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Case Report

Kikuchi-Fujimoto Disease with Subsequent Meningoencephalitis: Insights into Rare Complications – A Case Report

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Abstract

Kikuchi-Fujimoto Disease (KFD) is a rare, benign, self-limiting condition primarily affecting young adults and is often misdiagnosed due to its nonspecific symptoms. We present a rare case of a 36-year-old man who presented with high-grade fever, cervical lymphadenopathy, and weight loss. Despite a comprehensive workup, involving imaging studies and laboratory investigations, the diagnosis remained elusive until a lymph node excisional biopsy confirmed the Kikuchi disease. The patient developed meningoencephalitis, a rare but severe complication of KFD, characterized by seizures and altered mental status.Supportive care including non-steroidal anti-inflammatory drugs, and corticosteroids are the mainstay of management. The patient was discharged with a good prognosis. This case highlights the diagnostic challenges and potential severe neurological complications of KFD, emphasizing the need for heightened awareness and vigilant follow-up.

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Introduction

Kikuchi-Fujimoto disease (KFD) is a rare, mysterious, non-threatening, self-limiting syndrome characterized by localized lymphadenopathy with tenderness, primarily in the neck area.[1] The common presenting symptoms are fever and night sweats; less frequent symptoms are weight loss, nausea, vomiting, and sore throat.[2] Fever could be associated with upper respiratory symptoms. KFD has also been reported to cause prolonged fever of unknown origin and cervical lymphadenopathy.[3] It is important to highlight that approximately one-third of patients display atypical peripheral blood lymphocytes.[4] Although KFD is a rare disease documented worldwide, most of these cases reported are in Asia with more prevalence among females aged 20-3.[5] KFD has been frequently misdiagnosed[6] So, it is essential to distinguish it from other potential diagnoses like lymphoma, infectious diseases, and autoimmune conditions such as systemic lupus erythematosus. The etiological factors of Kikuchi's disease remain a topic of debate; nevertheless, certain microorganisms, including the Ebstein-Barr virus and herpesviruses 6 and 8, are considered possible culprits.[7] Histologically, KFD is characterized by subacute necrotizing lymphadenopathy, paracortical lymph node expansion with patchy, well-circumscribed areas of necrosis showing abundant karyorrhectic nuclear debris and the absence of neutrophils and eosinophils.[8] This case study will emphasize the unusual clinical presentation and encephalitis, a rare complication, thus highlighting the necessity of timely diagnosis and management.

Case Presentation

A 36 years man, a quality inspector at a factory by occupation, having no comorbid but smoker for 15 years presented in emergency with complaints of high-grade fever with rigors and chills for 3 months which was on and off initially but continuous for 1 month, Neck swellings (lymphadenopathy) for 3 months. He also complained of dyspnea on exertion, body aches, headache, and neck pain. The headache was pan-cephalic and associated with fever. Constipation and nausea were his recent complaints for 3 days but there was no history of cough, loose stools, or burning micturition. He had undocumented weight loss but no history of tuberculosis contact or travel. On physical examination, systemic examination of respiratory, gastrointestinal, neurology, and genitourinary systems was unremarkable except lymphadenopathy. There was a 3×2 cm enlarged lymph

node on the right side and multiple small lymph nodes on the left side of the neck, medial axillary, and inguinal region. Signs of meningeal irritation were also negative. The patient was vitally stable but had a fever recorded at 103 F. The temperature chart is attached as Figure 1. Previously he had a history of chronic suppurative otitis media (CSOM) 10 years ago which was resolved after taking treatment at that time. He was in good health 3 months back when the fever started. First, he went to quacks where he was treated with unknown medication. Later on, he went to a tertiary care hospital where was advised to take a co-amoxiclav and clavulanic acid combination for 1 month along with analgesic and antipyretics after which he improved little, neck swellings reduced in size but he used to have high-grade fever. When he presented to us he was taking advised medication. We stopped antibiotics and admitted him for the workup of pyrexia of unknown origin including tuberculosis and lymphoma. His laboratory findings are shown in the table 1.

Table 1: *Frequency of allergies in a sample of 300 medical students in Lahore, Pakistan, in 2014*

Laboratory Parameter	Normal Range	Results Day 1	Results Day 10
Hemoglobin	14-18 g/dl	11.8 g/dl	11.1 g/dl
MCV	75-95 fl	99.5 fl	90.8 fl
WBC count	4-11 k/microlitre	3.3 k/ microlitre	3.3 k/ microlitre
Neutrophils	45-70%	38.5%	63%
Lymphocytes	20-50%	40.9%	26.5%
Monocytes	2-10%	18.5%	6.3%
Platelet count	150-450 k/ microliter	140 k/ microlitre	272 k/ microliter
ESR	0-10 mm/hr	85 mm/hr	
Creatinine	0.7-1.2 mg/dl	0.8	
Liver Function Test	Bilirubin/ALT/AST/ALP	Normal Range	
Viral Screening	HBsAg/ Anti HCV	Negative	
Blood Culture and Sensitivity	No Growth was obtained after incubation of 7 days		

Chest X-rays were performed in the initial workup in which he was reported to have coarse broncho-vascular markings and flattening of the left heart border. Echocardiography was advised and possible cardiac conditions were ruled out. A peripheral blood smear showed no significant findings except leukopenia and macrocytosis of red blood cells. Abdominal ultrasonography was also unremarkable. An otorhinolaryngology evaluation revealed the presence of old chronic suppurative otitis media (CSOM), which is currently dry and not contributing to the present illness. When the washout time of antibiotic was completed we sent his blood culture during the fever spike which resulted in no growth. Brucella serology was sent which was also negative. Meanwhile, we decided to start a prophylactic antibiotic, Meropenem, and later on doxycycline. Besides that, he was on Paracetamol thrice a day he had un-affected fever spikes. His lymph node excisional biopsy was performed and sent for a histopathology examination. The histopathology report showed reactive lymphoid follicular hyperplasia with karyorhectic changes suggestive of Kikuchi lymphadenitis. The patient was given NSAID (Ibuprofen) after the first dose of which the patient was afebrile. He was discharged on ibuprofen with a follow-up of 7 days. On the 7th day of the discharge, he was improved with a reduction in lymph node size. But a dramatic twist comes when he got fits with tongue bite and urinary incontinence followed by an altered state of consciousness, between the 12th -and 14th day of discharge. He was brought to the emergency of a nearby public tertiary care hospital where he was admitted on the lines of tuberculous meningitis. Computed tomography (CT)

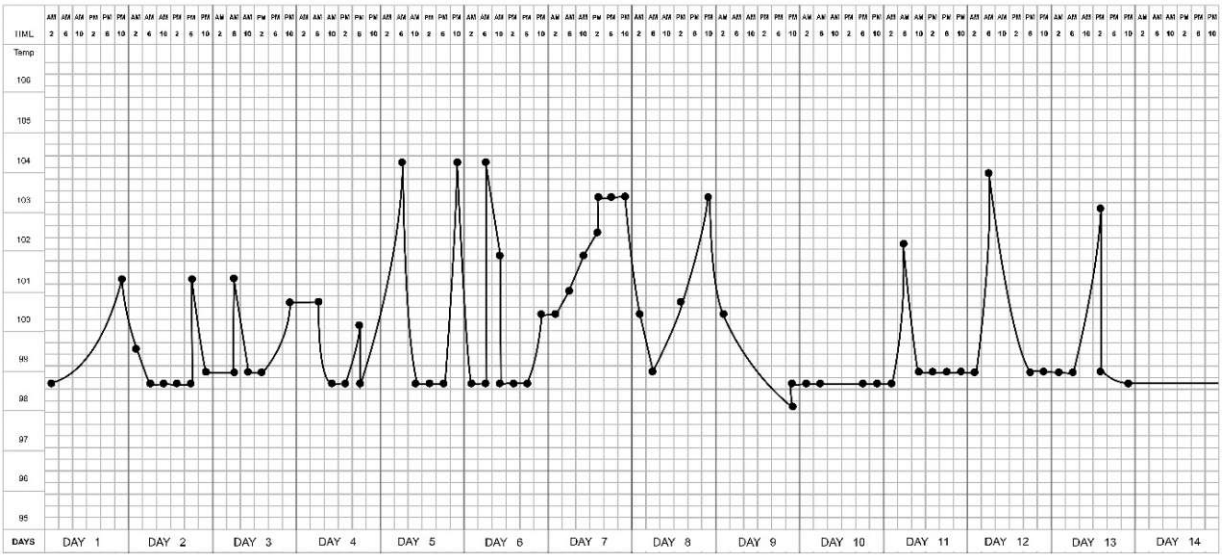

Figure 1: *Graph showing temperature charting*

brain was performed followed by magnetic resonance imaging (MRI) of the brain, which was unremarkable. The patient was discharged on request from there and admitted to a private teaching hospital. He was asked for a review of histopathology slides from a well-known laboratory. The lumber puncture was followed by a CSF examination, which did not reveal any significant findings. The revised histopathology report revealed a lymph node section showing focal, well-circumscribed foci of necrosis with abundant karyorrhectic debris and fibrin deposits. Lymphocytes and plasmacytoid monocytes are seen at the periphery of necrotic zones. Immunohistochemical staining was positive for CD 20 which highlights the reactive follicles. Histopathology images could not be availed due to outsourced reporting. Meanwhile supportive treatment was carried on. Finally, the patient improved clinically and was discharged.

Discussion

Kikuchi Fujimoto is a rare disorder, predominantly found in Japan.[9] A study conducted in Saudi Arabia revealed that only 0.5% of 920 lymph node biopsies exhibited characteristics of Kikuchi disease.[10] However, regional variation exists as demonstrated in a Korean study where 34% of cervical lymph node biopsies concluded for Kikuchi disease.[11] The cause of Kikuchi disease is not well understood, although infectious and autoimmune causes have been proposed.[12] Case reports have also described vaccination and COVID-19 infection serve as triggers.[12–15] This disease has three histological stages. First-Proliferative stage, with follicular hyperplasia with infiltrates of lymphocytes and histiocytes. The necrotizing- second stage, is distinguished by nuclear breakdown (karorrhexis) and multiple necrotic foci. The third stage, the xanthomatous stage, is characterized by foamy histiocytes with regression of necrotic areas.[16]

Table 2: *Overview of Comparative Studies*

Study	Patient Age (Years)	Clinical Presentation	Laboratory Findings	Diagnostic Methods	Management and Outcome
Khan et al. [17]	22y/F	Fever, Fatigue, Anorexia, Cervical lymphadenopathy (2x3cm) Duration: 2 Months	WBC: $12x10^9$/L	Excisional lymph node biopsy: lymph node hyperplasia and histiocytosis	Prednisolone and Paracetamol. Improved
MK et al.[18]	25y/F	Fever, Arthritis, Cervical lymphadenopathy (2x2cm) Duration: 15 Days	WBC: Not mentioned	FNAC: Reactive lymphadenitis,	NSAIDs Improved
Sarfraz et al.[19]	25y/M	Low-grade fever, Fatigue, and swelling in the neck (1.6x1cm) Duration: 1 Month	WBC: $5x10^9$/L	Ultrasonography, Excisional biopsy: Necrotizing lymphadenitis, histiocytic and interspersed nuclear debris	Paracetamol; Improved in 2 months
Kelner et al.[20]	25y/F	Painful neck swelling, intermittent fever, night sweats, and abdominal pain. Duration: 2-3 Weeks	WBC: $3.7x10^9$/L ANA: Negative Anti-DsDNA: Negative	CT Neck: Multiple lymph nodes with necrotic changes PET-CT: Hypermetabolic lymphadenopathy, Core Needle Biopsy: Necrotic tissue Excisional Biopsy: Lymphohistiocytic inflammation, karyorrhectic nuclear debris	Prednisolone; Rapidly improved but symptoms recurred after several months, second course of steroids was given leading to adverse effects. Hydroxychloroquine started; symptoms resolved in 4 months.
Song et al.[21]	20y/M	Fever, Headache, Skin rash, Cervical lymphadenopathy (2.1x8cm) Duration: 5 Days	WBC: $3.2x10^9$/L	Ultrasonography, Lymph node biopsy: lympho-histiocytic cells and karyorrhectic debris CT Brain plain, CSF examination	Prednisolone; The patient improved, No recurrence detected in 10 months follow-up

We present a rare case of Kikuchi Fujimoto disease complicated by meningoencephalitis. Only 41 cases of aseptic meningitis in Kikuchi disease have been reported.[21] The younger patients present with fever and tender lymphadenopathy whereas myalgia and weight loss are more common in adults.[22] Our patient, an adult male, presented with high-grade fever, cervical lymphadenopathy, and a history of weight loss which initially raised the suspicion for pulmonary tuberculosis due to the high prevalence of tuberculosis in our region. The physical examination was unremarkable except for cervical lymphadenitis and the laboratory results were either in the normal range or inconclusive, making the case challenging to diagnose. Cervical lymphadenopathy, a frequent finding of KFD, usually presents as unilateral cervical lymph node enlargement rather than bilateral nodal involvement.[23] Although our patient had bilateral lymph node involvement, the one-sided lymph node was markedly enlarged in size as compared to sub-centimeter lymph nodes on the other side of the neck. The size of the lymph node is about 1-2 cm which can be large up to 7cm; our patient had a lymph node of 3cm.[23] In a review of 244 cases of Kikuchi disease, Kucukardali et al. described common presenting symptoms after fever and lymphadenopathy including leucopenia (43%), high erythrocyte sedimentation rate (40%), anemia (23%), erythematous rashes (10%), joint pain (7%), and fatigue (7%).[24] The patient of our study had a high-grade fever for more than a month which is rarely found in this disease, rather studies suggest that Kikuchi disease commonly presents with low-grade fever which can persist for weeks.[25]

On peripheral blood smear leukopenia, anemia, and atypical cells have been reported in the literature which are consistent with our case except for atypical cells.[26] The type of anemia in our patient was macrocytic anemia as confirmed on blood film. In contrast, studies have reported microcytic and autoimmune hemolytic anemia in association with Kikuchi disease.[26,27] Macrocytic anemia has not been reported in KFD but it has been reported in VEXAS disease which mimics Kikuchi disease.[28] The complete blood count in our case also revealed a higher monocyte count as shown in the study of Song et al. where this differential monocyte count was 92%.[21] The diagnosis of Kikuchi disease is established through an excisional biopsy of the enlarged lymph node along with histopathology examination which is also crucial to rule out other possible conditions such as tuberculosis or lymphoma.[16]

We planned to start broad-spectrum antibiotics after sending blood culture and screening for Brucella as supported by the literature. Even though most of the patients presented with lymphadenitis have already taken empirical antibiotics for staphylococcus aureus and streptococcus pyogenes, still these bacteria should be considered along with other possible causes including Brucella, Bartonella, Yersinia, Toxoplasmosis, and mycobacterium which can trigger the disease. Nevertheless, cultures and other infectious investigations in Kikuchi Fujimoto give negative results.[16]

The mainstay of the management of Kikuchi disease is supportive care which involves using antipyretics and analgesics for symptomatic relief. However, corticosteroids can be used in severe cases.[16] Other treatment options, successfully used in the past, are hydroxylchloroquine, minocycline, and intravenous immunoglobulin.[16] The complications in KFD include weight loss in adult patients, hemophagocytic syndrome, arthritis, myocarditis, and hepatic dysfunction. Central nervous system involvement presents as aseptic meningitis, meningoencephalitis, acute cerebellar symptoms with tremors and ataxia, and optic neuritis.[1] Our patient had developed meningoencephalitis on recurrence of the disease as established by clinical presentation, brain imaging, CSF examination, and reconfirmation of histopathology report.

KFD, a self-limiting disease, carries a good prognosis, symptoms resolve spontaneously in 1 to 6 months duration. Nevertheless, affected patients should be on regular follow-up for years due to their conversion to lupus erythematosus.[1] A Korean study elaborates on this fact, 2.7% of their patients developed autoimmune diseases after KFD diagnosis.[29] Positive fluorescent antinuclear antibodies have been associated with a significant recurrence rate.[1] The fatality rate of the disease in severe and fatal cases has been reported at 2.1%, associated with hemophagocytic syndrome or connective tissue diseases.[1]

Conclusion

Kikuchi Fujimoto remains a diagnostic challenge due to its rarity and non-specific clinical presentation. Although it is a self-limiting disease with a favorable prognosis, the patient should be on regular follow-up for potential complications like aseptic meningitis or meningoencephalitis. Future studies should be focused on genetics and triggering factors that can drive the disease to these fatal complications.

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