Review

Cutaneous manifestations of primary Sjögren's syndrome are underestimated

A.-M. Roguedas[1,2], L. Misery[2], B. Sassolas[2], G. Le Masson[3], Y.-L. Pennec[4], P. Youinou[1]

[1]Laboratory of Immunology, [2]Unit of Dermatology, [3]Laboratory of Histopathology, and [4]Department of Internal Medicine, Brest University Medical School, Brest, France

Anne-Marie Roguedas, MD; Laurent Misery, MD; Bruno Sassolas, MD; Gilles Le Masson, MD; Yvon-Louis Pennec, MD; Pierre Youinou, MD, PhD, Professor of Rheumatology.

Please address correspondence to: Pierre Youinou, MD, Laboratory of Immunology, Brest University Medical School Hospital, BP824, F-29609 Brest Cedex, France.
E-mail: youinou@univ-brest.fr

Received on July 6, 2004; accepted on July 29, 2004.

Clin Exp Rheumatol 2004; 22: 632-636.

Key words: Sjögren's syndrome, skin, xerosis.

ABSTRACT

The association of kerato-conjunctivitis sicca and xerostomia has been termed Sjögren's syndrome (SS). Although this disease is referred to as a non-organ-specific autoimmune condition, the vast majority of the deleterious effects of primary SS are restricted to the exocrine glands. Among them, the lacrymal and salivary glands are at the foreground, owing to the severity of the objective consequences and the importance of the subjective manifestations. As a result, cutaneous manifestations are minimized, albeit relatively common. We have carefully analyzed the literature to draw up an inventory of the possible skin complications of this syndrome. In addition to xerosis and epidermal IgG deposits, they include vasculitis and cutaneous B cell lymphoma. Alopecia, vitiligo and papular lesions have also been reported to be associated with primary SS .

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease of unknown etiology which is characterized by the disruption of those epithelial cells that surround the acini and make up the ducts of exocrine glands. Be it the cause or the consequence of lymphoplasmocytic infiltration, such a process leads to the dryness of the organs watered by the product of the surrounding exocrine glands (1). Although uncommon in the setting of usual medical care (2), the disease turns out to be relatively frequent when the patients are identified in the context of an epidemiological survey (3). It may occur alone as a primary condition and represent an autoimmune epithelitis (4). In contrast the secondary variants of the syndrome are associated with diverse connective tissue diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (5). Thus, SS presents as a heterogeneous non-organ-specific autoimmune entity, encompassing a wide spectrum of clinical manifestations, serological abnormalities, and scattered complications. The vast majority reflect a reduction in the flow of the exocrine gland throughout the body. Among its deleterious effects, noteworthy are xerostomia and xerophtalmia which result from defects in the tears and saliva, respectively. The nasal, pharyngeal, vulval and gastric exocrine glands have also been cited among the targets of the disease. Although SS often remains a relatively benign condition, some patients develop systemic features, such as Raynaud's phenomenon, non-erosive arthritis, renal tubulopathy and interstitial pneumonitis.

In fact, other exocrine glands as well may be affected by the disease process. These include the sebaceous, sweat and apocrine glands which are the three classes of exocrine structures located in the skin. There are absolutely no reasons for the cutaneous glands to be set apart from the exocrine system and to escape this striking immunopathological offense. As pointed out by Fye and Talal (6), dermatological manifestations are therefore likely to be more common than usually acknowledged (5). Consistent with this view is the fact that more and more skin complications are being recorded throughout the course of primary SS and, to a lesser degree, throughout that of secondary SS.

Intriguingly, the number of studies specifically dedicated to cutaneous involvement, or which simply mention these clinical features in SS is limited (7-11). Awareness that such manifestations have been understimated prompted us to review these studies, together with anecdotal case reports, as an attempt to re-examine the current view

that involvement of the skin is exceptional. In addition, we wished thereby to underline the importance of a dermatological approach to SS.

Skin involvement

Xerosis

Although often neglected, dryness of the skin due to defective sweating has been shown to be common in SS. For example, of 62 patients enrolled in the pioneering study of Bloch *et al.* (7), 42 patients or 68% were recognized as presenting with cutaneous dryness. Of these 17 had noticed an exhaustion of their sweating. Similarly, 56% of their patients with primary SS were defined by Markusse *et al.* (8) as suffering from dryness of the skin at least on one occasion over a mean follow-up period of 9 years. Across the same range, Fye and Talal (6) observed xerosis in 65% of their cases, whilst Whaley *et al*. (9) found it in as few as 23% of theirs (Table I). A valid point was raised by Bernacchi *et al*. (10) who found that the level of xerosis was significantly higher in the primary (43% of the cases) than in the secondary form of SS (26% of the cases).

At first glance, it may be difficult to understand why these frequent complications are minimized. However, not only does the subjective feeling of skin dryness cause the patient merely unpleasantness, but this complaint can be drowned out by xerostomia and xerophtalmia which are much more tormenting than xerosis. With this in mind, it becomes less surprising that cutaneous manifestations are spontaneously so neglected by the patients. In addition, their development is particularly dilatory. According to Bernacchi *et al*. (10), the most classical subjective symptoms of xerosis are non-specific pruritus, sensation of dryness, and a "pin prick-like" feeling, which are associated with various objective signs such as rough, inelastic, hypotrophic or fine scaling skin. These disorders are often accompanied by angular cheilitis. The physiological reasons why the skin protects itself against a variety of injuries (including winter xerosis, hereditary ichthyosis, atopic dermatis or psoriasis) by inducing dryness remains unclear. This physiological reaction may even be encountered in elderly, otherwise healthy controls.

The sebaceous glands constitute the main known source of cutaneous lubrication. But the sweat glands may also be incriminated in the drying of the skin. In this respect, it is worth remembering that sweat comprises lactates which participate in skin homeostasis through continuous desquamation of the skin cells. Alternatively, xerosis may be accounted for by decreased eccrine sweating in primary and secondary SS. Studies of cholinergic-stimulated flow have indeed established that there is a reduction in sweating in SS patients, compared with normal controls.

Katayama *et al*. (12) have assessed the capacity to sweat in 49 patients with primary SS. The secretion was induced by mental stimulation through hand grasping, measured with a perspirometer, which continuously recorded the local sweat volume, and compared it with that of normal volunteers and disease controls. Stastically significant reductions in sweat volume were seen in SS. Sweat flow was significantly diminished in patients under 50 years of age compared with normal controls. The same held true irrespective of the primary or secondary presentation of SS. Patients with other forms of dermatitis also displayed a reduction in the volume of their sweat, but their flow was not statistically significantly lower than that of normal controls. Differences between SS patients and disease controls support the view that impairment of sweat flow may be specific for SS, especially in young individuals when compared with patients suffering from another dermatitis or with normal controls under 50 years of age.

A flurry of cases reports have recently emerged that further substantiate such an interpretation. For example, Mitchell *et al.* (13) examined a 55-year-old man with primary SS who had experienced difficulty in perspiring and became easily overheated in direct sunlight. A punch biopsy of the skin revealed a marked reduction in the number of eccrine glands and ductal structures within the reticular dermis, and all the remaining epithelial structures were heavily infiltrated by lymphocytes, plasmacytoid lymphocytes and plasma cells. Eccrine sweat testing was performed by the intradermal injection of metacholine into both forearms, the upper part of the arms, the anterior part of the chest, the back, and the thighs, and Bromophenol blue powder was used as a visualization agent. Very few scattered dots were identified, suggesting that eccrine sweating had virtually dried up.

The sweat secretion rate stimulated by iontophoresis of pilocarpine was also measured in 22 patients with primary SS and in 22 age- and sex-matched normal controls (14). Disappointingly, there was no significant difference in the measured sweat rates between these two groups of subjects. Here it should, however, be pointed out that sweating

Table I. Xerosis in primary Sjögren's syndrome (SS)

Authors	Number of patients	Frequency (%)
Markusse *et al*. 1992 (ref. 8)	46 primary SS	56
Bloch *et al*. 1965 (ref. 7)	62 (23 primary SS)	67
Whaley *et al*. 1973 (ref. 9)	171	23
Fye and Talal 1973 (ref. 6)	NA	65
Bernacchi *et al*. 2004 (ref. 10)	93 (62 primary SS and 31 secondary SS)	56 in primary SS and 26 in secondary SS

NA: not available

was induced on the flexor side of the forearm. Based on the scarcity of local sweat glands in this site, one may argue that this is not a suitable place to test.

Of the 7 patients of Whaley *et al*. (9) who underwent a systematic skin biopsy there was only one who showed evidence of a chronic inflammatory process destroying the sweat glands. A non-specific perivascular lymphocytic infiltrate was detected in the remaining 6 patients.

Another possibility is that the production of sebum is abated or abnormal. In his very early case report, Feuerman (15) described a complete absence of sebaceous glands in association with severe skin dryness and atrophy of the sweat glands. Similar abnormalities have since been confirmed by several (16), but not all investigators (11). Nonetheless, this reduced synthesis of sebum could also be offered as an explanation for dryness of the hair and decreased luster (17).

At present the function of apocrine glands is poorly understood. They may be suspected to play a role in the development of cutaneous dryness. Their dysfunction along the external auditory meatus was first mentioned by Henking *et al*. (18). Half of their patients suffered from the deficient production of cerumen, associated with pruritus, scaling and crusting of the external ear canal.

Epidermal IgG deposit

The most common serological finding in SS is hypergammaglobulinaemia which has been attributed to polyclonal B cell hyperreactivity. This inflation in immunoglobulin (Ig) incorporates a number of autoantibodies, most notably those directed against ubiquitous antigens such as rheumatoid factor and antinuclear antibodies to Ro/ SSA and/or La/SSB.

Using a direct immunofluorescence technique, deposits of IgG were detected in the intercellular areas of the epidermis in two-thirds of patients with primary SS (19-21). Remarkably, these deposits were found in as few as 13% of those patients with secondary SS. Hardly any was found in the dermo-epidermal junction, and there were neither Ig, nor C3 or fibrinogen in the skin specimens from healthy controls. Although pemphygus vulgaris is another well-known condition associated with *in vivo* intercellular epidermal Ig deposits, related bullous skin lesions have never been reported in patients with SS.

Two hypotheses have been forwarded to explain these Ig deposits. Oxholm *et al*. (19, 21) suggested that they reflect antibody reactions of which the target antigens would be buried in the intercellular space of epidermis. However, these *in situ* immune complexes are unlikely to occur, given the absence of histopathological signs of skin inflammation, such as accumulated fibrinogen. Interestingly, the situation of IgG deposits reproduces that of the Langerhans cell within the epidermis. Inasmuch as they expose Fc-gamma receptors, such pseudo-deposits might be made up by the insertion of bystander IgG into these receptors.

Velthuis *et al.* (20) have highlighted the association between deposition of IgG and the presence of circulating SSA/Ro and SSB/La antibodies. Subsequently, they speculated that epidermal staining would reflect the cellular localization of SSA, SSB or other ribonucleoproteins (RNP). Native RNPs are confined to the nucleus, whereas SSA and SSB particles are translocated from the nuclear to the cytoplasmic RNAs. In Wil-2 cells (a human lymphoid cell line) and in KB cells (a human epithelial cell line), speckled nuclear and cytoplasmic staining was observed, using whole sera containing anti-SSAand SSB antibodies.

Cutaneous complications

Vasculitis

By far the most severe cutaneous complications are generated by vasculitis. The histopathological hallmark of vasculitis consists of perivascular cellular infiltrates of small vessels, and its clinical presentation fluctuates from the most benign manifestations, such as petechiae, to the most serious complications, such as palpable purpura or widespread ecchymoses. The morphology of these inflammatory lesions is dependent on the level of blood vessel involvement in the skin and the magnitude of the inflammatory response.

Purpura is a common vasculitis-related manifestation. This appears as recurrent crops of round, pink, separated or confluent lesions. After a few days the lesions turn dull purple then brown, finally leaving a pale brown stain. This purpura may be regular or palpable. Bloch *et al.* (7) claimed that 17% of their primary SS patients had non-thrombocytemic purpura. Components of SS preceded the development of purpura in 2 patients, by 2 and 7 years, respectively. At disease onset, purpura was found in 28% of the 47 patients described by Pavlidis *et al.* (22), and in 15% of those 253 analyzed by Garcia-Carrasco *et al*. (23). Of the 62 primary SS patients included by Bernacchi *et al*. (10) in their remarkable retrospective study, 19 presented with cutaneous vasculitis, whereas there were only 9 in the group of 31 secondary SS patients. In most of the cases, palpable purpura was identified.

Thirty-seven patients with primary SS were examined by Oxholm *et al*. (19), in search of the presence of vasculitis: 6 of them complained of cutaneous vasculitis, consisting of purpura in 4. Alexander and Provost (24) also evaluated the cutaneous vasculitis in 22 patients with primary SS selected on the basis of clinical evidence of skin disease: 9 of them (45%) had purpura, and 7 (32%) had urticaria-like lesions. The latter constitute the second most common complications vasculitis. According to Provost and Watson (16), such lesions predominate in the lower extremities, and urticaria-like vasculitic lesions persist for days, whereas common hives usually come and go over a period of 3 to 6 hours.

Nailfold capillaroscopy can also be used as a simple non-invasive method to evaluate the microvascular abnormalities in SS patients (25), particularly in those with Raynaud's phenomenon and those with anticentromere antibodies.

In fact, vasculitis seems to be much more frequent than originally thought (26), since skin vasculitis was observed in 33% of the cases in the clinical study by the European concerted action on

malignant lymphoma in SS. Vasculitis appeared indeed to be more frequent in primary SS with non-Hodgkin's lymphoma (NHL) than in the general primary SS population. Histopathological examination of skin biopsies reveals two different patterns in these two clinically distinct settings (27). They may show the conventional leukocytoclastic vasculitis pattern with neutrophils, i.e. neutrophilic inflammatory vascular disease (NIVD), while mononuclear cells predominate within the lesions of mononuclear inflammatory vascular disease (MIVD). These two distinct patterns occurred in either clinical type of vasculitis, so that one cannot predict which type of cutaneous vasculitis lesions will tend to develop by analyzing the morphologic features of the skin biopsy (21).

Given the lack of specific tests (28), it is advisable to remain alert to the possibility of a disease superimposed on vasculitis, e.g. cancer (29) or infection (30). In the context of SS, NIVD is statistically associated with antinuclear antibodies, high titers of anti-Ro/SSA and/or anti-La/SSB antibodies, hypergammaglobulinemia, rheumatoid factor and hypocomplementemia. This does not occur in MIVD (21). Of note, the fact that urticaria-like vasculitis is accompanied by hypocomplementemia is consistent with the thesis of an immune complex-induced tissue lesion, but the proposed pathogenesis of the mononuclear vasculitis, which is not associated with hypocomplementemia, is less clear.

The prognostic implication of these cutaneous manifestations has been deciphered by Ioannidis *et al*. (31) in a sizeable group of 723 patients followed on a regular basis, over a period of 20 years. Two groups of primary SS were thus delineated: type I SS patients characterized by the presence of palpable purpura and low C4 levels at the first visit, as opposed to type II SS patients with an uncomplicated disease course. Importantly, the initial presentation of primary SS determines the subsequent outcome (32). The overall mortality of patients with primary SS is increased only in patients with adverse predictors.

Cutaneous B-cell lymphoma

B cell proliferative disorders include increased plasma cell infiltrates, as well as frank B cell lymphoma. In between these polar forms, there is a grey area of so-called pseudo-lymphomas. Lymphomas are the most worrying complications of primary SS. Nevertheless, data on the incidence of B-cell lymphoma associated with SS are lacking. Most of the studies have been limited by the small size of the cohorts. In contrast to cutaneous lymphoma which derive from T cells, those complicating primary SS are B cell lymphomas. The risk of developing NHL which is equivalent for primary and secondary SS, was estimated by Kassan *et al*. (33) to be 44 times greater than that observed in the normal population. Comparable results have been reported by Selva-O'Callaghan *et al*. (34). In their review of 16 NHLs in SS patients, Royer *et al*. (35) identified 3 cases located in the skin. Ioannidis *et al*. (31) ascribed one of 5 deaths in patients with primary SS to lymphoma, but in essence life-threatening lymphomas are high grade tumors which affect exceptionally the skin.

Miscellaneous

Alopecia

Alopecia in patches has been linked to primary SS by Fye and Talal (6). Its areata form is a common dermatological disease that could well be of autoimmune origin (36). Its association with autoimmune conditions such as autoimmune thyroid disease or diabetes mellitus has been repeatedly demonstrated, but its association with SS has not been established thus far. The possibility, however, exists that lymphocytic infiltration of the sebaceous gland leads to damage and destruction of the hair follicles.

Papular or nodular lesions

Teramoto *et al*. (37) observed 4 primary SS patients with a peculiar annular erythema mimicking that of Sweet's disease. This developed as an elevated edematous border with central pallor, and manifested on the face in 3 cases, and on the cheek in the fourth. Common findings included marked edema of upper epidermis, coat sleeve-like blood vessel-surrounding infiltrates of lymphocytes throughout the dermis, and the nuclear dust circumscribing blood vessels and between collagen bundles. Such lesions are reminiscent of those of classical annular erythemas, but those of Sweet's disease. Infiltrating lymphoid cells were not confined to the sweat glands, but distributed across the entire dermis. Histopathological studies did not however reveal Ig or complement along the basement membrane zone or around blood vessels, nor in affected or unaffected skin. This negative observation allows us to rule out the diagnosis of cutaneous lupus erythematosus.

Provost and Watson (17) have reported persistent plaque-like lesions (erythema multiforme-like lesions) in 9% of their patients with primary SS. There were also ill-defined superficial patches, i.e. erythema persistans, in 4% of them. Sweet's syndrome, which is characterized by erythematosous oedematous plaques and reflects inflammatory infiltration of the dermis with neutrophils, has been occasionally reported in primary SS (38, 39). Lichen planus is even less common than Sweet's syndrome. Including the patient described by Collet *et al*. (40), there are indeed as few as 4 cases reported in the literature. Even if it can be associated with an autoimmune disease such as SLE, immune hepatitis or RA, it is infrequent in SS.

Vitiligo

Of 34 patients with primary SS, 2 were found to present vitiligo (6). Fye and Talal noted pigment changes consisting of localized areas of hypopigmentation and also hyperpigmentation. The pathophysiological meaning of this observation remains unclear, although it is also believed to be of autoimmune origin.

Conclusion

The skin manifestations of SS seem to be frequent and various. However, it is quite difficult to be sure of the link between skin involvement and primary SS. Most importantly, some of these complications carry a poor prognosis

and may lead to palpable purpura (31). Oxholm *et al*. (19-21) have also found intraepidermal IgG deposits in the unaffected skin of 68% of primary SS patients, whereas similar deposits were found in only 13% of secondary SS patients. The search for intra-epidermal IgG deposits could possibly be instrumental in the differential diagnosis between primary and secondary SS. We thus believe it is important to checklist skin manifestations, and study their histology abnormalities.

Acknowledgements

Thanks are due to Simone Forest and Cindy Séné for their expert secretarial assistance.

References

1. TZIOUFAS AG, YOUINOU P, MOUTSOPOULOS HM: Sjögren's syndrome. *In* ISENBERG DA, MADDISON P, WOO P, GLASS P and BREEDVELD F (Eds.): *Oxford Textbook of Rheumatology*, 3rd ed., Oxford, Oxford Medical Publications (in press).
2. PILLEMER SR, MATTESON EL, JACOBSSON LT *et al*.: Incidence of physician-diagnosed primary Sjögren's syndrome in residents of Olmsted County, Minnesota. *Mayo Clin Proc* 2001; 76: 593-9.
3. DAFNI UG, TZIOUFAS AG, STAIKOS P, SKOPOULI FN, MOUTSOPOULOS HM: Prevalence of Sjögren's syndrome in a closed rural community. *Ann Rheum Dis* 1997; 56: 521-5.
4. MOUTSOPOULOS HM: Sjögren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994; 72: 162-5.
5. MOUTSOPOULOS HM, WEBBER BL, VLAGOPOULOS TP, CHUSED TM, DECKER JL: Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. *Am J Med* 1979; 66: 733-6.
6. FYE K, TALAL N: Skin manifestations of Sjögren's syndrome. *In* FITZPATRICK TB, EISEN AZ and WOLFF K (Eds.): *Dermatology in General Medicine*, 2nd ed., Maidenhead, McGraw Hill, 1979: 1883-7.
7. BLOCH KJ, BUCHANAN WW, WOHL MJ, BUNIM JJ: Sjögren's syndrome: a clinical, pathological and serological study of sixty-two cases. *Medicine (Baltimore)* 1965; 44: 187-231.
8. MARKUSSE HM, OUDKERK M, VROOM TM, BREEDVELD FC: Primary Sjögren's syndrome: clinical spectrum and mode of presentation based on an analysis of 50 patients selected from a department of rheumatology. *Neth J Med* 1992; 40: 125-34.
9. WHALEY K, WILLIAMSON J, CHISHOLM DM, WEBB J, MASON DK, BUCHANAN WW: Sjögren's syndrome. 1. Sicca components. *Q J Med* 1973; 166: 279-304.
10. BERNACCHI E, AMATO L, PARODI A *et al*.: Sjögren's syndrome: a retrospective review of the cutaneous features of 93 patients by the Italian group of immunodermatology. *Clin Exp Rheumatol* 2004; 22: 55-62.
11. VEKI H, INAGAKI Y, HAMASAKI Y, ONO M: Dermatologische manifestationen des Sjögren-syndrome. *Hautarz* 1991; 42: 741-7.
12. KATAYAMA I, YOKOZEKI H, NISHIOKA K: Impaired sweating as an exocrine manifestation in Sjögren's syndrome. *Br J Dermatol* 1995; 133: 716-20.
13. MITCHELL J, GREENSPAN J, DANIELS T, WHITCHER JP, MAIBACH HI: Anhidrosis in Sjögren's syndrome. *J Am Acad Dermatol* 1987; 16: 233-5.
14. REES JL, PAL B: Stimulated eccrine gland function in primary Sjögren's syndrome. *Clin Exp Dermatol* 1989; 14: 191-3.
15. FEUERMAN EJ: Sjögren's syndrome presenting as recalcitrant generalized pruritus. Some remarks about its relation to collagen diseases and the connection of rheumatoid arthritis with the sicca syndrome. *Dermatologica* 1968; 137: 74-86.
16. THIERS H, MOULIN G, CUFFIA C, ROBILLARD J: Syndrome de Gougerot-Sjögren associé à une dermatose de type parapsoriasis lichenoide. *Bull Soc Fr Dermatol Syphiligr* 1966; 73: 326-7.
17. PROVOST TT, WATSON R: Cutaneous manifestations of Sjögren's syndrome. *Rheum Dis Clin North Am* 1992; 18: 609-16.
18. HENKIN RI, TALAL N, LARSON AL, MATTERN CF: Abnormalities of taste and smell in Sjögren's syndrome. *Ann Intern Med* 1972; 76: 375-83.
19. OXHOLM P, OXHOLM A, MANTHORPE R: Epidermal IgG deposits in patients with chronic inflammatory connective tissue diseases: diagnostic value and correlation to clinical and immunological parameters in patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 1987; 5: 5-9.
20. VELTHUIS PJ, NIEBOER C, KATER L, HENE RJ: A prospective immunofluorescence study of immune deposits in the skin of primary Sjögren's syndrome. *Acta Derm Venereol* 1989; 69: 487-91.
21. OXHOLM A, MANTHORPE R, OXHOLM P: Immunoglobulin deposits in the epidermis of patients with primary Sjögren's syndrome. *Rheumatol Int* 1984; 4: 9-12.
22. PAVLIDIS NA, KARSH J, MOUTSOPOULOS HM: The clinical picture of primary Sjögren's syndrome: a retrospective study. *J Rheumatol* 1982; 9: 685-90.
23. GARCÍA-CARRASCO M, RAMOS-CASALS M, ROSAS J *et al*.: Primary Sjögren syndrome. Clinical and immunological disease patterns in a cohort of 400 patients. *Medicine (Baltimore)* 2002; 81: 270-9.
24. ALEXANDER E, PROVOST T: Sjögren's syndrome. *Arch Dermatol* 1987; 123: 801-10.
25. TEKTONIDOU M, KASKANI E, SKOPOULI FN, MOUTSOPOULOS HM: Microvascular abnormalities in Sjögren's syndrome: nailfold capillaroscopy. *Rheumatology (Oxford)* 1999; 38: 826-30.
26. VOULGARELIS M, DAFNI UG, ISENBERG DA, MOUTSOPOULOS HM: Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European concerned action on Sjögren's syndrome. *Arthritis Rheum* 1999; 42: 14765-14772.
27. MOLINA R, PROVOST T, ALEXANDER E: Two types of inflammatory vascular disease in Sjögren's syndrome. *Arthritis Rheum* 1985; 28: 1251-8.
28. GONZALEZ-GAY MA, GARCIA-PORRVA C, SALVARANI C, LO SCOCCO G, PUJOL RM: Cutaneous vasculitis, a diagnostic approach. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): 585-588.
29. GONZALEZ-GAY MA, GARCIA-PORRVA C, SALVARANI C, HUNDER GG: Cutaneous vasculitis and cancer, a clinical approach. *Clin Exp Rheumatol* 2000; 18: 305-7.
30. GARCIA-PORRVA A, GONZALEZ-GAY MA: Bacterial infection presenting as cutaneous vasculitis in adults. *Clin Exp Rheumatol* 1999; 17: 471-3.
31. IOANNIDIS JP, VASSILIOU VA, MOUTSOPOULOS HM: Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum* 2002; 46: 741-7.
32. SKOPOULI FN, DAFNI U, IOANNIDIS JP, MOUTSOPOULOS HM: Clinical evolution morbidity and mortality of primary Sjögren's syndrome. *Semin Arthritis Rheum* 2000; 29: 296-304.
33. KASSAN SS, THOMAS TL, MOUTSOPOULOS HM *et al*.: Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978; 89: 888-93.
34. SELVA -O'CALLAGHAN A, PEREZ-LOPEZ J, SOLANS-LAQUE R, LOPEZ-PEIG C, ANGEL-BOSCH GIL J, VILARDEL-TARRES M: Primary cutaneous large B-cell lymphoma of the legs in a patient with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2003; 21: 672.
35. ROYER B, CAZALS-HATEM D, SIBILIA J *et al*.: Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997; 90: 766-75.
36. HUMBERT P, DUPOND JL, VUITTON D, AGACHE P: Dermatological autoimmune diseases and the multiple autoimmune syndromes. *Acta Derm Venereol* 1989; 148: 2-8.
37. TERAMOTO N, KATAYAMA I, ARAI H *et al*.: Annular erythema: a possible association with primary Sjögren's syndrome. *J Am Acad Dermatol* 1989; 20: 596-601.
38. PRYSTOWSKY SD, FYE KH, GOETTE KD, DANIELS TE: Acute febrile neutrophilic dermatosis associated with Sjögren's syndrome. *Arch Dermatol* 1978; 114: 1234-5.
39. VATAN R, SIRE S, CONSTANS J, RAGNAUD JM: Association syndrome de Gougerot-Sjögren primitif et syndrome de Sweet: A propos d'un cas. *Revue Med Interne* 1997; 18: 734-35.
40. COLLET E, DALAC S, BRICHON P, LORCERIE B, BESANCENOT JF, LAMBERT D: Association lichen plan et syndrome de Gougerot-Sjögren primitif. *Ann Dermatol Venereol* 1989; 116: 483-6.