HIV Disease Presenting as Parotid Lymphoepithelial Cysts: A Presumptive Diagnosis of Diffuse Infiltrative Lymphocytic Syndrome (DILS)

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Abstract

Diffuse infiltrative lymphocytic syndrome (DILS), is a rare manifestation of human immunodeficiency virus (HIV) disease which is characterized by a diffuse visceral CD8 lymphocytic infiltration, a persistent CD8 lymphocytosis, bilateral parotid swelling and cervical lymphadenopathy. We describe a case of a HIV positive female, who had bilateral parotid swelling and CD8 lymphocytosis, to illustrate this rare clinical entity.

INTRODUCTION

Diffuse infiltrative lymphocytic syndrome (DILS) is a subset of HIV disease manifestation characterized by a diffuse visceral CD8 lymphocytic infiltration, a persistent CD8 lymphocytosis, bilateral parotid swelling and cervical lymphadenopathy. Embryologically, five to ten lymph nodes are trapped within the parotid gland. These nodes contain salivary gland acini and ducts. With HIV-1 virus replication, salivary gland lymphoid hyperplasia develops and parotid swellings ensue.1 About 40 percent of HIV-positive patients have head and neck related symptoms/signs. Parotid enlargement occurs in roughly 5 percent of this group.2 DILS is a unique illness of presumed autoimmune origin found in about 1-2% of patients with HIV infection.3

CASE REPORT

A 35 years old female patient came to HIV clinic in January, 02 with past history of pulmonary tuberculosis (treated adequately for 1 year) and history of intermittent fever, diarrhea and generalized weakness for previous three years. The patient was found HIV positive and was given supportive treatment. She was on regular follow up since then. Investigations reports at that time were: Hemoglobin - 9.5 gm%, TLC - 6700 cells/cu mm, DLC - P57 L41 E01 M01, general blood picture - normocytic normochromic, s. bilirubin - 0.5 mg%, SGPT (AST) - 24 IU/L, SGOT (ALT) - 35 IU/L, serum alkaline phosphatase - 209 IU/L, CD4/CD8 count was 264/1118 and the ratio was 0.24.

In December, 2002, patient presented with unilateral facial swelling. In two months time, (by Feb, 2003) she developed persistent, painless, non-fluctuating, moderate bilateral parotid gland swellings. (Figs. 1, 2) Cervical lymphadenopathy (unilateral, left) was also evident. On intraoral examination, the oral mucosa was normal in appearance. Upon milking of both parotid glands there was a clear salivary flow through Stenson’s orifice. General and systemic examination was found to be normal. There was no evidence of involvement of other organs like lung, liver, kidney, gastrointestinal tract and peripheral nerves. Investigations revealed: Hemoglobin - 12.0 gm%, TLC - 5010 cells/cu mm, DLC - P74 L26 E0 M0, general blood picture - normocytic normochromic, random blood sugar - 96 mg%, b. urea - 30 mg%, s. creatinine - 0.5 mg%, s. bilirubin - 0.5 mg%, ALT - 23 IU/L, s. protein - 7.3 gm%, s. albumin - 3.5 gm%. Absolute value of CD4/CD8 count was 159/1550 and the ratio was 0.17. X-ray chest and CT scan lung were normal. Ultrasound abdomen was found to be normal. Test for antinuclear antibody (ANA) was negative. Autoantibodies for Ro (SS-A) were found negative. The FNAC of parotid gland shows mainly lymphocytes and few polymorphs with occasional epithelial cells. Cytology was suggestive of nonspecific inflammation.

The patient’s history (bilateral parotid gland swelling for more than six months duration), the clinical examination and the investigations (FNAC report showing lymphocytic infiltration and CD8 lymphocytosis) pointed to a presumptive diagnosis of parotid lymphoepithelial cysts associated with DILS.

By August, 2003, swelling decreased in size (not completely resolved) on conservative treatment only. Antiretroviral therapy was suggested to the patient but she was unable to afford it.
Diffuse infiltrative lymphocytic syndrome (DILS) is characterized by the presence of dryness of the eyes and mouth and often massive enlargement of the parotid glands. The histopathologic findings in the minor and major salivary glands are similar to those in Sjogren’s syndrome, but the conditions differ in their underlying immunopathology and genetics.

The histopathogenesis of parotid lymphoepithelial cysts is, however, still uncertain. The parotid swellings originate either as hyperplastic activity of intraglandular lymphocytes, as described above, and/or as an extraglandular infiltration into the salivary gland tissue. It is argued that lymphoid proliferation could cause ductal obstruction and result in duct dilatation mimicking the appearance of a true cyst. On the other hand, ductal obstruction may not be a factor in all cases, since fluctuating levels of swelling are not observed during increased salivary flow.

The transient expansion of the CD8+ T cell pool normally occurs in the early phase of HIV infection. Persistent expansion of this pool is observed in two related settings: diffuse infiltrative lymphocytic syndrome (DILS) and HIV associated CD8+ lymphocytosis syndrome. The infiltrating lymphocytes are CD8 cells, which are often numerically expanded in both tissue and peripheral blood. The entry of lymphocytes into tissues involves interactions between specific cell adhesion molecules and their ligands. Studies have suggested that both the circulating and the infiltrative CD8+ lymphocytes in HIV infected patient with DILS represent an antigenically driven and immunogenetically determined host response to HIV infection. The cellular and molecular responses and the presence of HIV encoded proteins in salivary gland macrophages localized in close proximity to lymphoid aggregates suggest that the systemic response to HIV infection, in certain immunogenetically predisposed persons, give rise to specific oligoclonal CD8+ T-cell response that infiltrates certain tissues, such as salivary glands.

Based on the observations of the experiments in rhesus and cynomolgus macaques infected with primary simian immunodeficiency virus, it was suggested that the magnitude of the lymphocytosis might depend primarily on the level of viral replication in mucosal sites. These cells infiltrate multiple organs, but the salivary glands and the lung constitute the major sites involved in this process. This infiltrative process resembles in many aspects a Sjogren-like syndrome, owing to the visceral lymphocytic infiltration. DILS differs from Sjogren’s syndrome in the degree of salivary gland enlargement, high frequency of extraglandular manifestations, paucity of autoantibodies, and distinct immunogenetic associations. Salivary gland B-cell lymphoma is a complication common to both conditions. Unilateral parotid gland enlargement in a patient with HIV infection should prompt clinicians to suspect DILS. In addition, clinicians should be aware that the pulmonary process associated with DILS (lymphocytic interstitial pneumonitis) may mimic clinically and radiographically the pneumonic process caused by Pneumocystis carinii. Other extraglandular manifestations of DILS to consider include a severe form of peripheral neuropathy and bilateral seventh nerve palsies; lymphocytic
infiltration of the liver, evident as hepatitis; myositis; interstitial gastrointestinal disease and lymphocytic interstitial nephritis. Curiously, the natural history of patients with DILS includes the relatively slow progression of their underlying HIV infection but with a high frequency of high-grade lymphoma.

Diagnosis is often suspected clinically with parotid gland enlargement and/or marked CD8 expansion in peripheral blood combined with a minor salivary gland biopsy demonstrating a CD8-predominant sialadenitis. The diagnostic criteria developed by Itescu and Winchester require that the subject be HIV-seropositive, have bilateral salivary gland enlargement or xerostomia for more than six months, and have histologic confirmation of salivary or lacrimal gland lymphocytic infiltration in the absence of granulomatous or neoplastic involvement.

Clinically, parotid gland cysts are usually bilateral, painless and soft to palpation. Single or multiple, these cysts often become very large with the progression of the disease. Superficial lobes of the gland are most often involved. Histologically, the cysts are lined by squamous or cuboidal epithelium. The lumen contains pale homogenous material with foamy macrophages and lymphocytes. The cyst wall has germinal centers and dense infiltrate of lymphoidal cells with a fibrous capsule. The histology suggests the cyst’s origin within an intra- glandular lymph node.

Management of DILS is determined by the severity of glandular and extraglandular features. Several treatment approaches have been proposed for this clinical entity.

a. Up to twelve years ago, surgical removal of the superficial lobe of the gland was the treatment of choice. The danger of this treatment lies in the possible surgical damage of the facial nerve and possible morbidity in an immunocompromised patient.

b. For treatment of the parotid gland enlargement, which is frequently cystic and occasionally highly disfiguring, antiretroviral therapy has been associated with a major degree of clinical regression. Medications such as combination of AZT with the newer protease inhibitors seem to be the most successful measures in treating the parotid swellings of patients with DILS.

c. Enucleation, low-dosage radiation, and aspiration all have been reported with some success. Radiation therapy should generally be avoided because of concerns regarding malignant transformation.

d. Corticosteroids may temporarily shrink enlarged glandular tissues, but swelling generally returns with tapering of the medications.

e. For more serious and occasionally life-threatening forms of extraglandular involvement, high-dose corticosteroids or even cytotoxic drugs (i.e. cyclophosphamide, chlorambucil and others) may at times be necessary.

In patients with DILS, a great concern is often a cosmetic one. Since the facial swelling in this patient are not severe enough to affect the quality of life, the best treatment for her remains conservative. However, the possibility of transformation into a B-cell lymphoma should be kept in mind by the clinician. The patient should be examined periodically at six-month intervals. In general, an HIV patient presenting with DILS has a better prognosis than a patient with HIV alone.

The variation in CD8 count in the course of HIV disease is less understood. The variation in CD8 lymphocytes is implicated in the pathogenesis of a number of clinical manifestations in HIV diseases including diffuse infiltrative lymphocytic syndrome (DILS) and HIV associated CD8+ lymphocytosis syndrome. This highlights scope for further research into this area, particularly focusing on the response to different regimens of antiretroviral therapy on CD8 cell counts and its relationship with morbidity and mortality in the patient. Further studies are also needed to correlate the plasma viral load with CD8 lymphocyte count in patients with HIV disease.

**CONCLUSION**

DILS, a subset of HIV disease manifestation, may present as parotid gland swellings. In the case presented, a presumptive diagnosis of DILS is made based on classic clinical and histological (FNAC) features of DILS. Treatment often is not necessary due to the benign nature of this disease, unless cosmetics become a concern. Clinicians should watch for the possible transformation into B-cell lymphoma. A six monthly check-up is recommended, supplemented by a fine needle aspiration biopsy when indicated by the clinical behavior of the lesion.

**REFERENCES**