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Kikuchi-fujimoto disease in Rwanda: A rare disease with a common presentation.

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ABSTRACT:

CASE PRESENTATION: We describe a 28-year-old female patient who presented at the Kigali University Teaching Hospital with a one-week history of right cervical lymphadenopathy, fever and headache. She later developed uveitis of the left eye. Her septic work-up was remarkable for aseptic meningitis. During the second week of her hospitalization, her symptoms resolved completely. Lymph node biopsy results were consistent with Kikuchi-Fujimoto disease (KFD).

KFD, also known as histiocytic necrotizing lymphadenitis, is a rare and self-limiting disease. It is commonly seen in the young adult Asian population. Although its pathophysiology is not well understood, it is thought to be a result of an immune response of T cell histiocytes. KDF usually presents with unilateral lymphadenopathy and fever. The Diagnosis is made by histopathology of an involved lymph node. Symptoms usually resolve within 1 to 4 months.

Aseptic meningitis and/or uveitis, though rare, can be part of KFD. In our current practice, we start patients on anti-tuberculosis medications based on raised white blood cells in cerebrospinal fluid with lymphocytic predominance. However, it is very unlikely that all of them have tuberculous meningitis.

CONCLUSION: KFD is a rare condition that presents like common conditions, such as tuberculosis and lymphoma. We underline the importance of pursuing pathological diagnosis, before starting a long and potentially harmful treatment.

KEYWORDS (MeSH): Lymphadenitis; Lymphadenopathy; Fever; Aseptic Meningitis.

CASE PRESENTATION

The patient is a 28-year-old previously healthy female, who presented at Kigali University Teaching Hospital with a one-week history of unilateral, painless, right neck swelling, fever and headache. She consulted a private clinic where she was given ibuprofen, paracetamol and cloxacillin without improvement of her symptoms. She lives and works in an urban environment with no history of obvious contact with *Tuberculosis*. She was born in the neighboring Democratic Republic of Congo and moved to Rwanda at a young age and has not traveled outside Rwanda since then.

On physical examination, she was fully alert with neck rigidity, febrile (39.2°C), tachycardic (113 bpm), normotensive (132/80mmHg), tachypneic (24cpm) and saturating at 90% on room air. She had a right cervical, mildly tender lymph node measuring 5X3 cm. The remainder of her physical exam was normal. Septic workup was unremarkable. The following are her laboratory tests and imaging.

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Table 1: Laboratory tests.

Laboratory tests	Value	Normal range
Complete blood count		
WBC	4.62*10³/ul	4.0 - 10.0
Hb	12.5g/dl	11.0 - 16.0
Platelets	238*10³/ul	150 - 400
Hemocultures (3)	Negative	
Urinalysis		
WBC	0/hpf	0 - 5
Gram stain	Negative	
CSF analysis		
Total protein	1.075 g/L	0.1 - 0.45
WBC	30/mm³	0 - 5
Lymphocytes	70%	
Neutrophils	30%	
Gram stain	Negative	
Culture	Negative	
Genexpert for MTB	Negative	
Others		
VDRL	Negative	
TPHA	Negative	
HBsAg	Negative	
Anti-HC Ab	Negative	
HIV	Negative	
Creatinine	66 umol/L	50 -110
AST	60 u/L	10 - 40
ALT	33u/L	7 - 50
Total serum protein	6.2g/L	6 - 8

WBC: white blood cells, Hb: hemoglobin, CSF: cerebrospinal fluid, MTB: MycobacteriumTuberculosis, VDRL: Venereal Disease Research Laboratory, TPHA: Treponema pallidum hemagluttin antigen, HBsAg: hepatitis B surface antigen, Anti-HC Ab: Anti-hepatitis C antibody, HIV: human immunodeficiency virus, AST: Aspartate aminotransferase, ALT: Alanine transaminase.

Chest CT scan revealed mediastinal lymphadenopathy. A fine needle aspirate of the cervical lymph node revealed fibrinoid material with mixed inflammatory infiltrate mainly neutrophils in hemorrhagic background. Lymph node biopsy revealed extensive necrosis, foamy histiocytes and small mature lymphocytes. The findings were consistent with KFD.

Three days after admission she developed left eye redness and blurred vision. Ophthalmology examination was consistent with left eye uveitis which was successfully treated with atropine, neomycin and dexamethasone eye drops. After one-week in the hospital, while we were pursuing further investigations, the patient's fever and headache resolved. One week later the patient's cervical lymphadenopathy also completely resolved and the patient was discharged. She remained asymptomatic one-year after discharge.

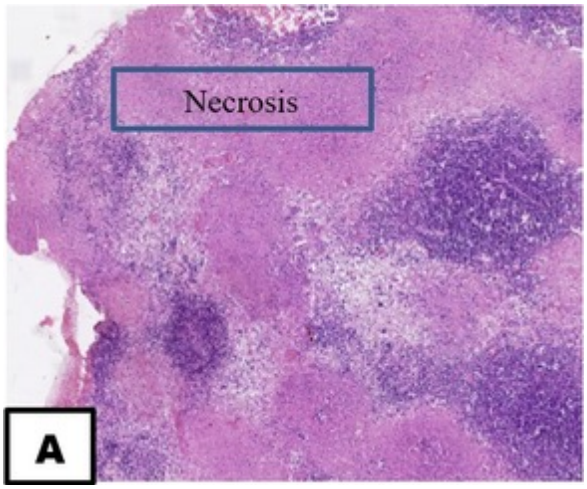

Fig. A: H&E stained (low power) microscopic images showing well encapsulated tissue with extensive necrosis and lymphocytic follicles.

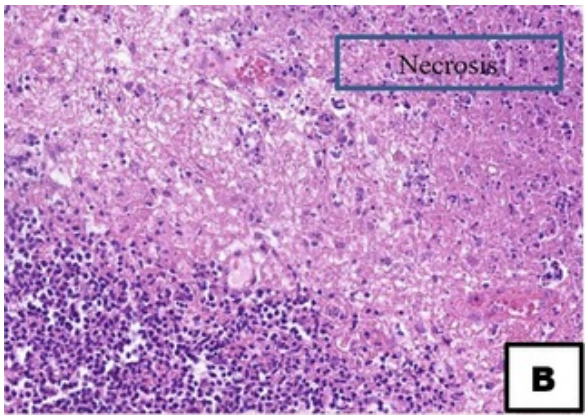

Fig. B: H&E stained (high power) microscopic images showing extensive necrosis (karyorrhexis, fibrin deposits), foamy histiocytes and small mature lymphocytes.

DISCUSSION:

Kikuchi-Fujimoto disease (KFD), also known as, histiocytic necrotizing lymphadenitis, is a self-limiting disorder involving mainly cervical lymph nodes. It was first described in Japan by Fujimoto and Kikuchi in 1972. It is common in Asian individuals below the age of 40, but it can also affect other populations [1]. The mean age at presentation is 32 years old. The female to male ratio of presentation is 3:1 [2].

Though the pathophysiology is not well understood, the extensive cell death seen in this condition is attributed to early apoptosis of CD8+ T-lymphocytes, which is characterized by excessive nuclear fragmentation (i.e. karyorrhexis). There are suggestions of an immune response of T cells and histiocytes to an infectious agent. Proposed infectious agents include Ebstein-Barr Virus (EBV), Human Herpes Virus 6 (HHV-6), Human Herpes Virus 8 (HHV-8), Human Immunodeficiency Virus (HIV), Parvovirus B 19, Yersinia Enterocolitica, and Toxoplasma [3]–[7].

KFD commonly presents with unilateral lymphadenopathy (56-98%), and sometimes with bilateral lymphadenopathy (31-46%). Lymph nodes size varies between 0.5 – 4cm [1]. Comparing the clinical presentation between male and female patients, males tend to be more symptomatic.

Table 2: Clinical presentation, comparing male and female patients

	Male	Female
Fever	67%	48%
Headache	20%	9%
Bilateral lymphadenopathy	46%	31%
Thrombocytopenia	29%	14%
Elevated CRP	78%	35%
Elevated LDH	80%	61%
Elevated ANA	10%	32%

CRP: C-reactive protein, LDH: lactate dehydrogenase, ANA: antinuclear antibody

Complete Blood Count (FBC) and Erythrocyte Sedimentation Rate (ESR) are usually normal. Granulopenia can be found in 25 - 58% of patients.

The diagnosis of KFD is made by clinical presentation, a characteristic disease progression, and histopathology demonstrating nodal architecture distortion, paracortical necrosis, and a large number of histiocytes. Differential diagnoses to consider include lymphomas with necrosis, tuberculosis, cat scratch disease, systemic lupus erythematosus, EBV, and herpes virus infection [1].

There is no treatment recommended for KFD, because symptoms usually resolve within 1 to 4 months. There are reports of use of steroids with some benefits in patients with severe symptoms [8]. Patients may have recurrent KFD, hence, they should be followed-up for several years [9]. In a case series of 102 patients, 7.8% of them had early relapse and 12.7% had late recurrence [10].

In our practice, the leading two differentials diagnoses in patients with fever and lymphadenopathy are tuberculosis and lymphoma. To our surprise none of these differentials were suggested by the pathologist. A second biopsy gave similar results, so we started to broaden our differentials. Considering that KFD is a rare condition, a second opinion sought in Japan confirmed our impression.

Our diagnosis KFD was based on the clinical presentation, disease evolution, and histopathology findings. Self-limiting unilateral cervical lymphadenopathy is typical for KFD. Usually symptoms resolve within 2 to 6 weeks [11]. Our patient presented with high CSF white cell count with lymphocytic predominance and high protein level. After having a negative Gram stain and culture, and a negative Genexpert for tuberculous meningitis, we concluded to aseptic meningitis. Aseptic meningitis, though rare, can be part of KFD [12].
The finding of lymphocytosis in the CSF is in our practice often followed by initiating treatment for tuberculous meningitis simply based on clinical presentation.

It is wrong to assume that, in our setting, every patient with lymphocytosis in the CSF has tuberculous meningitis. We know TB medications can be toxic with side effects ranging from a simple rash to hepatic fulminant failure [13]. A case of a 14 year-old boy with KFD who developed fulminant hepatic failure after starting empirical TB treatment illustrates the risk [13].

Uveitis is not common in KFD but it can occur [14],[15]. KFD is known to be associated with some viral and bacterial infections. However, there is no established causal relationship [11]. It is possible that our patient had a concomitant infectious process that we were not able to diagnose.

CONCLUSION:

The diagnosis of KFD should be included in patient with necrotizing lymphadenitis in the absence of other compelling diagnoses. In our setting, sometimes patients with lymphocytic-predominant cerebrospinal fluid are empirically treated for tuberculous meningitis. The present case report reminds us that it is worth thinking twice before starting a long, potentially harmful anti-tuberculous treatment in patients with such clinical presentation.

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