Lymphoepithelial Sialadenitis Involving HIV-Infected and Sjogren Syndrome Patients: A Cytologic Study

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Abstract Lymphoepithelial salivary gland cysts are rarely seen in autoimmune diseases particularly Sjogren syndrome as well as in HIV for which medical management is advocated. To study the morphology of these cysts, correlate with the disease process and assess the final outcome. Case series. Fine needle aspiration clinic. HIV-infected and autoimmune disease patients with lymphoepithelial cysts. Antiretroviral therapy for HIV-patients and anti-inflammatory drugs for Sjogren syndrome. Three HIV-infected patients (two children and one adult) and three middle aged female patients presented with parotid and submandibular cysts, two of which were bilateral along with submandibular (one each in the HIV and the autoimmune group). In the adult HIV-patient, the cyst was found at the inception of the disease while the other pediatric HIV-patients just crossed a decade. Of the other three cases of Sjogren syndrome, two were primary and one, secondary to rheumatoid arthritis. All the cysts

regressed completely with treatment of the respective diseases which was confirmed by ultrasonograms. Lymphoepithelial cysts are produced by release of serous secretion by the acinar and ductal cells within the epithelial islands in the process of their destruction. Possibly, antibody mediated increased secretion in the initial stages also plays a role. Lymphoepithelial cysts of HIV patients may occur in the course of treatment, not necessarily in the beginning, though it resolves spontaneously. Lymphoepithelial cysts of primary or secondary Sjogren syndrome may be repressed sufficiently by anti-inflammatory/immunosuppressant treatment.

Keywords Lymphoepithelial cysts · HIV · Sjogren syndrome · Lymphoepithelial sialadenitis

Introduction

Lymphoepithelial sialadenitis (LESA) occurs in the parotid (90%) or submandibular gland and consists of a benign lymphocytic infiltrate, leading to parenchymal atrophy and foci of ductal hyperplasia with lymphocytic epitheliotropism. Elderly women in 40–70 s in the ratio of 3:1 over men are more commonly affected. It is ostensibly an autoimmune lesion and may be found as a component of autoimmune diseases like Sjogren's syndrome (SS) [1]. They are also reported as an early manifestation of human immunodeficiency virus (HIV) infected patients, unexpectedly and most commonly affecting children [2]. This study was performed because of their rarity, difficulty in diagnosis, association with HIV and SS, and predisposition to Non-Hodgkin's Lymphoma. We have also attempted to analyze the clinical attributes that color the diagnostic complexities of such lesions.

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Table 1 Clinical features of all cases

Sl. no.	Age	Gender	HIV	Location
1	42	Female	Negative	Left parotid cyst
2	47	Female	Negative	Bilateral parotid and submandibular cysts
3	12	Female	Positive	Bilateral parotid and submandibular cysts
4	67	Female	Negative	Left parotid cyst
5	37	Female	Positive	Right parotid cyst
6	10	Female	Positive	Right parotid cyst

Materials and Methods

The FNA records of 2 years (2011–2013) in the department of pathology yielded merely six cases included in our study. All the lesions were in the parotid with two affecting additionally the submandibular glands. After consent was taken from the patient, FNA was performed with a 22 gauge needle fitted with a 10 ml syringe mounted on a Cameco syringe holder. Four to five passes were made keeping a constant suction and the aspirate thus obtained, was smeared on glass slides frosted at one end. Most of the swellings were large enough to be pierced at three discrete points and thus the procedure was repeated thrice. Any bias or the possibility of any particular cells being obtained by chance were thus eliminated. Both air dried and 100% methanol fixed smears were prepared which were subsequently stained with May-Grunwald-Giemsa (MGG) and Papanicolaou (Pap) stain respectively and then DPX mounted.

Clinical history was obtained for all the cases, particularly noting the patients' investigations leading to the diagnoses. The titers of serum autoantibody tests, if performed were also documented. Labial minor salivary gland biopsy to obtain incriminating foci as established by Greenspan and Daniels (Chisholm and Mason modified version) were performed as requested by the rheumatologist in the non-HIV patients [3].

HIV status was searched for or asked directly from the caregiver of the patients themselves. Maternal history, history of birth, immediate and subsequent medicines administered along with maternal treatment history were sought from the orphanage where these patients were housed. Milestone development and vaccination history were pursued. The information was gleaned by verbal questioning of the head of the orphanage since direct visualization of the patient files was denied.

Results and Observations

Only six patients could be unearthed in a 2-year FNA case database search at our cytology laboratory. Apparently, it was the female's prerogative to suffer from this ailment.

The elderly women, two in their 5th and one in 7th decade suffered from autoimmune parotitis. The others, including two in the 2nd decade were born to HIV positive mothers and were thus HIV positive themselves. The lone 37-year-old woman with a unilateral parotid swelling was also HIV positive. Bilateral parotid cysts were also accompanied simultaneously by corresponding submandibular swellings. These observations are summarized in Table 1.

Both the groups, the HIV and the non-HIV painted similar pictures by virtue of their aspirates with minor differences as depicted in Figs. 1 and 2. The lymphoid infiltrate consisted of a polymorphous population, densely populated on the smears of the HIV patients and sparse on those of the non-HIV. The ductal cell clusters with squamous metaplasia, albeit immature were very rarely found but was densely infiltrated with centrocyte like lymphocytes. The lymphoepithelial cysts from the non-HIV patients additionally contained a scarce smattering of neutrophils and histiocytes. In all the aspirates, occasional salivary gland acini were found, indicating undeniably the provenance of these cysts from salivary glands.

The 37-year-old HIV positive woman was initially equivocally reported at the integrated counseling and testing center (ICTC) testing positive with just two kits. Subsequently, qualitative DNA PCR was performed for verification. CD4 counts were 346/ml estimated by flow cytometry at the commencement of treatment and clinically, she was deemed to be in WHO stage 1 disease with mild weight loss and bilateral posterior cervical lymphadenopathy. She is currently on Zidovudine (AZT), Lamivudine(3TC) and Nevirapine(NVP) [4]. She was not suffering from Tuberculosis (pulmonary or lymph node), at the time of performing FNA, at 1-year follow-up and 2 years later. About 0.8 ml turbid semi translucent fluid was aspirated. The cysts had regressed at 1 year follow-up and remained in remission 2 years later as confirmed by ultrasonograms.

The two children were born to HIV positive mothers who tested positive as part of routine antenatal screening. Their initial CD4 counts (exact counts unknown) were low and both of them died within a year of their childbirth. Knowledge of Antiretroviral prophylaxis to the mother

Fig. 1 Photomicrographs of LESA in HIV positive patients (high cellularity). **a, d** Shows polymorphous population of lymphocytes along with tingible body macrophages. **b** Shows ductal epithelial cells infiltrated by lymphocytes. **c** Shows plump histiocytes admixed with lymphoid cells

remained obscure but the children were not administered syrup Nevirapine post birth. Cotrimoxazole preventive therapy was started at 6 weeks. At 6 weeks age, both the infants were strongly suspected to be infected with HIV-1 by dried blood spot (DBS) DNA PCR at ICTC followed by confirmation at antiretroviral therapy (ART) center by wet blood sample (WBS) DNA PCR. Immunization with vitamin A supplementation were administered according to the national immunization schedule. They were started on AZT, 3TC and NVP. Baseline total blood counts and serum chemistry including basic liver function and renal function tests performed before commencement of treatment were found to be within normal limits. CD4 counts were 690 and 684/ml of blood of the older and the younger child respectively. Developmentally, there had been slight delay but no regression of milestones. At present, both the girls suffered from stunted growth as well as sexual maturity. They appeared not older than 8–9 years of age. Their CD4 counts had fallen down to adult levels of 352 and 348/ml of blood respectively. None suffered from Tuberculosis,

pulmonary or lymph node at 3 year follow-up as well as at the time of performing the FNA. The quantity of aspirate was about 0.5 ml from each of these patients, translucent and mildly turbid. At 1 year follow up, the cysts had completely regressed and did not recur 2 years later which was confirmed by ultrasonograms.

The other three middle aged women for the past few months all struggled with gulping mouthfuls of food especially if dry and suffered transient failure in articulating words if asked to speak continuously (feeling of tongue and palate sticking together). They also complained of itchy, red eyes, foreign body sensation inside the eye lid, sticky mucoid secretions in eyes. In addition, the youngest of these women, a housewife aged 42, whose symptoms were milder, was quite bothered about her fingers being stiff and inept at preparing her two children for school in the morning. Examination of the mouth revealed in varying degrees of severity, the youngest showing the mildest, reddened mucosa and atrophic filiform papillae of tongue. The oldest 67-year-old female had raised Anti-SSA (18 IU/

Fig. 2 Photomicrographs of LESA in HIV negative patients. **a** Shows lymphoid cells with few neutrophils. **b** Shows streaked lymphocytes with few admixed histiocytes

ml) and Anti-SSB (17 IU/ml) antibody titers. The 47-year-old female had increased Anti-SSA (19 IU/ml) antibody titers. The youngest 42-year-old female had increased Antinuclear antibody (ANA) (84 units/ml), raised rheumatoid factor (RF) (12 IU/ml) levels and cyclic citrullinated peptide antibodies (CCP) (46U/ml) titers. They also had >1 focus (50 lymphocytes constituting lymphoepithelial sialadenitis/4 mm²) in their labial biopsy. Thus, the younger female was diagnosed as a patient of rheumatoid arthritis with secondary Sjogren syndrome (RA–SSS) and the older two, primary SS. The mildly turbid, thinly mucoid semitransparent aspirate was approximately 1 ml from the cyst of 42-year-old and 1.5 ml from each of 47 to 62-year-old females respectively. They had almost receded after the initial aspiration and they did not recur at 1-year follow-up and 2 years later. Overall, the parotid gland enlargement in all the cases had shrunk though still visibly larger than normal. There was no sudden increase in size. Uric acid, lactate dehydrogenase (LDH) and β 2-microglobulin levels were normal in all

cases at 2-year follow up along with absence of any abnormal cells in peripheral smear.

Discussion

Lymphoepithelial lesions are an inevitable phenomena of autoimmune diseases like Sjogren syndrome. In the salivary glands of these cases of SS, the initial lymphocytic infiltrate thus becomes acquired mucosa-associated lymphoid tissue (MALT). Often a bilateral disease due to autoimmunity, SS prefers females over males in a ratio of 3:1 [1]. The lymphoid population is arranged in follicles with germinal centers containing a polytypic population of B and T lymphocytes. Epithelial islands infiltrated and surrounded by monocytoïd B cells are also noted, a clonal proliferation of which engenders MALT lymphomas in the prolonged course of the disease [5, 6]. These epithelial islands may contain basement membrane like substance within them or may form cyst like structures [7–9]. There is usually ample evidence of ductal basal cell hyperplasia without significant myoepithelial component [6, 9]. Whether the lymphoid population is predominated by T or B cells is still debatable. While some authors opine favoring chiefly T cell infiltration in the salivary gland with B cells dominating the lymphocyte population exclusively in the lymphoepithelial lesions [9], other authors support a B cell dominated lymphoid population, both within the lymphoepithelial lesions and the larger lymphoid proliferation seen throughout the salivary gland [8]. The concept of B cell predominance is also supported by the leading textbook authors at present [7]. Lymphoid proliferation and lymphoepithelial lesions are also seen in other autoimmune diseases like Hashimoto thyroiditis [8]. It ultimately concludes in hypothyroidism owing to excessive and decompensated loss of thyroid follicular cells terminating in a fibrotic thyroid gland with few nodular polymorphous lymphoid aggregates, plasma cells and devoid of any native follicles. However, at the outset of this disease and infrequently, though not rarely, is observed a clinical event of transient thyrotoxicosis, which in the commoner parlance is also termed ‘Hashitoxicosis’. The pent up thyroid hormones in the follicular cells are released simultaneously into the bloodstream from a very large number of these follicular cells due to their antibody mediated destruction. Alternatively, the spectrum of autoimmune thyroiditis that includes Hashimoto thyroiditis at one end and Graves disease at the other, may incorporate Hashitoxicosis somewhere in between [10]. It may not be too erroneous to surmise the antibodies responsible for eventual destruction of the thyroid follicles may, fleetingly, in the initial stages of the disease stimulate the follicular cells. Between Hashimoto thyroiditis and SS, the histological predicament

of the respective organ involved share striking similarity; in the late stage fibrosis, loss of follicles in the thyroid corresponding to loss of acini and ducts in the parotid and the eventual diffuse lymphoid infiltrate. Akin to thyrotoxicosis in Hashimoto thyroiditis, therefore, transient overproduction of seromucinous secretion in the salivary glands in SS may not be unexpected but may be rarely seen. These secretions build up inside the epithelial islands to form cysts.

With an entirely different etiology and thereby pathogenesis, the picture of lymphoid infiltrate destroying the salivary acini, lymphoepithelial lesions of the ducts, initial ductal epithelial hyperplasia with focal squamous metaplasia seen in the LESA of HIV infection is similar to that seen in SS. Thus, cyst formation in HIV infection analogous to that seen in SS may share similar pathogenesis. It appears the lymphocytic infiltrate in HIV infection is CD8+ T cells, polyclonal and instigated by unknown antigens related to the putative virus [11].

It is, however proven in one study the lymphocytes responsible for LESA in HIV infection are B cells like that of SS, centrocyte like in morphology in contrast to the monocytoid appearance in similar lesions of SS though Bcl2 negative contrary to the Bcl2 positive cells in the LESA of SS. CD8+ T cells are predominant in the lymphoid infiltrate of the salivary glands in cases of SS [12], but are more numerous in the LESA of HIV infection [8].

The cysts in the HIV positive patient in both the parotid and submandibular glands is probably due to diffuse infiltrative lymphocytosis syndrome (DILS) that also affects the minor labial salivary glands. A similar diffuse lymphocytic infiltrate involving also the minor labial salivary glands is appreciated in SS and thus, lymphoepithelial cysts in both parotid and submandibular glands may be an anticipated incident. In a landmark study, the previously supposed notion that these lymphoepithelial cysts should be surgically excised had been overturned in favor of wait-and-watch strategy in the course of medical treatment of HIV. The cysts regressed totally in patients who tolerated the medical treatment but partially diminished in patients in whom treatment had to be curtailed due to intolerance [2]. Similarly, lymphoepithelial cysts in SS can be restrained with anti-inflammatory drugs used to treat autoimmune diseases [13]. The normal uric acid, LDH and β 2-microglobulin levels along with a normal peripheral smear at 2-year follow-up suggest absence of development of lymphoma. At present, there exists complete lack of evidence that lymphoepithelial lesions in HIV infections, though bearing a striking morphologic similarity with their autoimmune counterpart, are harbingers of MALT-lymphoma.

Diagnosis of the Sjogren syndrome in all our cases was strictly made based on the American-European-consensus-group (AECG) criteria. The AECG criteria included ocular

dryness symptoms, oral dryness symptoms, ocular signs (Schirmer's test ≤ 5 mm/5 min), focus score ≥ 1 focus/4 mm² on minor salivary gland biopsy, salivary gland involvement (unstimulated whole salivary flow ≤ 0.1 ml/min), positive anti-SSA or anti-SSB antibodies. A person deemed to be suffering from SS should possess any four of the six criteria with at least the criteria involving focus score or positive antibodies or any three of the last four criteria [14]. The patient with RA–sSS was diagnosed with SS concurring with the AECG criteria, the only difference being that her propensity to develop MALT-lymphomas comes at par with those of primary SS than those suffering from RA alone. The disease course of RA remains unaffected by the development of SS [15].

The diagnosis and ART treatment of HIV patients were conducted according to the NACO guidelines 2013 [4, 16]. Fortunately, none of these patients had any untoward effects of the drugs impeding their management. Notably, the cysts of the two children were noticed much later in the course of the treatment. There was no possibility of their occurring at the outset of the disease, though the cyst in the adult female arose at the beginning of treatment. In a similar study, all the cysts except one surfaced as the first sign of infection [2].

We have no conflicts of interest. There was no source of funding for the study. The study was conducted after obtaining the approval of the institutional scientific and ethics committee. FNAC procedure was performed after obtaining an informed consent from the patient.

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