Kikuchi-Fujimoto's Disease and Systemic Lupus Erythematosus

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Abstract

Kikuchi and Fujimoto's Disease, also known as Histiocytic Necrotizing Lymphadenopathy, is a rare and usually benign disorder of unknown etiology. Symptoms generally include cervical lymphadenopathy and fever. Its association with systemic lupus erythematosus is recognized, and it can be diagnosed before, simultaneously with, or after the diagnosis of lupus. The authors report a clinical case of a female patient who was diagnosed with Systemic Lupus Erythematosus ten 10 years after Kikuchi and Fujimoto's Disease in complete remission.

Key words: Kikuchi and Fujimoto's Disease, Histiocytic Necrotizing Lymphadenopathy, Systemic Lupus Erythematosus, Discoid Lupus Erythematosus.

Introduction

Kikuchi and Fujimoto's Disease (KFD), or Histiocytic necrotizing lymphadenopathy, was first described in 1972 in Japan, by Kikuchi and Fujimoto.[1-3] It is a rare disease that is four times more common among females than males, particularly in the second and third decades of life.[2-4] It is more prevalent in Asiatic countries, although it is distributed worldwide.[2,5]

Its etiology remains unknown, but an association with some infectious agents has been suggested, such as the Epstein-Barr virus, the parvovirus B 19, the cytomegalovirus, the herpes virus type 6, the human lymphotropic-T virus, acquired human immunodeficiency virus, brucella, yersinia, toxoplasma gondii, and bartonella.[1-4,6,7] However, the negative results of serological studies and microbiological research make this hypothesis controversial.[1] Its probable autoimmune etiology, indicated by several authors, is based on the clinical, laboratory and histopathological similarity between some cases of systemic erythematous lupus (SEL) and KFD, and on the fact that KFD may represent a reaction of delayed hypersensitivity to an antigen, the nature of which still has not been identified.[1] On the other hand, some patients initially diagnosed with KFD end up developing SEL which, for some authors, may be a sign that KFD represents a frustre form of an autoimmune disease, although many of these patients have had SEL from the beginning.[2] For certain authors, the higher frequency of episodes of lupus reactivation, which generally accompanies the start of KFD in these patients, and the simultaneous occurrence of these two entities, appears to indicate that they are not two independent diseases, and that KFD may represent a manifestation of lupus.[8]

It is characterized by the presence of adenopathies, generally involving the posterior cervical chains, although in rare cases, it may occur in any of the other ganglionar chains, either generalized, or in the form of a hidden adenomegalia.[1,2,4,5] They are usually painless, unilateral and firm, generally not larger than 3 cm at the widest point, and accompanied by fever in 50% of cases.[1,4] The involvement of extra-nodal locations is not common, but may involve the skin, liver and spleen.[2,5,7] Other associated manifestations are: asthenia, weight loss, sweating, myalgias, arthralgias, generalized maculopapular exanthema (25% of cases), malar erythema (sometimes in the form of a butterfly's wing), nausea, vomiting, diarrhea, abdominal pain, hepatosplenomegaly and chest pain.[1,2,4]

KFD generally begins in subacute form, developing over a period of 2 to 3 weeks.[2]

The laboratory exams are often normal. However, the following may occur: neutropenia (in 50% of cases), lymphocytosis, atypical lymphocytes (in 25% of

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cases), anemia, thrombocytopenia, increased speed of sedimentation and protein C reaction, and an increase in lactic dehydrogenase and hepatic enzymes.[1,2,4] Antinuclear antibodies, anti RNP, anti-DNA and lupic anticoagulant may be positive.[1]

The diagnosis of KFD is anatomical-pathological, and is made through excisional biopsy of an affected ganglion.[1,2,4] There is destruction of the ganglionar architecture by zones of necrosis, generally paracortical, as well as nuclear residues, and a cellular infiltrate emerges in the periphery of the areas of necrosis, formed by histiocytes, macrophages and activated T lymphocytes.[1,4] Three anatomopathological types of KFD are described, which appear to represent stages of evolution of the disease. The initial stage, known as the proliferative type, is featured by a predominance of lymphocytes, immunoblasts and histiocytes, but without necrosis; the necrosing type, the most frequent, is associated with necrosis, and the final, post-necrotic stage, known as the xanthomatous type, is associated with a predominance of xanthomatous hystiocytes.[2,4]

It may appear in association with other entities, particularly SEL, and its diagnosis may come before, simultaneously with, or after the diagnosis of SEL.[9,10] Thus, patients with KFD should be studied and followed-up, in order to evaluate the presence or future development of SEL, which have different prognoses and therapeutic approaches.[10-12] In rare cases, it may be associated with: discoid lupus erythematosus (DLE), Hashimoto thyroiditis, mixed disease of the conjunctive tissue, Still disease of adults, lymphomas, hemophagocytic syndrome, or polymyositis.[2,4,5]

The differential diagnosis includes lymphoma, particularly in the initial stages, in which there are few zones of necrosis and immunoblasts emerge among the nuclear residues. Immunophenotyping is a valuable process for differentiating between the two entities. The clinical, anatomopathological and serological similarity between KFD and SEL, and the possibility of association or evolution to SEL, can present problems when attempting to make a differential diagnosis between these two entities, which have completely different clinical evolution and therapeutic needs.[1,11,13] However, in lupic lymphadenitis, there are hematoxiphilic bodies which appear to represent degenerated nuclei after reaction with antinuclear antibodies, as well as Azzopardi phenomenon, which is characterized by incrustation of the walls of the blood vessels with nuclear material. Despite this, these important characteristics for the differential diagnosis between lupic adenitis and KFD may not be present in all patients with lymphadenitis associated with SEL, and may be similar to the histological alterations of KFD. Thus, a differential diagnosis between these two entities cannot always be made based on histological alterations alone.[2,14]

Infectious adenitis such as tuberculosis, adenitis with formation of microabscesses, such as cat-scratch disease, Yersinia infection, toxoplasma Gondii, Acquired Immunodeficiency Virus, Herpes Virus, and infectious mononucleosis are other differential diagnoses to take into consideration.[1,3,4]

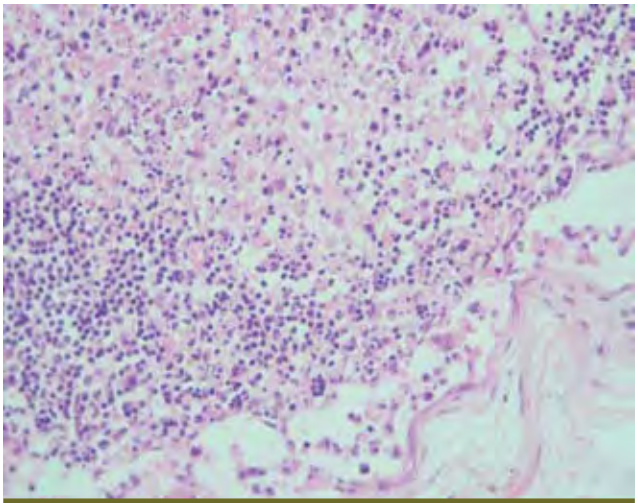
KFD has a benign and self-limited evolution in the majority of cases, with complete regression of the symptoms in around 3 months and of the adenomegalies up to 6 months of evolution.[1,2] It recurs in 5% of cases.[2] In cases where it is associated with other pathologies, such as SEL, its evolution follows that of the SEL.[3,4] Known cases of fatal KFD are extremely rare.[15]

Therapy is symptomatic, and may not be necessary in milder cases. Non-steroid anti-inflammatories may be used in patients with more marked symptoms. Therapy with corticosteroids, generally with low dose and short duration regimes, is reserved for clinically severe, persistent cases.[1,3,4]

Clinical case

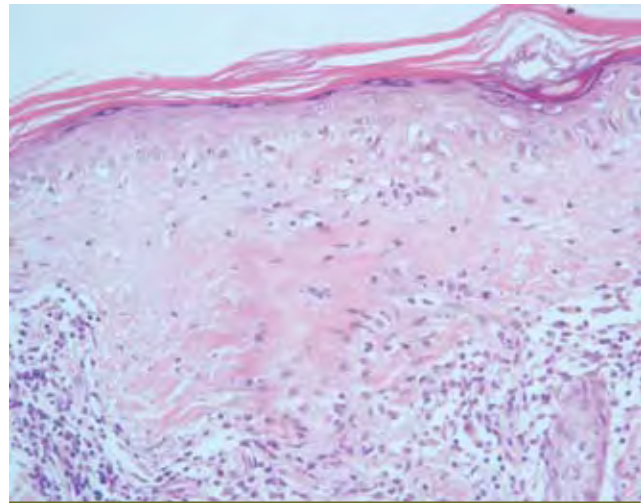
Female patient, currently aged 39 years, Caucasian, born and residing in Ilha da Madeira, a professional sales agent. At 26 years of age she was admitted for clarification of a condition consisting of asthenia, adynamia, weight loss and multiple adenopathies in the cervical, axillary and inguinal regions, bilaterally, with elastic, mobile consistency and slightly painful on touch, and with four months of evolution. The remainder of the objective exam was normal. The patient had a gynecological history of spontaneous abortion, requiring uterine curettage at the age of 19, and fetal death in uterus at 30 weeks, when she was 22 years of age. She bore two live children, born after full-term pregnancy, by eutocic labor, at 24 and 30 years of age.

Analytically, leucopenia (1900 cel/µL), thrombocytopenia (70.000cel/µL), TGO – 205 U/L, TGP – 224 U/L and LDH – 900 U/L are present. The serologies for EBV, CMV, toxoplasmosis, hepatitis A, B



Biopsy of the ganglion of the left jugular chain, suggestive of Kikuchi and Fujimoto disease.

FIG. 1



Skin biopsy, suggestive of chronic discoid lupus.

FIG. 2

and C, HIV 1 and 2 and VDRL were negative, as was the auto-antibody research (ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SS-A, anti-SS-B and anticardiolipin,). Abdominal echotomography, CT of the chest, abdomen and pelvis and the medullogram showed no alterations.

Biopsy of a ganglion of the left jugular chain confirmed the diagnosis of KFD. It showed a ganglion with a faded structure, large areas of necrosis, sometimes confluent, abundant nuclear residues and diffuse histiocytic reaction, with an absence of polymorphonuclear cells, suggestive of histiocytic necrotizing lymphadenitis (*Fig. 1*).

Six months after the start of symptomatic therapy with non-steroid anti-inflammatories, complete regression of the above-mentioned clinical condition was observed.

Some months later, erythematous plates appeared, dispersed on the scalp, which were scaling, itchy, and accompanied by focal alopecia. This was observed in the Dermatological consultation and medicated with Betamethasone solution and Salicylic Acid. Despite the therapy, the lesions continued, and after three months, had extended to the face. Skin biopsy, carried out at that time, showed a cluster of small, mature lymphocytes in the dermis, particularly periannexial, suggestive of chronic discoid lupus (*Fig. 2*). Auto-antibodies ANA, anti-dsDNA, anti-SSA, anti-SSB, anti-sm, anti-RNP and anticardiolipin continued to be negative and persisted until the patient was 36 years of age, at which time she developed light sensitive malar rash, Raynaud's phenomenon and arthritis of the proximal and distal interphalangeal joints in both hands. The laboratory study carried out at that time showed leucopenia (3000cel/µL), mild thrombocytopenia (145.000 cel/µL) and positivity for the antibodies ANA, anti-dsDNA, anti-Ro, anti-RNP and anticardiolipin. Patient also presented, at that time, criteria of SEL, and therapy was initiated with Indomethacin 25mg 3*/day, Hydroxychloroquine Sulfate 400 mg/day and Prednisolone 30mg/day, with regression of the clinical state after 3 months of treatment.

At 39 years of age, the patient was diagnosed with idiopathic arterial hypertension, and 4 months later, suffered left parietal lacunar ischemic vascular accident, with complications of right hemiparesis. The patient is currently being followed up by the Internal Medical Clinic of the Hospital Central do Funchal, and is being medicated with Clopidogrel 75 mg/day, AAS 100 mg/day, Hydroxychloroquine Sulfate 400 mg/day, Prednisone 5 mg/day, Candesartan 16 mg/day, Indapamide 2,5 mg/day, Nifedipine 30 mg/day and Simvastatin/Ezetimibe 20/10 mg/day.

Discussion

In a young patient, the subacute appearance of generalized adenopathies, with benign characteristics, accompanied by general symptoms, leucopenia,

thrombocytopenia, increased lactic dehydrogenase and laboratory signs of hepatic cytolysis is suggestive of KFD, which was confirmed by the anatomopathological exam of the excised ganglion. During the follow-up at the Internal Medicine consultancy, the patient developed state of DLE and subsequently, SEL, confirming the already known association between KFD and lupus.

SEL is a systemic disease of unknown cause, the diagnosis of which is based on the presence of at least 4 of the 11 criteria established by the American College of Rheumatology.[2,16] The occurrence of adenopathies in SEL is not rare, occurring in 15% of cases, particularly in the phases of active disease.[9,16] However, at 26 years of age, when adenopathies appeared, the patient did not present the necessary criteria for diagnosis of SEL, as only hematological alterations (leucopenia and thrombocytopenia) were present. On the other hand, at that time, the anatomopathological exam of the ganglion confirmed the diagnosis of KFD, and the manifestations regressed after 6 months, with only symptomatic therapy, as is typical of this entity. However, as mentioned above, the anatomopathological characteristics that differentiate lymphadenitis of SEL from KFD may not be present, leading to an erroneous histological diagnosis of KFD in some cases of SEL.[2,14] Furthermore, some months after the spontaneous disappearance of the adenopathies, cutaneous lesions of DLE appeared, which occur in up to 20% of patients with SEL[16], and which were also confirmed histologically and continued to progress, despite therapy with topical corticoid. Thus, knowing the association between KFD and SEL, and the fact that its diagnosis can be made before, simultaneously with, or after the diagnosis of SEL[9,10], it is likely that the patient began a state of SEL at 26 years of age, under the form of KFD, although diagnosis was not possible at that time as the patient did not meet of the necessary criteria. The definitive diagnosis of SEL was only possible at 36 years of age (10 years after the start of the complaints), by which time the patient had 6 of the 11 criteria of SEL of the American College of Rheumatology, such as: malar rash, light sensitivity, arthritis, hematological alterations, positive ANA and positive anti–dsDNA and anticardiolipin antibodies. Is KFD therefore an initial manifestation of SEL? Or are these two entities independent phenomena?

As we can see in the case presented here, follow-up of patients with KFD is of vital importance for evaluating whether this is a self-limited process or evolves to SEL, which has a manifestly different prognosis and therapeutic approach.[10-12] ■

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