



Original Research Article

Kikuchi-Fujimoto disease on aspiration cytology: diagnostic dilemma and clinicopathological correlation – A retrospective study in a tertiary care hospital

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ABSTRACT

Introduction: Kikuchi - Fujimoto disease (KFD), also known as Histiocytic necrotizing lymphadenitis is a benign, uncommon, self-limited disease of unknown etiology. Young females are primarily affected and it manifests primarily as cervical lymphadenopathy with tenderness at times. Kikuchi and Fujimoto, way back in 1972, reported it from Japan, independently and simultaneously, as a type of lymphadenitis associated with numerous histiocytes and extensive nuclear debris. The present study aims to study the key cytomorphological features of KFD along with its clinicopathological correlation.

Materials and Methods: This present study was carried out in a tertiary care hospital for a period of one year. The cases that were diagnosed as KFD on Fine needle aspiration cytology (FNAC) and whose follow up histopathology was confirmatory were included in the present study. Papanicolaou stain (PAP stain), Hematoxylin and eosin stain (H&E), and May-Grunwald Giemsa stain (MGG stain) was done on smears. Following cytological features were evaluated; cellularity, crescentic histiocytes, plasmocytoid monocytes, karyorrhectic debris and intra and extra cytoplasm apoptotic bodies.

Result: Females in the age group of 31-40 years were most commonly affected with cervical lymphadenopathy as the presenting feature. The most common clinical diagnosis rendered by clinicians was tuberculosis. Karyorrhexis, crescentic histiocytes and plasmacytoid monocytes were the key cytological features.

Conclusion: This study emphasizes on the key cytological features of the rare entity of KFD and its clinicopathological correlation. Knowledge and timely diagnosis of this rare entity avoids unnecessary surgical intervention and helps in timely management.

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1. Introduction

Kikuchi and Fujimoto disease (KFD), also known as (Histiocytic necrotizing lymphadenitis) is a benign, uncommon, self-limiting disease of unknown etiology. Young females are primarily affected and it manifests primarily as cervical lymphadenopathy with tenderness at times.¹

Kikuchi² and Fujimoto,³ way back in 1972, reported it from Japan, independently and near about simultaneously, as a type of lymphadenitis associated with numerous histiocytes and extensive nuclear debris.

Autoimmune and viral etiologies have been suggested, though its etiopathogenesis is not fully understood.⁴ It is often diagnosed clinically, and misdiagnosed on pathology as reactive lymphoid hyperplasia, metastasis, malignant lymphoma, tuberculosis, systemic lupus erythematosus (SLE) lymphadenopathies and Kawasaki disease.⁴ Accurate diagnosis by fine needle aspiration cytology (FNAC) can obviate the need for excisional biopsy. In patients with typical clinical features and characteristic findings in lymph node cytology, is sufficient enough to diagnose KFD. Clinicians and as well as many pathologists are not very familiar with this rare entity. The aim of the present study is to identify the key cytological features of KFD along with

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its clinicopathological correlation and address its diagnostic dilemmas.

2. Materials and Methods

This present study was carried out in Department of Pathology, G.K General Hospital, Bhuj for a period of one year. The cases that were diagnosed as KFD on Fine needle aspiration cytology (FNAC) and whose follow up histopathology was confirmatory were included in the present study. Details of age, sex, sites of FNAC and their clinically diagnosis were recorded. FNAC was done with 23 & 24 Gauge needle and alcohol fixed and air dried smears were prepared, stained and examined. Papanicolaou stain (PAP stain) (BIO LAB) and Haematoxylin and eosin stain (H&E) (J.K. Diagnostics) were done on wet fixed smears. May- Grunwald Giemsa stain (MGG stain) (HIMEDIA) was done on air dried smears. Ziehl-Neelsen stain (ZN stain) (HIMEDIA) was done where ever needed. Smears were examined carefully and detailed cytomorphological features were assessed. Following points were noted in cytology-Cellularity, crescentic histiocytes, plasmacytoid monocytes, karyorrhectic debris and intra and extra cytoplasmic apoptotic bodies.

3. Results

1. Cytological examination revealed the presence of karyorrhectic debris in 94.73% cases. Polymorphous population of lymphoid cells were present in 63.15%. (Table 1)
2. Corresponding histopathology of the lymph node in cases of KFD shows the presence karyorrhectic nuclear debris, abundant crescentic histiocytes and plasmacytoid monocytes. (Figure 1a, 1b)
3. Kikuchi histiocytes are crescentic histiocytes with eccentrically placed twisted, crescentic or distorted nuclei with ingested intracytoplasmic karyorrhectic debris. They were present in 89.47% cases. [(Table 1) (Figure 2)]
4. Plasmacytoid monocytes (acidophilic cells) with eccentric, pyknotic nuclei and pink condensed cytoplasm, were present in 73.68% cases. [(Table 1)(Figure 3, thin arrow)]
5. Non phagocytic histiocytes were also present in the present study. These are histiocytes with lobulated or twisted nuclei without intracytoplasmic debris.(Figure 3, thick arrow)
6. Maximum smears were moderately cellular in 73.68% cases. (Table 2)

4. Discussion

Kikuchi- Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis is a rare, benign, self limiting

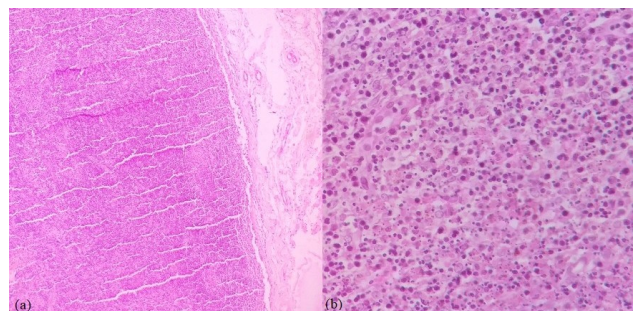


Fig. 1: (a) H&E (100 X) Corresponding histology of the lymph node shows the presence of karyorrhectic debris; (b) H&E (400 X) Corresponding histopathology shows the presence karyorrhexis, abundant crescentic histiocytes and plasmacytoid monocytes.

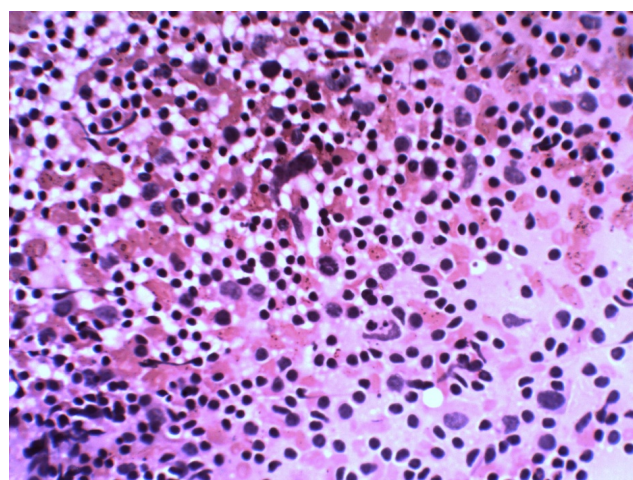


Fig. 2: H&E (400 X) Cytological examination shows the presence of kikuchi histiocytes, lymphocytes and plasmacytoid monocytes.

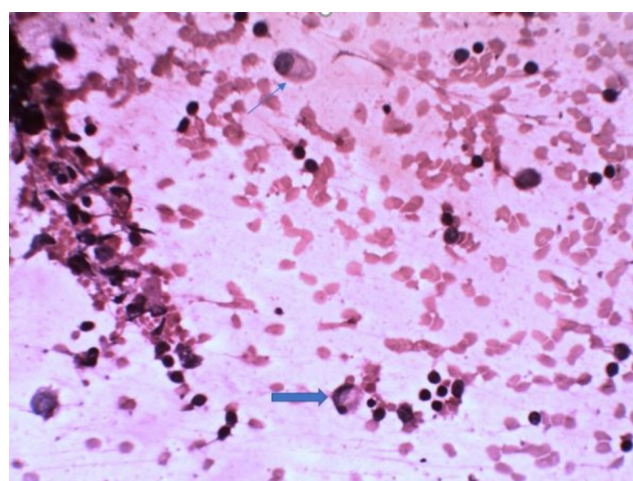


Fig. 3: H&E (400 X) Cytological examination shows the presence of nonphagocytic histiocytes (thick arrow), lymphocytes and plasmacytoid monocytes (thin arrow).

Table 1: Presence of different cell types in KFD

S.No	Cell type	Number	Percentage (%)
1.	Phagocytic crescentic histiocytes	17	89.47
2.	Plasmacytoid monocytes(acidophilic cells)	14	73.68
3.	Karyorrhectic debris	18	94.73
4.	Polymorphous lymphoid cell population	12	63.15
5.	Neutrophils	1	5.26
6.	Plasma cells	2	10.52

Table 2: Presence of cellularity in KFD

Cellularity	Number	Percentage (%)
Low	2	10.52
Moderate	14	73.68
High	3	15.78

disease of unknown etiology. It primarily affects young females presenting as cervical lymphadenopathy.⁵ Kikuchi disease is a benign uncommon disease reported almost simultaneously, though independently by Kikuchi² and Fujimoto³ in 1972 from Japan.

Many speculations regarding the etiology of this disease have been put forward. Earlier *Yersinia enterocolitica*, *Brucella*, *Bartonella henselae*, *Entamoeba histolytica* and *Toxoplasma gondii* were suggested as possible causative agents on the basis of the positive serological tests, but there was not enough evidence to support this hypothesis.⁶ Infectious and autoimmune are the two most common theories explored in literature. Role of Epstein barr virus (EBV) and other viruses have been questioned, as serological tests have proved non confirmatory.⁷

Role of viral infection due to the presence of upper respiratory tract infection prodrome, presence of atypical lymphocytes, necrosis, immunoblasts and expansion of para cortical zone has also been suggested.⁸ KFD has a world wide distribution with Asiatic and Japanese population having a higher prevalence.⁸

The age range in the present study was 20-50 years. Out of 19 cases, females were maximally affected (15/19 cases) in the age group, 31-40 years. Cervical lymphadenopathy was the most common site of lymphadenopathy [(14/19) (73.68%)].

Most common clinical diagnosis was tuberculosis [(10/19) (52.63%)] followed by reactive lymphoid hyperplasia [(8/19) (42.10%)].

Precise diagnosis of KFD can be made on FNAC, though it is difficult at times. This unnecessitates the need for excisional biopsy, as medical treatment with corticosteroids in patients with more severe clinical course gives rewarding results at times.⁴ Studies have stated that SLE, tuberculous lymphadenitis malignant lymphoma, benign lymphadenopathies and infectious lymphadenitis are the important differential cytopathological diagnosis of KFD.^{4,5} This was also the findings in the present study

when evaluating the other differentials of the cytological features of necrosis, polymorphous population of lymphoid cells, histiocytes and reactive immunoblasts.

It is the constellation of these cytopathological features, which permits the accurate diagnosis of KFD on FNAC, viz the presence crescentic histiocytes also known as the kikuchi histiocytes, plasmacytoid monocytes and karyorrhectic debris. Neutrophils are usually sparse or absent.⁹ In the present study also neutrophils were present in only one case. (Table 1)

Few studies^{9,10} state that non phagocytic histiocytes, with twisted and folded nuclei can also be present along with immunoblasts. Non phagocytic histiocytes were also present in our study that prompted us to search for the kikuchi histiocytes (Figure 3). We recommend that in the absence of the epithelioid histiocytes and neutrophils, and in the presence of necrosis, if non phagocytic histiocytes are seen, one must search for the pathognomic kikuchi histiocytes.

In the present study also, 89.47%, 76.68% and 94.73% cases respectively (Table 1) showed the presence of crescentic histiocytes, plasmacytoid monocytes and karyorrhectic debris. These findings were similar to other studies.^{9,10}

Kuo TT in their study¹¹ described three stages of this disease, viz ; proliferative, necrotizing and xanthomatous. Crescentic histiocytes, plasmacytoid monocytes, karyorrhectic debris and atypical lymphocytes are present in the proliferative stage. Karyorrhectic debris, eosinophilic necrosis, plasmacytoid monocytes, abundant histiocytes and variable number of lymphocytes are present in necrotizing adenitis stage. The ancillary studies for acid fast bacilli are usually negative in most cases. Karyorrhectic debris, abundant foamy histiocytes, minimal or no necrosis are seen in xanthomatous stage. Necrosis is present in most of the stages, hence the synonym necrotizing histiocytic lymphadenitis.⁸ Karyorrhexis an exclusive feature of KFD.¹⁰⁻¹² These findings were similar to our study also.

Karyorrhectic debris was present in 94.73% cases. (Table 1)

SLE lymphadenopathy can be mistaken for KFD, hence differentiation is very critical. SLE like KFD usually occurs in young women. Lymphadenopathy is usually cervical or generalized.¹³ SLE is an autoimmune disorder, characterized by the presence of antinuclear antibodies (ANAb) and anti double stranded (ds) DNA antibodies. On FNAC polymorphous population of reactive lymphoid cells, macrophages, immunoblasts of different morphology and Hematoxylin bodies (nuclear debris) and scant granular necrotic debris are present similar to KFD.^{14,15}

It is the presence of this necrotic debris, polymorphous population of lymphoid cells and macrophages that places it in the differential diagnosis of KFD. Moreover, at times in areas of necrosis, blood vessels showing the Azzopardi phenomenon may be seen. Cervical lymphadenitis present in both the conditions (SLE&KFD). However, the presence of increased ESR, clinical features of the disease, presence of double standard DNA positivity aims at the diagnosis of SLE. In SLE, plasma cells are prominent. In KFD, plasma cells and neutrophils are sparse.^{15–17} In the present study also plasma cells and neutrophils were present in 10.52% and 5.26% respectively. (Table 1) Plasmacytoid monocytes is an exclusive feature of KFD that was present in 73.68% cases. (Table 1) (Figure 3)

The presence of extensive necrosis of cytology and histopathology makes KFD difficult to differentiate from tuberculous lymphadenitis. ZN stain must be done in all these cases.

The necrotizing form of KFD may be difficult to differentiate from SLE and tuberculous lymphadenitis.^{18,19} Though abundant karyorrhectic debris may be seen in tuberculous lymphadenitis, it is the presence of caseous necrosis admixed with epithelioid histiocytes, Langhans giant cells that confirms the diagnosis of tuberculous lymphadenitis. Neutrophils are also present at times. Neutrophils are usually conspicuous by their absence in KFD as was seen in the present study also.²⁰

At times it may be difficult to differentiate reactive lymphoid hyperplasia from KFD. However the presence of the plasmacytoid monocytes (acidophilic cells) helps to differentiate KFD from reactive lymphoid hyperplasia.²⁰

High grade lymphoma may be difficult to differentiate to KFD due to the presence of abundant immunoblasts of reactive nature found in the proliferative phase of KFD.^{18,19}

KFD is a type of cervical lymphadenitis that occurs rarely in children.²¹ KFD is rarely reported in children and is misdiagnosed as reactive lymphoid hyperplasia or malignancy clinically and pathologically also.^{1,4,22} Most of clinical diagnosis in our study was that of tuberculous lymphadenitis and reactive lymphoid hyperplasia. The present study addresses the clinicopathological correlation along with cytopathological features in KFD. Few studies have been reported so far.^{11,21}

In this regard interpretation errors are the most important causes of missing out of the diagnosis of KFD. Immunohistochemistry findings suggestive of KFD are CD3+, CD8+, CD20-, CD4, lymphoid cell population and CD68+ and myeloperoxidase (MPO) positive kikuchi histiocytes in the affected foci.²¹ A variable number of CD8+ T cells can be present, but B cells are nearly always absent in KFD. No immunohistochemical stain is a substitute for a Well fixed Hematoxylin and eosin stained section.

Following are the key features that need to be evaluated on FNAC of KFD -

1. Plasmacytoid monocytes many a times are absent. In such cases one must look for crescentic histiocytes with ingested debris and karyorrhectic nuclear debris.
2. Plasmacytoid monocytes if present along with necrosis, it's an important diagnostic clue.

Following are the key features that need to be evaluated on histopathology of KFD-

1. Neutrophils and eosinophils are conspicuously absent, an important clue in the diagnosis of this entity.
2. Patchy, well circumscribed areas of necrosis are present in Kikuchi – Fujimoto disease.
3. Abundant histiocytic accumulation at the edge of necrosis.
4. At the edge of necrosis, clusters of plasmacytoid monocytes, dendritic cells and immunoblasts are present.
5. Presence of thrombosed vessels at periphery are seen.^{16,23}
6. Predominance of the different cell types depend upon the histologic phase of Kikuchi Fujimoto disease as described by Kuo TT in their study.¹¹
7. Low power patterns for recognition of lymph nodes are very important.²⁴

Morphological evaluation is the predominant mode of diagnosis of Kikuchi Fujimoto disease. Hence the importance of identification of the key points and addressing the diagnostic dilemmas.

Diagnostic dilemmas arise many a times in KFD. At times on FNAC the presence of patchy necrosis in the absence of the crescentic histiocytes is misdiagnosed as tuberculosis or SLE. Though on meticulous search the presence of crescentic histiocytes and presence of plasmacytoid monocyte points to the diagnosis.⁹ Plasmacytoid monocytes are usually not easily observed and hence also missed at times on cytological evaluation of smears for KFD.⁹ However in the present study, plasmacytoid monocytes were seen in 73.68 % cases (Table 1)(Figure 3). The same situation also applies for histopathology. The presence of the key features of kikuchi histiocytes, karyorrhectic nuclear debris along with

plasmocytoid monocytes points to the diagnosis of KFD.¹¹ (Figure 1a, b)

Similar to the study by William et al⁹, our study emphasized that the presence of the triad of karyorrhectic debris, kikuchi histiocytes and plasmocytoid monocytes in the background of polymorphous population of lymphoid cells for the diagnosis of kikuchi lymphadenitis.

5. Conclusion

This benign, enigmatic self limiting rare entity is a dilemma for both the clinician and pathologist. This present study emphasizes on the key cytopathological features of this entity and the diagnostic dilemmas of this entity. Clinicians as well as many pathologists are unfamiliar with this entity. Timely diagnosis of this entity avoids unnecessary surgical excision.

6. Source of funding

None.

7. Conflict of Interest

None.

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