When is the last time you looked for diffuse infiltrative lymphocytosis syndrome in HIV patients?

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Abstract

Background: Diffuse Infiltrative Lymphocytosis Syndrome (DILS) is characterised by a persistent $CD8^+$ lymphocytosis and lymphocytic infiltration of various organs. The exact prevalence isn't known but some studies have reported between 0.85 – 3%, and appears to be more common in African population. Patients with DILS tend to have higher CD4 cell counts and survive longer than those patients without DILS. Most patients present with bilateral parotid gland enlargement and features of the Sicca syndrome. Common sites of extra glandular involvement are the lungs being the most common site, followed by peripheral neuropathy and liver. With the high incidence of HIV in our population it is likely that DILS is under diagnosed probably due to our ignorance of this disease. Awareness of its various presentations may bring to light undiscovered patients with DILS.

Objective: To review pathogenesis, diagnostic approach and current trends in the management of diffuse interstitial lymphocytic syndrome.

Data source: Literature review of relevant published literature from both Africa and the rest of the world.

Data synthesis: Pathologically, under light microscopy, DILS resembles the focal sialadenitis seen with Sjogren's syndrome, although it tends to be less destructive of the glandular architecture than in Sjogren's syndrome. Most of the inflammatory infiltrate is composed of $CD8^+$ lymphocytes unlike Sjogren's which are $CD4^+$. Lymphoepithelial cysts are frequently observed in the parotid glands of patients with DILS. 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. 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 may mimic clinically and radiographically the pneumonic process caused by *pneumocystis carinii*. Other manifestations of DILS to consider include a severe form of peripheral neuropathy; lymphocytic infiltration of the liver, evident as hepatitis; myositis; and lymphocytic interstitial nephritis. Management of DILS is determined by the severity of glandular and extra glandular features. Data on therapeutic trials are lacking although there are isolated reports of good response to antiretroviral and steroid therapy.

Conclusion: DILS, a subset of HIV disease manifestation, may present as parotid gland swellings. In general, an HIV patient presenting with DILS has a better prognosis than a patient with HIV alone. With the high incidence of HIV in our population it is likely that DILS is under diagnosed probably due to our ignorance of this disease. Awareness of its various presentations may bring to light undiscovered patients with DILS. Clinicians should watch for the possible transformation into B-cell lymphoma. There is still paucity of data about this disease from pathophysiology to treatment to studies correlating the plasma viral load with $CD8^+$ lymphocyte count in patients with HIV disease.

Introduction

The Diffuse Infiltrative Lymphocytosis Syndrome (DILS) in HIV-infected persons is characterized by a presence of circulating $CD8^+$ lymphocytosis. Their response to the HIV infection is to developing an oligoclonal expansion of $CD8^+$ lymphocytes. These cells infiltrate multiple organs with the salivary glands and the lungs being the major sites involved

in this process. This infiltrative process resembles in the salivary glands many aspects a Sjogren's-like syndrome, owing to the visceral lymphocytic infiltration. Clinicians should suspect DILS in HIV patients who present with unilateral parotid gland enlargement. In addition, clinicians should be aware that the pulmonary manifestation associated with DILS may mimic clinically and radiographically *pneumocystis carinii* infection. Other ways in which it manifests of DILS include peripheral neuropathy; lymphocytic infiltration of the liver as a hepatitis; myositis; and lymphocytic interstitial nephritis. It was first reported in 1989 from New York in a cohort of 12 patients who were HIV positive with parotid gland enlargement, pulmonary insufficiency and lymphadenopathy[1]. There is limited literature on the exact prevalence of the disease with estimates ranging from 0.8% to 7.8% in HIV-infected persons[2,3]. In West African review it was reported to be as high as 48% in HIV patients with features of DILS on lymph node biopsy[4]. The prevalence in the United States of America (USA) was found to be 3% (definitive) and 3.4% (possibly) in an HIV positive outpatient population[3]. It is reported to be more common in African Americans (60%) than American whites (26%)[2, 4]. A French retrospective study found a prevalence of 2.5%[5].

Pathophysiology

The histopathogenesis is however, still uncertain. Analysis of the $CD8^+$ lymphocytes infiltrating the salivary glands of patients who have DILS has provided evidence that DILS represents an MHC-restricted, antigen-driven oligoclonal selection of $CD8^+CD29^+$ lymphocytes that express selective homing receptors, such as CD29, the integrin CD11a/CD18 (lymphocyte function-associated antigen-1 [LFA-1]), and CD57. These receptors allow $CD8^+$ to become sequestered and infiltrate the salivary glands, lung, and other organs. There is also a strong expression of CD54 (intracellular adhesion molecule-1 [ICAM-1]) molecules on post-capillary venule endothelium within lymphoid aggregate. Therefore, the entry of lymphocytes into tissues involves interactions between specific cell adhesion molecules and their ligands, such as between LFA-1 and ICAM-1[6]. Research has suggested that both the circulating and the infiltrative $CD8^+$ lymphocytes in HIV-infected persons with DILS represent an antigen driven and immunogenetically determined host response to HIV infection. The cellular and molecular responses described above together with 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, gives rise to a specific oligoclonal $CD8^+$ T-cell response that infiltrates certain tissues, such as the salivary glands[7]. 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.

Clinical presentation

It commonly presents with features similar to Sicca Syndrome. Patients typically presents with bilateral parotid gland enlargement with xerostomia in 82% and xerophthalmia in 35%. It's rarely unilateral parotid swelling[1,2,8]. Generalized lymphadenopathy is seen in 80-100% of the patients[9,10]. How to differentiate it from Sjogren's syndrome?? Degree of gland enlargement (firm and tender) and extra glandular involvement together with relative of antibodies and differing HLA associations[11]. The lung is the most common extra glandular site of disease, affecting 31% of patients in the largest patient group investigated for DILS to date[3]. 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*. The most common presenting symptoms are cough (71%) and worsening dyspnea (61%) which is slowly progressive over months and in rare cases several years[12-14]. Other symptoms and/or signs include weight loss (16%), fevers (10%), pleuritic chest pain (6%), fatigue and arthralgia. Examination findings are finger clubbing, cyanosis though rare and crackles on respiratory system. One should also look out for extra respiratory findings that may point towards LIP which are hepatosplenomegaly, lymphadenopathy, parotid gland enlargement, and arthritis. Peripheral nervous system involvement has been reported in association with DILS. Both a symmetric sensorimotor neuropathy and an asymmetric neuropathy have been described[15-17]. These polyneuropathies might be confused with the very common distal sensory polyneuropathy of late HIV infection or with a toxic polyneuropathy related to antiretroviral nucleoside analogue drugs. Both of the neuropathies associated with DILS may present with predominating distal sensory symptoms and (less commonly) with either mononeuritis multiplex or a demyelinating polyneuropathy. Peripheral neuropathy has been reported with DILS occurring in approximately 20–25% of patients[4,5]. Other extraglandular manifestations of DILS to consider include seventh nerve palsies due to compression by the parotid gland; lymphocytic infiltration of the liver, evident as hepatitis; myositis; interstitial gastrointestinal disease and lymphocytic interstitial

nephritis[18]. 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

Diagnosis should be suspected in a HIV-patient with parotid gland enlargement and/or marked $CD8^+$ expansion in peripheral blood combined with a minor salivary gland biopsy demonstrating a $CD8^+$ predominant sialadenitis. Itescu and Winchester[19] developed a diagnostic criteria that requires a subject to 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. The diagnosis of DILS can be made from a labial salivary gland biopsy by demonstrating a $CD8^+$-predominant focal lymphocytic infiltrate unlike the $CD4^+$-predominant infiltrate in Sjögren syndrome[4,20]. MRI and CT scans can be of use in the diagnosis. They may reveal benign lymphoepithelial cysts, which can be a feature of DILS. Scintigraphy with gallium citrate Ga 67 has been shown to be extremely useful as a substitute for salivary gland biopsy in two different studies in which a classic, intense uptake of tracer occurred, provided that the patient has persistent bilateral parotid gland enlargement[2,3]. The intense gallium activity in DILS patients reveals the extensive lymphocytic infiltration of the salivary glands

Therapy

There are no randomised controlled trials that have evaluated therapy for DILS. Surgical removal of the superficial lobe of the gland was abandoned because the danger of this treatment was the possible surgical damage of the facial nerve and possible morbidity in an immunocompromised patient[21]. 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. 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. Therapy for DILS focuses on the use of prednisone and antiretroviral drugs[24]. Corticosteroids in moderate to high doses tend to elicit a good response, but their use is recommended only for patients with significant symptoms[20.22]. The lymphocytic interstitial pneumonitis associated with DILS requires higher doses of corticosteroids (up to 60 mg/d), as suggested by Reveille[20]. Reports of low-dose radiotherapy suggest good short-term efficacy in reducing parotid gland enlargement in DILS patients but with frequent relapses occurring in patients with less favourable initial responses[22,23]. The prevalence of DILS seems to be decreasing since the advent of HAART[2,20]. This supposition is based on the results of T-cell receptor analyses that show oligoclonal expanded $CD8^+$ T cells to be significantly diminished during HAART[24], with the entire $CD8^+$ T-cell repertoire decreasing after 8 weeks[25]. These results suggest that with HAART, there may be an interruption of chronic antigenic stimulation and that persistently replicating viral populations are required to maintain elevated levels of HIV-1-specific $CD8^+$ lymphocytes[24,26]. The response of $CD8^+$ lymphocytes to antiretroviral therapy was seen even from the onset of use of antiretroviral therapy, when monotherapy with zidovudine was used for HIV-related Kaposi's sarcoma[27]. In addition, many reports have shown significant improvement in $CD8^+$ lymphocytosis and reversal of visceral infiltration with the institution of antiretroviral therapy[20,21,28]. Others have shown that HAART is also effective in resolving parotid epithelial cysts[29]. The initiation of HAART seems to be the best modality for treating DILS in patients with HIV infection. 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 reasons for the better prognosis have not been identified.

Conclusions

DILS, is a subset of HIV disease manifestation and is characterized by the presence of dryness of the eyes and mouth and often massive enlargement of the parotid glands. Other manifestations of DILS include lymphoid interstitial pneumonitis, peripheral neuropathy; lymphocytic infiltration of the liver, evident as hepatitis; myositis; and lymphocytic interstitial nephritis. 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. Few reports of DILS have been made from southern Africa. This may be due to a lack of knowledge concerning this disease or that in our population of patients with HIV. DILS may be an uncommon complication or presentation. 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.

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