

Kikuchi-Fujimoto Disease: A Study Of 67 Cases From Coastal South India

Basavaprabhu Achappa

Kasturba Medical College, Mangalore, Manipal Academy Of Higher Education, Manipal

Nipuni Chamathka Herath

Kasturba Medical College, Mangalore, Manipal Academy Of Higher Education, Manipal

Jyoti Ramanath Kini

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

Ramesh Holla

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

Bodhi Sebastian

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

Nikhil Victor Dsouza (✉ dmikhildsouza@outlook.com)

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

<https://orcid.org/0000-0001-6627-1987>

Deepak Madi

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

Soundarya Mahalingam

Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal

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Abstract

Background Kikuchi-Fujimoto disease is a rare, benign condition, of unknown etiology, presenting as cervical lymphadenitis, usually tender and maybe associated with systemic symptoms. Despite the extensive literature on this disease, it continues to be misdiagnosed owing to its misleading clinical presentation. Results The mean age in our study was 26.9 (± 11.3) years with a female majority of 65.7%. The clinical presentation of most cases was, tender swelling over the side of the neck (n =50, 74.6%). On local examination, the mean length and width were 2.3 (± 1.0) cm and 2.2 (± 0.7) cm respectively. Histopathological examination revealed that most patients presented in the proliferative stage (n =40, 59.7%). In 83.6% of the patients lymphadenopathy resolved in less than 2 months. Follow up of these patients over 9 months revealed that a vast majority of the patients underwent full recovery with symptomatic treatment (n =42, 62.7%). Conclusions The disease is prevalent in young, female patients of Asian descent and often presents as cervical lymphadenopathy. Early diagnosis with excisional lymph node biopsy is crucial to avoid unnecessary investigations and treatment. Treatment is only symptomatic unless complicated, where steroid therapy is considered. Kikuchi's disease has an excellent prognosis with almost no risk of fatality.

Background

Kikuchi-Fujimoto disease (KFD), also known as "histiocytic necrotizing lymphadenitis" is a rare condition of unknown etiology. This benign condition presents as cervical lymphadenopathy, usually tender and is often associated with systemic symptoms like fever¹.

Identified first by 2 Japanese pathologists, independent of each other in the year of 1972, KFD was noted to have a higher incidence in Asian patients², Kikuchi disease continues to be misdiagnosed till date¹. Therefore, the awareness of this condition amongst clinicians and pathologists alike would be fruitful as it would aid in the early detection and prevention of life threatening sequelae such as malignancies³.

Kikuchi's disease is seen more frequently in young adults, with a mean age between 20–30 years⁴ but it can occur in any age group¹. Even though a female predominance is reported in many previous cases, some studies done in Asia show a male to female ratio of 1:1¹. The rare involvement of the heart, liver and lungs increases the fatality of an otherwise self-limiting disease².

The most common clinical feature is cervical lymphadenopathy, with or without systemic features, such as fever, fatigue, headache and night sweats⁵. The lymphadenopathy is usually under 4 cm⁶, and in most cases can be tender or painful². Hepatosplenomegaly has been reported in a few cases¹.

Both the etiology and pathogenesis of this disease is still unknown¹. Clinically and histologically, the disease is often misdiagnosed as tuberculosis, lymphoma or systemic lupus erythematosus (SLE)⁴. KFD can be seen in patients with previous history of SLE, it can coexist with SLE or complicate into SLE⁷. This

association with SLE was more common in Asian than European patients⁶. Meanwhile, a significant number of patients were found to have underlying viral infections⁶.

The gold standard investigation for diagnosis is by histopathological examination of an excisional biopsy obtained from the affected lymph node⁷. Histologically, altered lymph node architecture by nodules in the cortex, and apoptotic cells with areas of necrosis accumulation of crescentic histiocytic, and the absence of eosinophils and basophils are typical fine-needle aspiration cytology features seen in KFD^{6,8}. Due to challenges faced in diagnosing KFD, three evolving histologic patterns have been proposed by pathologists based on key morphologic features. Namely, they are proliferative, necrotizing and xanthomatous⁷. Most patients have normal laboratory findings¹. However, a few cases with mild anemia, elevated Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP), along with leucopenia, and elevated Lactate Dehydrogenase (LDH) have been reported rarely³.

Even though, this disease almost always runs a benign course and resolves in several weeks to months in most patients^{6,9}, it is seen to increase the risk of SLE and lymphoma⁷. Treatment if necessary is symptomatic with analgesics and antipyretics¹. Kikuchi's disease has a very low recurrence rate of and only a few fatalities have been reported¹. The use of corticosteroid therapy is still under debate for the management of recurrent cases¹.

Despite the extensive studies done on Kikuchi's disease, it continues to be misdiagnosed till date. The objective of this study was to promote awareness among clinicians and pathologists alike. Therefore, this study discusses the clinico-epidemiological presentations of the disease, the pathological morphology commonly found in these cases and the importance of follow up of these patients to ensure complete recovery and avoid possible sequelae and complications.

Results

The baseline characteristics of the results are shown below in the in Table 1. The age of our study population ranges from 4 to 77 years. The mean age is 26.9 (\pm 11.3) years and a median age of 27 years (IQR: 18–32 years). As shown below Kikuchi's disease commonly affects younger adults between the ages of 21 to 40 years (n = 44, 65.7%). Kikuchi's disease was seen more in female patients (n = 44, 65.7%). When the occupation of the study population was analyzed, most of the patients were found to be homemakers (n = 27, 40.3%).

Table 1
Baseline characteristics of Kikuchi Fujimoto disease
patients (N = 67)

Baseline Characteristics	Number	Percentage
Age group (years)		
< 21	18	26.9
21–40	44	65.7
41–60	03	04.5
61–80	02	03.0
Sex		
Female	44	65.7
Male	23	34.3
Occupation		
Homemaker	27	40.3
Minors/students	21	31.3
Business	14	20.9
Semi-skilled worker	02	03.0
Retired	01	01.5

Table 2 demonstrates the distribution of chief complaints at presentation in Kikuchi's patients. A vast majority of the patients presented with tender swelling over the side of the neck (n = 50, 74.6%). Local examination revealed, the length and width of the cervical lymph nodes ranged from 0.5 to 5 cm and 1 to 5 cm respectively, with mean length of 2.3 (\pm 1.0) cm and mean width of 2.2 (\pm 0.7) cm. Patients also presented with complaints of fever (n = 35, 52.2%) and hepatosplenomegaly (n = 10, 14.9%) due to the systemic involvement of the disease.

Table 2
Distribution pattern of the clinical presentation of KFD (N = 67)

Presenting complaints	N*	n (%)
Tender swelling over side of neck	50	74.6
Fever	35	52.2
Hepatosplenomegaly	10	14.9
Non tender neck swelling	07	10.4
Axillary lymph node enlargement	06	09.0
Associated cough	03	04.5
*Multiple responses		
The histopathological profile of all patients was analyzed after classifying the findings of excision biopsies to the three morphological stages are given in Table 3. As shown in the table given, most of the patients were in the proliferative stage (n = 40, 59.7%).		

Table 3
Histopathological profile of Kikuchi's disease patients (N = 67)

Histopathological profile of KFD	N	n (%)
Proliferative phase	40	59.7
Necrotizing phase	16	23.9
Xanthomatous phase	11	16.4

The duration of lymphadenopathy in Kikuchi's disease patients ranged from a few days to 6 months. In most patients, lymphadenopathy resolved in less than 2 months (n = 56, 83.6%).

Table 4
Duration of Lymphadenopathy of Kikuchi's disease patients (N = 67)

Duration of Lymphadenopathy	N	n (%)
0 to 15 days	24	35.8
15 to 2 months	32	47.8
2 months to 6 months	09	13.4
> 6 months	02	03.0

The patients were followed-up over a period of 9 months to observe the outcomes of Kikuchi's disease as seen in Table 5. A vast majority of the patients recovered with symptomatic treatment (n = 42, 62.7%). Meanwhile steroid use was successful in treatment of KFD patients with systemic symptoms (n = 17, 25.4%), and 1 such patient presented with signs of neurological involvement which also resolved following treatment with steroids. A few patients were found to have a self-limiting course of Kikuchi's disease (n = 6, 12.2%). Recurrence of Kikuchi's disease was observed after treatment only in 2 patients during this study period.

Table 5
Outcomes of Kikuchi's disease patients (N = 67)

Outcomes	N	n (%)
Complete recovery with symptomatic treatment	42	62.7
Complete recovery with steroids	17	25.4
Complete recovery with no treatment	06	09.0
Recurrence	02	03.0

Discussion

Kikuchi Fujimoto disease is a rare, self-limiting condition that is usually prevalent in Asian countries, clinically presenting as tender cervical lymphadenopathy with or without systemic symptoms. The etiology of the disease is yet to be uncovered, although certain studies have suggested an underlying viral infection or autoimmune disease to trigger the onset of Kikuchi Fujimoto disease². A hospital based case study was conducted on 67 patients diagnosed with Kikuchi's disease, in order to determine the sociodemographic profile, symptomatology, and the outcome of the disease.

The mean age of Kikuchi's disease prevalence was found to be 27.1 years in this study while in a study done in Sub-Saharan Africa, in October 2017, an average of 21 years was recorded¹⁰. The youngest patient in our study was a 4 year old girl and the oldest, a 77 year old man. Of the study population 16 were children (ranging from 4–18 years old) with confirmed cases of Kikuchi's disease. A study done on 6 confirmed pediatric cases of Kikuchi's disease, in North India, in September 2019 reported a mean age of 10.8 years¹⁵.

On analysis of the gender prevalence in this study, a female predominance of 1.91:1 was observed. Meanwhile, in a study done South India, there was a significant female majority of 2.4:1⁹. However, a gender comparison of 1:1 was observed in the results obtained from a study conducted in Italy, in September 2016⁵. A reversal of the gender ratio in our study was observed in a study carried out in Korea which showed a significant male majority of 2.8:1¹⁶, and another conducted in North India where the ratio was 2:1¹⁵.

Younger females were noted to be more predisposed to KFD in our study with ages ranging from 4–38 years, all considerably younger than their male counterpart in this study. A study of 9 patients was conducted in Sri Lanka by Abeysekara R A et al, where all the cases were female patients in the age group of 12–30 years¹³. A similar study was carried out by Adhikari R C et al, in Nepal where 5 of the 6 cases were females and the age range was 13–32 years¹⁴.

The most common clinical presentation of these patients was tender swelling on the side of the neck (74.6%). Similar results were obtained from a study done in Michigan, in May 2018 with 60–90% of the cases having posterior cervical lymphadenopathy¹. Systemic symptoms such as fever (52.2% of the cases) and hepatosplenomegaly (14.9% of the cases) was found abundantly in this study. Fever was noted to be associated frequently with tender cervical lymphadenopathy (n = 30, 44.8%). This coexistence of symptoms was replicated in the Michigan study in 35–77% of the patients¹. Tender cervical lymphadenopathy was the most common symptom in studies done in Italy⁵ (60–98%), Saudi Arabia² (56–98%) and Michigan¹ (60–90%). The involvement of axillary lymph nodes was encountered in 9% of the cases in this study, while the same in a study conducted on 24 cases in Bangalore yielded, 13%⁹.

One 22 year old male patient in this study presented with symptoms of cervical lymphadenopathy for 15 days associated with systemic symptoms of fever, neck stiffness and meningitis, was treated with steroids, tapered over a period of 1 month. Follow-up over 2 years revealed that lymphadenopathy subsided in 3 months and the patient recovered fully with no recurrence reported. In a study done in Japan by Komagamine T et al, which reported 5 cases of recurrent aseptic meningitis associated with Kikuchi's Disease, all the cases resolved within several months with 3 requiring treatment with steroids¹¹. Thus the use of steroids in patients with recurrence of Kikuchi Fujimoto disease with neurological involvement is considered beneficial following extensive investigation to ensure its safety¹¹.

The histopathology findings of the excisional lymph node biopsy remains gold standard for confirming Kikuchi's disease. In this study, the findings were sub grouped into 3 morphological phases as done in previous studies^{5,7,8}, and a vast majority of the confirmed cases presented in proliferative phase of KFD (n = 40, 59.7%).

In contrast to a study that was conducted in Bangalore, in 2013, where the lymphadenopathy lasted from 1 week to 3 months⁹, this study results suggested a longer duration of symptoms and varied from, 2 weeks to 6 months.

The follow up outcomes of the patients over a period of 9 months revealed that all recovered fully with no complications in this study.

A significant majority of our patients recovered after symptomatic management (62.7% of the cases), which was the choice of initial treatment in previous studies as well^{1,11,15}. One fourth of the patients in this study were treated successfully with steroids (25.4%). A similar result was obtained in a study done

by Guleria et al in 2019, where 2 of the 6 patients required steroid therapy¹⁵. In a study done in Florida, in 2014, the treatment with methylprednisolone showed a drastic response within 24 hours⁶.

Even though Kikuchi's disease is known to be a self-limiting condition, this study showed that only a small fraction of patients recovered completely without any treatment (9%). In contrast, in Florida, majority of the patients had self-limiting cases of KFD which typically lasted 1 to 4 months⁶, while in a study conducted in England, following the hospital visit for the lymph node biopsy, most of their symptoms resolved spontaneously within 6 months⁷.

There was minimal recurrence of 3% when patients were followed up for 9 months in this case study, similar results were observed in a studies done in Michigan¹, Saudi Arabia² and Spain¹² where the recurrence rate reported was 3–4%. Even though there was no recurrence of symptoms in the children reported in our study, Han H J et al in Korea, recorded a recurrence rate of 27% after a follow up of 1 year¹⁶. Meanwhile, a study done in Florida revealed that recurrences in Kikuchi's disease can occur as late as 8 years following the initial presentation and in this study the recurrence was reported as 15%⁶. Therefore, long-term follow-up is essential to determine the rate of recurrence of KFD.

Conclusion

Kikuchi-Fujimoto disease is a rare, idiopathic condition which presents as a diagnostic challenge to both pathologists and clinicians due to its misleading presentation. Demographically, the disease is prevalent in young, Asian, female patients and often presents as cervical lymphadenopathy. Early diagnosis with excisional lymph node biopsy is crucial to avoid unnecessary investigations and treatment for this self-limiting condition. Treatment is only symptomatic unless complicated, where steroid therapy is considered. KFD has an excellent prognosis with almost no risk of fatality. Long term follow up of patients is vital to prevent recurrence and complications of this condition.

Therefore, KFD patients should not only be diagnosed early, but long term follow-up with annual screening for SLE and blood ESR levels is advised to prevent misdiagnosis and complications⁷.

From a clinical standpoint, early diagnosis is essential to prevent extensive investigations, unnecessary treatment and to avoid rare complications. Kikuchi-Fujimoto disease should be considered in young females presenting with cervical lymphadenopathy with nodal biopsy showing necrosis and karyorrhexis.

Methods

The study was a record based retrospective study was carried out among all patients diagnosed with Kikuchi's disease in Mangalore. The diagnosis was confirmed following histopathological examination of the excision biopsy of the lymph nodes of suspected patients in the Pathology Department in Kasturba Medical College, Mangalore. The Institutional Ethics Committee (IEC) of Kasturba Medical College, Mangalore (Manipal Academy of Higher Education) approval was obtained prior to starting the study.

The permission to access the medical records of Kikuchi's patients was obtained from the Pathology department.

The records of KFD patients during the period of April 2011 to April 2019 was reviewed and information on demographics, clinical profile and histopathological data of Kikuchi's patients seeking medical care (of the histopathologically confirmed cases through excision biopsy) was recorded in a semi structured proforma. The proforma included the relevant clinico-epidemiological information about the patient inclusive of clinical presentation, associated co-morbidities, examination findings, investigations done, pathological morphology as well as any complications or sequelae on follow up over a period of 9 months.

Histopathological examination of the excision biopsy of all suspected cases of KFD was carried out. The results obtained were categorized into 3 phases. Namely, proliferative phase, xanthomatous phase and necrotizing phase. The classical presentation of the proliferative stage was histiocytes, dendritic cells, lymphocytes and nuclear fragments. In the xanthomatous phase the predominant feature was foamy histiocytes within the lesions. Necrotizing phase typically shows extensive necrosis with karyorrhectic nuclear debris and coagulative necrosis and complete loss of lymph node architecture. The diagnosis of KFD was confirmed based on these morphological findings.

The data collected was analyzed using Statistical Package for Social Sciences (SPSS) version 20 to analyse the clinico-epidemiological data, clinical presentation, local examination findings, histopathological presentation as well as outcomes on follow up. This data was expressed as proportions, mean, standard deviation, median and Inter Quartile Range (IQR).

Abbreviations

KFD: Kikuchi Fujimoto disease;

SLE: Systemic Lupus Erythematosus;

ESR: Erythrocyte Sedimentation Rate;

CRP: C-Reactive Protein;

LDH: Lactate Dehydrogenase;

IQR: Inter Quartile Range;

IEC: Institutional Ethics Committee;

SPSS: Statistical Package for Social Sciences

Declarations

Ethics approval and consent to participate

The Ethics approval was obtained from the Institutional Ethics Committee, Kasturba Medical College, Mangalore (IEC KMC MLR10-19/505)

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

- NVD, BA and JK contributed to the conception, design and analysis of the study and drafted the manuscript.
- CH and BS contributed to the acquisition of data and have drafted the manuscript.
- RH contributed to the analysis and interpretation of study data
- DM and SM contributed to the analysis and interpretation of study data.
- All authors have read and approved the final manuscript

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Not Applicable

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