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A COMPARITIVE STUDY OF CLINICAL FEATURES AND LABORATORY CHARECTERISTICS OF HISTOPATHOLOGICALLY CONFIRMED KIKUCHI VS NON KIKUCHI DISEASE AND TO EVALUATE THEIR USEFULLNESS IN THE DIAGNOSIS OF KIKUCHI-FUJIMOTO DISEASE.

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ABSTRACT

INTRODUCTION: Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a benign and self-limiting disease that mainly affects young women. Patients present with localized lymphadenopathy, fever, and leukopenia in up to half of the cases. Kikuchi disease usually gets better (resolves) on its own within one to four months (although it may take up to a year), with or without treatment. The primary threat is a misdiagnosis of an infective, tuberculous or even a malignant pathology.

OBJECTIVES: To study of clinical features and laboratory characteristics of histopathologically confirmed Kikuchi vs non Kikuchi disease and to evaluate their usefulness in the diagnosis of Kikuchi-Fujimoto disease.

METHODOLOGY: 160 cases of cervical lymphadenopathy between August 2013 and July 2018 were studied and the results analysed using Chi square test.

CONCLUSIONS: Clinical features and lab parameters included in the study are significantly associated with presence of Kikuchi disease.

KEYWORDS

Kikuchi-Fujimoto Disease (KFD), Lymphadenitis, Fine Needle Aspiration Cytology (FNAC), Histopathological Examination (HPE), Immunohistochemistry (IHC).

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a benign and self-limiting disease that mainly affects young women. Patients present with localized lymphadenopathy, fever, and leukopenia in up to half of the cases[1]. Kikuchi disease usually gets better (resolves) on its own within one to four months (although it may take up to a year), with or without treatment. KFD can occur in association with multiple disorders[2]. This disorder causes the lymph nodes to become enlarged, inflamed and painful. The exact cause of Kikuchi's disease is not known. Although viruses such as human herpes viruses 6 and 8, parvovirus B 19, EBV, and hepatitis B have been linked to Kikuchi disease[3,4].

An autoimmune mechanism has also been proposed because KFD is seen in conjunction with systemic lupus erythematosus (SLE). There are several reports suggesting an association between Kikuchi's disease and systemic lupus erythematosus (SLE). However no convincing evidence is available to confirm such association[5]. Diagnosis is based on histopathological findings of a lymph node biopsy. Morphologically, it is characterized by irregular para cortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce[6].

The immunophenotype of Kikuchi's disease is primarily composed of mature CD8-positive and CD4-positive T lymphocytes. High rate of apoptosis is also seen among lymphocytes and histiocytes. The histiocytes express histiocyte associated antigens such as lysozyme, myeloperoxidase (MPO) and CD68 which can be detected by immunohistochemistry. Plasmacytoid monocytes are also positive for CD68 but not for myeloperoxidase[7].

The absence of granulocytes in areas of necrosis and the lack of follicular hyperplasia differentiate these cases from lymphadenitis caused by cat-scratch disease and other bacterial infections. Early-stage lesions without overt necrosis may be distinguished from malignant lymphoma by (a) the focal nature of the lymph node involvement with incomplete architectural effacement; (b) the presence of plasmacytoid dendritic cells at the periphery of the lesion; and (c) bland cytological features of the mixed-cell population in areas of involvement[8].

Perhaps the primary threat in clinical practice is a misdiagnosis of an infective, tuberculous or even a malignant pathology. Hence this study was conducted among 160 patients with cervical lymphadenopathy to compare the clinical features and lab parameters between kikuchi and non kikuchi patients and to study their usefulness in diagnosis of Kikuchi disease.

AIMS AND OBJECTIVES:

1. To study of clinical features and laboratory charecteristics of histopathologically confirmed kikuchi vs non kikuchi disease
2. To evaluate the usefullness of clinical features and laboratory characteristics in the diagnosis of kikuchi-fujimoto disease.

MATERIAL AND METHODS:

This study was done among 160 patients who underwent cervical lymph node biopsy at a tertiary care hospital during the period between August 2014 and July 2018. The clinical features, FNAC findings and histopathological findings were recorded. The presence of fever (>98.4F), painless lymphadenopathy, laterality (Unilateral vs Bilateral), leukopenia (<$4x10^3$/uL) and FNAC suggestive of Kikuchi disease (necrotic debris with paucity of neutrophils) were compared between patients with and without Kikuchi disease confirmed on HPE study.

Histopathologically, Kikuchi disease is characterized by irregular para cortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce.

The diagnosis was confirmed immunohistochemically by presence of CD8 and CD4 positive T lymphocytes, histiocytes expressing MPO and CD68[7]. The data collected was statistically analysed and presented.

STATISTICAL ANALYSIS:

The data regarding the clinical features and laboratory parameters of

Kikuchi and non Kikuchi patients was collected. Clinical features like fever, tenderness of lymphnodes and laterality of involvement were considered and analysed using Microsoft Excel and the statistical significance was analysed by Chi square test. A p value <0.05 was taken as statistically significant.

RESULTS:

Among the 160 cases studied, 18 were diagnosed histo-pathologically and confirmed by immunohistochemistry as Kikuchi-Fujimoto Disease (KFD). Among the patients (18), majority were females (16) with a female to male ratio of 8:1. The mean age among the Kikuchi patients was 26 years.

All but one of Kikuchi patients presented with a fever (94%) while 14 (78%) had leukopenia. The average size of lymph nodes was 19mm, of which 15(84%) were painless.

Among the non Kikuchi patients, 99(70%) had fever, 40(28%) had leukopenia and 23(16%) had tender lymph nodes. 85(60%) had unilateral cervical lymphadenopathy.

FNAC was not conclusive of Kikuchi disease in the study population

TABLE 1: Distribution of clinical features and lab parameters among Kikuchi and non-Kikuchi patients.

Clinical &laboratory characteristics	Kikuchi disease (n=18)	Non Kikuchi disease (n= 142)
Sex ratio(Female : Male)	8:1	1.5:1
Fever	17(94%)	99(70%)
Leukopenia	14(78%)	40(28%)
Non tender Lymph Nodes	15(84%)	119(84%)
Unilateral Lymph node	18(100%)	85(60%)

The sensitivity, specificity, positive and negative predictive values for the different clinical findings and lab parameters were tabulated (Table 2) and analysed.

TABLE 2: Sensitivity, specificity, Positive and Negative predictive value of various factors.

Clinical and lab characteristics	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)
FEVER	94.4	30.3	14.7	97.8
LEUCOPENIA	77.8	71.8	25.9	96.2
TENDER LYMPHNODES	16.7	83.8	11.5	88.8
UNILATERAL LYMPH NODE INVOLVEMENT	100	40.1	17.5	100

The data obtained was statistically correlated using Chi square test and p values were calculated. Table 3.

TABLE 3: p values of factors studied

	p value	Interpretation
Fever	0.03	Significant
Leukopenia	2.75×10^{5}	Significant
Tender Lymph nodes	0.96	Not significant
Unilateral LN involvement	0.0008	Significant

DISCUSSION:

Among the 160 cases studied, 18 were diagnosed to have Kikuchi disease by histopathology and confirmed by immunohistochemistry. Various clinical and laboratory parameters were considered and their usefulness in diagnosing Kikuchi disease were considered.

The present study showed that majority of patients with Kikuchi disease were females (89%) similar to the finding of study by Norris et.al[9].

Fever was present among 94% of Kikuchi patients and 70% of other cases of cervical lymphadenopathy, while leukopenia was among 78% of Kikuchi patients and 28% of non Kikuchi patients. Non tender lymph nodes were seen among 84% of Kikuchi and non Kikuchi patients. All Kikuchi patients had unilateral lymph node involvement while 60% non Kikuchi patients had unilateral involvement[10].Presence of Fever, leukopenia and unilateral lymph node involvement were found to be significantly associated with the presence of Kikuchi disease as shown by p values of 0.03, 2.75×10^{5} and 0.008 respectively.

Among the factors studies, unilateral lymph node involvement had 100% sensitivity for Kikuchi Disease while absence of tender lymph nodes had maximum specificity (83.8%). Leukopenia had a positive predictive value of 25.9% while unilateral lymph node involvement has 100% negative predictive value.

CONCLUSION:

The present study concludes that diagnosis of Kikuchi disease is primarily based on histopathological findings and confirmed by immunohistochemistry. Other parameters studied here like fever, leukopenia and unilateral lymph node involvement are significantly associated with Kikuchi disease. However they cannot serve as a replacement for histopathology supplemented with IHC continues to be the gold standard for diagnosis of Kikuchi disease.

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