

CASE REPORT

HISTIOCYTIC NECROTIZING LYMPHADENITIS (KIKUCHI LYMPHADENITIS) IN AN HIV-POSITIVE PATIENT

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SUMMARY

Histiocytic necrotizing lymphadenitis, or Kikuchi's lymphadenitis (KL), is an unusual form of lymphadenitis, generally with self-limited clinical course. KL has been reported in rare patients infected with the human immunodeficiency virus (HIV). Pathogenesis of the lesion is probably related to an impaired immune function. The purpose of the present article is to report on one case in which KL was diagnosed in an HIV-infected patient. Histomorphology and immunophenotype were similar to previous reports, but a focus of activated CD30+ macrophages was seen, what might be due to the immunological status of the patient. EBV was not detected on the sections using the *in situ* hybridization technique. Although rare, the occurrence of KL in HIV-infected subjects must be emphasized, because of the potential misdiagnosis of malignancy, especially in the presence of CD30+ cells.

KEYWORDS: Histiocytic necrotizing lymphadenitis; Kikuchi lymphadenitis; AIDS; HIV.

INTRODUCTION

Kikuchi first described histiocytic necrotizing lymphadenitis in 1972 as an unusual lymphadenitis of unknown etiology, which was more frequent in young women in Japan, with benign self-limiting clinical course. Histologically it presented with focal reticulum cell hyperplasia, nuclear debris and phagocytes, but no granulocytic infiltrate. It was subsequently described outside Japan^{8,17} and also in Brazil^{2,13}.

In a study of 108 cases, DORFMAN & BERRY⁸ reported 2 cases of Kikuchi lymphadenitis (KL) related with the acquired immunodeficiency syndrome (AIDS). Other rare cases of KL associated with the HIV infection were also reported^{1,7,9,16,18}. As KL presents histological differential diagnosis with infectious processes (such as tuberculosis in patients infected with the human immunodeficiency virus - HIV¹²), and with malignant lymphoma^{8,15}, the precise recognition of this morphological pattern is important in order to establish the correct therapy. Therefore, it is our purpose to report one case in which KL was diagnosed in a patient with AIDS.

CASE REPORT

In September 2000, a 37 year-old homosexual black male, school teacher, came for consultation with complaint of diplopia 2 months before the onset of bilateral blindness, right hemiparesia, headache, mental

confusion, evening fever and cough. Physical examination showed oral moniliasis and moderate enlargement of cervical anterior lymph nodes. Liquor analysis showed alterations consistent with neurotoxoplasmosis. Serology for toxoplasmosis was positive for IgG and negative for IgM. He was also positive for VDRL (1:32). Serology for HIV was positive, with high viremia. Lymph node biopsy was performed. Vision was recovered after therapy for toxoplasmosis. Oral moniliasis and syphilis were also treated. Antiviral therapy for HIV was started. In December 2000 he resumed his professional and normal social activities. At present, his status is stable, with undetectable viremia.

Histologically the lymph node showed complete effacement of normal architecture due to large areas of histiocytic and medium sized blast proliferation, with frequent debris of apoptotic cells. Some areas of preserved lymphoid population were present, without germinal centers. In some areas, necrosis was present, as well as xantomatous foci. No granulocytes, plasma cells or eosinophils were seen (Fig. 1). Atypical large cells were absent. Search for alcohol-fast bacilli (Ziehl stain) and fungus (Grocott silver stain) was negative.

Immunohistochemical analysis was performed using the EnVision-peroxidase method on paraffin sections (all reagents were provided by Dakopatts, USA). Residual areas of CD20-positive lymphocytes were detected. CD3 (polyclonal) was detected in medium sized blastoid T-cells, most of which surrounding necrotic areas (Fig. 2). Immunodetection

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of CD45RO/UCHL-1 and CD43 was present in more frequent cells, as these markers label T-cells and monocytes. Numerous macrophages stained positively for CD68/KP-1 (Fig. 3). Foci of CD30 activated cells with morphology consistent with macrophages were also seen (Fig. 4). Scarce numbers of blasts showed cytoplasmic light chains of immunoglobulin kappa and lambda, in a polyclonal pattern. Using the *in situ* hybridization technique with the EBER (Epstein-Barr virus Early RNA) probe (Novocastra, UK) no reactivity was seen.

DISCUSSION

KL is an uncommon lymphadenitis, which affects patients around the age of 25-30 years, slightly more frequent in women. Fever may be present in 30-50% of the cases. Lymphadenopathy is more frequently cervical, but some authors report generalized lymph node enlargement (1.3-22.2%). About half of the cases may be associated with painful lymphadenopathy. Leukopenia is reported in 25-50% of the cases and leukocytosis in less than 5% of the cases¹¹. It generally regresses spontaneously, without any specific therapy, but in some cases symptoms may persist up to 5 months, causing anxiety both for the patient and clinician¹⁵. Recurrence is reported in about 4% of the cases¹¹.

This pattern of lymphadenitis is rarely present in HIV-positive patients, as already reported^{1,7,8,9,16,18}. Some aspects of previous reports on KL in HIV-positive patients are summarized on Table 1. Diagnosis can be made simply by conventional histomorphology, but it may be misinterpreted as malignant lymphoma or tuberculosis. In our patient, the histological pattern may be classified as predominantly "necrotizing type", as reported by

KUO¹¹. This author described three histological patterns of KL: proliferative, necrotizing and xantomatous types. He discussed that these morphological types might correspond to different stages of the disease, or different underlying etiologies or pathogenesis. Immunophenotype in our case is also in agreement with previous reports^{11,15}. However, in our patient, an increased number of CD30 positive cells, with morphological features of macrophages, was evident in areas. SPIES *et al.* reported that only rare CD30+ cells were present in their 5 cases of cutaneous KL¹⁹. In another case report, CD30+ cells were found in the bone marrow and peripheral blood⁵. It is well known that CD30+ macrophages can be present in some infections⁶. CD30 was also found in late stages of maturation in macrophage cell cultures³. In our case a specific damage in the immunological system of the patient by the HIV could be responsible for the increased number of CD30+ macrophages.

KL is more frequently misdiagnosed as malignant lymphoma by pathologists^{8,15}, what may lead to aggressive and unnecessary therapy, causing potentially medico-legal problems. This is particularly true in HIV-positive patients, which have more frequently high grade non-Hodgkin's lymphomas. An erroneous diagnosis could precipitate death in an already debilitated individual. Necrotizing lymphadenitis in HIV-positive patients is frequently associated with mycobacterium infection¹². In such cases, mycobacteria are numerous in histiocytes, as detected by the Ziehl stain, what was not the case in our patient.

Etiology of KL is still unclear. As morphology is similar to lupus erythematosus lymphadenitis, a relationship between these two processes has been debated. Some authors consider KL as a *forme fruste* of lupus.

Table 1
Selected data in previous reports on Kikuchi lymphadenitis in HIV-positive patients

Reference	Number of cases	Age	Sex	Topography of lymph node	Histological pattern	CD30	EBV	Follow-up
1	2	NI	NI	NI	NI	NI	NI	One patient died on AIDS
16	1 (drug addict)	26 y	Female	cervical	Partial involvement; predominant necrosis + blasts	NI	Serology negative; <i>in situ</i> not done	Fever recovered spontaneously after 25 days
17	1 (drug addict)	17 y	Female	Generalized lymphadenopathy	Extensive necrosis + histiocytic and blastic proliferation	CD30 positive in T-activated blasts	NI	Alive after 3 years
7	3	26-35 y	2 males, 1 female	Cervical (1); axillary (1); multiple (1)	Predominant necrosis + foamy histiocytes	NI	Elevated serum titres for EBV; <i>in situ</i> not done	NI
9	1 (drug addict)	34 y	Female	Cervical and axillary	Predominant necrosis	NI	NI	Alive and well 2 months later

NI: no information; EBV: Epstein-Barr virus; y: year-old.

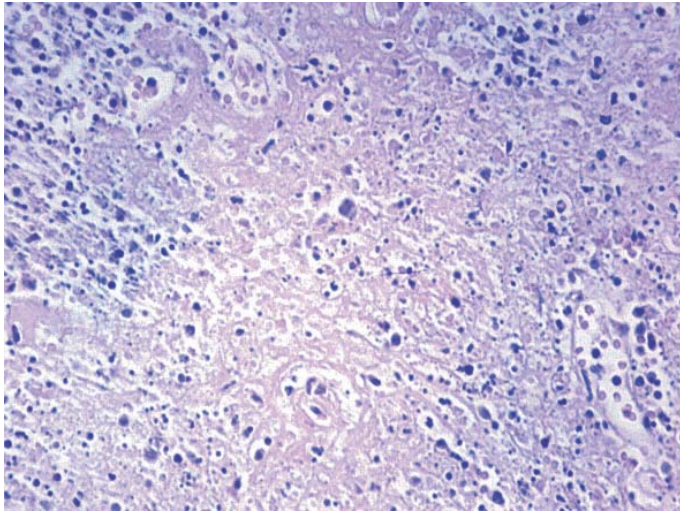


Fig. 1 - Kikuchi lymphadenitis. Extensive areas of necrosis, with cellular debris, but no granulocyte infiltration. (HE, original magnification 250x).

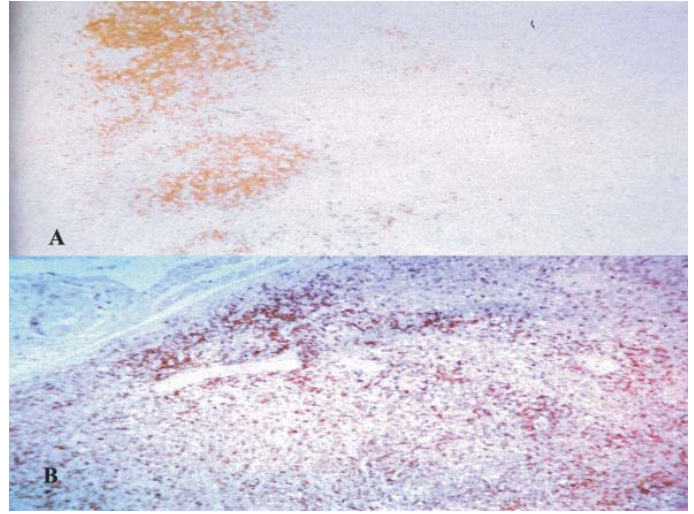


Fig. 2 - Kikuchi lymphadenitis. Residual cortical lymphocytes labeled with anti-CD20 (A), and many paracortical lymphocytes labeled with anti-CD3 (B). (250x).

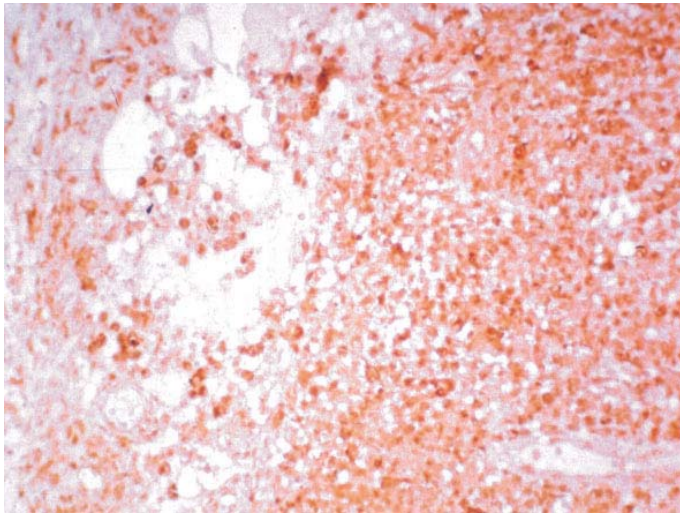


Fig. 3 - Kikuchi lymphadenitis. Strong labeling of histiocytes with anti-CD68/KP-1. Histiocytes are diffusely distributed throughout lymph node and sinuses. (250x).

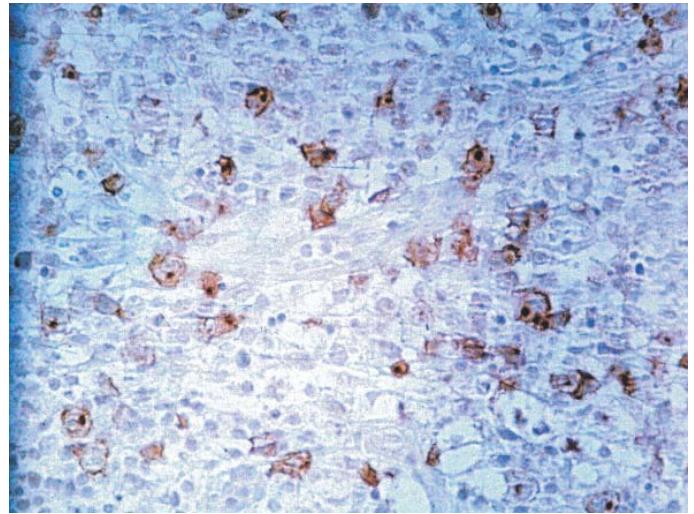


Fig. 4 - Kikuchi lymphadenitis. A focus of cells with morphological features of histiocytes labeled with anti CD30 in membrane and dot pattern. (400x).

Although some reports have associated KL to infection by viruses as EBV, human herpesvirus-6 (HHV-6), parvovirus B-19²⁰ and HTLV-1⁴, no confirmation was possible by others. MARTINEZ-VAZQUEZ *et al.* did not find viral DNA using the sensitive PCR technique, searching herpes simplex virus 1/2, varicella zoster virus, cytomegalovirus, HHV-6, EBV and HHV-8¹⁴.

There are strong evidences that the pathogenesis of KL is predominantly linked to apoptosis mediated by cytolytic lymphocytes. FELGAR *et al.* found evidences of apoptosis (DNA fragmentation, using the *in situ*-end labeling technique, ISEL) in lymphocytes and histiocytes within and in surrounding areas of necrosis¹⁰. They found also an increase

in CD8+ and TIA1+ lymphocytes, whereas CD56+ cells were present in few numbers. These authors concluded that their findings corroborated a viral (still unknown) or autoimmune (perhaps initiated by a viral infection) pathogenesis in KL. As this pattern of lymphadenitis is rare both in the general population and among HIV-positive patients, it may reflect a particular immunological response, due to individual genetic constitution and/or to the immunological status due to HIV infection⁷.

Whatever the etiology and pathogenesis, it is highly important to recognize KL as a distinctive clinical-pathologic process, which, although rare, may be related to HIV-infected individuals, in order not to misdiagnose malignancy.

RESUMO

Linfadenite necrosante histiocítica (linfadenite de Kikuchi) em um paciente HIV-positivo

A linfadenite necrosante histiocítica, ou linfadenite de Kikuchi (LK), é uma forma rara de linfadenite, geralmente de curso clínico auto-limitado. Raros casos de LK associados à infecção pelo vírus da imunodeficiência humana (HIV) foram relatados, sendo sua patogênese atribuída à disfunção imunológica destes pacientes. O objetivo do presente artigo é relatar um caso de associação de LK em um paciente HIV-positivo. A histomorfologia e a imunofenotipagem foram semelhantes aos casos anteriormente descritos na literatura, mas focos de macrófagos ativados positivos para o CD30 foram vistos, o que pode ser devido ao estado imune do paciente. A pesquisa de EBV por hibridização *in situ* foi negativa no tecido. Embora rara, a ocorrência de LK em pacientes HIV-positivos deve ser lembrada, por causa do potencial erro diagnóstico com linfoma maligno, especialmente na presença de células CD30+.

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