Pathogenesis of Vaginal Dryness in Primary Sjögren’s Syndrome: A Histopathological Case-control Study

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Background/Purpose: Women with primary Sjögren’s syndrome (pSS) often experience vaginal dryness, but the pathogenesis of this symptom is unknown. Previously, we reported impaired vaginal health and presence of a subepithelial infiltrate in the vagina of women with pSS. In the current analysis, we quantitatively studied changes in lymphocyte subsets, endothelial cells and soluble immune markers in the vagina and endocervix of women with pSS, compared to age-matched controls, which may explain vaginal dryness.

Methods: Gynaecological examinations were performed in 10 premenopausal women with pSS, fulfilling the ACR-EULAR criteria, with symptoms of vaginal dryness, and 10 premenopausal non-pSS controls scheduled for laparoscopic procedures. Participants with inflammatory or infectious gynaecological morbidity were excluded. Endocervical swab and cervicovaginal lavage samples were collected, in which levels of pro-inflammatory chemokines and cytokines were analyzed using a multiplex bead based immunoassay. Mid-vaginal biopsies and endocervical biopsies were collected and stained for leucocyte markers, caldesmon for smooth muscle cells, ERG for endothelial cells and anti-podoplanin (clone D2-40) for lymphatic endothelium. The number of positive pixels/µm² was calculated digitally using Aperio ImageScope v 12.1.

Results: One pSS patient was excluded due to chlamydia, and 2 controls due to discovery of endometriosis during their laparoscopy. In the remaining 9 patients and 8 controls, median age was 36 years (IQR 33-46) and 41 years (36-44), respectively (p=0.61). A higher level of CXCL10 was measured in endocervical swabs of pSS patients (median 37.1 pg/ml, IQR 19.4-66.1) compared to controls (median 12.6 pg/ml, IQR 5.9-31.1, p= 0.046). No differences were found in levels of APRIL, BAFF, RANKL, TNF-α, CCL2, CXCL11, CXCL13, IL6, IL7 or IL8. One vaginal biopsy from a control was excluded from analysis as it was too superficial, consisting for 98% of epithelium. Three pSS and two control cervix biopsies which did not show representative endocervical tissue were excluded from analysis. The number of CD45+ and CD3+ cells (expressed as number of positive pixels/µm²) in vaginal biopsies was significantly higher in pSS patients (p=0.012 for CD45, p=0.008 for CD3). Lymphocytic infiltration was mainly located in the subepithelial layer, with aggregates in dermal papillae. Endocervical CD45+ leucocytic infiltrates were seen in patients as well as controls, but CD20+...
positive pixels/µm² were significantly higher in pSS patients (p=0.041). Importantly, there was a significantly lower number of vascular smooth muscle cells (caldesmon+ pixels/µm²) in the vagina of pSS (p=0.031). In the endocervix, no significant differences were seen in endothelial or smooth muscle cells.

**Conclusion:** Our findings indicate that in addition to chronic inflammation, vascular disturbances in the vaginal mucosa are likely to contribute to vaginal dryness in women with pSS.


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