Section: Clinical Immunology and Rheumatology

Case Series

UNMASKING KIKUCHI-FUJIMOTO DISEASE IN SOUTH INDIA: A CASE SERIES HIGHLIGHTING CLINICAL FEATURES AND DIFFERENTIATION FROM COMMON MIMICS

Nidhi Prabhu[1], Rajeswari Sankarlingam[2], Balaji Chilukuri[3], Lakshmi Tejaswi K[1], Vishwa Prakash Tiwari[1], Sharmin Mohmmed Ashraf Memon[1]

[1]*Postgraduate, Department of Clinical Immunology and Rheumatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India*
[2]*Professor and Head, Department of Clinical Immunology and Rheumatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India*
[3]*Professor, Department of Clinical Immunology and Rheumatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India*

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Corresponding Author:
Dr. Nidhi Prabhu,
Postgraduate, Department of Clinical Immunology and Rheumatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India
Email: nidhiprabhu44@gmail.com

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ABSTRACT

Kikuchi-Fujimoto Disease (KFD) is an uncommon, benign, and self-limiting condition characterized by lymph node inflammation. Due to its overlapping clinical features with tuberculosis and autoimmune conditions, it is frequently misdiagnosed. This case series aims to enhance clinical awareness by outlining the presenting features, histopathological findings, and outcomes of patients diagnosed with KFD. A retrospective analysis was performed on 12 confirmed KFD cases managed at the Department of Rheumatology, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, over a six-year period. The most frequent clinical presentation was painless cervical lymphadenopathy, often accompanied by systemic symptoms such as fever, hepatosplenomegaly, and skin rash. Histopathological evaluation commonly revealed necrotizing lymphadenitis, with CD68-positive histiocytes in several samples. Laboratory investigations showed leukopenia in most patients and features of macrophage activation syndrome (MAS) in a few. The majority of patients responded well to NSAIDs; however, corticosteroids and hydroxychloroquine were used in more severe cases. Outcomes were favorable in all monitored patients.

Keywords: Cervical Lymphadenopathy, Differential Diagnosis, Histopathology, Kikuchi- Fujimoto Disease

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), also referred to as histiocytic necrotizing lymphadenitis, is an uncommon, benign, and self-limiting inflammatory disorder first described in 1972 by Kikuchi and Fujimoto in Japan.[1,2] It predominantly affects young females, especially those under the age of 30, and has a higher prevalence in Asian populations, although cases have been documented globally across various age groups and ethnicities.[3]

The disease often presents with a sudden or gradual onset of unilateral, painful, and mobile cervical lymph node swelling, typically accompanied by systemic symptoms such as fever, fatigue, night sweats, weight loss, and skin rashes.[4] These cutaneous manifestations can vary from maculopapular eruptions to lesions that mimic lupus, making clinical diagnosis challenging.[5] Given its overlapping features with infections, malignancies, and autoimmune disorders—particularly systemic lupus erythematosus (SLE)—KFD may be misdiagnosed.[6]

The exact etiology remains unknown, although viral and autoimmune mechanisms are suspected. Multiple infectious agents, including Epstein-Barr virus, cytomegalovirus, human herpesviruses, and bacteria like Toxoplasma gondii and Bartonella henselae, have been investigated, but no definitive causative agent has been confirmed.[7-9] A genetic

predisposition has also been proposed, particularly involving HLA class II alleles (HLA-DPA1 and HLA-DPB1), especially in Asian individuals.[10]

Excisional lymph node biopsy remains the cornerstone for diagnosis, typically revealing foci of necrosis with karyorrhectic debris, numerous histiocytes, and plasmacytoid dendritic cells, notably without neutrophils or eosinophils. Immunohistochemistry findings often show the presence of CD8+ T lymphocytes and CD68+ histiocytes.[11,12] Importantly, the absence of hematoxylin bodies helps distinguish KFD from SLE-associated lymphadenitis.[13]

Management is primarily supportive, relying on antipyretics and analgesics for symptom relief. In severe or persistent cases, corticosteroids or immunomodulatory drugs like hydroxychloroquine may be considered.[14] Most patients recover spontaneously within 1 to 4 months. Recurrence is rare among adults (about 3–4%) but is relatively more common in children, reaching up to 39% in some reports.[15] Rarely, KFD may be complicated by conditions such as hemophagocytic lymphohistiocytosis (HLH).[16]

Awareness of KFD is crucial to prevent its misidentification as lymphoma or autoimmune disease. Regular follow-up is advisable, particularly due to the slight but recognized risk of developing SLE after resolution of KFD.[6,17]

Objective

The main aim of this case series is to report on the demographic characteristics, clinical features, histopathological patterns, and treatment outcomes observed in patients diagnosed with Kikuchi-Fujimoto Disease (KFD).

MATERIALS AND METHODS

This retrospective case series was carried out in the Department of Rheumatology at Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, spanning a six-year period from June 2018 to 2024. Patient records with a confirmed diagnosis of KFD were systematically reviewed.

Inclusion was restricted to individuals with a histopathological confirmation of KFD based on lymph node biopsy findings.

Laboratory parameters analyzed included:

- Complete blood count (CBC)
- Renal function tests (RFT)
- Liver function tests (LFT)
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Antinuclear antibody (ANA) testing
- Workup for macrophage activation syndrome (MAS), including serum ferritin, triglyceride levels, fibrinogen, and lactate dehydrogenase (LDH)

Patients with insufficient documentation or those identified with alternate etiologies for lymphadenopathy were excluded from the review.

RESULTS

This observational case series included 12 patients diagnosed with Kikuchi-Fujimoto Disease (KFD) confirmed by lymph node histopathology. Patient ages ranged from 10 to 31 years, with a mean age of 20.5 years. There was a notable female predominance, with a female-to-male ratio of 5:1. The most frequently observed symptom was non-tender cervical lymph node enlargement, followed by axillary lymphadenopathy. One case involved mesenteric lymph node enlargement.

Symptom duration prior to diagnosis varied from two weeks to three months, with a median of one month. Three individuals were initially misdiagnosed and treated for presumed tuberculous lymphadenitis. Features suggestive of macrophage activation syndrome (MAS) were noted in two patients. EBV serology was negative in eight patients, while one tested positive for Parvovirus. ANA positivity was seen in one case. Management approaches included NSAIDs for milder cases and corticosteroids or hydroxychloroquine for more severe presentations.

Table 1: Clinical Profile of Patients with Kikuchi-Fujimoto Disease (n = 12).

Parameter	Patients (n)
Mean Age (years)	20.5 (Range: 10–31)
Sex (Female : Male)	10 : 2
Lymph Node Tenderness	1
Cervical Lymphadenopathy	11
Axillary Lymphadenopathy	9
Other Lymphadenopathy (e.g., mesenteric)	3
Fever	6
Hepatosplenomegaly	5
Rash	2

The disease predominantly affected young females. Cervical lymphadenopathy was the most common site of involvement. Constitutional symptoms like fever and hepatosplenomegaly were also common. Only one patient had tender lymph nodes, emphasizing the typically non-tender presentation.

Table 2: Laboratory Findings, Histopathology, Treatment, and Outcome (n = 12).

Investigations / Treatment / Prognosis	Patients (n)
Histopathology Patterns	
Necrotizing (N)	4

Necrotizing + Proliferative (N/P)	5
Necrotizing + Xanthomatous (N/X)	2
All 3 Patterns (N/P/X)	1
CD68 Positivity	5
Leukopenia	9
MAS (Macrophage Activation Syndrome)	2
Treatment Regimens	
NSAIDs only	6
NSAIDs + Steroids	4
Hydroxychloroquine (HCQ)	4
HCQ + NSAIDs	2
Prognosis	
Resolution after 4 months	3
Resolution after 3 months	1
Lost to follow-up	2

Histopathological examination revealed necrotizing features in all patients, often with overlapping proliferative and xanthomatous changes. CD68 positivity, a key immunohistochemical marker, was noted in less than half. Most patients exhibited leukopenia, and two developed MAS requiring corticosteroid therapy. NSAIDs were the mainstay of treatment, with additional steroids or HCQ used in more severe or refractory cases. Most patients experienced resolution of lymphadenopathy within 3 to 4 months, though two were lost to follow-up.

[Figure 1] CD68 Immunohistochemistry Showing Histiocyte Positivity in Kikuchi-Fujimoto Disease

The image represents a histopathological section stained for CD68, a macrophage/histiocyte marker. The brown-stained cells indicate CD68-positive histiocytes, characteristic of Kikuchi-Fujimoto Disease (KFD). The circled area highlights a cluster of these positive histiocytes amid a background of small lymphocytes. This immunohistochemical finding supports the diagnosis of KFD by demonstrating the prominent histiocytic infiltrate, a hallmark of the necrotizing lymphadenitis seen in this condition.

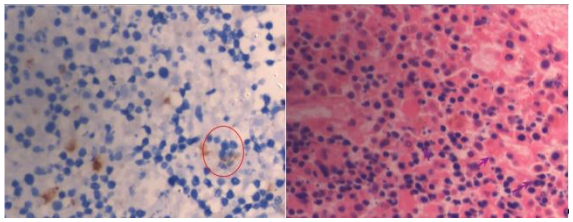

Fig: 1 CD 68 Positive & IHC-68+

DISCUSSION

Kikuchi-Fujimoto disease (KFD) is a rare, self-limiting lymphadenitis more frequently observed in Asian populations, potentially due to genetic susceptibility associated with specific HLA haplotypes such as HLA-DPA1 and HLA-DPB1.[18,19]

In our study, the mean age of presentation was 20.5 years, consistent with previous reports. Kim et al. reported a median age of 21.5 ± 11.8 years,[20] Dumas et al. reported 30 ± 10.4 years,[18] and Supari and Ananthamurthy observed a median of 26 years.[21]

A clear female predominance was observed (F:M = 10:2), echoing the findings of Dumas et al. who found a 77% female majority.[18] Kim et al. also noted a predominance of female patients among adults aged 20–29, whereas male preponderance was seen in children under 9 years, suggesting a possible interaction between sex and age in disease susceptibility.[20] Supari and Ananthamurthy similarly reported female preponderance.[21]

Cervical lymphadenopathy was the most common presentation, consistent with findings from Dumas et al. (90% cervical, 52% polyadenopathy),[18] Kim et al. (90% cervical, 8.8% axillary, 6.3% inguinal),[20] and Supari and Ananthamurthy (100% cervical among 74% of those with lymphadenopathy).[21] In our study, axillary lymphadenopathy was seen in 9 patients, and mesenteric lymphadenopathy was reported in one, comparable to the 2.5% rate in Kim et al.[20]

Only one of our patients had tender lymph nodes, whereas Kim et al. found lymph node tenderness in 60% of cases.[20] Fever and rash were additional features in our cohort. Dumas et al. reported fever in 67% and rash in 32.9%,[18] while Kim et al. noted these symptoms were more common in pediatric patients.[20]

Histopathologically, necrotizing lymphadenitis was the most common pattern in our study, which is consistent with Dumas et al., who observed necrotic subtype in 76.55% of cases, followed by xantho-granulomatous (19.1%) and proliferative (4.4%) subtypes.[18]

CD68 positivity, a key histiocytic marker, was observed in 5 of our patients, reinforcing the diagnosis of KFD and aligning with previously described immunohistochemical findings.[18,22]

Leukopenia was seen in the majority of our patients (75%), similar to Supari and Ananthamurthy, who reported it as the most common lab abnormality (65%),[21] and Dumas et al., who reported lymphocytopenia in 63.8%.[18]

Two patients had associated macrophage activation syndrome (MAS), a rare but severe complication of KFD, also described in prior case reports.[23]

Viral association was notable in one parvovirus-positive case, while 8 patients were EBV-negative. This corresponds to Dumas et al., who reported viral co-infections in 8 patients—2 with parvovirus, 4 with

EBV, and others with herpes and coxsackie viruses.[18] Kim et al. also observed higher EBV positivity in male children.[20]

In terms of treatment, NSAIDs were the most frequently used intervention in our study, followed by hydroxychloroquine (HCQ) and corticosteroids in severe cases. This parallels Kim et al., where NSAIDs were the mainstay, and corticosteroids were added if fever persisted [20]. Dumas et al. reported steroid use in 32% and HCQ in 17.6% of cases, while 3 patients received intravenous immunoglobulin.[18] Supari and Ananthamurthy initiated treatment with antibiotics, followed by corticosteroids in 3 patients.[21]

Although follow-up was incomplete for several patients, 3 showed complete resolution. This reflects the typically favorable prognosis of KFD.

Limitations of this study include the small sample size and retrospective design, which constrain the generalizability and depth of analysis. Nevertheless, the findings affirm known clinical, histological, and therapeutic patterns of KFD and underscore the need for clinician awareness.

CONCLUSION

Kikuchi-Fujimoto Disease (KFD) should be included in the differential diagnosis of not only typical cases involving cervical lymphadenopathy but also when lymph node enlargement occurs in atypical regions, such as the axillary or mesenteric areas, particularly if the nodes are painful. Due to its clinical and histopathological resemblance to conditions like tuberculosis and autoimmune disorders—especially systemic lupus erythematosus (SLE)—KFD is at risk of being misdiagnosed, potentially resulting in unnecessary or incorrect treatments.

Clinicians must remain vigilant and consider KFD in patients presenting with signs of infection or features indicative of macrophage activation syndrome (MAS). Prompt and accurate diagnosis is essential, as the disease generally resolves on its own and carries a favorable prognosis when managed with supportive therapy.

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