Kikuchi Disease Unveiling Systemic Lupus Erythematous: A Rare Case of Initial Manifestation

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Abstract

Background: Kikuchi disease is a rare presentation, which typically presents with cervical lymphadenopathy and fever. Its association with Systemic Lupus Erythematous (SLE) is well established, although majority of SLE cases does not present with Kikuchi disease. We report a case, in which a young patient presented with fever and cervical lymphadenopathies for two weeks duration. This carries a broad differential and initially raising the possibility of infections or malignancies. However, after further clinical evaluation including cervical node biopsy, direct histological examination revealed Kikuchi disease. Combining all clinical information and laboratory data, we concluded that the patient's condition was consistent with Kikuchi disease associated with SLE with probable autoimmune hepatitis (AIH). This case illustrates a young female patient with clinical presentations of SLE associated with Kikuchi disease as first manifestation.

Keywords: Kikuchi Disease; Systemic Lupus Erythematous; Kikuchi Fujimoto Disease; Kikuchi Disease Related Autoimmune; Kikuchi Disease Related SLE; Multiple Lymphadenopathies.

Introduction

Kikuchi- Fujimoto's disease (KFD), also called Kikuchi histiocytic necrotizing lymphadenitis is a clinicopathologic diagnosis characterised by cervical lymphadenopathy, that usually runs a self- limiting course. As the name implies, lymph node microscopic examination shows foci of necrosis and histiocytic cellular infiltrate. It predominantly affects the young females with a male to female ratio of 1:4.[1,2] Given its association with auto immune diseases, it is important to exclude SLE, which may present concomitantly or several years after the diagnosis of Kikuchi disease.[1]

Besides lymphadenopathy, other frequently reported symptoms included fever (35%), malar rashes (10%), fatigue (7%) and joint pain (7%).[3] As for blood investigation, common abnormalities reported included leukopenia (18%), high ESR (16%) and anemia (9%).[3] Not to forget, KFD can also present with thrombocytopenia, normal count and sometimes with thrombocytosis.[4] KFD may carry risk of thrombophilia and thrombosis or association of Budd Chiari syndrome if there is concomitant presentation with SLE/APLS.[5]

Case Report

A 26-year-old lady, works as assistant pharmacist, previously a healthy individual presented to us with complaint of fever for two weeks, associated with intermittent abdominal discomfort, loose stool and vomiting. The patient had loss of appetite and documented weight loss about 6kg within two weeks. She noted multiple neck swellings, which were gradually increasing in size. She complained of multiple symmetrical polyarthralgia as well. Otherwise, she denied alopecia, oral ulcers, photosensitivity rash. There was no family history of connective tissue disorders. Denied previous history of tuberculosis or tuberculosis contacts. On clinical assessment she had bilateral cervical

lymphadenopathies, which were mobile, non-tender, non-matted with largest node measuring about 2x2cm. No enlarged lymph nodes elsewhere or hepatosplenomegaly present. Her initial laboratory investigations revealed leukopenia, transaminitis and elevated Lactate dehydrogenase(LDH). The laboratory findings are summarized in Table 1. Our differential diagnosis at that point were lymphoproliferative disease or tuberculosis lymphadenitis. Workup for lymphadenopathy was done. Her chest x-ray did not show any abnormalities. Blood and urine cultures were sterile. An otolaryngology consult was obtained for the neck swelling. A nasal endoscopy was done which showed no abnormalities.

Table 1: Blood investigation on admission.

Blood Parameters	Reference Ranges	On admission
Hemoglobin (g/dL)	12-16	12.5
Total white cells (per/µL)	40000-11000	2.93
Platelet (10^9/L)	150,000-400000	153
Sodium(mmol/L)	135-145	137
Potassium (mmol/L)	3.4-4.8	3.7
Urea(mmol/L)	2.4-7.4	3.8
Creatinine(µmol/L)	54-110	57
Corrected calcium(mmol/L)	2.2-2.7	2.22
Total bilirubin (µmol/L)	3.4-20	12.0
Alanine Transferase(u/L)	<55	153
Aminotransferase (u/L)	5-34	249
Alkanine Phosphatase (u/L)	40-150	71
Albumin (g/L)	35-54	38
Lactate Dehydrogenase (u/L)	<140	1444
C-reactive protein(mg/L)	<5	1.9
Erythrocyte Sedimentary Rate (ESR)	20mm	57
UFEME		Protein 2+,others: Neg
24 hours urine protein		1.29g/24 hour
Dengue serology NS1/IgM/IgG		Negative
Blood smear Malaria Parasite		No malaria parasites identified

Excisional biopsy was carried out and HPE composed of histocytes, plasmacytoid dendritic cells, eosinophilic material and abundant karyorrhectic debris, surrounding a central zone of overt necrosis which was consistent with Kikuchi lymphadenitis [Figures 1 and 2]. Additionally, no granuloma, atypical cells or malignancy seen. Epstein Barr was also ruled out by EBER ISH – Epstein Barr encoding region in-situ hybridization methodology. Her platelets ranged from 80-130 x 10^9/L .Considering the prevalence of malaria and tuberculosis in our region, screening for both conditions were done. On of D10 admission, her white blood cells started to drop further with an ANC of 0.6 Peripheral blood film did not show atypical cells. In addition to this her transaminitis were worsening. Serological test performed for viral hepatitis, as a potential cause for elevated liver enzyme.

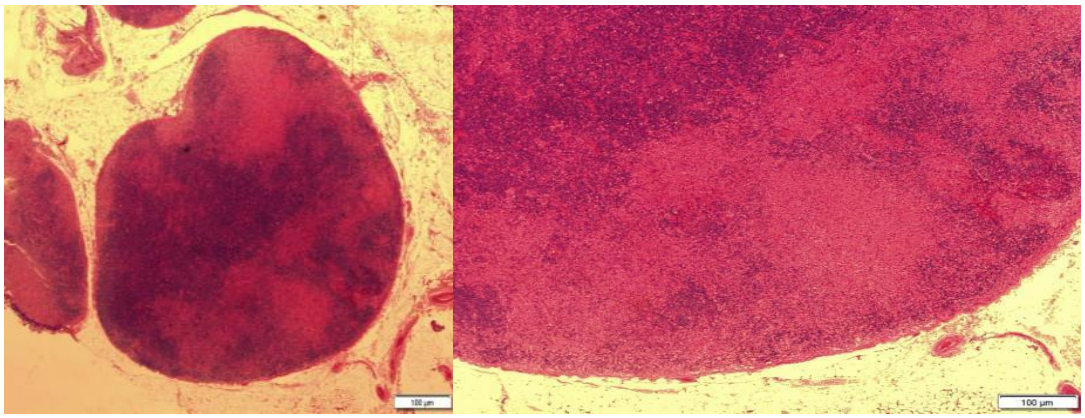

Figure 1: Showing the lymph node is effaced with expanded interfollicular areas.

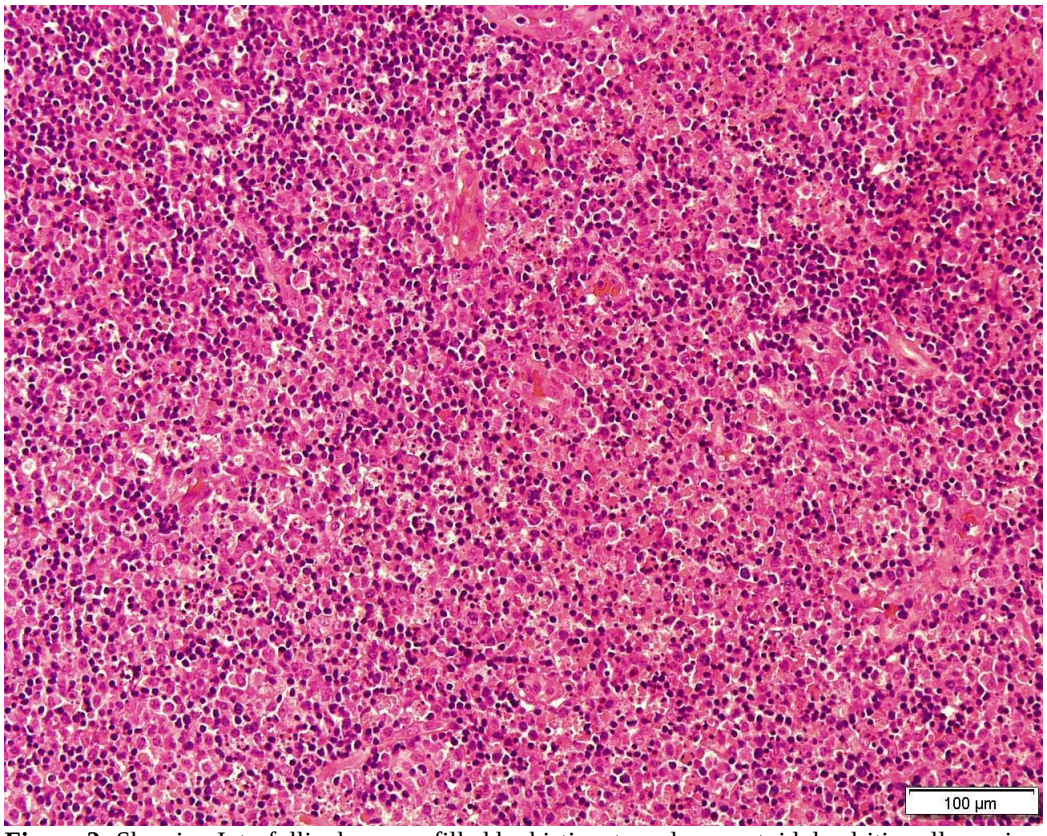

Figure 2: Showing Interfollicular areas filled by histiocytes, plasmacytoid dendritic cells, eosinophilic granular material and abundant karyorrhectic debris.

Additionally, autoantibodies for autoimmune hepatitis (AIH) were also analysed, which may be associated with SLE. Upon receiving the results of her connective tissue disease work up, namely Anti- nuclear antibody ANA which showed, homogenous pattern with a titre of 1:640, Anti-Smith, Anti- Ribosomal P, with low C3 along with presence of leukopenia and arthralgia, we reached a diagnosis of Systemic Lupus erythematous (SLE) which meets the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria. The elevated liver enzymes could have been part of SLE manifestation, lupoid hepatitis, or Autoimmune hepatitis or simply part of manifestation of Kikuchi disease. A definite confirmation requires further assessment, such as liver biopsy, which was not done in this case. By using simplified diagnostic criteria for autoimmune hepatitis, she was classified as probable autoimmune hepatitis without liver biopsy.

She was started on glucocorticoids therapy and hydroxychloroquine. She responded well following steroids initiation with improvement of symptoms. She was discharged with prednisolone 1mg/kg/day. Her final diagnosis was Systemic Lupus Erythematous (SLE) associated with Kikuchi disease with probable auto immune hepatitis

(AIH). She was reviewed two weeks post discharge, and she continued to improve clinically the cervical lymphadenopathies, which were reducing in size and blood parameters normalizing [Table 2]. Three months after her admission patient continued to remain well with regression of lymph nodes, normal blood parameters and resolution of other symptoms.

Table 2: Post discharge 2 weeks.

Blood Parameters	Reference Ranges	2 weeks post discharge
Hemoglobin (g/dL)	12-16	9.6
Total white cells (per/µl)	40000-11000	7.8
Platelet (10^9/L)	150,000-400000	244
Sodium(mmol/L)	135-145	139
Potassium (mmol/L)	3.4-4.8	3.8
Urea(mmol/L)	2.4-7.4	3.5
Creatinine(µmol/L)	54-110	46.5
Total bilirubin (µmol/L)	3.4-20	24.6
Alanine Transferase(u/L)	<55	79
Aminotransferase (u/L)	5-34	58
Alkaline Phosphatase (u/L)	40-150	127
Albumin (g/l)	35-54	37
Lactate Dehydrogenase (u/L)	<140	644
C-reactive protein(mg/l)	<5	12

Discussion

The Kikuchi-Fujimoto disease is also known as histiocytic necrotizing lymphadenitis and was initially described in Japan by Kikuchi and Fujimoto in 1972.[6] Kikuchi disease presence alongside SLE suggests possible underlying autoimmune mechanism. Numerous reviews have observed frequent co-occurrence of KFD, either diagnosed concurrently with or after the diagnosis of SLE.[7] In this case, SLE developed alongside KFD, as an initial presentation. Kikuchi's disease shares a sex and age predisposition with SLE which typically are young women, less than 30 years of age.[8] Though uncommon, Kikuchi disease also been reported in association to other autoimmune conditions and manifestations such as Autoimmune hepatitis, antiphospholipid syndrome, polymyositis, systemic juvenile idiopathic arthritis, bilateral uveitis, rheumatoid arthritis, and cutaneous necrotizing vasculitis.[9,10]

The exact cause of KDF is unknown, but few hypotheses suggest that they are possibly triggered by viral infection, given that often presentation is flu like symptoms. Possible viral association are Epstein Barr Virus (EBV), Human Herpes (HH8),Human Herpes 6 viruses, Human immunodeficiency virus (HIV), parvovirus B19, and parainfluenza viruses.[11,12] Diagnosing KDF can be challenging as it may mimic other diseases such as lymphoma, TB, viral lymphadenopathies or even SLE lymphadenopathies and often presents with leukopenia, transaminitis and raised LDH as the initial presentation which can overlap with the other diseases. Lymphadenopathy in SLE is a common presentation however its less recognized, as it is not a criterion for SLE diagnosis. A lymph node histology in KDF may show areas of necrosis and presence of histocytes and T-cells and may share similar histologic features with SLE. However, SLE-associated lymphadenopathy can be distinguished from KFD histologically by presence of Hematoxylin bodies; or lupus erythematous (LE) cells, Azzopardi phenomenon; and abundance of plasma cells. Yu et al. retrospectively studied the clinical and pathological features and found that C4d deposition, which reflected autoantibody-mediated complement activation, was noted in SLE but not in KFD.[13]

In conclusion, in this case the presentation of cervical lymphadenopathies, with constitutional symptoms, leukopenia and transaminitis and raised in LDH and ESR, prompted us for extensively workup for malignancy and tuberculosis. It is important to recognise Kikuchi disease as a cause of cervical lymphadenopathy in young patients and its diagnosis should prompt further evaluation for autoimmune association especially SLE. KDF, while infrequently encountered, tend to be a self- limiting condition with favourable prognosis, emphasizing the

importance of accurate diagnosis. It is essential to recognize this condition as it may be misinterpreted for other causes of lymphadenopathies and minimizes unnecessary laboratory investigations, misdiagnosis, and inappropriate treatment.

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