Kikuchi-Fujimoto's disease in a black patient

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Abstract

Kikuchi-Fujimoto's disease is a benign, self-limited, rare condition of unknown aetiology. It presents cervical lymphadenopathies associated to constitutional symptoms and it is frequently associated with other systemic diseases. Differential diagnosis with lymphoproliferative (ex: Lymphoma), infectious (ex: tuberculosis) and autoimmune (ex: SLE) diseases should be made. Diagnostic confirmation is histological, and treatment is usually symptomatic.

The authors report a case of a 22 year old black female patient, with no relevant past medical history, admitted with a 15 day on-going complaints of high fever, associated with profuse sweating and discrete cervical and axillary lymphadenopathies.

After performance of several negative or inconclusive diagnostic studies, an excisional biopsy of a cervical node showed a morphologic pattern suggesting Kikuchi´s disease. Differential diagnosis with lymphoma, tuberculosis and systemic erythematosus lupus was then made. Repetition of EBV serologies, as an outpatient, confirmed a likely association of this virus with the disease, with descending titers.

Key words: Kikuchi-Fujimoto's disease, histiocytic necrotizing lymphadenitis, lymphadenopathy.

INTRODUCTION

Kikuchi-Fujimoto's disease, also known as hystiocytic necrotizing lymphadenitis, is a rare clinical-pathological entity, described for the first time in 1972 in Japan, by Kikuchi, Fujimoto et al.[1]

It mainly affects women, at a ratio of 4:1, aged between 20 and 30 years.[2] It is a benign disease, self-limited, and of unknown etiology, characterized by the presence of cervical adenopathies, generally associated with non-specific symptoms.[1,3] It is often associated with other systemic diseases, and histological diagnosis is generally obtained by lymph node biopsy, being characterized by destruction of this structure, with areas of necrosis circumscribed to the paracortical region with nuclear detritus that causes a marked reaction to macrophages.[2] It is essential to make a differential diagnosis with certain lymphoproliferative diseases (e.g: lymphoma), infectious diseases (e.g. lymph node tuberculosis, and auto-immune diseases (e.g. SLE).[1,3,4] Treatment is usually symptomatic.[3,4]

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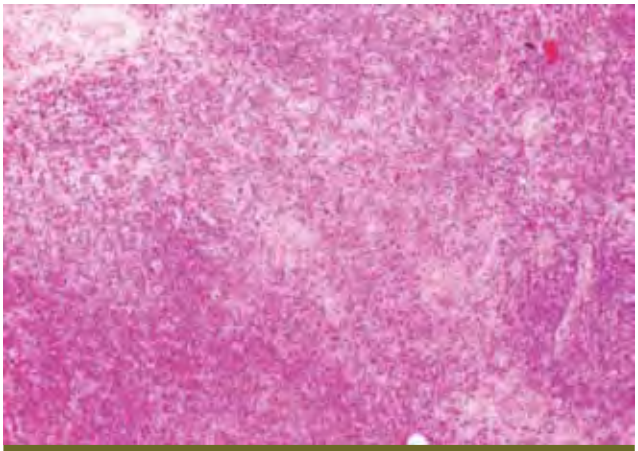
CLINICAL CASE

The authors present the case of a woman, aged 22, Black, originally from Cape Verde but living in Portugal from the age of four. There was no relevant pathological history, except that one and a half years earlier, she had had an elective cesarean due to fetal-pelvic incompatibility. The patient reported no relevant family or epidemiological history, or history of smoking.

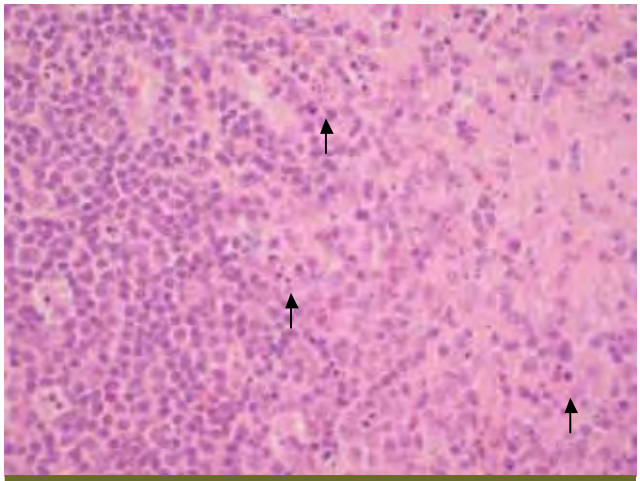
She was admitted by the emergency unit (EU) on 19/7/2007 with symptoms evolving for a fortnight, characterized by high fever in the evenings (axillary temperature of 38-39ºC) and profuse sweating, with was only partially relieved with antipyretics. She did not have any other accompanying symptoms. The symptoms were treated in the outpatient department, and subsequently with empirical antibiotherapy due to probable acute pharyngitis (Azithromycin, 500 mg/day, p.os. for 3 days). As there was no clinical improvement, she was admitted for etiological study.

The following data are highlighted from the objective examination on admission (positive data). high fever (39º C, axillary temperature) and enlarged lymph nodes (from 1-2 cm at the widest point) cervical lymph nodes (bilaterally), right axillary and left supraclavicular nodes: painless, with hard-elastic consistency, not adhering to the deep layers. Laboratory tests were as follows: a hemogram revealed leukopenia (2,530/µL) with lymphocytosis [N=1,15x10^3 (45.6%); L=1,27x10^3 (50.2%)] and a slight elevation in transaminases (ALT-44 U/L), the HIV Check and monotest were both negative. Electrocardiogram



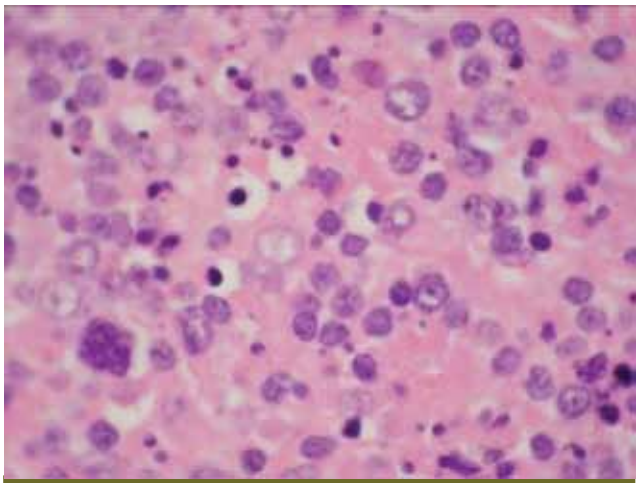
"Starry sky" pattern (histological section stained with HE).

FIG. 1



Area of necrosis on the right and lymphoid population with several blasts on the left (histological section stained with HE). Numerous apoptotic cells can be seen (arrows).

FIG. 2



Apoptotic cells and immunoblasts (histological section stained with HE).

FIG. 3

(ECG) and radiography of the chest did not show any relevant changes.

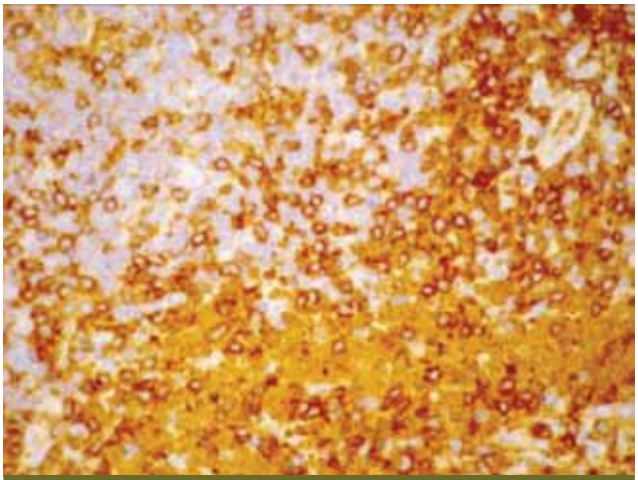
The patient had high fever until the tenth day of admission, and no fever thereafter. The adenopathies described above continued, becoming painful. She initially received 5 days of empirical antibiotherapy, with Amoxicillin + Clavulanic acid (1.2 gr 8/8h, iv), but there was no clinical improvement. In terms of laboratory results, the following were found: persistence of leukopenia with lymphocytosis [2,050 leucocytes/µL; L=0.98x10^3 (48%)] and increased sedimentation rate (ESR=52mm/1st h), associated with mild hepatic cytolysis (ALT-42 U/L; AST-54 U/L), a gradual increase in LDH (741 U/L) and the appearance of mild normocytic, normochromic anemia (Hb-11 gr/dL; MCV-84 fL; MCH-27.2 pg).

From the remainder of the diagnostic study, the following are highlighted: hemocultures, uroculture and screening for atypical pneumonias - negative. Serology for hepatitis (A B, C, D and E) was suggestive of immunization for HBV and former infection for HAV; the Mantoux test was non-reactive; transthoracic ultrasound of the abdomen and pelvis showed no relevant changes; CT of the chest, abdomen and pelvis showed small axillary and mediastinal adenopathies associated with homogenous enlarged liver and possible retroperitoneal adenopathy.

In this phase of the diagnostic investigation, it was necessary to rule out lymphoproliferative disorder, for which two aspiration biopsies were carried out (Fine Needle Aspiration Cytology - FNAC) of the cervical adenopathies, both of which were inconclusive.

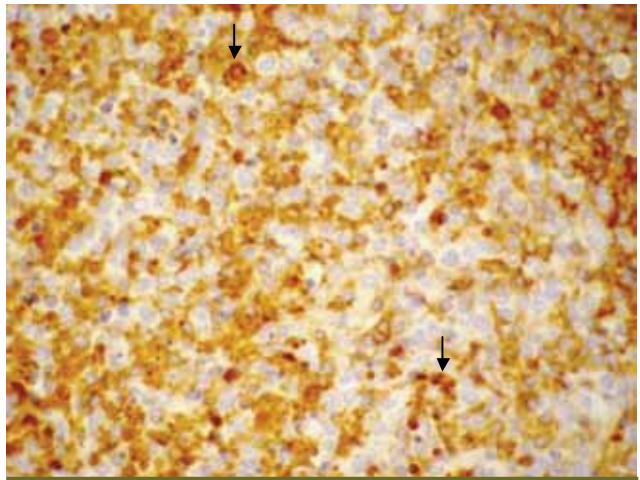
Finally, excisional biopsy of a left cervical lymph node *(Fig. 1)* showed marked proliferation of the interfolicular zone associated with fibrinoid necrosis of the follicular centers, as well as extensive areas of apoptotic cells with macrophages, with bodies with dye uptake *(Fig. 2 and 3)* – proliferation of the monocytoid cells with whitened chromtin and irregular nucleus, compatible with immunoblastic proliferation.

The immunocytochemical study with CD3 (T



Imunocytochemistry with CD3.

FIG. 4



Imunocytochemistry with CD8. Numerous apoptotic cells can be seen (arrows).

FIG. 5

lymphocytes) and CD20 (B lymphocytes) showed the polyclonality of the lymphoid population *(Fig. 4)* and CD68 the existence of numerous macrophages *(Fig. 5)*.

This morphological pattern, suggestive of Kikuchi's lymphadenitis, obliged us to carry out a differential diagnosis with the lymphadenitis associated with the SLE and with the lymphoma, among others.

The Widal, Huddletson, Bengal Rose, RPR and TPHA reactions were negative. Protein electrophoresis and autoimmune study [Immunoglobulins: A, G, M and E; complement study: C_3 and C_4, Rheumatoid factor, Ac. Anti-ds-DNA; ENA's screening: Anti-SS-A (Ro), Anti-SS-B (La), Anti-Scl70, Anti-Jo-1, Anticentromere; ANA screening: SS-A (Ro), SS-B (La), RNP (Sm), ds-DNA] did not show any changes.

The serologies (Enzyme Linked Fluorescent Assay – ELFA) for cytomegaloirus (CMV = IgG - 53 U/ml; IgM - negative), Epstein-Barr virus (EBV = IgG – 282 U/ml; IgM – 5 U/ml) and Toxoplasmosis (IgG – 48 U/ml; IgM - negative) were compatible with previous infections, therefore serology for EBV may represent an infection in the subacute phase.

The patient was discharged on the 26th day of Admission, asymptomatic.

In the outpatient department, serial serologies for CMV and EBV confirmed decreasing titers of EBV (at 6 weeks: IgG – 180 U/mL; IgM – negative; at 12 weeks: IgG – 120 U/mL; IgM - negative), indicating a probable association with this virus.

DISCUSSION AND CONCLUSIONS

Kikuchi-Fujimoto's disease is a benign disease, usually self-limited, and usually affecting young women (male-to-female ratio of 4:1), an average of 25 years, and more frequent in Asian countries.[3,4] Its etiology remains unknown, although an infectious etiology has been suggested [Epstein-Barr virus (EBV), parvovirus B19, type 6 herpes virus, cytomegalovirus (CMV), lymphotropic human T virus (HTLV), human immunodeficiency virus (HIV), Brucella, Yersinia, Toxoplasma and Bartonella].[3-5]

The association with other clinical entities is common, particularly with systemic lupus erythmatous (SLE), and also, although less commonly, with discoid lupus, Hashimoto's thyroid, mixed disease of the conjunctive tissue, Still's disease in adults, non-Hodgkin lymphomas, hemophagocytic syndrome and polymyositis.[3-9]

Clinically, it is characterized by the appearance of adenopathies, generally in the neck, although in rare cases they may be more widespread (the following have also been described: axillary, mesenteric, mediastinal, inguinal, intraparotid, iliac, celiac and peripancreatic involvement[10]). These adenopathies are voluminous, firm, sometimes painful and never ulcerated. Other common manifestations are fever (in around 50% of cases),[11] astenia, weight loss, sweating, myalgias and arthralgias, and in rare cases, generalized maculopapular exanthema (described in 25% of

cases), malar or butterfly rash,[12] enlarged liver and enlarged spleen.[1,3,5]

Laboratory tests may include an increase in inflammatory parameters (CRP and ESR), leukopenia (in around 50% of patients)[1] with neutropenia and lymphocytosis, mild anemia or thrombocytopenia, an increase in LDH or alterations compatible with hepatic cytolysis (increase in transaminases).[2-5] May present ANA, Anti-RNP, anti-DNA and positive lupus anticoagulant.[2]

The diagnosis is histological and is characterized by the presence of areas of necrosis, generally circumscribed to the paracortical region, with numerous nuclear detritus and cellular infiltrates consisting of histiocytes, macrophages and activated T-cells. Polymorphonucleated netrophils are typically absent.[3,13]

Three histological stages can be defined:[2,14]

Proliferative – The initial stage; numerous atypical mononuclear cells are observed.

Necrotising – The most frequent, intermediary stage; numerous histiocytes are observed.

Xanthomatous – The final stage: post-necrotic stage.

Immunohistochemical studies show that the lesion is comprised of CD15+ histiocytes, CD4+ T cells (in the initial stages) and CD8+ T cells (in the late stages) with relative scarcity of B cells and NK cells.[2,15]

A differential diagnosis should be performed, particularly with lymphoproliferative diseases, infectious diseases associated with lymph node necrosis (e.g. lymph node tuberculosis) and with SLE.[1,3]

The evolution of Kikuchi's Disease is typically benign, with spontaneous regression of the symptoms at the end of three months,[11] therefore most cases do not need therapy, or only symptomatic therapy.[3,4] The most commonly used drugs are Paracetamol, AINEs, and corticosteriods in low doses and short-duration regimens[3] (reserved for cases with severe and persistent symptoms).[2] Recurrences are rare, although they can occur (2-3% of patients),[2] and two fatal cases have been described in the literature.[16,17]

In relation to the clinical case presented, it was the imaging exams (CT of the thorax, abdomen and pelvis) that, on confirming the existence of axillary and mediastinal lymphadenopathies, and revealing the presence of homogenous enlarged liver, led us to carry out excisional biopsy and exclude lymphoproliferative disease (since the fine needle aspiration biopsies performed were inconclusive). It also seems likely to us that there is an association with infection by EBV, which reinforces our diagnostic hypothesis, as described in the literature. We also feel it is important to highlight that because DKF is, by itself, a rare disease, it is also less frequent among Black individuals. In most cases, the course of the disease is benign. ■

Bibliografia

1. Norris AH, Krasinskas AM, Salhany KE et al: Kikuchi-Fujimoto disease: a benign cause of fever and lymphadenopathy. Am J Med 1996; 171: 401-405.

2. Reichert A, Correia T, Freitas O, Almeida T, Lino Rosado: Doença de Kikuchi e Fujimoto. Acta Méd Port 2005; 18: 231-234.

3. Meyer O: La maladie de Kikuchi. Ann Med Interne 1999; 150: 199-204.

4. Magnani G, Cocca G, Mezzadri S et al. Kikuchi's disease: an uncommon cause of fever of unknown origin. Ann Ital Med Int 1999; 14: 205-208.

5. Vodoff MV, Petit B, Vinh D et al. La maladie de Kikuchi-Fujimoto. Arch Pediatr 2001; 8: 611-613.

6. Yoshino T, Mannami T, Ichimura K et al. Two cases of histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) following diffuse large B-cell lymphoma. Hum Pathol 2000; 31(10): 1328-1331.

7. Mahadeva U, Allport T, Bain B et al. Haemophagocytic syndrome and histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease). J Clin Pathol 2000; 53(8): 636-638.

8. Wilkinson CE, Nichol F: Kikuchi-Fujimoto disease associated with polymiositis. Rheumatology (Oxford) 2000; 39(11): 1302-1304.

9. Lyberatos C: Two more cases of Still's disease and Kikuchi's. J Rheumatol 1990; 17: 568-569.

10. Dorfman RF, Berry GJ: Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol 1988; 5: 329-345.

11. Pina R., Fonseca I, Saldanha M.H: Doença de Kikuchi-Fujimoto: Uma causa pouco frequente de adenopatias cervicais, Medicina Interna 2004, 11 (4): 187-190.

12. Lopez C, Olivier M, Olavarria R, Sarabia MA, Chopite M: Kikuchi-Fujimoto necrotizing lymphadenitis associated with cutaneous lupus erythematosus: a case report. Am J Dermatopathol 2000; 22 (4): 328-333.

13. Diebold J: Lymphadénite histiocytaire nécrosant sans réaction granulocytaire

de Kikuchi-Fujimoto. Rev Med Interne 1996; 15: 981-983.

14. Kuo TT: Kikuchi disease (histyocytic necrotizing lymphadenitis): a clinicopathologic study of 79 cases with analysis of histologic subtypes, immunohistology, and DNA ploidy. Am J Surg Pathol 1995; 19: 798-809.

15. Ohshima K, Kikuchi M, Sunlyoshi Y et al. Proliferating cells in histiocytic necrotizing lymphadenitis. Virchows Arch B Cell Pathol Incl Mol Pathol 1991; 61: 97-100.

16. Chan JK, Wong KC, Ng CS: A fatal case of multicentric Kikuchi's histiocytic necrotizing lymphadenitis. Cancer 1989; 63: 1856-1862.

17. Shih-Hua L, Wang-Sheng K, Herng-Sheng L et al. Kikuchi's disease associated with lupus-like syndrome – a fatal case [Letter]. Journal of Rheumatology 1992; 19: 1995-1996.