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Original Research Article

Clinicopathological study of non-granulomatous necrotizing lymphadenopathies

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ABSTRACT

Context: Non-granulomatous necrotizing lymphadenopathy (NGNL) is not a specific entity. It is seen in various conditions like Kikuchi-Fujimoto disease (KFD), Systemic Lupus Erythematosus (SLE), tuberculosis, lymphoma/metastasis and lymph node infarction. These conditions mimic each other histologically but it is necessary to identify the correct pathology as the treatment differs significantly.
Aim of the study: To highlight the subtle morphological features which lead to the etiological diagnosis in NGNL.
Materials and Methods: The lymphnode biopsies (N=198), reported in our institute as NGNL, over 4$\frac{1}{2}$ year study period, were retrieved. Of these, the benign cases were 64 in total, with 40 cases of KFD and 8 cases of SLE. H&E, special stains and immunohistochemistry slides were reviewed by two pathologists. Histomorphological features like amount of necrosis, apoptotic debris, vasculitis, presence of neutrophils, eosinophils, histiocytes, plasma cells, hematoxylin bodies, Azzopardi phenomenon and thrombus formation were studied.
Statistics: Logistic regression analysis was performed to identify the most significant histopathological parameter with each disease. Kendall's Tau matrix plot analysis was used to measure the correlation between the disease and the histopathologic variables.
Results: Features like vasculitis, hematoxylin bodies and Azzopardi phenomenon showed strong correlation with SLE and inverse correlation with KFD. Apoptotic debris, paucity of neutrophils and eosinophils had a strong positive association with KFD.
Conclusion: The histological features help in differentiating the various entities associated with NGNL. It is necessary to correlate with clinical details and various laboratory parameters to reach a conclusive diagnosis because these conditions have varied treatment modalities.

1. Introduction

Necrotizing granulomatous lymphadenopathies are commonly encountered in developing countries like India, and are usually due to infectious etiologies like tuberculosis. Whereas, non-granulomatous necrotizing lymphadenopathy (NGNL) is seen in various conditions like Kikuchi-Fujimoto disease (KFD), Systemic Lupus Erythematosus (SLE), malignancies (Lymphoma/metastasis), infarction and infections like tuberculosis.[1] Histologically, these conditions have very subtle differences. It is necessary to identify the exact etiology, as the treatment and prognosis differs significantly.

The etiological diagnosis of NGNL cannot be made, purely on morphology. Ancillary techniques like special stains, immunohistochemistry and other investigations like peripheral blood picture and auto-antibody profile along with clinical and treatment history like chemoradiotherapy, are needed.

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This study is being done to highlight the subtle morphological features, which can lead to the diagnosis in cases of NGNL.

2. Materials and Methods

This was an observational study (partly retrospective & partly prospective). Cases diagnosed as NGNL, over $4\frac{1}{2}$ year study period, were retrieved from the histopathology records and reviewed. Lymph node biopsies received as part of large specimen were excluded from the study. Patient details including age, sex, presenting symptoms, past history, site & size of lymph node, and organomegaly were recorded. Laboratory findings like Coomb's test, auto-antibody profile, culture for TB, Mantoux test and imageological data were collected, wherever available.

Hematoxylin & Eosin-stained lymph node biopsy slides were studied to look for amount of necrosis, apoptotic debris, evidence of vasculitis, presence of neutrophils, eosinophils, histiocytes, plasma cells, hematoxylin bodies, Azzopardi phenomenon and thrombus formation. Special stains like Ziehl-Neelsen, Gomori's Methenamine Silver were done in all cases. Periodic acid Schiff was done in few cases. Immunohistochemistry was done in suspicious cases of malignancy. In case of lymphoma, various combinations of immunohistochemistry were used, which included CD3, CD20, PAX5, CD15, CD30, ALK, CD5, CD10, Cyclin D1, CD23, Bcl2, Tdt and Ki67. Similarly, in case of metastasis, depending on the clinical history and morphology, immunohistochemistry was used for the diagnosis. Approval was obtained from the institutional ethics committee.

2.1. Statistical analysis

Demographic and relevant clinical and biochemical parameters were presented as mean and percentage. The categorical data was analyzed as percentage. Chi-square test was also used. Logistic regression analysis was performed to identify the most significant histopathological parameter with the disease and Odds ratio (OR) was obtained. A p-value <0.05 was considered statistically significant. In addition, Kendall's Tau matrix plot analysis was used to measure the correlation between the disease and the histopathologic variables. GraphPad prism software was used for the analysis of the data.

3. Results

During the study period, total number of lymph node cases showing necrosis without granulomas was 198. Of these, 134 cases were associated with malignancy (either denovo or post-therapy) and 64 were benign. The malignant cases were aged between 1.5-90 years (median 48), with cervical lymphadenopathy as the most common presentation. The other lymphnode sites affected were supraclavicular (3), axillary (3), inguinal (1), mediastinal (1) and parotid region (1). Site was unknown in 3 cases. Based on morphology and immunohistochemistry results, the etiological diagnosis of necrosis associated with lymphoma (n=68) or metastasis (n=66) was made.[2] Chemotherapy related necrosis was seen in eight cases of lymphoma.

The 64 benign cases are the main focus of interest in this study. Based on the morphology and ancillary tests like special stains (AFB, SM stain) and immunohistochemistry, the benign cases were divided etiologically into KFD (n=40), SLE (n=8), Kikuchi in SLE (n=4), tuberculosis/Mycobacterial (n=4), suppurative necrotizing inflammation (n=3), Infarction (n=1) and necrosis-NOS (not otherwise specified, n=4).

All the entities show similar age group distribution, with an average in the third decade of life, and female predominance (M:F ratio-1:3). The most common presenting complaint was fever followed by cervical lymphadenopathy. Lymph node size varied between 0.4- 2.3 cms. Lymphadenopathy involving multiple sites was seen in 36% (23/64) cases (Table 1). Splenomegaly was noted in two cases of KFD. Hepatomegaly was not seen. Rash, arthritis and alopecia was seen in two SLE patients each. A summary of other laboratory data is given in Table 2.

In cases diagnosed as KFD, the architecture of the lymph node was partially effaced in the majority (77.5%). There was variable amount of necrosis mainly involving the subcapsular area of the cortex (Table 3, Figure 1). The necrosis contained apoptotic nuclear debris, surrounded by lymphocytes, histiocytes, immunoblasts and few plasma cells. The histiocytes were seen in 62% (25/40) cases, plasma cells in 10% (4/40) and presence of thrombi in 7% (3/40) cases. There was paucity of neutrophils and eosinophils in 92% (37/40) of the cases (Table 4).

KFD has been divided into four subtypes on histology as lymphohistiocytic, phagocytic, necrotic and foam cell types.[3] Necrotic subtype was the most common (52.5%). One case could not be subdivided further because of mixed morphology (Table 5). Due to the increased proliferation of immunoblasts, there was a suspicion of lymphoma in four of these cases. Immunohistochemistry with CD3, CD20, CD68 and Ki67 was performed and lymphoma was ruled out.

In cases diagnosed as SLE, there was variable amount of necrosis surrounded by histiocytes, immunoblasts and plasma cells. In addition, evidence of vasculitis, hematoxylin bodies and Azzopardi phenomenon were noted in six, three and two cases respectively (Table 4, Figure 2).

In four cases of clinical SLE, KFD was diagnosed on histology, as they did not show the characteristic features of SLE like vasculitis, hematoxylin bodies and Azzopardi phenomenon.[4,5] These were labelled as Kikuchi in SLE.[6]

Three cases were diagnosed as suppurative necrotizing lymphadenitis, due to the presence of dense neutrophilic infiltrate along with the necrosis. Four cases could not be

characterised further into any of the etiological diagnostic groups and were labelled as necrotizing lymphadenopathy NOS. The histopathology findings in the 16 cases diagnosed as Kikuchi in sle, Koch's, suppurative necrotizing inflammation, infarction and necrosis-nos are summarized in Table 6.

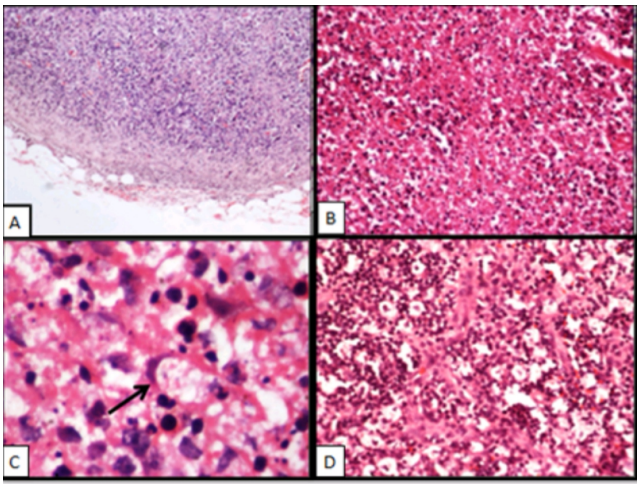

Fig. 1: Kikuchi-Fujimoto disease; **A:** Lymph node biopsy showing subcapsular necrosis with apoptotic debris. H&E X 40; **B:** Necrosis with apoptotic debris. H&E X 100; **C:** Crescentic nuclei of histiocytes. H&E X 400; **D:** Lymph node showing foamy histiocytes. H&E X 100.

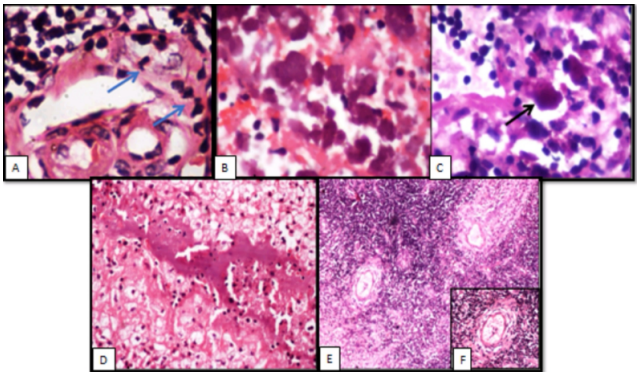

Fig. 2: Systemic Lupus Erythematosus; **A:** Vasculitis. H&E X 400; **B,C:** Hematoxylin bodies. H&E, PAS X 400; **D:** Azzopardi phenomenon. H&E X 100; **E,F:** Lymph node biopsy showing subcapsular necrosis with onion skinning around the blood vessels. H&E X 100,400.

Chi-square test and logistic regression analysis was performed to identify the most significant histopathological parameter with the disease and Odds ratio (OR) was obtained, but due to the disparity in the total number of cases in Kikuchi's disease (n=40) and SLE lymphadenopathy (n=8), these statistical analyses comparing the histological features of the two conditions, were not possible. Hence, Kendall's Tau Rank Correlation Coefficient was used to measure the correlation between the disease and the histopathologic variables. Features like evidence of vasculitis, hematoxylin bodies and Azzopardi phenomenon showed strong correlation with SLE and strong inverse correlation with KFD. Whereas, features like presence of apoptotic nuclear debris and paucity of neutrophils and eosinophils have shown a strong positive association with KFD (Figure 3).

Variable	SLE	NOS	Kikuchi	SNI	Koch
Necrosis	0.033	0.018	-0.122	-0.026	0.162
Nuclear debris	0.128	-0.537	0.626	-0.462	-0.372
Histiocytes	0.138	-0.322	0.151	0.026	-0.058
Paucity/ absence of N/E	-0.056	-0.269	0.553	-0.355	-0.413
Vasculitis	0.67	-0.083	-0.477	-0.071	-0.083
Thrombosis	0.258	-0.083	-0.014	-0.071	-0.083
H. bodies	0.462	-0.057	-0.329	-0.049	-0.057
Azzopardi phenomnenon	0.374	-0.046	-0.266	-0.04	-0.046
Plasma cells	0.182	-0.098	-0.051	0.14	-0.098

Fig. 3: Kendall's - Tau matrix plot showing disease wise association of variables. Abbreviations: NOS- not otherwise specified; SNI- Suppurative necrotizing inflammation; N/E- neutrophils/eosinophils; H.bodies- Hematoxylin bodies.
Interpretation: Red- strong positive association; Green- strong inverse association.

4. Discussion

This study is done on lymph node biopsies showing necrosis, without any evidence of granulomas. There were 198 such cases, of which 134 had some kind of associated malignancy and 64 cases had benign etiology, like KFD, SLE, tuberculosis/mycobacterial, infarction, etc. It is important to differentiate between the above entities, as the treatment and prognosis varies significantly.

KFD is an uncommon disease. This study included 40 cases of KFD. It can occur over a wide age range (2-75 years), and most commonly affects young females.[10] The mean age in this study was 29 years. As expected, females outnumbered males (M:F=1:2.5). The most common presenting complaint was fever followed by cervical lymphadenopathy (Table 7). Three cases presented with generalized lymphadenopathy, which is considered a rare presentation.[11,12]

On histology, the features were largely consistent with the literature.[1,6,7,13] But the degree of necrosis differed from Supari et al and Sanpavat et al (table-3).[1,7] Majority of our cases showed partially effaced architecture with large areas of necrosis mainly involving the subcapsular area of the cortex. There was paucity of neutrophils, eosinophils and plasma cells.[6,13]

Table 1: Clinical features of the Necrotizing LAD in benign cases.

N=64	Kikuchi	SLE	T/M	Kikuchi-SLE	Necrosis-NOS	Suppurative inflammation	Infarct? cause
Number of cases	40	8	4	4	4	3	1
M:F	1:2.5	0, 8	1:3	0, 4	0, 4	3:1	1:0
Median Age	27	22.5	31	22	24	52	19
Presenting complaint	Fever-29, cervical LAD-22	Fever-8, LAD-5, rash-2	Fever-3, LAD-3	Fever-2, LAD-2	Nonspecific	LAD-3	Parotid swelling
LN site *	Cervical-36	Cervical-5	Cervical-3	Cervical-3	Cervical-4	Supraclavicular-2	Parotid region
LN size (cm)	0.4- 2.2	0.4-1.8	0.7-1.2	1.3-1.8	1-1.8	0.7-2.3	1.5
Cases with multiple LN's	17	2	1	1	1	1	None

Abbreviations: T/M- tuberculosis/Mycobacterial; LAD-lymphadenopathy; LN-lymphnode; *-most common.

Table 2: Summary of auto-antibody profile among the benign entities.

	KFD	SLE	Kikuchi in SLE	Necrosis NOS
ANA (n=10)	4 (negative)	3 (positive)	2(positive)	1(positive)
Anti-ds-DNA(n=7)	3 (negative)	2 (positive)	1(positive) 1(negative)	
Anti-Sm(n=2)	1 (negative)	1 (positive)		
Anti-histone(n=1)		1 (positive)		
RA-factor, aCL, IgM-RF	1 (negative) each			

Abbreviations: ANA- antinuclear antibody; aCL-anticardiolipin.

Table 3: Comparison of various histomorphological features of KFD with other studies.

	Current study	Sanpavat et al [1]	Supari et al [7]
Number of cases	40	17	24
Architecture			
Completly effaced	15%	-	17%
Partially effaced	**77.5%**	-	**75%**
Preserved	7.5%	-	9%
Location of necrosis			
Paracortical	7.5%	47%	-
Cortical (subcapsular)	**92.5%**	**53%**	-
Extent of necrosis			
Small areas	32.5%	**70.6%**	**70%**
Large areas	**67.5%**	29.4%	30%

Table 4: Comparison of the histopathology features in Kikuchi and SLE.

	Paucity of neutrophils	Histiocytes	Plasma cells	Vasculitis	Thrombi	Hematoxylin bodies	Azzopardi phenomenon
Kikuchi (n=40)	92%(37)	62%(25)	10%(4)	0	7%(3)	0	0
SLE(n=8)	63%(5)	63%(5)	25%(2)	75%(6)	25%(2)	37%(3)	25%(2)

Table 5: Comparison of various histological subtypes of KFD with other studies.

	Current study	Susheelan et al [8]	Seong et al [9]
Number of cases	40	96	40
Proliferative	25%(10): lymphohistiocytic-(4), phagocytic-(6).	Rare	37.5%
Necrotic	**52.5%(21)**	**Predominant**	**55%**
Foam cell/ xanthomatous	20%(8)	Rare	7.5%
Kikuchi-NOS	2.5%(1)	-	-

Table 6: Comparison of histological features among the other groups.

	Kikuchi in SLE(n=4)	Tuberculosis/ mycobacterial (n=4)	Necrosis NOS (n=4)	Infarct (n=1)	Suppurative necrotizing inflammation (n=3)
Necrosis					
Small area (%)	25	0	25	0	33.3
Large area (%)	75	100	75	100	66.6
Neutrophils					
Excess (%)	50	100	75	100	100
Paucity (%)	50	0	25	0	0
Nuclear debris					
Absent (%)	25	75	100	100	100
Present (%)	75	25	0	0	0
Histiocytes					
Absent (%)	0	50	100	0	66.6
Present (%)	100	50	0	100	33.3

Table 7: Comparison of clinical features of KFD with other case series.

	Current study	Sanpavat et al [1]	Supari et al [7]	Susheelan et al [8]	Seong et al [9]
Number of cases	40	17	24	96	40
Age	13-64 (29)	27.5	9-55 (26)	10-60 (22.5)	29.3
Female: male	2.5:1	7.4:1	2.4:1	3.8:1	2.6:1
Presenting complaints					
Fever	72.5%	5.9%	54%	1.04%	62.5%
LAD	55%	100%	100%	83%	70%
LN site- MC	Cervical (90%)	Cervical (100%)	Cervical (100%)	Cervical (88%)	Cervical (92.5%)
LN number					
Single-	64%	23.5%	58%	-	77.5%
Multiple-	36%	76.5%	42%	-	22.5%
LN size	0.4-2.2	1-3 cm	0.5-3.5 cm	-	
Splenomegaly	5%	-	13%	0	2.5%
Hepatomegaly	0	-	4%	0	0

Abbreviations: LAD- lymphadenopathy; LN- lymph node; MC- most common.

The histological classification proposed by Kuo,[14] which divides KFD into proliferative, necrotizing and xanthomatous subtypes, was followed by the previous studies. The proliferative phase in Kuo's classification encompasses both lymphohistiocytic and phagocytic subtypes. Necrotic subtype was the most common type in our study, similar to the other studies reported from India and Korea (table-5).[8,9] In four cases, where the immunoblasts were increased, leading to suspicion of lymphoma, immunohistochemistry with CD3, CD20, CD68 and Ki67 was performed to rule out lymphoma.

Although the number of lymph node biopsies done to diagnose SLE has reduced, after the 1982 revised criteria for the classification of SLE (which is dependant mainly on the clinical and serological criteria).[15] It is still important to know the histologic features of SLE, to differentiate it from other benign conditions, as the treatment differs. Eight cases were diagnosed as SLE on histology. All were young females, who came with complaints of fever (8/8), cervical lymphadenopathy (5/8) and rash (2/8). Lymphadenopathy is seen in 23-34 % of SLE patients,[16,17] and cervical nodes are commonly involved,[5] more so in younger patients.[18] Auto-antibody profile was available in 3/8 cases. All of these were ANA-positive, two were positive for ds-DNA and one was positive both for anti-Sm and anti-histone antibodies (table-2). As majority of these patients, were being treated on out-patient basis, it was not possible to get all the serologic data. Histology showed variable amount of necrosis surrounded by histiocytes, immunoblasts and plasma cells. In addition, evidence of vasculitis, hematoxylin bodies and Azzopardi phenomenon were noted in six, three and two cases respectively.

Four cases were diagnosed as Kikuchi's disease in SLE patients, based on the histological features like necrosis with nuclear debris, presence of histiocytes, paucity of neutrophils, eosinophils, plasma cells and lack of diagnostic features of SLE lymphadenopathy like vasculitis, hematoxylin bodies or Azzopardi phenomenon.

KFD has been reported to coincide with, precede, or follow a diagnosis of SLE. Kucukardali et al found

KFD to be associated with SLE in 32 of 244 SLE cases.[19] Some authors have considered KFD to be a precursor of SLE.[20,21] But no clear relation has been found between the two entities.[22] The two diseases have common clinical features like lymphadenopathy, erythematous skin rash, fever, arthralgia and cytopenia. But auto-antibody profile was consistently found to be negative in KFD, not supporting the hypothesis of similar autoimmune disease process of KFD and SLE.[23] Hence, the diagnosis of SLE needs correlation with clinical features, serology and other laboratory data like blood picture, etc.[24]

Among the four cases reported as Koch's, three were young adults with fever and cervical lymphadenopathy and histology showed large areas of necrosis without any epithelioid granulomas. However, stains for AFB were positive. The fourth case had complaints of cough, bilateral cervical lymphadenopathy and histopathology revealed extensive areas of necrosis with calcification and hyalinization, which was suggestive of a healed granuloma. Therefore, even in the absence of granulomas, when there is a strong clinical suspicion, special stains for AFB should be performed as an aid for the diagnosis of tuberculosis/Mycobacterial etiology.

The study included only one case of near-total infarction. Infarction is caused by a wide range of benign and malignant conditions. Hence, any viable area of the node should be examined for organisms and for possible malignancies. It is essential to look for perinodal fat infiltration by neoplastic cells and thrombi in blood vessels. Special stains and immunohistochemistry can aid the diagnosis.[1,25]

To conclude, the histological features help in differentiating the various entities associated with non-granulomatous necrotizing lymphadenopathy like KFD, SLE, tuberculosis, infarction and malignancies. Although, it's necessary to correlate with clinical details, laboratory parameters (culture studies, auto-antibody profile), and ancillary histotechniques like special stains and immunohistochemistry, to reach a conclusive diagnosis, as the treatment options vary.

5. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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None.

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