

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

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## ABSTRACT

Kikuchi disease is a rare condition, typically characterized by cervical lymphadenopathy and fever. Although its association with systemic lupus erythematosus (SLE) is well established, the majority of SLE cases do not present with Kikuchi disease. We report a case of a young patient who presented with fever and cervical lymphadenopathies for two-weeks. This presents a broad differential, initially suggesting 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 and probable autoimmune hepatitis. This case illustrates a young female patient with clinical presentations of SLE associated with Kikuchi disease as the first manifestation.

**K**ikuchi-Fujimoto's disease (KFD), also called Kikuchi histiocytic necrotizing lymphadenitis, is a clinicopathologic diagnosis characterized by cervical lymphadenopathy that usually follows a self-limiting course. As the name implies, lymph node microscopic examination shows foci of necrosis and histiocytic cellular infiltrate. It predominantly affects young females with a male-to-female ratio of 1:4.<sup>1,2</sup> Given its association with autoimmune diseases, it is essential to exclude systemic lupus erythematosus (SLE), which may present concomitantly or several years after the diagnosis of KFD.<sup>1</sup>

Besides lymphadenopathy, other frequently reported symptoms included fever (35%), malar rashes (10%), fatigue (7%), and joint pain (7%).<sup>3</sup> Regarding blood investigations, common abnormalities reported included leukopenia (18%), high erythrocyte sedimentation rate (16%), and anemia (9%).<sup>3</sup> KFD can also present with thrombocytopenia, a normal count, and sometimes with thrombocytosis.<sup>4</sup> KFD may carry the risk of thrombophilia and thrombosis or association with Budd-Chiari syndrome if there is a concomitant presentation with SLE/APLS.<sup>5</sup>

## CASE REPORT

A previously healthy 26-year-old woman, working as an assistant pharmacist, presented with a complaint of fever for two weeks, associated with intermittent abdominal discomfort, loose stool, and vomiting. She reported a loss of appetite and a weight loss of about 6 kg within two weeks. She noticed multiple neck swellings that were gradually increasing in size, and multiple symmetrical polyarthralgia. She denied alopecia, oral ulcers, photosensitivity rash, and a previous history of tuberculosis or tuberculosis contacts. There was no family history of connective tissue disorders. On clinical assessment, she had bilateral cervical lymphadenopathies, which were mobile, non-tender, and non-matted, with the largest node measuring about 2 × 2 cm. There were no enlarged lymph nodes elsewhere or hepatosplenomegaly present. Her initial laboratory investigations revealed leukopenia, transaminitis, and elevated lactate dehydrogenase (LDH) [Table 1]. The differential diagnosis at that time was lymphoproliferative disease or tuberculosis lymphadenitis. Further workup for lymphadenopathy was done. Her chest X-ray showed no abnormalities. Blood and urine cultures were sterile. An otolaryngology consult was obtained for the neck swelling. A nasal endoscopy showed no abnormalities.

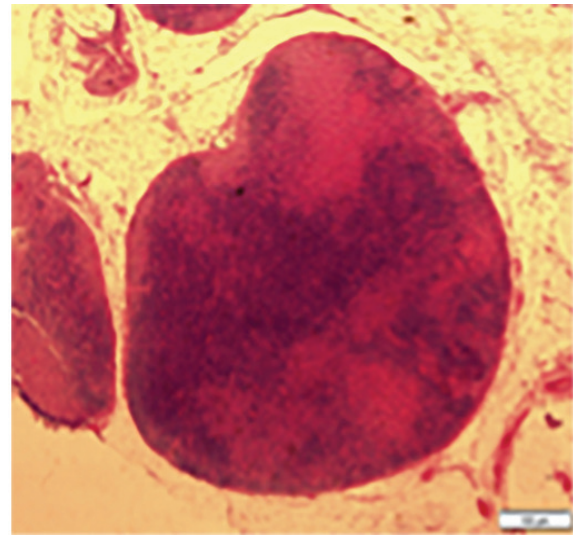
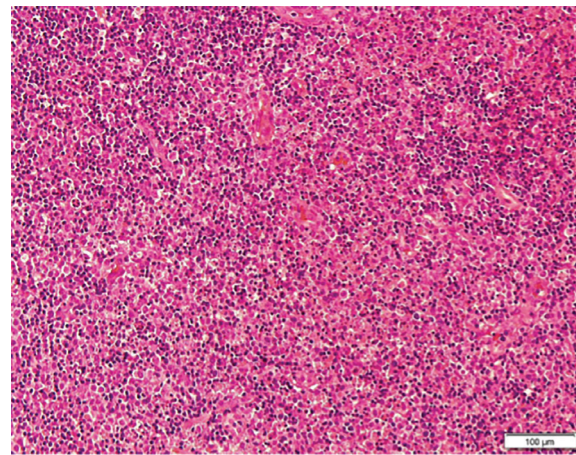
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**Table 1:** Blood investigation on admission.

| Blood parameters                   | Reference ranges | On admission            |
|------------------------------------|------------------|-------------------------|
| Hemoglobin, g/dL                   | 12–16            | 12.5                    |
| Total white blood cells, / $\mu$ L | 40 000–11 000    | 2.9                     |
| Platelet, $10^9$ /L                | 150 000–400 000  | 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, $\mu$ mol/L            | 54–110           | 57                      |
| Corrected calcium, mmol/L          | 2.2–2.7          | 2.2                     |
| Total bilirubin, $\mu$ mol/L       | 3.4–20.0         | 12.0                    |
| Alanine transferase, u/L           | < 55             | 153                     |
| Aminotransferase, u/L              | 5–34             | 249                     |
| Alkaline phosphatase, u/L          | 40–150           | 71                      |
| Albumin, g/L                       | 35–54            | 38                      |
| Lactate dehydrogenase, u/L         | < 140            | 1444                    |
| CRP, mg/L                          | < 5              | 1.9                     |
| ESR                                | 20 mm            | 57                      |
| Urinalysis                         |                  | Protein 2+, others: Neg |
| Urine protein, g/24 hours          |                  | 1.2                     |
| Dengue serology NS1/IgM/IgG        |                  | Negative                |
| Blood smear                        |                  | No malaria              |
| Malaria parasite                   |                  | parasites identified    |

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NS1: non-structural protein 1; IgM: immunoglobulin M; IgG: immunoglobulin G.

An excisional biopsy was carried out, and histopathological examination revealed histiocytes, 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 were observed. Epstein-Barr was also ruled out by Epstein-Barr encoding region in situ hybridization. Her platelet count ranged between 80 and  $130 \times 10^9$ /L. Considering the prevalence of malaria and tuberculosis in our region, screening for both conditions was done. On day 10 of admission, her white blood cell started to drop further with an absolute neutrophil count of 0.6. Peripheral blood film showed no atypical cells. In

**Figure 1:** The lymph node is effaced with expanded interfollicular areas.**Figure 2:** The interfollicular areas filled with histiocytes, plasmacytoid dendritic cells, eosinophilic granular material, and abundant karyorrhectic debris.

addition, her transaminitis was worsening, and she was evaluated for autoimmune hepatitis (AIH), which demonstrated positive AIH serology. Based on results of the connective tissue disease workup, namely antinuclear antibody with a homogenous pattern at a titre of 1:640, along with anti-Smith, anti-Ribosomal P, with low C3 levels, with leukopenia and arthralgia, the patient was diagnosed with SLE, meeting the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria. The elevated liver enzymes may have been part of SLE manifestation, lupoid hepatitis, AIH, or a manifestation of KFD. A definite confirmation requires further assessment, such as

**Table 2:** Blood investigation two-weeks post-discharge.

| Blood parameters                   | Reference ranges | 2-weeks post-discharge |
|------------------------------------|------------------|------------------------|
| Hemoglobin, g/dL                   | 12–16            | 9.6                    |
| Total white blood cells, / $\mu$ L | 40 000–11 000    | 7.8                    |
| Platelets, $10^9$ /L               | 150 000–400 000  | 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, $\mu$ mol/L            | 54–110           | 46.5                   |
| Total bilirubin, $\mu$ mol/L       | 3.4–20.0         | 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                    |
| CRP, mg/L                          | < 5              | 12                     |

CRP: C-reactive protein.

liver biopsy, which was not done in this case. By using simplified diagnostic criteria for AIH, the patient was classified as probable AIH 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 1 mg/kg/day. Her final diagnosis was SLE associated with KFD and probable AIH. At a two-week post-discharge follow-up, the patient continued to improve clinically, with decreasing cervical lymphadenopathies and normalization of blood parameters [Table 2]. At three months after admission, she remained well with regression of lymph nodes, normal blood parameters, and resolution of other symptoms. Informed consent was obtained from the patient.

## DISCUSSION

KFD, also known as histiocytic necrotizing lymphadenitis, was first described in Japan by Kikuchi and Fujimoto in 1972.<sup>6</sup> The association between KFD and SLE suggests a possible underlying autoimmune mechanism. Numerous reviews have observed frequent co-occurrence of KFD, either diagnosed concurrently with or after the SLE diagnosis.<sup>7</sup> In this case, SLE developed alongside KFD as an initial presentation. KFD shares a similar sex and age predisposition with

SLE, typically affecting young women age < 30 years.<sup>8</sup> Although uncommon, KFD also been reported in association with other autoimmune conditions and manifestations such as AIH, antiphospholipid syndrome, polymyositis, systemic juvenile idiopathic arthritis, bilateral uveitis, rheumatoid arthritis, and cutaneous necrotizing vasculitis.<sup>9,10</sup>

The exact cause of KFD is unknown; however, a few hypotheses suggest a possible viral trigger, given that the presentation is often flu-like symptoms. Possible viral association are Epstein-Barr Virus, Human Herpes 8, Human Herpes 6, HIV, parvovirus B19, and parainfluenza viruses.<sup>11,12</sup> Diagnosing KFD can be challenging as it may mimic other diseases such as lymphoma, tuberculosis, viral lymphadenopathies, or even SLE lymphadenopathies. Patients often present with leukopenia, transaminitis, and elevated LDH as the initial presentation, which can overlap with other diseases. Although lymphadenopathy is a common presentation of SLE, it is not a criterion for SLE diagnosis. A lymph node histology in KFD may show areas of necrosis and the presence of histiocytes and T-cells, and may share similar histologic features with SLE. However, SLE-associated lymphadenopathy can be distinguished histologically from KFD by presence of hematoxylin bodies or lupus erythematosus cells, Azzopardi phenomenon, and abundance of plasma cells. Yu et al,<sup>13</sup> 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.

## CONCLUSION

In this case, the presentation of cervical lymphadenopathies with constitutional symptoms, leukopenia, transaminitis, and elevated LDH and erythrocyte sedimentation rate, prompted extensive workup for malignancy and tuberculosis. It is essential to recognize KFD as a cause of cervical lymphadenopathy in young patients and its diagnosis should prompt further evaluation for autoimmune association especially SLE. Although KFD is infrequently encountered, it tends to be a self-limiting condition with favorable 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.

**Disclosure**

The authors declare no conflicts of interest.

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