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Sjögren's syndrome in a 25-year-old female: A case study

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ABSTRACT

Sjögren syndrome (SS) is an autoimmune epithelitis characterized by lymphocytic glandular infiltration and various extraglandular manifestations. SS is usually encountered in middle-aged females (>50 years). Immunological, viral, hereditary, environmental and hormonal etiologic factors are controversially proposed with regard to the pathogenesis of SS with no upper hand given. The present study reports an atypical case of SS in a 25-year-old female who was closely followed up for three years. Being pregnant in 2015, SS ran a total remission course but did relapse more aggressively after delivery. Immunologically implicating, the possible interpretation, which may account for such a pathological fluctuation, is also tackled.

Keywords: Sjögren syndrome Xerophthalmia Xerostomia Parotid ultrasound Diagnostic biopsies

1. Introduction

Sjögren's syndrome (SS), either primary or secondary, has been defined as an autoimmune epithelitis characterized by lymphocytic glandular infiltration and various extraglandular manifestations [1,2]. Transcending Copenhagen diagnostic praxis, SS is nowadays diagnosed according to the European-American inclusion and exclusion criteria and classification [3]. Although the exact etiology of SS is not totally fathomed, immunological, genetic and environmental predisposing factors, are blamed for priming this disease. There, apoptosis, IFN signaling, cytokine levels, expression of autoantigens, and T-cell and B-cell dysfunction are all likely to be of (a) salient role(s) in understanding the etiopathogenesis of SS [4,5].

Clinical manifestations of SS develop gradually along its pathological course. The first clues in primary SS are, most often, lacrimal hypofunction (xerophthalmia), and dry mouth (xerostomia) secondary to hyposalivation which result from self-perpetuating immune-mediated loss of acinar and ductal cells of lacrimal and salivary glands. In secondary SS, rheumatoid factors and several extraglandular manifestations are concomitant with such xerophthalmia and xerostomia. This includes neural, renal, rheumatological, vascular, gastric and pulmonary manifestations [4]. Propensity of malignant transformation to lymphoma in SS has added up to 5% of the reported cases. Developing oral squamous cell carcinoma has been also documented. Follow up is therefore mandatory [4]. The present study reports an atypical case of SS in a 25-year-old wife who was closely followed up for three years. Although SS is epidemiologically encountered in middle-aged and old females (9:1 female-to-male ratio), children and teenagers might be, quite rarely, affected. If so, the juvenile form of SS is self-limiting [6]. The rarity of this reported case is permanently developing SS in a young female with a remarkable fluctuation in the aggression course over three years.

2. Case presentation

A 25-year-old female visited our outpatient clinic in April 2013 with badly decayed teeth. Careful intraoral and extraoral examinations revealed xerostomia, candidal infection on her tongue, difficulty in swallowing and parotidomegaly (Fig. 1). Familial sociological profile of the patient included preference of consanguineous marriage. No history of drinking or smoking was reported.

The ultrasound study showed a bilateral heterogeneous echo-pattern of the major salivary glands. The glandular parenchyma was atrophic with diffuse cystic cavities (diameter of the largest cyst was less than 0.9 cm) Mililiary sporadic calcifications were conspicuous. The overall picturesque was giving the impression of the so-called “cribriform” appearance. (Fig. 2). Cervical lymph nodes maintained their normal oval shape, yet mildly enlarged, and their normally appearing hilum. Both thyroid lobes and isthmus

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displayed a normal echopattern and texture. MRI on the head and neck was run annually in order to assess the status of the salivary glands and cervical lymph nodes (Fig. 3).

Serological results revealed an elevated ESR, positive ANA, strongly positive anti-Sjögren’s syndrome-A (SS-A) and positive anti–Sjögren’s syndrome-B (SS-B). The rheumatoid factor was, however, negative. Lymphocytopenia, absolute neutropenia, hypochromic microcytic anemia and thrombocytopenia were evident in her deferential CBC. Under local anesthesia, four minor salivary glands from a normally appearing labial mucosa were harvested. The extract was immersed immediately in 10% formalin to be submitted for microscopic examination. The histologic picture viewed a confluence of lymphocytic infiltrate and a few macrophages which replaced most of the glandular parenchyma (greater than fifty lymphocytes in several foci). Acinar degeneration and sporadic epimyoepithelial islands were also observed. No germinal centers were observed (Fig. 4). All in all, a diagnosis of Sjögren’s syndrome was established. The patient was referred to a rheumatologist and an ophthalmologist for managing her condition but multidisciplinary follow-up was highly recommended. A low-dose corticosteroid was prescribed by her rheumatologist (20–30 mg of daily Hostacortin).

Following this young female up, an ultrasound study was periodically conducted every three months while MRI on the head and neck was run annually in order to assess the status of the salivary glands and cervical lymph nodes (Fig. 3).

In July 2016, a minor salivary gland was obtained, under local anesthesia, from a normally appearing buccal mucosa and was immersed immediately in 10% formalin to be submitted for microscopic examination. The histologic picture viewed a higher intensity of inflammatory lymphocytic infiltrate which effaced totally architecture of the glandular structures except for maintaining few epimyoepithelial islands (Figs. 5–7). However, the sonographic and MRI pictures demonstrated no signs of malignancy. Running immunohistochemical confirmatory tests, the minor salivary gland specimen was also stained for CD20, C30, BCL6, MUM1 and Pan cytokeratin to exclude any malignant transformation into lymphoma or squamous cell carcinoma. All tests came back negative except for non-specific immunopositivity of epimyoepithelial islands for Pan cytokeratin. The patient was educated about the possibility of evolving low-grade lymphoma ex-SS and was advised to get her minor salivary glands re-biopsied in February 2018. She was also assured about the conservatively successful management of the evolving MALT lymphomas ex-SS if the close follow-up program was continued. The patient was referred back to her rheumatologist for managing the progressive case. Recruiting a therapeutic line, other than corticosteroid intake, was recommended because Hostacortin did not prove effective in alleviating the severity of inflammation in the minor salivary glands.
3. Discussion

Although the triad of xerostomia, xerophthalmia and rheumatoid arthritis was academically considered cardinal signs of SS, this concept has been jettisoned. Furthermore, dozens of other signs and symptoms were included [2-4]. On the one hand, general symptoms comprise fatigue, arthralgia/arthritis, myalgia/myositis, and lymphadenopathy. Internal organ changes include neuropathy, thyroiditis, interstitial lung disease, chronic atrophic gastritis, celiac disease, primary biliary cirrhosis and other liver manifestations, vasculitis, glomerulonephritis, hearing troubles, vaginal dryness, dyspareunia, and interstitial cystitis. Complicating matters, SS is frequently associated with other connective tissue diseases. Oral manifestations, on the other hand, include xerostomia, high caries index, periodontal disease, early tooth loss, gnathic pain, osteomyelitis, difficulty in swallowing and chewing, chronic erythematous mucosa, candidiasis, stomatopyrosis, halitosis, dysgeusia, crusting/numbness of lips, parotidomegaly as well as angular cheilitis [3]. Such heterogeneous manifestations are explained at two levels: glandular and systemic extraglandular levels. Hitherto, the analyses of gene expression profiles of salivary gland tissues, obtained from...
patients with SS, confirmed the presence of T cells, B cells, dendritic cells and macrophages. Systemically, chronic inflammation in several organs, mostly immunologically-induced, is responsible for the extraglandular manifestations [7]. Pursuing the dysfunctional pathways, genetic background was identified in SS patients. More often, the inflammatory fire is attributed to abnormal regulation of ApoE, BAFF, CCR5, Fas, Fasl, GSTM1, HA-1, IgKM, IkB, IL-1, IL-6, IL-10, IL-4R, IRS1, MBL, PTPN22, STAT4, TcRBV, TGF-B, TNF-α, and 52 kDa Ro/SS-A [3].

The question of ameliorating or exacerbating the severity of SS during pregnancy is rarely negotiated in the medical literature. However, hormonal contribution to the pathogenesis of SS was suggested especially after demonstrating higher ratios of prolactin/progesterone and estrogen/progesterone in a number of SS patients [8].

Furthermore, microchimeristical involvement of cells transfer between fetus and mother during pregnancy, which can persist in both decades later, has been suggested to cause autoimmune disease including SS [9]. Moreover, acinar cells of minor salivary glands were demonstrated to fail maintaining cysteine-rich secretory protein-3 and dihydrotestosterone in SS and so is the case in female-dominant autoimmune exocrinopathy. This was attributed to androgen depletion and defective dehydroepiandrosterone (DHEA) in SS salivary glands [10]. However, restoration of systemic androgen levels by DHEA treatment did not correct local androgen depletion [11]. This can be simply attributed to secondary role of DHEA in SS salivary glands. Given the impairing influence of elevated levels of DHEA on dendritic cells but not on lymphocytes [12], failure of treating SS by restoring DHEA can be comprehended.

Nevertheless, this case study demonstrated that pregnancy had totally recovered the glandular architecture of major salivary glands which was relapsed three months after delivery. In 11-month time, the intensity of lymphocytic infiltrates within salivary glands was much greater than was the case in 2013. This suggests that luteinizing hormones, or one of them, can improve the patient’s condition. The setback may be attributed to the later diminishing of such hormones after delivery.

In a trial to explain the initial dramatic improvement and relapse, intercalated duct cells are postulated to carry a heavier weight than acinar cells in restoring the normal function of salivary glands. Given the overexpression REG Iα in salivary ductal cells is induced by IL-6 but not by IL-8 at the transcriptional level. IL-6-JAK-STAT3 is expected to play the major pathogenic role in maintain the chronic inflammatory status of SS salivary glands [13]. Estrogen, which is decreased after menopause and after delivery, may be of therapeutic effect on SS via regulating immune tolerance (growth, differentiation and proliferation of lymphocyte; antigen presentation; cytokine production; antibody production; as well as cell survival and apoptosis). In early pregnancy, low molecular mass polypeptide (LMP) 2 and LMP7, which underlie the downregulation of human leukocyte antigen class I antigen, may be responsible for promoting SS. TAP-LMP genetic abnormality is known to be responsible for several autoimmune conditions [14].

Taken together, pregnancy, which is immunosuppressant, can cause a total, yet transient, remission of SS thanks to the several secretions which fire down the inflammatory status and regulate JAK/STAT pathway. Given the proven IL-6 role in regulating SS, the glandular manifestations in SS can be considered a localized autoinflammation.

Phlogistic measures are mandatory in order not to aggravate the severity of SS. Dietary and beverage must be caffeine-free and non-cariogenic. Exposure to ionized radiation must be avoided unless very necessary. Radiological Follow up should be confined to sonography and MRI. Scrupulous oral hygiene is mandatory [2].

Treating Sjögren’s syndrome is also problematic and banks heavily on alleviating the severity of symptomatic signs and symptoms as well as on educating patients about their medical condition. Applying topical fluoride and remineralizing solutions, using artificial saliva and oral lubricants, sipping water, washing eyes, wetting skin, and artificial tears are useful. Therapeutic effect of corticosteroid in SS patients is controversial [2,15]. Our patient was initially treated with low-doses of corticoids which were suspended during pregnancy and on.

4. Conclusions

Sjögren syndrome may behave more aggressively if encountered in young patients. Although ultrasound and MRI are excellent non-ionizing diagnostic tools which can be useful in close follow-up, the minor salivary gland biopsy can be more informative. Pregnancy can cause a total, yet transient, remission of SS thanks to several secretions which fire down the inflammatory status and regulate JAK/STAT pathway. However, the severity of SS after delivery cannot be anticipated.

Conflict of interest

None.

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Ethics committee approval

Not required.

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References


