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Original Article

Women With Primary Sjögren Syndrome and With Non-Sjögren Sicca Syndrome Show Similar Vulvar Histopathologic and Immunohistochemical Changes

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Summary: The goal of this study was to evaluate the characteristics and the prevalence of histopathologic and immunohistochemical changes in vulvar biopsies, in women with Primary Sjögren Syndrome (pSS) and non-Sjögren Sicca Syndrome (nS-SS). Twenty-one women with pSS and 11 with nS-SS (investigated by xerophtalmia and xerostomia tests, biopsy of minor salivary glands, gynecological history, and gynecologic symptoms score) underwent vulvar biopsies, evaluated for histopathologic and immunohistochemicalchanges, and compared with those obtained from 26 patients with lichen sclerosus. An inflammatory infiltrate was present in 31/32 biopsies (96.9%); biopsies from pSS patients showed a mild infiltrate in 10 cases and a moderate infiltrate in 11 cases; and patients with nS-SS had a mild infiltrate in 8 biopsies and moderate infiltrate in the other 2 biopsies. By immunohistochemistry, the infiltrate was composed predominantly of T lymphocytes ($CD3^+$), $CD20^+$ B cells were sparse and mean CD4:CD8 T-cell ratio was 1.5. No differences were observed between the grading of the inflammatory infiltrate in nS-SS and pSS; no correlation was shown between vulvar inflammatory infiltrate score (mild or moderate) and salivary glands inflammatory score. No differences were found in gynecologic symptoms, as well as in clinical and demographical characteristics between patients with mild and those with moderate vulvar inflammatory score. A higher prevalence of moderate inflammatory infiltrate was observed in biopsies from women with lichen sclerosus than in pSS and nS-SS patients (61.5% vs. 27.5%, $P = 0.02$). Women with pSS and nS-SS show a high and similar prevalence of vulvar inflammatory infiltrate. A gynecologic evaluation is needed both in pSS and nS-SS to assess genital involvement and, eventually, to address a therapy targeted to genital symptoms. **Key Words:** Sjögren Syndrome—Not Sjögren Sicca Syndrome—Histopathology—Vaginal dryness—Vulvar dryness.

Primary Sjögren Syndrome (pSS) is an autoimmune disease most frequently affecting women, characterized by a lymphocyte-mediated infiltration and destruction of several exocrine glands. This causes reduction of glandular secretion resulting in mucosal dryness, mainly at lachrymal and salivary glands (causing xerophtalmia and xerostomia) but also involving epithelia of respiratory, gastroenteric, tegumentary systems, and female genital tracts (1–3).

pSS is diagnosed in the presence of 4/6 of American and European Consensus Group (AECG) classification

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The authors declare no conflict of interest.

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criteria, as long as either histopathology or serology [antibodies to Ro(SSA) and/or to La(SSB)] is positive (4). Patients not fulfilling criteria but presenting with ocular and salivary symptoms are considered affected by non-Sjögren Sicca Syndrome (nS-SS) (5).

In women with pSS, the genital involvement, is characterized by vulvar and vaginal dryness, dyspareunia, and pruritus (5–18), and it is frequently present since disease onset. In a previous study, we demonstrated a high and similar prevalence of genital symptoms in women with pSS and nS-SS (80% and 91%, respectively) (17). Importantly, we also showed that genital symptoms, mainly vaginal and vulvar dryness and dyspareunia, notably affected sexual activity (in around 50% of subjects), reduced frequency in sexual intercourses (>80%), and affected the relationship with partners (>50%), with similar frequency similarly in pSS and nS-SS patients (17).

However, despite the high frequency of genital concerns in pSS and nS-SS, few data on pSS and no data on nS-SS have been published regarding the histopathology of external genitalia (9,10,19). This may be due both to technical problems in taking samples useful for the histologic examination (6,9,11) and for the difficulties in communication between patients and health professionals about sexual issues (17).

The studies performed until now have shown that vaginal and vulvar dryness is due to the presence of a vulvar inflammatory infiltrate (11) and to the atrophy of minor and major vestibular glands (6), whose secretions are important especially during the sexual intercourse.

The principal aim of this study is to evaluate the characteristics and the prevalence of histopathologic and immunohistochemical changes in vulvar tissue in women with pSS and nS-SS.

Moreover, we aimed to (i) quantify by a semiquantitative score the lymphocytic infiltrate in vulvar biopsies; (ii) assess the possible differences between the histopathologic vulvar score in pSS and nS-SS; (iii) correlate vulvar score with salivary Chisholm e Mason score (20) of salivary glands and with the clinical symptoms.

Finally, we compared the changes of vulvar biopsies of pSS and nS-SS with those found in patients affected by lichen sclerosus that we proposed as control group.

PATIENTS AND METHODS

Patients

In this study, 112 women with Sicca symptoms, followed at the Rheumatology outpatient clinic of the Department of Experimental and Clinical Medicine, Division of Medicine, University of Florence, were proposed to undergo to vulvar biopsies at the Vulvar Clinic of the Department of Science for Woman and Child Health, University of Florence, Italy.

The only inclusion criterion was the presence of symptoms related to ocular or oral dryness (xerophtalmia and xerostomia).

Exclusion criteria were the presence of other rheumatic conditions (secondary Sjögren syndrome) and the current or anamnestic presence (in the previous 5 yr) of gynecologic diseases.

Both pSS and nS-SS patients were investigated for: age, disease duration, ocular test for xerophtalmia (Schirmer, break up time, Lissamine green tests), salivary gland function (salivary gland scintigraphy) and histology (biopsy of minor salivary glands), autoantibodies patterns (ANA, ENA, particularly anti-SS-A, and anti-SS-B), and gynecologic history (including age at menarche, parity, menopause, years from menopause, hormone replacement therapy).

Symptoms and signs (itching, burning sensation, dyspareunia, subjective vulvar and vaginal dryness, objective genital dryness, reduced sexual drive, spontaneous genital pain, and dysuria) were collected for each patient. Each item was scored as: 0 if no symptoms, 1 if mild symptoms, 2 if moderate symptoms, and 3 if severe symptoms. Then, the scores for each patient were summed to obtain the total gynecologic symptoms score (range, 0–24) created by the Vulvar Clinic of the Department of Science for Woman and Child Health, University of Florence, normally used for the assessment of vulvar affections, especially for lichen sclerosus (21).

Seventy-one of the 112 patients initially proposed for gynecologic evaluation and vulvar biopsy (63.4%) accepted and 41 (36.6%) did not from lack of interest.

Thirty-nine patients who presented for the gynecologic evaluation were not biopsied (54.93%). Among them, 20 (51.28%) refused and 19 (48.72%) were not biopsied for the following reasons: 4 had concomitant gynecologic affections (candida or lichen), 1 was taking aspirin, 4 referred allergy to anesthetics, 5 for technical problems, and 5 for unspecified causes. Thus, 32/71 patients (45.07%) were biopsied. The study was approved by the local ethic committee and patients signed a written informed consent.

According to AECG classification criteria, 21 of the 32 patients who underwent biopsy were diagnosed with pSS patients and 11/32 with nS-SS (4,5).

The biopsies obtained from pSS and nS-SS patients were compared with those obtained from 26 consecutive women affected by early lichen sclerosus (mean age,

57.61 ± 10. 72 y), the most common chronic inflammatory sclerosing dermatosis of the vulva (18), that leads to clinical and sexual problems, similar to those reported by pSS and SS patients.

Biopsies

Biopsies were performed in the middle third of the lateral vestibule of the vulva by a 4 mm punch. This area was chosen because it is the least sensitive area of the vulva, easier to keep clean, and not in contact with urine.

The biopsy material was fixed in formalin and routinely processed for paraffin embedding. Serial sections (with thickness of 4 μm) were obtained for hematoxylin and eosin staining, as well as for immunohistochemistry.

Histopathology

Hematoxylin and eosin-stained sections were examined for the presence of surface squamous epithelium, including epithelial hyperplasia, dysplasia, orthokeratosis, parakeratosis, spongiosis, and for the infiltration by inflammatory cells. The presence of subepithelial edema and/or fibrosis was also examined. The inflammatory infiltrate of the mucosa was scored semiquantitatively as absent (0), mild (1), and moderate (2).

In mild infiltrate, inflammatory cells are evenly and sparsely distributed in the subepithelial stroma (Fig. 1A); in moderate infiltrate, inflammatory cells are numerous and more often distributed in a "band-like" fashion within the stroma (Fig. 1B).

Immunohistochemistry

The inflammatory infiltrate was characterized immunohistochemically by using monoclonal antibodies against CD20, CD3, CD4, and CD8. Paraffin section (4 μm thickness) were dewaxed, hydrated, and after inactivation of endogenous peroxidase were immunostained using the BenchMark XT stainer (Ventana Medical Systems Inc., Tucson, AZ), and revealed with the iVIEW DAB detection kit, yielding a brown reaction product.

The primary monoclonal antibodies used were CD3 (prediluted; Ventana Medical Systems Inc.), CD4 (prediluted; Cell Marque, Rocklin, CA), CD8 (prediluted; Ventana Medical Systems Inc.), and CD20 (prediluted; Ventana Medical Systems Inc.).

After the staining run was completed, the slides were removed from autostainer, counterstained with hematoxylin, dehydrated, and mounted with permanent mounting medium.

As negative controls, we substituted the primary antibody with a dispenser filled with nonimmune serum at the same concentration for each immunohistochemical reaction.

Statistical Analysis

Data are presented as mean ± SD and as numbers and percentages. To compare for the clinical and clinimetric characteristics of groups, Fischer exact or χ^2 tests (when appropriate) were used to test for binomial variables and Student t test for continuous variables. Pearson or Spearman test (when appropriate) were used for the correlations.

Data were analyzed by SPSS 18 for Windows.

RESULTS

The clinical and gynecologic characteristics of pSS and nS-SS are shown in Table 1.

Vulvar Biopsies

The biopsy specimens consisted of mucosa fragments with nonkeratinizing squamous epithelium and underlying stroma.

An inflammatory infiltrate was evidenced in 31 of 32 biopsy specimens (96.9%). The infiltrate was composed of mature lymphocytes, histiocytes, and few plasma cells.

According to our semiquantitative analysis, 1 biopsy showed absence of inflammatory infiltrate, 18 were scored as mild, and 13 as moderate.

Biopsies of pSS patients showed a mild infiltrate (score 1) in 10 cases and a moderate infiltrate (score 2) in 11 cases; patients with nS-SS had a mild infiltrate in 8 biopsies and a moderate infiltrate in the other 2 biopsies.

Other histopathologic changes observed were the presence of ortho-keratosis and para-keratosis (2 biopsies), and mild spongiosis (1 biopsy). No dysplastic changes of the surface epithelium were observed in any of the biopsies. Two biopsies showed mild interstitial edema, and 1 presented mild fibrosis of the subepithelial connective tissue, with thickening of collagen fibers.

The immunohistochemical analysis showed that the inflammatory infiltrate was composed predominantly of T lymphocytes ($CD3^+$), whereas $CD20^+$ B cells were sparse. The mean CD4:CD8 T-cell ratio was 1.5 (range, 1.1–1.9) (Fig. 2).

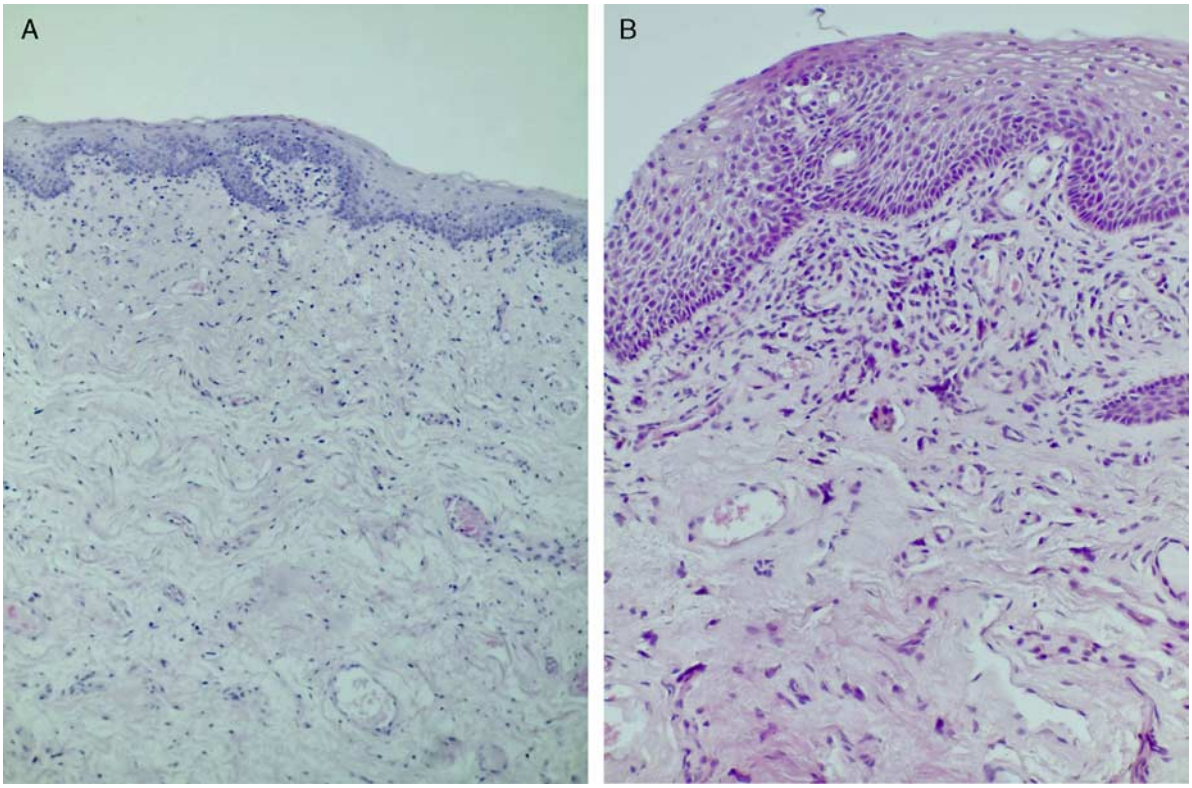

FIG. 1. (A) Punch biopsy showing unaltered surface squamous epithelium and a mild inflammatory infiltrate in the underlying lamina propria in a patient with non-Sjögren Sicca Syndrome. (B) Punch biopsy showing a slightly acanthotic squamous epithelium and a moderate inflammatory infiltrate distributed in a "band-like" fashion within the superficial lamina propria in a patient with Primary Sjögren Syndrome. Hematoxylin and eosin staining, original magnification $\times 10$ in (A), $\times 20$ in (B).

TABLE 1. *Demographical, clinical, and gynecologic characteristics of patients with Primary Sjögren Syndrome and non-Sjögren Sicca Syndrome*

	pSS (21 patients)	nS-SS (11 patients)	*P*
Age (yr) (mean ± SD)	64.33 ± 11.06	65.36 ± 9.11	NS
Disease duration (y) (mean ± SD)	3.81 ± 3.26	4.63 ± 4.59	NS
Menopausal state	17/21 (80.9%)	9/11 (81.8%)	NS
Age at menopause (yr) (mean ± SD)	46.88 ± 4.66 (n = 17)	50.78 ± 1.92 (n = 9)	0.025
Hormonal replacement therapy	5/17 (29.4%) (n = 17)	1/9 (11.1%) (n = 9)	NS
Autoantibodies positivity			
Anti-SSA	7/21 (33.3%)	0/11 (0%)	0.01
Anti-SSB	5/21 (23.8%)	0/11 (0%)	NS (0.14)
Schirmer test < 5 mm	10/21 (47.6%)	7/11 (63.6%)	NS
Objective genital dryness	12/21 (57.1%)	7/11 (63.6%)	NS
Score gynecologic symptoms	7.43 ± 4.75	6.45 ± 4.39	NS
Subjective genital dryness (vulvar or vaginal)	19/21 (90.5%)	7/11 (63.6%)	NS
Subjective vulvar dryness	18/21 (85.7%)	7/11 (63.6%)	NS
Subjective vaginal dryness	13/21 (61.9%)	7/11 (63.6%)	NS
Pruritus	8/21 (38.1%)	1/11 (9.1%)	NS
Burning	10/21 (47.6%)	1/11 (9.1%)	NS
Spontaneus genital pain	5/21 (23.8%)	0/11 (0%)	NS
Dysuria	4/21 (19.0%)	3/11 (27.3%)	NS
Dyspareunia	6/21 (28.6%)	8/11 (72.7%)	NS

NS indicates nonsignificant; nS-SS, non-Sjögren Sicca Syndrome; pSS, Primary Sjögren Syndrome.

Comparison of Vulvar Inflammatory Infiltrate Between pSS and nS-SS Patients

No differences were observed between the grading of the inflammatory infiltrate in vulvar biopsies in nS-SS and pSS ($P = 0.37$ by χ^2 test).

Correlation of Vulvar Inflammatory Infiltrate Score With Salivary Gland Biopsy Score in Patients With pSS and nS-SS

In nS-SS and pSS, no correlation was shown between the score of the vulvar inflammatory infiltrate (1 = mild; 2 = moderate) and the Chisholm and Mason score (20) of the minor salivary gland biopsy ($P = 0.26$, by χ^2 test).

Comparison of Vulvar Inflammatory Infiltrate Score With Clinical and Demographic Characteristics in Patients With pSS and nS-SS

No differences were found in clinical and demographical characteristics between patients with pSS and nS-SS with mild and those with moderate vulvar inflammatory infiltrate score (Table 2).

Comparison of Vulvar Inflammatory Infiltrate Score With Gynecologic Symptoms in Patients With pSS and nS-SS

No differences were observed in the gynecologic symptoms between patients with pSS and nS-SS with mild and those with moderate vulvar inflammatory infiltrate score (Table 2).

Comparison of Vulvar Inflammatory Infiltrate of pSS and nS-SS Patients With Lichen Sclerosus

The reviewed vulvar biopsies taken from women affected by early vulvar lichen sclerosus showed lichenoid or interstitial lymphoid infiltrate.

A significant higher number of biopsies showing moderate inflammatory infiltrate was observed in the group of women affected by lichen sclerosusthan in pSS and in nS-SS patients (61.5% vs. 27.5%, $P = 0.02$).

DISCUSSION

To the best of our knowledge, this is the first study evaluating the histopathologic and immunohistochemical characteristics of vulvar mucosa in both women with pSS and nS-SS.

Although genital tract symptoms, such as vulvar and vaginal dryness, dyspareunia, and pruritus are common in patients with pSS and nS-SS, their consequences on sexual ability have been rarely evaluated (17). Moreover, few data have been published on the histopathologic features of external genitalia of pSS women (6,8,11) and no data are available on nS-SS patients.

The few articles that assessed cervical and vaginal biopsies in pSS female patients have shown dystrophic processes resulting in the atrophy of the cervicovaginal mucosa in 50% of the cases, chronic cervicitis in 10% of the cases, (10) and perivascular infiltration with chronic inflammatory cells (11).

The aim of this study was the evaluation of the changes occurring in the vulvar tissue of patients affected by pSS and in patients who not fully meet the AECG criteria but who present the same symptoms.

We observed a very high incidence of inflammatory infiltrate both in pSS patients and in nS-SS patients (31 of 32 vulvar biopsies, 98.9%). The inflammatory infiltrate, composed by mature lymphocytes, histiocytes, and few plasma cells, was mainly distributed in the superficial stroma and tended to assume a subepithelial band-like appearance when becoming more intense. By using a semiquantitative score, in 18 biopsies the inflammation were scored as mild and in 13 as moderate.

No differences were observed in inflammatory infiltrate of vulvar biopsies of nS-SS and pSS patients, indicating a chronic inflammation also in nS-SS, despite that, not satisfying it AECG criteria, nS-SS is not usually considered as an inflammatory condition.

These results confirm the data of a previous study of our group, showing that a high percentage of patients with pSS and nS-SS present with gynecologic symptoms suggesting that gynecologic symptoms depend on vulvar inflammation irrespective of diagnosis (17).

Our present results confirm the hypothesis that patients fulfilling AEGC criteria (4) and those presenting only with Sicca symptoms and signs may be regarded as affected by the same condition, yielding a different disease expression (5). Some authors, however, consider patients fulfilling AECG criteria as affected by Sjögren disease and those with negative antibodies and biopsy as affected by Sjögren syndrome (3,5).

As we previously demonstrated, 80% of pSS and 90% of nS-SS patients have gynecologic symptoms, with vulvar and vaginal dryness and dyspareunia as the most reported concern, and sexual ability in both groups was more affected by gynecologic symptoms (mainly vulvar and vaginal dryness) than by muscle-skeletal concerns (17).

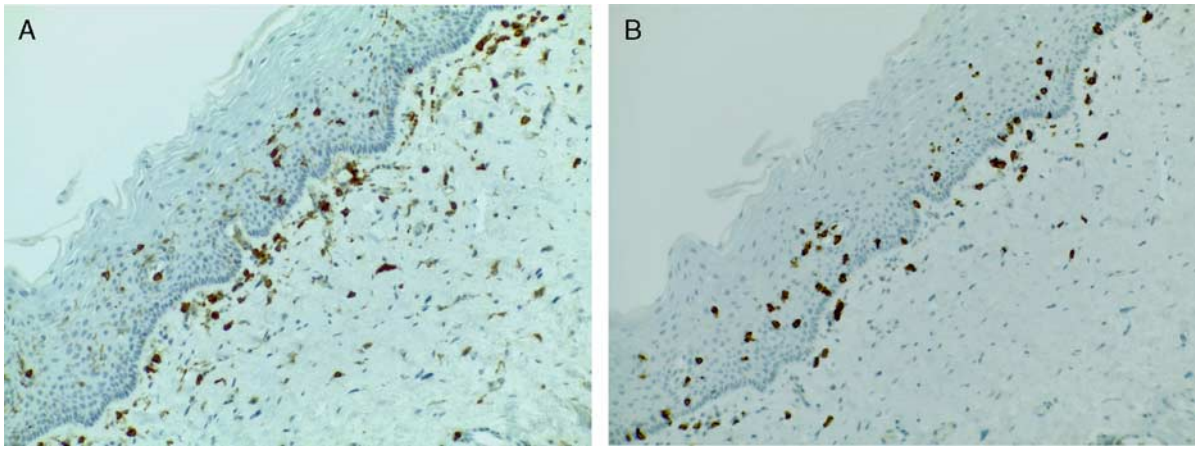

FIG. 2. Immunohistochemical staining showing the CD4 (A) and CD8 (B) lymphocyte distribution in the epithelium and lamina propria, in a vulvar punch biopsy showing mild infiltrate in a patient with non-Sjögren Sicca Syndrome. Original magnification: × 20.

Thus, according to the data presented in the current study, although based on a small sample of patients, dryness at external genitalia, one of the most annoying problem among Sicca symptoms, relies on tissue inflammation not only in women with pSS but also in women with nS-SS. Moreover, we investigated a possible correlation between the intensity of the vulvar inflammatory infiltration and the severity of the gynecologic symptoms. The lack of correlation of vulvar inflammatory score to gynecologic symptoms score is probably related to the small number of subjects assessed.

The lack of correlation between vulvar inflammation score and salivary gland biopsy score (20) may be due to the different extent of inflammation present in vulvar mucosa and in minor salivary glands.

According to our data, women with pSS and nS-SS have similar scores in vulvar inflammation. Conversely, patients with pSS, present a lymphocytic infiltrate and epimyoepithelial islands composed of keratin-containing epithelial cells in salivary glands biopsies.

These alterations are not found, or are present to a lesser extent, in nS-SS patients (22).

Also the immunohistochemical characteristics of the vulvar inflammatory infiltrate, that we evaluated for the first time, are different from those found in salivary biopsies. In vulvar biopsies of women with

TABLE 2. *Demographical, clinical, and gynecologic characteristics of patients with Primary Sjögren Syndrome and non-Sjögren Sicca Syndrome with gynecologic score 1 (mild) and 2 (moderate)*

	Score 1 (18 patients)	Score 2 (11 patients)	*P*
Age (y) (mean ± SD)	63.89 ± 9.6	65.15 ± 11.70	NS
Disease duration (y) (mean ± SD)	4.67 ± 4.31	3.54 ± 2.79	NS
Menopausal state	14/18 (77.8%)	11/13 (84.6%)	NS
Age at menopause (y) (mean ± SD)	48.93 ± 4.14	47.18 ± 4.71	NS
Hormon replacement therapy	4/14 (28.6%) (14 patients)	2/11 (18.2%) (11 patients)	NS
Autoantibodies positivity			
Anti-SSA	3/18 (16.7%)	4/13 (30.76%)	NS
Anti-SSB	3/18 (16.7%)	2/13 (15.38%)	NS
Schirmer test < 5 mm	10/18 (55.5%)	6/13 (46.15%)	NS
Objective genital dryness	10/18 (55.5%)	8/13 (61.5%)	NS
Score gynecologic symptoms	7.43 ± 4.75	6.45 ± 4.39	NS
Subjective genital dryness (vulvar or vaginal)	13/18 (72.2%)	13/13 (100%)	NS
Subjective vulvar dryness	13/18 (72.2%)	12/13 (92.3%)	NS
Subjective vaginal dryness	10/18 (55.5%)	10/13 (76.9%)	NS
Pruritus	5/18 (27.8%)	4/13 (30.8%)	NS
Burning	5/18 (27.8%)	6/13 (46.1%)	NS
Spontaneus pain	1/18 (5.5%)	4/13 (30.8%)	NS
Dysuria	5/18 (27.8%)	2/13 (15.4%)	NS
Dyspareunia	9/18 (50%)	5/13 (38.5%)	NS

NS indicates nonsignificant.

pSS and n-S-SS, we found an inflammatory infiltrate composed predominantly of T lymphocytes ($CD3^+$) and by rare $CD20^+$ B cells. Conversely, in salivary biopsies of pSS, $CD4^+$ T lymphocytes are the main cell population in mild lesions (23), and B cells, containing intracytoplasmic immunoglobulins, mainly with anti-Ro (SSA) and/or anti La (SSB) reactivity are also present (24,25). In salivary glands, germinal centers can be occasionally found, whereas macrophages and natural killer cells represent $< 5\%$ of the total cell population.

By comparing vulvar biopsies of women with pSS and nS-SS with those from lichen sclerosus, the most common vulvar sclerosing dermatosis (19), the latter showed a significant higher number of biopsies with moderate inflammatory infiltrate than in pSS and in nS-SS patients, indicating that vulvar inflammation in lichen sclerosus is more prominent than in pSS and nS-SS patients.

Vulvar biopsies taken from lichen sclerosus show atrophic epidermidis with interface change, hyalinization at the upper dermis, and inflammatory band at lower dermis. Early lesions may lack the characteristic sclerotic band, and may present with basement membrane thickening, acanthosis, sclerosis of the submucosa, and ectatic subepithelial blood vessels (26).

As for pSS and other autoimmune diseases, the prevalence of lichen sclerosus is higher in postmenopausal women. It can present with the same symptoms of pSS or nS-SS like itching, burning, and dyspareunia, leading to notable problems in sexual function (27,28).

Probably, in women with pSS and ns-SS, similarly to lichen sclerosus, inflammatory processes of vulvar mucosa are among the main causes of vulvar and vaginal dryness, dyspareunia, and pruritus and may indirectly lead to impairment of sexual ability (17).

The major limitation of our study is the small number of patients enrolled. As mentioned above, the low number of patients included in our study is due to the low number of women who accepted to undergo gynecologic evaluation. Moreover, not all the women who accepted, were biopsied (45%).

The refusal to undergo biopsy is due to the uncomfortable procedure and underlines the difficulty of the women with pSS and ns-SS in openly dealing with sexual issues, even with a medical doctor, although gynecologic symptoms are felt as prominent problems.

In agreement with previous data (17,29), 36.6% of the patients who were referred for gynecologic evaluation did not accept, declaring no interest and no gynecologic problems.

In contrast, in pSS and ns-SS, disease-related gynecologic and sexual problems, although frequent (17), are overshadowed by other symptoms and rarely assessed by health professionals, due to the scarce clinic importance given to them and to mutual problems in communication between rheumatologists and patients (17).

CONCLUSIONS

Women with pSS and nS-SS show a high and similar prevalence of vulvar inflammatory infiltrate.

Genital involvement is potentially impacting on sexual life; therefore every patient, independent of the diagnosis, needs a gynecologic evaluation, so that correct therapy could reduce symptoms and sexual discomfort.

Rheumatologists should inform women that gynecologic symptoms may arise in the course of pSS and nS-SS, take them into account and, if needed, refer patients to gynecologists for proper management.

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