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A Case of Progressive Transformation of Germinal Centers in an HIV-Infected Patient

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Abstract

Progressive Transformation of Germinal Centers (PTGC) is an uncommon condition, characterized by a reactive lymph node hyperplasia with enlarged follicles and expansion of mantle zone lymphocytes into adjacent germinal centers. The disorder presents with persistent asymptomatic lymphadenopathy, generally affecting cervical, inguinal and axillary nodes, and sometimes is associated with Hodgkin's lymphoma and other diseases. Prognosis is generally good, and treatment is conservative in most cases. We report a patient with HIV-infection who presented with persistent impressive lymphadenopathies due to PTGC.

Keywords: Progressive Transformation of Germinal Centers; HIV-Infection

Introduction

Progressive Transformation of Germinal Centers (PTGC) is an uncommon condition of uncertain origin. Histologically, it consists of a reactive lymph node hyperplasia with enlarged follicles and expansion of mantle zone lymphocytes into adjacent germinal centers [1]. The disease occurs mostly in young oriental males and is characterized by persistent or recurrent asymptomatic lymphadenopathies, generally affecting cervical, inguinal and axillary nodes, with other nodes or extranodal sites being involved infrequently [2,3].

In the HIV-infected population, lymphadenopathy is common, and may be caused by neoplasms, opportunistic infections, and many other conditions, but PTGC has been infrequently reported [4]. We describe a patient with longstanding HIV-infection who presented with persistent impressive lymphadenopathies due to PTGC.

Case Presentation

A 38-year-old white male presented with enlarged lymph nodes at both sides of his neck, of two months duration. His past medical record included remote intravenous drug abuse, alcohol abuse, smoking habit, genotype 4 hepatitis C, HIV infection diagnosed 18 years earlier, Pneumocystis jirovecii pneumonia, and cerebral toxoplasmosis. The patient was on treatment with tenofovir, emtricitabine and efavirenz for his HIV infection. He was in good health, but lipoatrophy was evident in his face and extremities, and nontender lymphadenopathies 2 to 4 cm in diameter were noted at both sides of his neck and both axillae, while the rest of physical exam was unrevealing. Routine blood analyses disclosed creatine kinase 218 U/l (normal value < 180 U/l), gamma-glutamyl transpeptidase 84 U/l (normal value < 40 U/l), and alanine aminotransferase 209 U/l (normal value < 40 U/l), with all other results normal. Hepatitis C viral load was 3.8 million IU/ml, HIV RNA was 14,589 copies/ml, and CD4 lymphocyte count was 382 cells per µl (normal value 600 to 1400 cells per µl). Hepatitis B and Epstein-Barr virus serologies were indicative of past infections, and human herpesvirus 8 serology was negative. Morphologic and phenotypic analysis of blood cells revealed no abnormalities. An electrocardiogram, chest radiographs and an abdominal ultrasound exam were normal. A Computed Tomography (CT) scan of the neck, chest and abdomen showed cervical, axillary and mediastinal lymphadenopathies, up to 4 cm in diameter. A transient elastography of the liver gave a result of 6.5 kPa (reflecting minimal or no fibrosis). A liver biopsy disclosed a mild portal inflammation and absence of fibrosis (METAVIR grade 1, stage 0). The histologic and immunohistochemical exam of a whole excised lymph node of the neck disclosed typical findings of PTGC: enlargement and fusion of follicles, which showed a preserved polarity, germinal center tangible body macrophages, and blurring and thickening of the mantle zone; flow cytometry identified a polyclonal population of B cells; immunohistochemical staining for bcl2 demonstrated infiltration of mantle zone lymphocytes into the germinal center; and staining of centrocytes with bcl6 in normal germinal centers was altered with islands of non-labeled cells.

Sixteen months later, while on treatment with tenofovir, emtricitabine and ritonavir boosted darunavir, the patient was in good health, lymphadenopathies in the neck and axillae had diminished in size to 1 cm the largest of them, HIV RNA was undetectable (limit of detection 20 copies/ml), and CD4 lymphocyte count was 794 cells per µl.

Discussion

PTGC is now considered an IgG4-related disease, along with multicentric Castleman disease-like, follicular hyperplasia, interfollicular expansion, and nodal inflammatory pseudotumor-like. All five conditions are characterized by an IgG4 plasma cell infiltrate of lymph nodes or other tissues [5,6].

Blood analyses in PTGC may show increased IgG4 level, as well as other nonspecific alterations. Fluor-18-deoxyglucose-positron emission tomography scan generally displays increased uptake in affected tissues [1], while other image studies show nonspecific changes. A biopsy is needed to establish the diagnosis.

There is a significant association between PTGC and lymphoma,

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especially with nodular lymphocytic predominant Hodgkin lymphoma, although evidence supporting a common pathogenesis is lacking [1]. Both conditions can present in a similar way, and must be differentiated on the basis of histologic, immunologic, and in situ hybridization analysis. An association of PTGC with autoimmune diseases, such as systemic lupus erythematosus, is also occasionally seen [1].

PTGC management is expectant in most cases, with close follow-up and additional investigations warranted should symptoms or new lymphadenopathy develops. Rituximab may have a role to prevent the development of relapsing Hodgkin's lymphoma in patients with PTGC.

Only a few cases of PTGC in the HIV-infected population have been described so far. A detailed histological description of those cases is available, but unfortunately clinical data regarding status of HIV infection is not reported [4]. We speculate that inadequate control of HIV infection along with a relatively preserved immune function could have a role in the pathogenesis of PTGC in our patient.

We considered other conditions in the differential diagnosis of our case, including infectious diseases such as tuberculosis [7], inflammatory or idiopathic conditions such as sarcoidosis [8], or Castleman's disease [9]. And most of all we considered the possibility of lymphoma [10]. Histologic findings and clinical evolution over time allowed us to rule out all those conditions, and establish the diagnosis of PTGC.

Our case is remarkable for the impressive size of lymphadenopathies, due to a benign condition, such as PTGC, in an HIV-infected patient.

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