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Review article

Lymphadenopathies in human immunodeficiency virus infection

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ABSTRACT

This article describes the various non-neoplastic lymphadenopathies that occur in patients infected with the human immunodeficiency virus (HIV), before or during the stage of acquired immunodeficiency syndrome (AIDS). The stages that develop during the HIV infection include: primary infection (acute infection, spread of the virus, development of host immune response, and acute retroviral syndrome), chronic infection or clinical latency, and finally, the AIDS stage. Non-neoplastic lymphadenopathies can occur at any of these phases of the infection and are due to multiple causes that can be divided into infectious causes (bacterial, fungal, parasitic, viral), and reactive causes (persistent generalized lymphadenopathy and a variety of situations that they also occur in immunocompetent people such as Castleman's disease and Kikuchi-Fujimoto's disease, among others). The general, histological and immunophenotypic characteristics of these pathologies are described.

Introduction

A significant increased number of infected HIV individuals has been reported since the discovery of the disease in the early 1980s. Currently, more than 70 million people infected with HIV have been documented and there are close to 35 million deaths from this cause. On average, at the end of 2016, there were 36.7 million people living with HIV. For that year, it has been estimated that the prevalence in adults (15–49 years) was 0.8%. Africa is the continent affected with the largest number of cases with 4.2% of adults infected (1 in 25 people), followed by the American continent (0.5%), Europe (0.4%), South East Asia (0.3%), countries of the West Pacific (0.1%) and countries of the Eastern Mediterranean (0.1%).[1–6] The condition of HIV infection is a known predisposing factor for various neoplastic and opportunistic infectious diseases, causing a progressive decline of CD4 helper T cells by different mechanisms previously described[7,8] The natural history of HIV infection consists of three well-established stages[7,8]:

Primary infection

a. Acute (early) infection, characterized by the infection of memory T cells, with an expression of CCR5, in lymphoid tissue of the mucous membranes, with the death of many HIV- infected cells. In this phase, the decrease of CD4 + T cells begins.
b. Dissemination of the virus and development of the host immune response.
c. Acute retroviral syndrome, as a clinical manifestation of viral dissemination and the immune response. It usually occurs between 40% and 90% of cases and occurs 3–6 weeks after infection and disappears spontaneously 2–4 weeks after initiation. It is self-limited, similar to the flu (a sore throat, myalgia, fever, fatigue and weight loss). In other cases there is also skin rash, cervical lymphadenopathy, diarrhea, and vomiting.

Chronic infection (clinical latency)

a. In this phase, the sites of HIV replication and cell destruction occur in lymph nodes and spleen. In this stage, there is a trend toward decreased expression of of CD4 + T cells.
b. Patients may be asymptomatic or have symptoms related to opportunistic infections (*Candida, Herpes zoster, Mycobacterium tuberculosis*).

Acquired Immunodeficiency Syndrome (AIDS)

in this stage there is a marked decrease in CD4 T lymphocytes, and symptomatic immunosuppression. It is characterized by the following events:

a. Clinical manifestation characterized by fever, low weight, diarrhea, and lymphadenopathy.
b. Opportunistic infections (parasites, fungi, bacteria, viruses)
c. Tumors (lymphomas, Kaposi sarcoma)

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Table 1
Main causes of non-neoplastic lymphadenopathy associated with HIV infection.

1. Infections
2. Reactive changes:
a. Persistent generalized lymphadenopathy
b. Castleman disease
c. Kikuchi-Fujimoto disease
d. Progressive transformation of germinal centers
e. IgG4-associated disease
f. Rosai Dorfman disease

As described, lymphadenopathies are among the most characteristic clinical manifestations of people with HIV infection, because the target of this virus is CD4 T lymphocyte.[9] Non-neoplastic lymphadenopathies can occur at any time during infection and the causes are diverse (Table 1).

In the present review, we describe the different types of lymphadenopathy in patients with HIV infection with special emphasis on the histological patterns and immunophenotypic profiles that characterize them.

Lymphenopathies associated with infections

The microorganisms vary according to the geographic region.[2,3,6,10–12] For example, in Africa the main cause of lymphadenopathy is tuberculosis (92%),[13] whereas in Colombia[6] this infection corresponds to 58%, and in USA[10] to 2.8%. Other infections described[11,14,15] are: infectious mononucleosis, infections by *Mycobacterium avium* complex or *M. tuberculosis*, cytomegalovirus infections, *Peumocystis jirovecii*, secondary syphilis, toxoplasmosis, histoplasmosis and other fungi, bacillary angiomatosis, hepatitis B, Lyme disease, and lymphogranuloma venereum, among others.

The pathological characteristics do not differ from those observed in cases without HIV infection. Next, we will review the most frequent ones:

Mycobacterias

In HIV-infected individuals, the risk of co-infection with *Mycobacteria tuberculosis* is around 30 times higher than for those who're uninfected and, according to a report from the WHO, 25% of these patients die from this cause.[16] The pathological characteristics of lymphadenopathies due to tuberculosis do not differ in those observed in patients without HIV infection. The affected lymph node presents a granulomatous inflammatory reaction with marked caseation. The granulomas are surrounded by epithelioid histiocytes usually with multinucleated giant cells of Langhans type, lymphocytes, and fibroblasts. Mycobacteria are identified in the ring of histiocytes and in the necrotic areas (Figs. 1 and 2), using AFB stain, which is non-specific to differentiate the different species of this bacterium (*M. tuberculosis, M. intracellular M. avium, M. atypical*). For this purpose, the molecular method of Polymerase Chain Reaction (PCR) must be used, which is also useful for determining microbial resistance to therapy.[12]In individuals with pronounced immunosuppression, well-formed granulomas might be absent, and a suppurative histiocytic and neutrophils process can be found.

Pneumocystis

In patients with HIV, *Pneumocystis jirovecii* (formerly known as *P. carinii*) usually produces pneumonia when the CD4 count are below 200/mm^3.[3,17] and is the most frequent cause of pneumonia in these patients.[18] Although in recent years its incidence has decreased with the use of chemoprophylaxis and antiretroviral therapy, it remains a serious clinical problem.[19,20] The lymphadenopathies associated with this microorganism are rare and occur in cases with pneumonia. In a recent report of 16 patients with HIV and *Pneumocystis jirovecii* pneumonia, approximately 43.8% and 50% of the cases had coexistent hilar and mediastinal lymphadenopathies, respectively.[17] Other affected region are the retroperitoneals lymph nodes.[21] Histologically, lymphadenopathies show granulomas with central eosinophilic necrosis. Microorganisms can be evidenced using silver stains, which allow seeing the classic "hull shape" in necrotic foci.[12] Nowadays; most labs perform direct immunofluorescence against the parasite in samples from bronchioalveolar lavages.

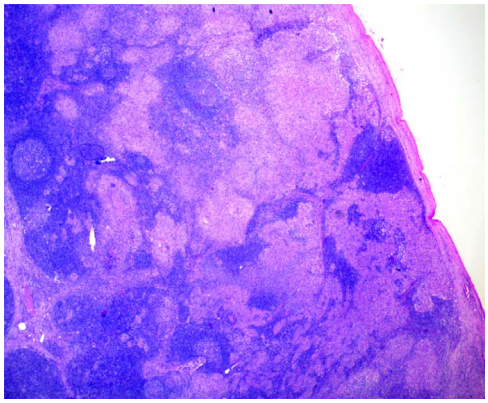

Fig. 1. *Tuberculous lymphadenitis in patient with HIV infection.* Characteristic granulomatous inflammation at low magnification.

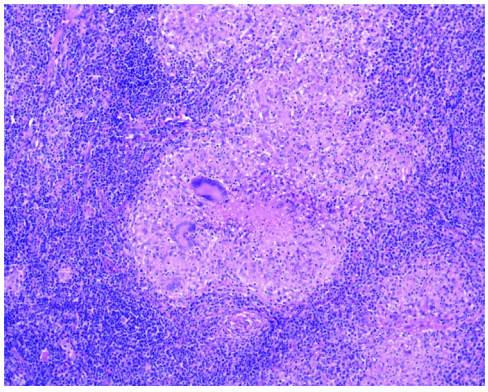

Fig. 2. *Tuberculous lymphadenitis in a patient with HIV infection.* Granulomatous inflammation and high magnification, shows central granular caseation surrounded by epithelioid and multinucleate giant cells.

Bacillary angiomatosis

Bacillary angiomatosis is caused by *Bartonella henselae* (formerly known as *B. rochalimaea*), the same bacteria that causes cat scratch disease, although it can also be caused by *Bartonella Quintana*.[22,23] Infection occurs almost exclusively in patients immunocompromised by HIV when the CD4 lymphocyte count is below 100/mm^3.[12] It is transmitted by a vector insect (mites, lice), or by trauma to an animal vector (cat).[12] The microorganism evades the immune system, stimulating the production of factors that induce hypoxia and angiogenesis in the host, causing granulomatous lymphadenitis.[24] Clinically, bacillary angiomatosis is characterized by reddish or violaceous cutaneous lesions, sometimes painful. The histopathology of the affected lymph nodes is similar to what's observed in the skin: there is a proliferation of small coalescent vessels that partially or totally distort the normal architecture of the lymph node. These vessels are lined by epithelioid endothelial cells with clear cytoplasm, sometimes with atypia, and nuclear anisocytosis, with intraluminal protrusion of their nuclei. These findings, together with numerous mitoses, can, in some cases, suggest malignancy. The interstitium shows granular, eosinophilic to