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Case Report

Atypical Histiocytic Necrotizing Lymphadenitis (Kikuchi-Fujimoto Disease) as a Trigger for Fibromyalgia-Like Symptoms: A Case Report

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Abstract

Kikuchi-Fujimoto disease is a rare clinical condition, the etiology of which remains unclear. Clinical presentation is acute or sub-acute and most cases resolve spontaneously, with recurrences being rare. The condition is more common in young women. It can be associated with autoimmune rheumatic diseases, particularly systemic lupus erythematosus. Biopsy, histology and immunohistochemistry are required to confirm diagnosis, while the differential diagnosis includes lymphoproliferative diseases and solid tumors. This report describes a case of Kikuchi-Fujimoto disease in a male patient whose symptoms took longer than usual until remission and progressed to fibromyalgia-like symptoms that failed to respond to steroids. This case is unique for the following reasons: (1) The disease occurred in a male patient; (2) It involved the inguinal lymph nodes rather than the cervical lymph nodes or those of the upper limbs; (3) Symptoms persisted for a prolonged amount of time (adenopathy for more than 3 months); and (4) Kikuchi-Fujimoto disease appeared to act as a trigger for the development of fibromyalgia-like symptoms in a male patient.

Keywords: Histiocytic Necrotizing Lymphadenitis; Kikuchi-Fujimoto Disease; Inguinal Lymphadenopathy; Histiocytes; Fibromyalgia-Like Symptoms.

Introduction

Kikuchi and Fujimoto, independently but concomitantly, were the first to describe necrotizing histiocytic lymphadenitis in Japan in 1972. The condition would later come to be known as Kikuchi-Fujimoto disease [1]. The characteristics of this rare, benign, self-limited condition with acute to sub-acute presentation that tends to resolve within three weeks [1,2] were originally reported based on findings of fever and painful cervical lymphadenopathy in young women. Nonetheless, the preliminary concept of a condition that affected Asian women under 30 years of age would change by the 1980s/1990s as many cases started being reported in the Western world [2]. Typically, the affected patients are previously healthy individuals who present with fever and painful, rarely generalized, cervical lymphadenopathy [2]. The etiology remains poorly understood. Many studies have suggested the involvement of microbial or viral pathogens; nevertheless, evidence is inconclusive. The pathogenic hypotheses include antigenic stimuli or an autoimmune process with apoptosis as the protagonist [1,2]. Although the differential diagnosis is with infectious, autoimmune, and malignant diseases, Kikuchi-Fujimoto disease sometimes occurs in patients with systemic lupus erythematosus (SLE). Fibromyalgia is a chronic pain syndrome, characterised by diffuse musculoskeletal pain and accompanied by stiffness, fatigue, tender points, sleep disturbances and cognitive and gastrointestinal symptoms. It affects predominantly middle-aged women (between 40 and 65 years of age) and is often triggered by environmental factors such as viral infections, physical or emotional stress, poor sleep, and changes in weather. The present report describes a case of a young male who developed fibromyalgia-like features after prolonged Kikuchi-Fujimoto disease.

Case Presentation

On February 11, 2021, a 29-year-old male was admitted to the Hospital Metropolitano da Lapa in São Paulo, Brazil complaining of bilateral headache with no warning signs, and myalgia, pain and swelling in the left inguinal region over the preceding two weeks. The patient had no recent history of weight loss, night sweats, fever, respiratory symptoms, mucocutaneous lesions, arthralgia, sicca syndrome or Raynaud's phenomenon. He was hypertensive and treated with 50 mg losartan. At admission, physical examination revealed a palpable, painful lymph node of approximately 3 cm in the left inguinal region, adhered to the deep planes. No other palpable lymph node chains or splenomegaly were found, and Traube's space was free. Ultrasonography confirmed an inguinal mass, with no signs of inflammation. Computed tomography showed inguinal adenomegaly, with no other lymph nodes affected. The node measured 3.4 x 2.0 cm in diameter (Figure 1). Blood count at admission was normal: erythrocyte sedimentation rate 8 (reference value ≤30), lactic dehydrogenase 190 (reference value ≤220) and beta-2 microglobulin 1.8 (reference value ≤2.5). Screening tests for rheumatic diseases including antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Ro/SSA, anti-ribonucleoprotein (anti-RNP), anti-Smith (SM) and antiphospholipid antibodies were all negative. Serum complement C3/C4 levels were normal. Serology was negative for hepatitis B and C, human immunodeficiency virus (HIV), syphilis, cytomegalovirus, HTLV 1 and 2, Epstein-Barr virus, Covid-19 and toxoplasmosis. Lymphoma was suspected and the patient remained in hospital receiving analgesia with dipyrone/metamizole and corticoids for the headache and, principally, for the pain in the inguinal region. Several specialists, including hematologists, examined the patient. On February 16, an ultrasound-guided core biopsy was performed. Histopathology showed abnormalities in the architecture of the lymph node due to the presence of a heterogeneous lymphocytic infiltrate, with large immunoblast-like lymphoid cells and histiocytes, and necrotic foci containing apoptotic cell debris. These findings were suggestive of necrotizing lymphadenitis (Figure 2A and 2B). The patient remained in hospital, receiving intravenous dipyrone/metamizole up to a maximum dose of 2 ml every six hours and prednisone (20 mg/day) for the pain. The headache, myalgia and inguinal pain improved; however, the adenomegaly in the left inguinal region persisted. The patient was discharged two days after biopsy, at which time he no longer required medication. On April 21, however, the patient returned complaining of severe pain in the inguinal region. Physical examination and imaging tests showed that the lymph node remained abnormally enlarged but no more so than at his previous admission to hospital. He was prescribed 50 mg of tramadol every 6 hours, as required, and was discharged on the same day. The assumption was that his condition was taking longer than usual to resolve and it was decided to implement expectant management. In December 2021, the patient returned to the hospital reporting severe muscle pain in the dorsal region and lower limbs over the preceding four months. He also reported severe fatigue, non-restorative sleep, tension headaches, difficulty in concentrating and overlapping anxiety. He denied having had anhedonia, weight loss, night sweats or fever and he had no recent history of having travelled. At physical examination, no lymph nodes were palpable, even in the inguinal region; however, there was pain at palpation of the muscles of the back, chest and upper and lower limbs. Blood samples were taken for further testing: full blood count, urea, creatinine, liver function tests, serology for hepatitis B and C, HIV, dengue, Zika virus, chikungunya, thyroid function (TSH and free T4), erythrocyte sedimentation rate, lactate dehydrogenase (LDH) and beta 2 microglobulin. All

results were within the normal range. Tomography of the neck, chest and abdomen was performed, with results showing no sign of adenomegaly or visceromegaly. Rheumatology screening tests were then performed, including rheumatoid factor, antinuclear antibody test (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Ro/SSA, anti-ribonucleoprotein (anti-RNP), anti-Smith (SM) antibody and anti-phospholipid antibodies, all of which were negative. Serum complement C3/C4 levels were normal.

Discussion

Kikuchi-Fujimoto disease is estimated to account for 0.5-5% of all cases of lymph node enlargement with a confirmed histological diagnosis [3]. In a retrospective study of 1,724 lymph node biopsy specimens, Kikuchi-Fujimoto disease was found in only 36 cases [4]. Several infectious agents have been investigated as possible antigenic stimuli, including the Epstein-Barr virus, herpesvirus types 6 and 8, HIV, parvovirus B19, parainfluenza virus, Yersinia spp. and Toxoplasma gondii [1]. No infection, however, was confirmed in the case described here. Kikuchi-Fujimoto disease classically presents with lymphadenopathy of the posterior cervical chain, often associated with involvement of the axillary and supraclavicular chains, and fever. Generalized lymphadenopathy is rare. Other infrequent symptoms include weight loss, nausea and vomiting, fatigue, headache, arthralgia, night sweats and symptoms of upper airway infection. Extra nodal involvement is rare, with other reported sites including the kidneys, liver, gastrointestinal tract, thyroid, parathyroid, adrenal glands and bone marrow [1,3]. Diagnosis of Kikuchi-Fujimoto disease is achieved by performing lymph node biopsy and ruling out other conditions that also present with fever and lymphadenopathy such as tuberculosis, lymphoma and Kawasaki disease [1,3]. Kikuchi-Fujimoto disease shares some characteristics with systemic lupus erythematosus such as the sex and age of patients as well as the abnormalities detected at histology. Consequently, it has been referred to as a lupus-like syndrome [1]. Another hypothesis is that this disease could be a manifestation of lupus or a stage of progression towards lupus, thus justifying monitoring these patients with immunological tests such as ANA. Patients may test positive at ANA, anti-RNP, anti-DNA and lupus anticoagulant [5]. Other autoimmune conditions such as antiphospholipid antibody syndrome, polymyositis, Still's disease, uveitis, scleroderma, thyroiditis, pulmonary hemorrhage and interstitial lung disease may be associated with Kikuchi-Fujimoto disease [2,6]. Notwithstanding, rheumatologic screening tests were all negative in this patient, both at diagnosis and during the patient's clinical course. As the disease evolved, the presence of signs and symptoms associated with a diagnosis of fibromyalgia became apparent, and may have been triggered by Kikuchi-Fujimoto disease. Fibromyalgia is a non-immune-mediated syndrome of chronic musculoskeletal pain that is often accompanied by fatigue, sleep disturbances, cognitive alterations and multiple somatic complaints. Its prevalence is higher in the fifth and sixth decades of life and it is more common in women (6:1). Its diagnosis is entirely clinical and based on the criteria established in the 2016 American College of Rheumatology Diagnostic Criteria for Fibromyalgia, which takes into consideration generalized pain and main symptoms such as fatigue, sleep disturbances, mood and cognitive alterations. Treatment is multidisciplinary and includes cognitive behavioural therapy and the use of antidepressant drugs such as tricyclic antidepressants. In the case in question, the patient was prescribed tricyclic antidepressants and psychotherapy, and advised to practice physical activities. His condition and symptoms have been improving. In Kikuchi-Fujimoto disease, histology shows lymph nodes with Para cortical necrosis surrounded by histiocytic aggregates [7,8]. Three subtypes have been described: proliferative, necrotizing and xanthomatous. These subtypes are believed to correspond to the different evolving or sequential phases, to different etiological agents or even to differences in patients' inflammatory responses [7,9]. In the case reported here, areas of necrosis with cell debris were found (Figure 2B). There is no known effective treatment for Kikuchi-Fujimoto disease. Signs and symptoms usually resolve within four months [5]. Patients with persistent or more severe symptoms have been treated with low-dose corticoids [5,6] as in the case reported here. Although pain improved with treatment, the lymph node remained enlarged for several months after his first admission to hospital. Long-term clinical follow-up is advisable due to the risk of recurrence in 3% of cases and the possibility of progression to lupus [5,6].

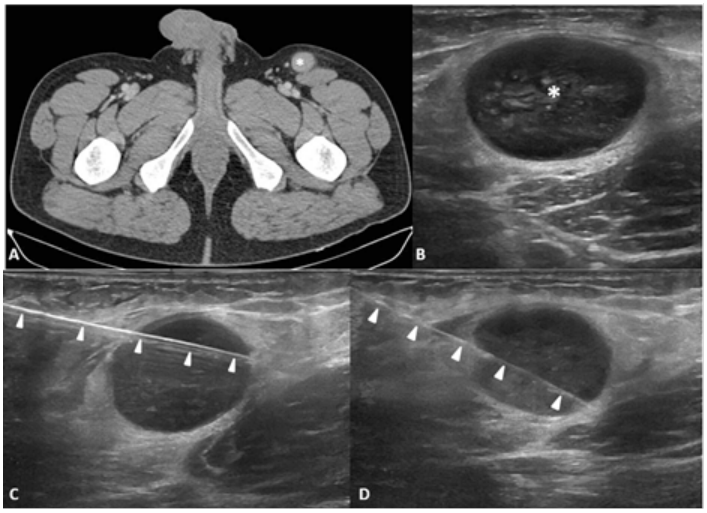

Figure 1: Pelvic computed tomography (A) and ultrasonography (B) showing lymph node enlargement in the left inguinal region (white asterisk). Large needle core biopsy (white arrowheads), with samples being obtained from different areas (C and D).

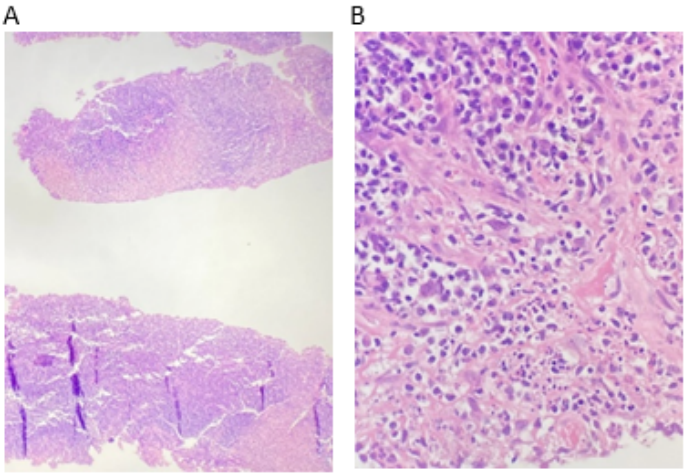

Figure 2: Optical microscopy image of left inguinal lymph node biopsy specimen (A), showing areas of necrosis with cell debris (B) Hematoxylin and eosin staining (magnification of panel A: 20 X; B: 40 X).

Conclusions

Kikuchi-Fujimoto disease, albeit rare, should be included in the differential diagnosis of cases of lymph node enlargement, particularly in young patients. Investigation for other clinical conditions is mandatory. As these patients could go on to develop rheumatic and autoimmune diseases, long-term monitoring is essential. Therapeutic intervention may be required in symptomatic cases and when the disease is progressive. The patient described here presented with nonspecific signs and symptoms, and the definitive diagnosis was only possible following biopsy. Twelve months after diagnosis of Kikuchi-Fujimoto disease, the patient met the criteria for fibromyalgia, while remaining negative at screening for other rheumatic diseases and apparently fully recovered from the original diagnosis. It is, therefore, reasonable to assume that Kikuchi-Fujimoto disease may have been a predictor of fibromyalgia in this patient. At his latest consultation in May 2023, he was asymptomatic, in use of antidepressants and undergoing regular psychotherapy and was being monitored by a rheumatologist.

Ethics: The institutional review board approved this study.

Informed Consent: The patient whose case was reported here gave his written informed consent for this report to be published.

Conflicts of interest: The authors declare that there are no conflicts of interest.

Authors' contributions: JCV, DD, LT, TZ, LF, AB, GP and NH provided direct care to the patient, interpreted his test results and collected all the data presented here. JCV obtained consent from the patient to publish this report. JCV and NH wrote the first manuscript draft. All authors revised the article and approved the final version for submission.

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