KIKUCHI-FUJIMOTO DISEASE- CLINICOPATHOLOGICAL ANALYSIS OF 35 CASES

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ABSTRACT

BACKGROUND

Kikuchi-Fujimoto disease has become a common cause of lymphadenopathy in many parts of the world. The cause and pathogenesis still remains a mystery. Systemic morphological studies of the disease are few from India.

Aims of this study were-

1. To delineate the clinical and lab features as well as lymph node morphology of Kikuchi-Fujimoto disease and to compare the above features with previous studies.
2. To compare the proliferative subtype of the disease with high-grade lymphoma and devise a scoring system that aids in differential diagnosis.

MATERIALS AND METHODS

35 consecutive patients diagnosed to have Kikuchi-Fujimoto Disease on lymph node biopsy in Calicut Medical College during the period January 2006 to December 2007 were evaluated for their clinical details. Their lymph node biopsies were reassessed; 15 lymph node biopsies reported as high-grade non-Hodgkin lymphoma were compared with proliferative subtype of Kikuchi Fujimoto Disease.

RESULTS

The mean age in the study was 25.4 years with female: male ratio of 2.5. Cervical nodes were involved in almost all the cases. Significant number of cases were associated with leukopaenia. Of the 35 cases 17 were proliferative type (48.6%), 16 were necrotising type (45.7%) and 2 were xanthomatous type (5.7%). A scoring system was devised for discriminating between KFD and high-grade lymphoma noting certain microscopic features.

CONCLUSION

Kikuchi-Fujimoto disease is a benign self-limiting condition, which commonly affects cervical lymph nodes of young women. Histologically, the node can be subtyped into 3 categories. A scoring system devised can be used to discriminate between proliferative subtype of Kikuchi-Fujimoto disease and high-grade lymphoma.

KEYWORDS

Kikuchi-Fujimoto Disease, Histological Subtypes, Scoring System to differentiate from Lymphoma.

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BACKGROUND

In 1972, Kikuchi[1] and Fujimoto et al[2] independently described Kikuchi-Fujimoto Disease (KFD) as unusual form of benign lymphadenitis. The majority of patients are under 30 years of age[3] with an increased incidence in females.[4,5] A viral or autoimmune cause has been suggested as aetiology. Various viruses include Epstein-Barr virus, cytomegalovirus, parvovirus B19, HHV-6 and HHV-8.[6,7] It is possible that KFD might represent an exuberant T cell-mediated immune response in genetically susceptible people to a variety of nonspecific stimuli.[8] KFD most frequently manifests as acute/subacute onset of cervical adenopathy associated with fever.[9,10] Less commonly other lymph nodes may be affected.[11] Unusual features include skin and neurological involvement.[12,13] SLE has developed in some patients, thought to have true KFD.[14,15,16,17] With regard to this topic in 2003, Hu and coworkers concluded that the KFD-like lymphadenitis coexisting with SLE should be regarded as a lupus lymphadenitis on the basis of several histologic criteria.[18] In patients with KFD, diagnostic laboratory and radiologic test findings are nonspecific. Complete blood count shows mild granulocytopaenia in 20% - 50% of patients.[3,5,9,10] The characteristic histopathologic findings of KFD include irregular areas of coagulative necrosis with abundant karyorrhectic debris.[19,20] The cells include histiocytes with varying morphology, plasmacytoid monocytes, immunoblasts and small and large lymphocytes. Atypia in the reactive immunoblasts can be mistaken for lymphoma. There usually are areas of paracortical hyperplasia. Neutrophils characteristically are absent and plasma cells are absent or scarce.[3,5] Kuo proposed classification of the histopathologic features of KFD into 3

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evolving histologic stages: proliferative, necrotising and xanthomatous.[5] The histologic differential diagnosis of KFD includes mainly reactive lesions such as lymphadenitis associated with SLE, herpes simplex and other microorganisms and non-Hodgkin lymphoma. KFD typically is self-limited and lasts 1 to 4 months. Only a very few fatal cases have been reported.[21,22,23]

Aims and Objectives

1. To delineate the clinical and lab features as well as lymph node morphology of Kikuchi-Fujimoto disease and to compare the above features with previous studies.
2. To sub-classify the disease based on node histology and probe for correlations of the different subtypes with clinical and laboratory features.
3. To compare the proliferative subtype of Kikuchi-Fujimoto disease with high-grade lymphoma and devise a scoring system that aids in accurate differential diagnosis.

MATERIALS AND METHODS

Subjects- 35 consecutive patients diagnosed to have Kikuchi-Fujimoto Disease on lymph node biopsy in Calicut Medical College during the period from January 2006 to December 2007. Patients were evaluated for the clinical details, haematological investigation and fine needle aspiration cytology if any. The patients were followed up to look for remission or recurrence and the results of anti-nuclear antibody assay were collected.

Their lymph node biopsies were reassessed. The parameters specifically noted and scored were-

1. Architecture of lymph node: Whether total or partial effacement of architecture were present.
2. Follicular hyperplasia.
3. Normal paracortex.
4. Paracortical hyperplasia.
5. Proliferation centers.
6. Geographic necrosis.
7. Apoptosis: (Mild/Moderate/Severe).
8. Foam cells.

Classification- Each node examined and grouped into the following categories.

1. Proliferative Type (PT): Proliferative centres predominate and necrotic area is less than 10% of the total.
2. Necrotic Type (NT): Area of geographic necrosis is more than 10% of the total.
3. Xanthomatous Type (XT): Foam cell collections account for more area than proliferation centers or necrosis.

Differentiation from High-Grade Lymphoma

15 lymph node biopsies reported as high-grade Non-Hodgkin Lymphoma (NHL) during the study period were compared with lymph nodes grouped as proliferative type of KFD. The presence or absence of following parameters were assessed.

1. Total effacement.
2. Follicles.
3. Normal paracortex.
4. Paracortical hyperplasia.
5. Geographic necrosis.
6. Mitotic count per high-power field.
7. Pleomorphism (Graded as 1: Nil or Minimal; 2: Moderate; 3: Marked).
8. Apoptosis (Graded as 1: Nil or minimal; 2: Moderate; 3: Marked uniformly distributed).
9. Foam cell collections.

The parameters that were significantly different in the two groups were used to devise a scoring system that is capable of discriminating between the two conditions.

Analysis- The data were entered in Excel 8 sheet and analysed using Epi Info 2000.

RESULTS

The age of the 35 cases in the study ranged from 8 years to 50 years. The mean age was 25.4 years. The female-male ratio was 2.5. Cervical nodes were involved in almost all the cases. More than two-thirds of the cases had lymphadenopathy of 4 to 6 weeks duration. The clinical and laboratory parameters of all the cases are shown in Table 1. The difference between cases with and without fever is shown in Table 2.

Parameter	Result
Fever	57.1% (20 cases)
Tenderness (%)	17.1% (6 cases)
Haemoglobin (mean g/dL)	10.9
TLC (mean/mm^3)	5170
Leukopaenia	27.3% (9 cases)
Lymphocytes (mean/mm^3)	2159
ESR > 60 mm/I^{st} hour	38% (13 cases)
ESR– 10 - 59 mm/I^{st} hour	62% (22 cases)
Antinuclear antibody	0%

Table 1. Clinical and Laboratory Parameters (N=35)

Parameter	Fever+ (20 Cases)	Fever- (15 Cases)	P
Tenderness (%)	25.0	6.7	0.17
TLC (mean/mm^3)	4475	6238	0.017
Leukopenia (%)	45.0	0	0.017
Lymphocytes (mean/mm^3)	1698	2868	0.003
ESR (mean mm^3/hr)	64	37	0.036

Table 2. Clinical and Laboratory Parameters in Cases with and without Fever (N=35)

Total leucocytes count, absolute lymphocyte count & ESR show statistically significant difference in groups with & without fever (P value of <0.05).

We have got followup in 22 cases. All had remission within 3 - 7 weeks' period.

Histopathology

Histology of the lymph node in KFD is a mixture of different patterns. All cases showed partial effacement of architecture. Retained follicles were seen in 9 out of 35 cases (25.7%). Most follicles were small and residual. Widened paracortex was a feature in most cases. Many cases showed areas of paracortical hyperplasia characterised by a starry sky appearance.

There were 5 distinct areas seen in lymph nodes affected by KFD.

1. Follicles.
2. Paracortex (normal or hyperplastic).
3. Proliferation centers.
4. Geographic necrosis.
5. Foam cell collections.

The proliferation centers were light staining areas within the paracortex with collections of transformed cells (Figure 1). There was varying degrees of apoptosis in the proliferation centers (Figure 2).

Areas of geographical necrosis varied from small foci to large patches (Figure 3). Foam cells were seen scattered (Figure 4) or as small groups.

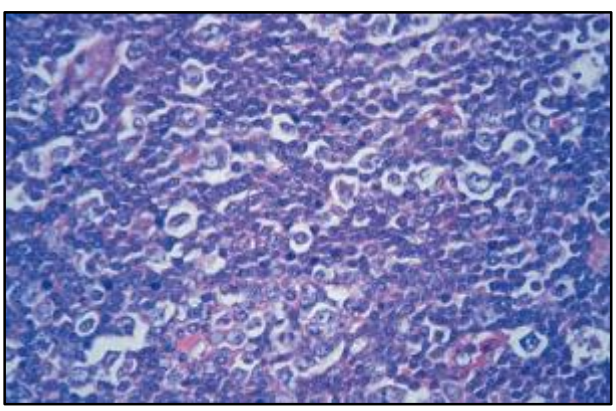

Figure 1. Transformed lymphocytes in the area of paracortical hyperplasia. The cells are surrounded by a clear space giving the starry sky appearance. H & E x 400

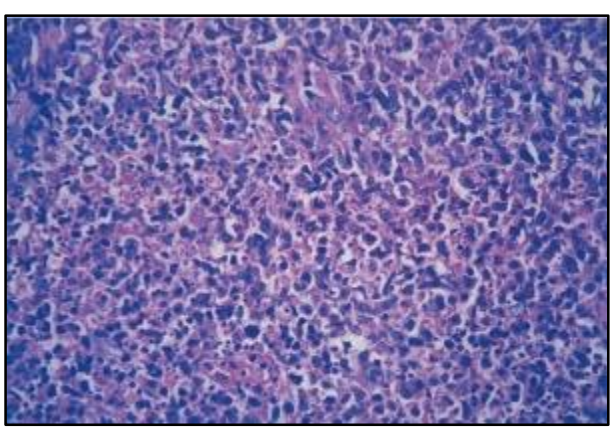

Figure 2. Proliferation center showing widespread apoptosis. H & E x 400

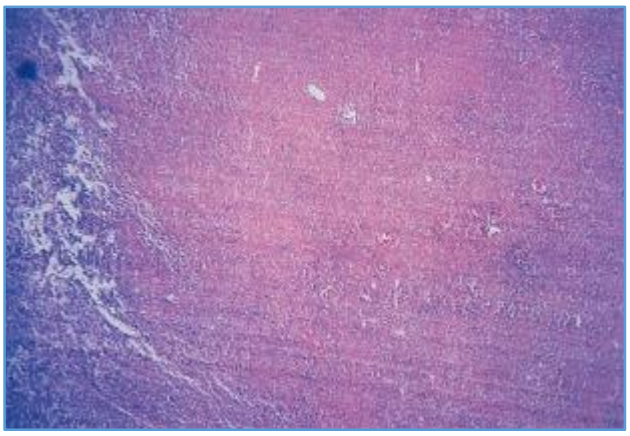

Figure 3. Area of geographic necrosis in a lymph node. H & E x 40

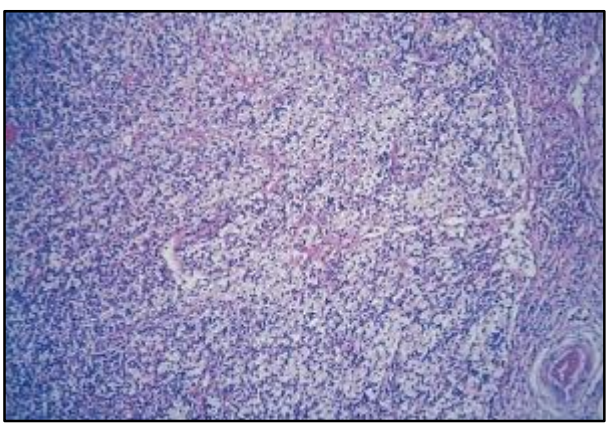

Figure 4. Widely scattered foam cells in the xanthomatous subtype. H & E x 100

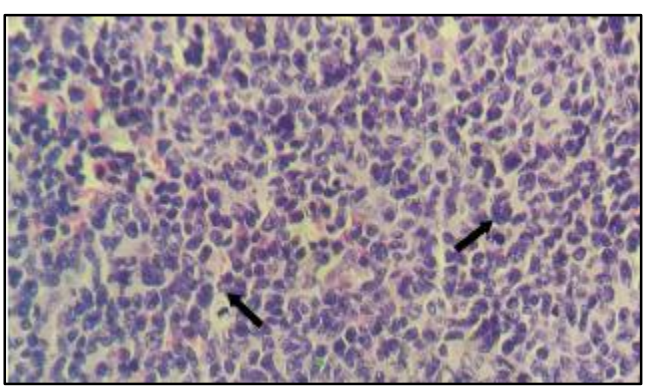

Figure 5. High-grade lymphoma with many mitoses. H & E x 400

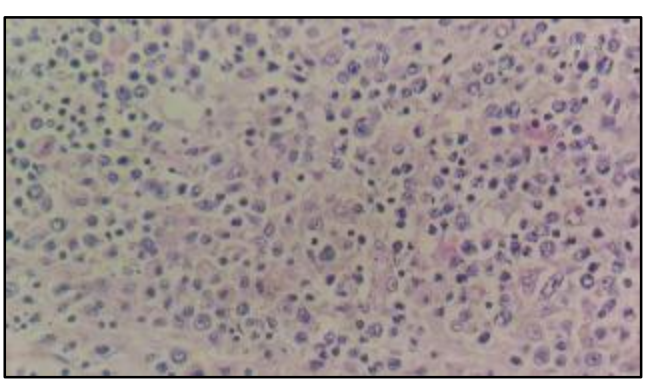

Figure 6. High-grade lymphoma with cells showing marked pleomorphism. H & E x 400

Of the 35 cases 17 were Proliferative type (PT 48.6%), 16 were Necrotising type (NT 45.7%) and 2 were Xanthomatous type (XT 5.7%). Comparison of clinical laboratory features between the subtypes is shown in Table 3. Statistical significance of the differences between PT and NT is also shown. XT was not included because of the small numbers.

Parameter	PT (17 Cases)	NT (16 Cases)	XT (2 Cases)	P value (PT vs. NT)
Mean age (Yrs.)	24.8	26.1	24.5	0.7446
Female (%)	58.8	87.5	50.0	0.0712
Fever (%)	47.1	62.5	100	0.2949
Tenderness (%)	5.9	25.0	50.0	0.1487
Haemoglobin (Mean g/dL)	11.2	10.7	10.5	0.2619
TLC (mean/mm^3)	5363	5007	4850	0.6566
Leukopaenia (%)	25.0	33.3	0.0	0.4537
Lymphocytes (mean /$mm^{3)}$	2445	1875	1993	0.1852
ESR > 60 mm/hr (%)	26.7	40.0	100	0.3499

Table 3. Comparison of Clinical and Laboratory Parameters in Different Subtypes (N = 35)

(PT- Proliferative type; NT- Necrotising type; XT- Xanthomatous type).

Fever, tenderness and percentage of leukopaenic patients were more with necrotising type than with the proliferative type. Differential lymphocyte count and ESR also showed substantial difference.

Of the 14 cases in which FNAC was done, only 4 (28.6%) were diagnosed correctly as KFD.

The comparison between Proliferative type of KFD (17 cases) and 15 lymph node biopsies reported as high-grade non-Hodgkin lymphoma is shown in Table 4.

Parameter	KFD (17 Cases)	Lymphoma (15 Cases)	P
Total effacement (%)	0.0	73.3	< 0.0001
Follicles (%)	40.0	20.0	0.2134
Normal paracortex (%)	100.0	13.3	< 0.0001
Paracortical hyperplasia (%)	80.0	0.0	< 0.0001
Geographic necrosis (%)	33.3	13.3	0.1949
Widespread apoptosis (%)	66.7	0.0	< 0.0001
Mitosis > 1/hpf (%)	0.0	66.7	< 0.0001
Marked pleomorphism (%)	0.0	26.7	0.0498
Foam cells (%)	20.0	6.7	0.2988

Table 4. N-KFD-17 Cases Comparison between KFD and High-Grade Lymphoma N-Lymphoma- 15 Cases

Total effacement of architecture was absent in all the KFD, while 73.3% of high-grade lymphoma showed total effacement of architecture. Paracortical hyperplasia noted in 80% of KFD, which was absent in lymphoma. Widespread apoptosis was noted in 66.7% of KFD and high mitotic count (> 1/hpf) was present in 66.7% of high-grade lymphoma. (Figure 5- High mitotic count in high-grade lymphoma; Figure 6- Marked pleomorphism).

DISCUSSION

The clinical and laboratory features of the present study were compared with those of other series reported in the literature. The age distribution of patients with KFD is comparable with the other series,[3,5] with the mean age of 25.4 years. There is a female preponderance with female-to-male ratio of 2.5 as shown in many series.[3,10] (Comparison is shown in Table 5). In 74% of cases, there was isolated cervical lymphadenopathy, while in 17% there was lymph node enlargement in other sites like axillary and supraclavicular in addition to cervical lymphadenopathy.

The duration of illness varied from 2 weeks to 24 weeks with more than 65% (24 cases) having lymph node enlargement for 4 - 6 weeks. Fever was an important associated finding in 20 cases (57.1%). One of laboratory data found significant was leukopaenia with particularly low absolute count of lymphocytes as described by Tsang et al[3] and Kuo.[5] About 38% of patients had high ESR (> 60 mm in 1^{st} hour). Others have ESR between 10 - 59 mm in I^{st} hour. Serum antinuclear antibody were negative in all the 19 patients tested.

Features	Tsang et al[3]	Kuo[5]	Present Study
No. of Cases	75	79	35
Sex ratio (F:M)	2.75:1	1.1:1	2.5:1
Age (Yrs.)			
Range	14-57	9 — 54	8 — 50
Mean	25.5	26.9	25.4
Median	25	26	26
Fever	38.5%	48.4%	57.1%
Lymphadenopathy			
Cervical	94.6%	97%	91.4%
Generalised	5.3%	1.3%	5.7%
Painful	?	59.2%	17.1%
WBC Count			
Leukopenia	45.5%	42.9%	27.3%
Leukocytosis	?	2.9%	0

Table 5. Clinical Feature- Comparison

Comparison of clinical and laboratory parameters in cases with and without fever was revealing. Statistically significant difference in total leukocyte count, absolute lymphocyte count and ESR were noted as shown in Table 2.

As the proliferative phase of KFD can be mistaken for high-grade malignant lymphoma, we tried to compare the

histological features in the two conditions as shown in Table 4. We devised a scoring system for discriminating between KFD and high-grade lymphoma by giving one point to the features favouring lymphoma, namely-

1. Total effacement of architecture.
2. Absence of normal paracortex.
3. Absence of paracortical hyperplasia.
4. Mitosis > 1/Hpf.
5. Marked pleomorphism.
6. Absence of uniformly scattered apoptosis.

The total score in cases of KFD were 0 or 1. In cases of Lymphoma, the scores ranged from 2 to 6. Thus, a total score of less than 2 by this scheme could effectively discriminate KFD from a high-grade lymphoma.

CONCLUSION

1. Kikuchi-Fujimoto disease is a benign self-limiting condition, which commonly affects cervical lymph nodes of young women (Female: male ratio 2:5).
2. The median age of presentation is 26 years.
3. Significant number of cases are associated with leukopenia.
4. There is substantial difference in the clinical and laboratory parameters in cases with and without fever.
5. Histologically, the node can be subtyped into 3 categories.
    1. Proliferative- If proliferation centers with transformed lymphocytes and apoptosis occupy a significant portion of area.
    2. Necrotising- If > 10% area of cross-section shows geographic necrosis.
    3. Xanthomatous- If foam cell collections are significant
6. A scoring system can be used to discriminate between proliferative subtype of Kikuchi-Fujimoto disease and high-grade lymphoma noting features favouring lymphoma, which includes 1. Total effacement of architecture, 2. Absence of normal paracortex, 3. Absence of paracortical hyperplasia, 4. Mitosis > 1/Hpf, 5. Marked pleomorphism and 6. Absence of uniformly scattered apoptosis.

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