our series cheilitis was associated with xerostomia in 95.5% of primary SS and in 100% of secondary SS cases. In addition, angular cheilitis was associated with xerosis in 70.8% of primary SS and in 60% of secondary SS patients. We can postulate that dryness and xerostomia may be predisposing factors for the development of angular cheilitis.

Finally, cutaneous vasculitis was present in 30.6% of our primary SS and in 29.3% of our secondary SS patients. Palpable purpura of the lower extremities was present only in 25.8% of our primary SS patients, however, unlike the 45% reported in previous studies (34), and none of our primary SS patients complained of urticaria-like lesions, described as the second most common form of vasculitis in SS (34). Palpable purpura was instead the most common clinical feature in primary SS patients with cutaneous vasculitis, being present in 84% of the cases.

Raynaud's phenomenon was detected in 35.4% of our primary SS cases, a higher incidence than the 20% reported by others (3,34-36). The incidence of Raynaud's was even higher in the subgroup of the primary SS cases with cutaneous vasculitis (11/19). In addition, primary SS cutaneous vasculitis was associated with FR in 57.6% and

with hypergammaglobulinemia in 52.6%.

Some studies have demonstrated both leukocytoclastic and mononuclear vasculitides in primary SS (34-36). The former was associated with high titers of anti-SSA+SSB autoantibodies, hypergammaglobulinemia, and rheumatoid factor, and a decreased complement level. On the other hand mononuclear vasculitis was associated with low titers of anti-SSA+SSB antibodies and with a general sero-hyporeactivity (34, 36). In the 2 biopsied primary SS patients with palpable purpura, leukocytoclastic vasculitis associated with hypocomplementemia and elevated serum SSA+SSB autoantibodies titres was demonstrated. Moreover the subgroup of primary SS patients with palpable purpura had lower levels of SSA+SSB antibodies and ANA and higher levels of FR than patients with primary SS cases + vasculitis generally. These data were not statistically significant, but could indicate a correlation between FR and palpable purpura.

Clinical, cerebral CT, and angiographic findings suggest that complications involving the peripheral nervous system (predominantly sensory-motor and sensory polyneuropathy) and the central nervous system (focal or multifocal lesions of the brain or the spinal cord) are frequent (20-40%) in primary SS patients (34,43) and may be ascribed to various immunopathological mechanisms (39,43). Our SS patients with cutaneous vasculitis did not show clinical symptoms or a positive history of peripheral or central NS complications, however.

Cryoglobulins were detected in 5% of primary SS, in 3.2% of secondary SS, and in 16.7% of primary SS patients with cutaneous vasculitis. Cryoglobulins were therefore more frequently associated with cutaneous vasculitis, but did not show a significant clinical association with palpable purpura (Table III).

In conclusion, our study confirms xerosis and cheilitis as the most frequent cutaneous manifestations of primary SS and also shows annular erythema to be typical of the disease, although it is very rare in Europe. Moreover, cheilitis and eyelid dermatitis are correlated with xerosis, xerostomia and xerophthalmia. Finally, skin dryness in primary SS should be considered a distinct form of primary xerosis not related to decreased sebaceous or eccrine gland secretion. In this regard a more detailed immunohistochemical evaluation of xerosis in SS would be useful to clarify its pathogenetic mechanism.

References

1. UEKI H, INAGAKI Y, HAMASAKI Y, ONO M: Dermatologische manifestationen des Sjögren-Syndrome. *Hautarz* 1991; 42: 741-7.
2. ALEXANDER EL, PROVOST TT: Cutaneous manifestations of Sjögren's syndrome. In: *Immunologic Diseases of the Skin*. Norwalk, Appleton & Lange, Inc. 1991, 401-9.
3. PROVOST TT, WATSON R: Cutaneous manifestations of Sjögren's syndrome. *Rheum Dis Clin North Am* 1992; 18: 609-15.
4. WHALEYK, WILLIAMSON J, CHISHOLM DM: Sjögren's syndrome sicca components. *Q J Med* 1973; 166: 279-302.
5. BLOCH KJ, BUCHANAN WW, WHOHL MJ: Sjögren's syndrome: A clinical, pathological and serological study of 62 cases. *Medicine* 1965; 44: 187-231.
6. VITALI C, BOMBARDIERI S, MOUTSOPOULOS MH *et al*.: Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: result of a prospective multicentre study. *Ann Rheum Dis* 1996; 55: 116-221.
7. FOX RI, SAITO I: Criteria for the diagnosis of Sjögren's syndrome. *Rheum Dis Clin North Am* 1994; 20: 391-407.
8. FOX RI: Sjögren's syndrome. *In* KLIPPEL JH (Ed.): *Primer on the Rheumatic Diseases*, Atlanta, Arthritis Foundation, Inc., 1997: 283-8.
9. CHISHOLM DM, MASON DK: Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* 1968; 21: 656-60.
10. CHERNOSKY ME: Clinical aspects of dry skin. *J Soc Cosmet Chem* 1976; 27: 365-76.
11. FISHER AA: Upper eyelid dermatitis syndrome. In *Contact Dermatitis.* Philadelphia, Lea & Febiger 1986: 378.
12. ANDERSON SG, ADDISON IE, DIXON HG: Antinuclear factor serum (homogeneous): An international collaborative study of the proposed research standard 66/233. *Ann NY Acad Sci* 1971; 177: 337-45.
13. CLARK G, REICHLIN M, TOMASITB: Characterization of a soluble cytoplasmatic antigen reactive with sera from patients with systemic lupus erythematosus. *J Immunol* 1969; 102: 117-22.
14. ABRASS C, NIES K, LOUIE J, BORDER WA, GLASSOCK RJ: Correlation and predictive accuracy of circulating immune complexes with disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 1980; 23: 273-82.
15. CARBONARA AO, MANCINI G, HEREMANS JF: Immunochemical quantitation of antigens by single radioimmunodiffusion. *Immunohistochemistry* 1965; 2: 235-54.
16. ANGELINI G, GRANDOLFO M, CUSANO F *et al*.: Commissione SIDEV/GIRDCA. Linee guida sulla diagnostica della dermatite da contatto. *G Ital Dermatol Venereol* 1999; 134: 521-38.
17. MOUTSOPOLOS HM, TZIOUFAS AG, TALAL N: Sjögren's syndrome: A model to study autoimmunity. *In* TALAL N (Ed.): *Sjögren's Syndrome.* New York, Academic Press 1991; 319-40.
18. TAN EM: Autoantibodies to nuclear antigens (ANA): Their immunobiology and medicine. *Adv Immunol* 1982; 33: 167.
19. CHAN E KL, ANDRADE LEC: Antinuclear antibodies in Sjögren's syndrome. *Rheum Dis Clin North Am* 1992; 18: 551-70.
20. BERRY N, CHARMEILC, GOUJON C *et al*.: A clinical, biomethodological and ultrastructural study of xerotic skin. *Int J Cosmet Sci* 1999; 21: 241-52.
21. ENGELKE M, JENSEN JM, EKANAYAKE-MUDIYANSELAGE S, PROKSH E: Effects of xerosis and ageing on epidermal proliferation and differentiation. *Br J Dermatol* 1997; 137: 219-25.
22. FEUERMANEJ: Sjögren's syndrome presenting as recalcitrant generalized pruritus. *Dermatologica* 1968; 137: 74-86.
23. KATAYAMA I, YOKOZEKA H, NISHIOKA K: Impaired sweating as an exocrine manifestation in Sjögren's syndrome. *Br J Dermatol* 1995; 133: 716-20.
24. HART IE, CASPI D, HULL RS *et al*.: Sweat gland function in Sjögren's syndrome. *Ann Rheum Dis* 1986; 45: 350-1.
25. REES JL, PAL B: Stimulated eccrine gland function in primary Sjögren's syndrome. *Clin Exp Dermatol* 1989; 14: 191-3.
26. TERAMOTO N, KATAYAMAI, ARAI H: Annular erythema: A possible association with primary Sjögren's syndrome. *J Am Acad Dermatol* 1989; 20: 596-601.
27. KATAYAMAI, ASAI T, NISHIOKA K: Annular erythema associated with primary Sjögren's syndrome: Analysis of T cell subsets in cutaneous infiltrates. *J Am Acad Dermatol* 1989; 21: 1218-21.
28. RUZICKA T, FAES J, BERGNER T, UWE PETER R, BRAUN-FALCO O: Annular erythema associated with Sjögren's syndrome: A variant of systemic lupus erythematosus. *J Am Acad Dermatol* 1991; 25: 557-60.
29. KATAYAMAI, TERAMOTO N, ARAI H, NISHIOKAK, NISHIYAMA S: Annular erythema. A comparative study of Sjögren's syndrome with subacute cutaneous lupus erythematosus. *Int J Dermatol* 1991; 30: 635-9.
30. OSTLERE LS, HARRIS D, RUSTIN MHA: Urticarial annular erythema: A new manifestation of Sjögren's syndrome. *Clin Exp Dermatol* 1992; 18: 50-1.
31. WATANABE T, TSUCHIDA T, ITO Y, KANDAN, UEDA Y, TAMAKI K: Annular erythema associated with lupus erythematosus/Sjögren's syndrome. *J Am Acad Dermatol* 1997; 36: 214-8.
32. KOIANO T, NISHIOKA K: Prevalence of eyelid dermatitis in primary Sjögren's syndrome. *Int J Dermatol* 1994; 33: 421-4.
33. SOTO ROJAS AE, VILLA AR, SIFUENTES-OSORNIO J, ALARCON SEGOVIA D, KRAUS A: Oral candidiasis and Sjögren's syndrome.

J Rheumatol 1998; 25: 911-5.

34. ALEXANDER EL, PROVOST TT: Cutaneous manifestations of primary Sjögren's syndrome: A reflection of vasculitis and association with anti-Ro(SSA) antibodies. *J Invest Dermatol* 1983; 80: 386-91.
35. MASON AMS, GUMPEI JM, GOIDING PL: Sjögren's syndrome – A clinical review. *Semin Arthritis Rheum* 1973; 2: 301-31.
36. MOLINA R, PROVOST TT, ALEXANDER EL: Two histopathologic prototypes of inflammatory vascular disease in Sjögren's syndrome: Differential association with seroreactivity to RF and antibodies to Ro-(SSA) and with hypocomplementemia. *Arthritis Rheum* 1985; 28: 1251-8.
37. MOLINA R, PROVOST TT, ALEXANDER EL: Peripheral inflammatory vascular disease in Sjögren's syndrome: Association with nervous system complications. *Arthritis Rheum* 1985; 28: 1341-7.
38. ALEXANDER EL, PROVOST TT: Sjögren's syndrome: Association of cutaneous vasculitis with nervous system disease. *Arch Der - matol* 1987; 123: 801-10.
39. ALEXANDER E: Central nervous system disease in Sjögren's syndrome. New insights into its immunopathogenesis. *Rheum Dis Clin North Am* 1992; 18: 637-72.
40. MOUCH E, VOLK C, KRATZCH G, KRAPF H: Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. *Acta Neurol Scand* 1994; 84: 31-5.
41. ALEXANDER EL, RAZEMBACH MR, KUMAR AT: Anti Ro(SS-A) antibodies in central nervous system disease associated with Sjögren's syndrome: Clinical, neuroimaging and angiographic correlates. *Neurology* 1994; 44: 899-908.
42. LAFITTE C: Neurologic manifestations of primary Gougerot-Sjögren's syndrome. *Rev Neurol* 1998; 154: 658-73.
43. LAFITTE C, AMOURAZ, CACOUB P: Neurological complication of primary Sjögren's syndrome. *J Neurol* 2001; 248: 577-548.