Kikuchi-Fujimoto Disease: Don't Forget it in the Differential

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Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is a rare, benign, self-limiting disease of unknown etiology. It has been reported worldwide but has a higher prevalence in Japanese and Asian populations. It is more frequently seen in women than men and commonly presents between 20 and 40 years of age. It is often characterized by cervical lymphadenopathy and fever lasting for a few months before spontaneous resolution [1]. We present the case of a 32 year old woman with this disorder.

CASE PRESENTATION

A 32 year old Israeli Jewish female of Iraqi origin presented to our department with persistent fever lasting for 3 weeks. She was previously admitted to another hospital for 17 days due to the persistent fever. There, she was diagnosed with brucellosis based on a positive Rose Bengal test and treatment with gentamycin, rifampicin and doxycycline was begun. During her hospitalization abdominal ultrasound demonstrated a hemangioma in the liver. Blood and urine cultures were negative. Transthoracic echocardiography showed no vegetations and nuclear bone scan was normal.

She had been previously healthy and her past medical history was not significant. She did not smoke, drink alcohol or use illicit drugs. Before her admission she had constantly taken paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve fever.

In our department she had continuous fever of 39.6°C accompanied by malaise, nausea but infrequent vomiting. She reported a 10 kg weight loss and loss of appetite. She had no obvious signs of lymphadenopathy, rashes, lesions, or organomegaly. Her heart, lungs, abdominal and neurological examinations were normal. She had no change in bowel habits or urinary symptoms.

Laboratory tests revealed normochromic normocytic anemia with hemoglobin level of 9 g/dl, leukopenia 2.9 k/µl and neutropenia 0.8 k/µl, and slightly elevated C-reactive protein (CRP) of 20 mg/L. Tests of creatinine and blood urea nitrogen (BUN) were normal. Her liver function tests were normal but lactate dehydrogenase (LDH) was mildly elevated. Urinalysis was normal, without nitrites. Her electrocardiogram (ECG) and chest X-ray were normal.

Tests for brucellosis, Q fever, Epstein-Barr virus (EBV), cytomegalovirus and Parvo B19 were all negative. The serum that was found to be positive for brucellosis in the previous admission was recalled and tested again for brucellosis and found negative.

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) excluded vegetations. Bone scan was normal. Abdominal ultrasound revealed a known hepatic hemangioma. Doppler of the lower limbs showed no abnormalities. Autoantibody tests for autoimmune disorders revealed elevated rheumatoid factor (RF), positive antinuclear (ANA), anti-RO, anti-LA, anti-SM and anti-RNP antibodies. Computed tomography (CT) scan revealed lymphadenopathy in the region of the liver and in the retroperitoneum.

The site of the lymphadenopathy was difficult to biopsy, so we performed PET-CT (positron-emission CT) of the body which showed the same lymphadenopathy without any other site of hypermetabolic tissue [Figure 1A].

Percutaneous core needle biopsy of the lymph node was performed. The biopsy showed cores of lymph node with distorted reactive architecture and area of apoptosis and eosinophilic necrosis. There was no evidence of granulocytes [Figure 1B]. A predominance of CD8+ cells over CD4+ cells in the necrotic areas was present [Figure 1C]. There was no evidence of malignancy. In situ hybridization for Epstein-Barr virus V and cytomegalovirus were negative, as was Ziehl-Neelsen staining for acid-fast bacilli. The pathological picture was highly suggestive of Kikuchi necrotizing lymphadenitis.

COMMENT

Kikuchi disease is a rare cause of lymphadenopathy, accompanied by fever and occasionally other systemic symptoms such as weight loss, nausea, vomiting, myalgia, upper respiratory symptoms, and maculopapular rash. Laboratory findings may be normal; however, many case reports have described findings of leukopenia, as well as elevated sedimentation rate, serum transaminases and LDL [1]. Typically the cervical lymph nodes

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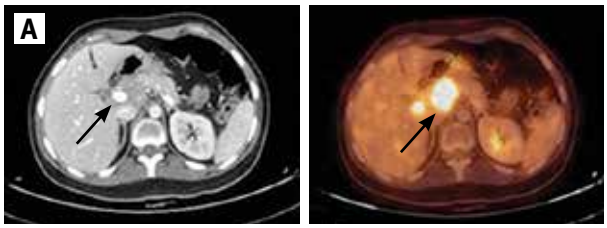
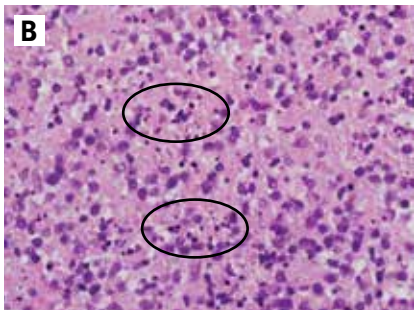
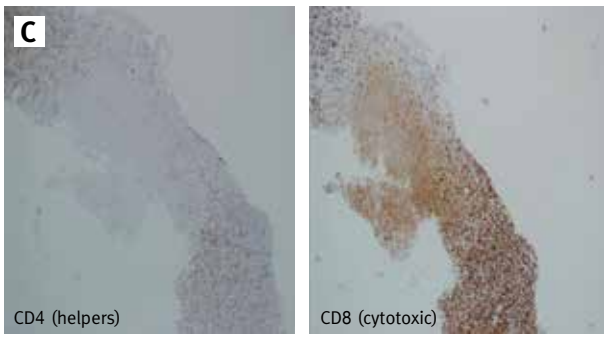
Figure 1. [A] PET-CT scan showing hypermetabolic lymphadenopathy in the port of liver and retroperitoneum without any other unexpected hypermetabolic sites





[B] Biopsy from lymph node shows eosinophilic necrosis with apoptotic bodies (in black circles), without granulocytes



[C] Lymph node biopsy showing the predominance of CD8+ cells over CD4+ cells

are involved; however, in our case the patient had retroperitoneal lymph node involvement which, although rare, is more common in Israeli patients [2]. The etiology of Kikuchi disease is still unknown. However, it is thought to be induced by a viral illness such as EBV or cytomegalovirus, although their involvement in the pathogenesis of the disease has not been confirmed [3]. Other etiological pathogens that were studied, such as *Toxoplasma*, *Yersinia* and *Brucella*, were inconclusive with regard to their involvement in the pathogenesis of Kikuchi disease [1]. An association with systemic lupus erythematosus (SLE) has also been explored in recent years. Studies have shown that patients may develop an autoimmune disease during the course of illnesses such as SLE or Still's disease, or they may have autoantibodies associated with autoimmune disorders [4]. Autoimmune manifestations are more frequent in women; therefore, follow-up and surveillance of female patients after recovery is crucial [5].

The pathogenesis of Kikuchi disease is a mystery. It has been proposed to be due to an immune response involving apoptosis of CD8 cells via the Fas/FasL pathway. Additionally, the abundance of plasmacytoid cells is thought to increase type 1 interferon, which induces a cytotoxic reaction leading to the necrotizing pathology in the lymph nodes [2,4,5]. Biopsy is necessary for diagnosis. Immunohistochemical stain is also frequently used to confirm the diagnosis as the cells express particular cell markers. Histocytes are MPO positive and CD68 positive. Plasmacytoid monocytes are positive for CD68 and cutaneous lymphocyte-associated antigen and positively stained by pan-macrophage monoclonal antibody Kim1P [1].

Once the diagnosis is made, treatment is supportive as there is no cure and the course of the disease is self-limiting and lasts between 1 and 4 months. Treatment of symptoms with antipyretics and analgesics is often given and rest is recommended. Corticosteroids are used to treat severe or relapsing cases. Various studies have described patients whose condition improved following minocycline (probably due to its anti-inflammatory effects); however, other antibiotics were not shown to be beneficial [1,2]. Kikuchi disease may mimic other disorders such as tuberculosis or lymphomas due to the constitutional non-specific symptoms; therefore, it is essential to reveal the underlying cause of the illness in order to prevent futile exposure to harmful treatments such as corticosteroids [1,2].

Following the diagnosis of Kikuchi disease in our patient, she was treated symptomatically, leading to a persistent complete clinical and laboratory remission. Due to the risk of developing consequent autoimmune disease she is maintained on follow-up.

CONCLUSIONS

Kikuchi-Fujimoto disease is a rare necrotizing lymphadenitis accompanied by various systemic signs, most commonly fever and cervical lymphadenopathy. This rare disease may mimic infections and malignancies. It is important to remember this disorder in the long list of differential diagnoses of fever of unknown origin and to pursue histological diagnosis in relevant cases.

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