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Morphological Spectrum of Peripheral T Cell Lymphomas and Utility of Immunohistochemistry in the Diagnosis

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Abstract

Context: Peripheral T cell lymphomas (PTCLs) are uncommon subtypes of non Hodgkin lymphoma (NHL). The diagnosis is often challenging and not infrequently misdiagnosed. *Aims:* To analyse the morphological and immunohistochemical profile of Peripheral T cell lymphoma. *Settings and Design:* This study was carried out at the Department of Pathology, where cases were recruited using consecutive sampling method. *Methods and Material:* Immunohistochemical staining was performed in all cases of lymphoma and results were analysed. *Statistical Analysis Used:* Frequency distribution of the diagnoses was studied. *Results:* There were six casesof Peripheral T cell lymphoma – unspecified (CD3+, CD20-), two cases of Angioimmunoblastic T cell lymphoma (AITL)(CD3+, CD10+, CD23+), one case of Lennert's lymphoma(CD3+,CD20-) and a hepatosplenic T cell lymphoma(CD3+,CD2+). *Conclusions:* PTCLs constituted for 20% of NHLs. Immunohistochemistry was helpful in diagnosis when differentiation from Hodgkin lymphoma was difficult morphologically.

Keywords: Angioimmunoblastic T Cell Lymphoma; Lennert's Lymphoma; Lymphoma; Non Hodgkin Lymphoma; Peripheral T Cell Lymphoma.

Introduction

The World Health Organization (WHO), 2008 [1] classifies mature T cell / NK cell neoplasm into four categories (nodal, extranodal, cutaneous and leukemic). Nodal group includes peripheral T cell lymphoma unspecified, angioimmunoblastic T cell and anaplastic large cell lymphoma. PTCLs constitute 4 to 12% in western [2,3] and 12-26 % in eastern countries [4]. Indian studies have shown a frequency of 9 to 12% [5]. PTCLs show a higher morphological and immunological diversity than any other lymphoma. Hence the diagnosis of PTCL remains a challenge to the histopathologist.Thus, this study aims to analyze the morphological and immunohistochemical features of PTCL, for better understanding of this rare variant.

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Key Messages

Immunohistochemistry (CD3, CD20, CD15, CD30, CD23, and CD5) is essential in differentiating peripheral T cell lymphoma from its mimics (Hodgkin lymphoma and reactive conditions) because of its varied morphological pattern on routine hematoxylin and eosin stained sections

Subjects and Methods

Between August 2011 and August 2013, 52 consecutive cases diagnosed as lymphoma in the histopathology department in a tertiary care hospital were included in the study.

Inclusion Criteria

Patients of all ages and both genders with both primary and/or extranodal lymphomas (treatment naïve) were included in the study.

Exclusion Criteria

Samples inadequate for light microscopy and

immunohistochemistry were excluded. Similarly, patients who were on treatment for lymphoma were excluded.

For histological and immunohistochemical studies, the samples were received in neutral buffered formalin. Routine Hematoxylin and eosin staining was done to study the pattern, cellular morphology and presence of key diagnostic features. A panel of immunohistochemical markers was chosen based on the histological differential diagnosis. For immunohistochemistry, 4μ sections were taken in specially coated slides. Slides were then deparaffinised and rehydrated in ethanol and xylene. Antigen retrieval was done by microwaving using two methods 1) by incubating sections with a Tris-EDTA solution, pH 9.0 for 20 minutes before staining with antibodies against CD3, CD15, CD30, CD2, TDT, CD23 and CD10 (mouse, monoclonal, biogenex), and 2) by incubating sections with 0.01 M citrate buffer solution, pH 6.0, for 20 min before staining with antibodies against CD45, CD20 (mouse, monoclonal, biogenex). The slides were then incubated under humid conditions at room temperature for 90 minutes.

The antibodies bound to antigens were detected by addition of secondary antibody conjugated with horse radish peroxidase polymer and diaminobenzidine substrate. The slides were counterstained with hematoxylin. Appropriate positive controls for the primary antibodies as per the manufacturer's instruction manual (biogenex) were used. The immunohistochemically stained slides were analyzed for the presence/absence of reaction and cellular localization. The positive reaction in the neoplastic cells was assessed. This study was conducted with approval of the Institutional ethical committee, in accordance with the ICMR guidelines for human research.

Statistical Analysis

Frequency distribution of gender and diagnoses were studied.

Results

Of the 52 cases of lymphoma, ten were peripheral T cell lymphomas. These ten cases included seven males and three females. The age of the patients ranged from four years to 90 years. All except one, presented with peripheral lymphadenopathy while the other presented with hepatosplenomegaly.

The diagnosis was made based on World Health Organization (WHO) 2008 classification. Six cases were diagnosed as Peripheral T cell lymphoma-unspecified (PTCL-U). These cases showed a heterogenous population of cells which were small to large with pleomorphic nuclei with irregular nuclear contours and variable amount of cytoplasm (Figure 1). Reactive population of cells included plasma cells, lymphocytes and eosinophils. Vascular channels were prominent in five cases. Occasional binucleated cells were seen in two cases (Table 1). The differential diagnosis included Hodgkin lymphoma as the reactive population of cells was seen in all the six cases and T cell rich B cell lymphoma in two cases as there were large neoplastic cells admixed with small lymphoid cells. Immunohistochemistry demonstrated absence of CD15, CD30 and CD20 staining in large cells. The neoplastic cells demonstrated membrane and cytoplasmic staining for CD3 (Figure 2) and CD2 (Table 2).

Two cases were diagnosed as angioimmunoblastic T cell lymphoma. Of the two cases one showed complete effacement of lymph node architecture by diffuse proliferation of small to medium sized lymphoid cells with scattered eosinophils and few histiocytes. The other showed partially preserved lymph node architecture with follicular hyperplasia and paracortical expansion by the polymorphic infiltrate of cells with few cells having clear cytoplasm (Figure 3 and 4). Pale eosinophilic areas comprising of cells with eosinophilic cytoplasm and indistinct cell membrane were observed in one case. Numerous branching and arborizing vascular channels lined by plump endothelial cells and few immunoblast like cells were noted in both the cases. Immunohistochemistry demonstrated CD 3 (Figure 5) and CD10 positivity. CD23 staining highlighted the extrafollicular dendritic cell network (Table 3) (Figure 6).

One case showed loss of nodal architecture by diffuse proliferation of small lymphoid cells and confluent clusters of epithelioid cells (microgranulomas). Scattered large atypical cells and few reactive cells composed of eosinophils and plasma cells were seen. There were no classical Reed Sternberg cells. This was diagnosed as Lennert's lymphoma. The differential diagnosis included reactive lymphadenitis and Hodgkin lymphoma. Immunohistochemistry showed absence of CD15 and CD30 in the large atypical cells, thus excluding Hodgkin lymphoma (Table 3).

In the single extranodal case, the site of biopsy was liver as the patient (four years old female) presented with hepatosplenomegaly without any lymphadenopathy. Histology showed sinusoidal

expansion by dense infiltration of monotonous small to medium sized lymphoid cells. Periportal involvement was also noted. Hepatocytes appeared normal. This was diagnosed as Hepatosplenic T Cell Lymphoma with a differential diagnosis of acute lymphoblastic leukemia. On immunohistochemistry, the lymphoid cells were positive for CD3, CD2 and negative for Terminal deoxynucleotidase(TdT) and thus Lymphoblastic leukemia was ruled out because of TdT negativity (Table 3).

Table 1: Morphological features of PTCL- U

Morphological Features	Distribution of the features (N = 6)
Effacement of architecture	6 (100%)
Heterogenous population of cells	6 (100%)
Reactive population of cells	5 (83%)
Reed Sternberg like cells	2 (33%)
Prominent vascular channels	2 (33%)

Table 2: Immunhistochemical profile of PTCL-U

IHC	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
CD45	+	+	+	+	+	+
CD3	+	+	+	+	+	+
CD2	ND	+	+	+	+	+
CD20	+ in reactive cells	-	-	-	Focally +	-
CD15	-	-	-	-	-	-
CD 30	-	-	-	-	-	-

ND – Not done, IHC- Immunohistochemistry

Table 3: Morphological and immunohistochemical features of other PTCLs

	Clinical features	Morphology	IHC	Diagnosis
1	70/M cervicalnode	Microgranulomas and small lymphoid infiltrates	Positive for CD45,CD3,CD2 and negative for CD20, CD15,CD30	Lennerts lymphoma
2	50/F cervical node	Arborizing vascular channels , polymorphic infiltrates and immunoblast like cells	Positive for CD3, CD10 AND CD23. Negative for CD20, CD15, CD30.	Angioimmunoblastic T cell lymphoma
3	50/M inguinal node			
4	4/F, liver biopsy	Sinusoidal expansion by atypical lymphoid cells	Positive for CD3, CD2. Negative for CD20, TdT.	Heptosplenic T cell lymphoma

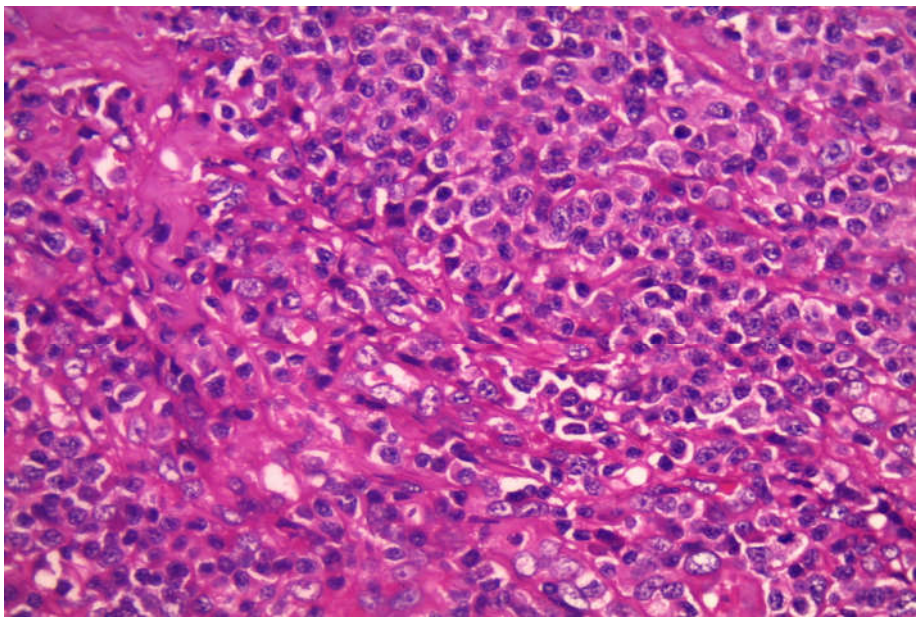

Fig. 1: Peripheral T cell lymphoma–U: heterogeneous population of cells with few reactive cells (40X, original magnification)

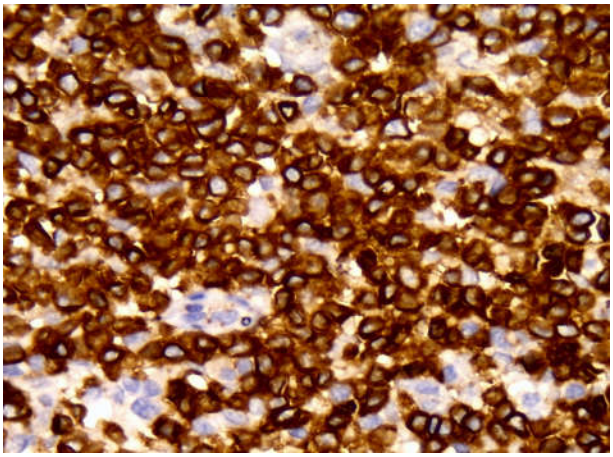

Fig. 2: *Peripheral T cell lymphoma–U:* CD3 positive tumour cells (40X, original magnification)

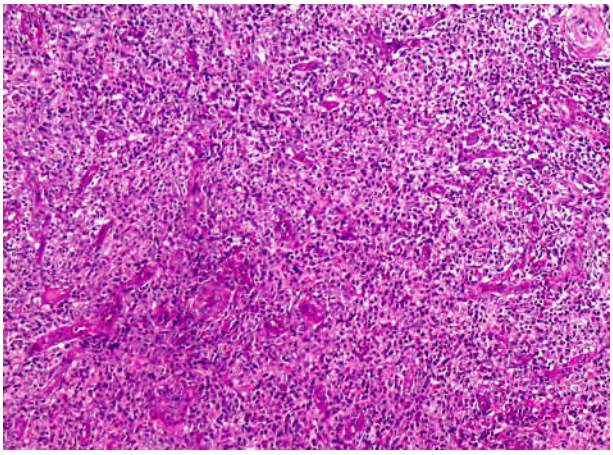

Fig. 3: *Angioimmunoblastic T cell Lymphoma:* arborizing vascular channels, effacement of architecture (4X, original magnification)

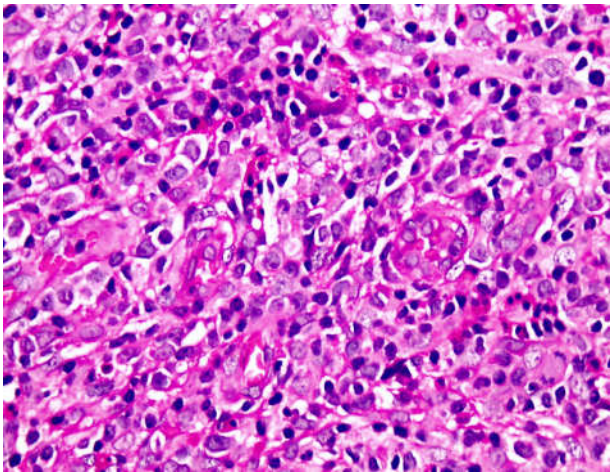

Fig. 4: *Angioimmunoblastic T cell Lymphoma:* neoplastic cells (few with clear cytoplasm), prominent vascular channels and eosinophils. (40X, original magnification)

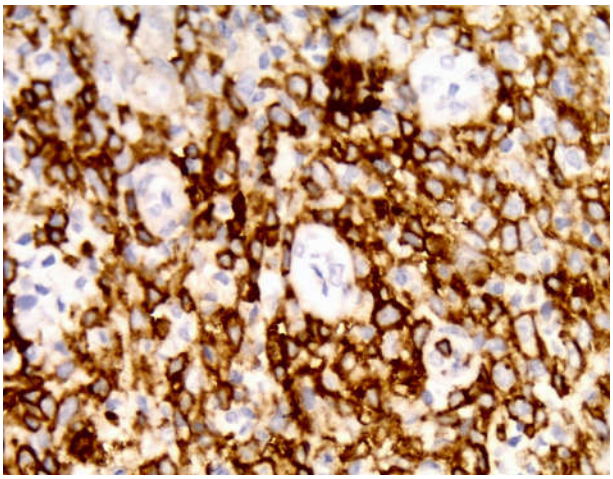

Fig. 5: *Angioimmunoblastic T cell Lymphoma:* CD3 positive neoplastic cells. (40X, original magnification)

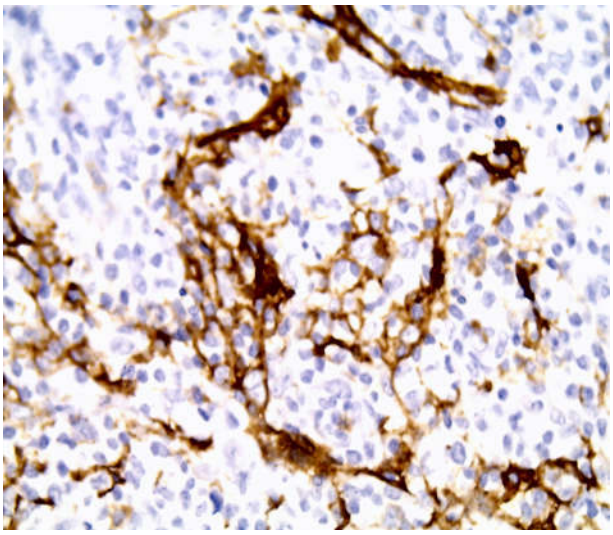

Fig. 6: *Angioimmunoblastic T cell Lymphoma:* Extrafollicular follicular dendritic cell network highlighted by CD 23 staining (40X, original magnification)

Discussion

In the present study, PTCL constitutes 20 % of NHL. This is much higher when compared to other Indian studies [5]. In our study, Nodal PTCLs accounted for about 90% of PTCLs.

PTCL U is a heterogenous group of lesions which do not fit into any of the subtypes of peripheral T cell lymphoma and thus is a diagnosis of exclusion. It is the most common subtype of Mature T cell lymphoma, typically occurring in adults at sixth decade. Lymphadenopathy is the usual presentation. In this study PTCL- U accounts for about 60% of PTCLs which is comparable to other studies [5,6]. As found in other studies, there was a male predominance and 90% of cases had lymphadenopathy. The immuno-histochemistry demonstrated positivity for T cell markers CD3 and CD2 and also showed abberant loss of CD5 expression.

Lennert's lymphoma (lymphoepithelioid lymphoma) is a variant of PTCL-U. It is a rare entity displaying monomorphic small tumor cells, few scattered immunoblasts, epithelioid cells in clusters and absence of high endothelial venules and follicular dendritic cells (FDC) networks [7,8]. In our study, the patient presented with bilateral cervical lymphadenopathy and hepatosplenomegaly. The lymph node showed the unique histological features characterized by epithelioid cell clusters and infiltrates of small lymphoid cells. Immunoblastic cells were noted in this case. CD30 positive cells were not identified.

Angioimunoblastic T cell lymphoma forms approximately 15-20% of PTCLs [9,10]. In the present study, it constituted about 20 % of PTCLs. AITL is a systemic disease clinically characterized by lymphadenopathy, hepatosplenomegaly and skin rash. Polyclonal hypergammaglobulinemia and hemolytic anemias are other associations [10]. Both the patients in the present study presented with lymphadenopathy and hepatosplenomegaly while one patient also had skin rash. The presence of hemolytic anemia and hypergammaglobulinemia were not evaluated. However they showed the classical morphological findings which include arborizing high endothelial venules, polymorphic infiltrates and presence of clear cells. The vascularity was more pronounced in AITL when compared to other PTCLS. Extrafollicular follicular dendritic cell proliferation was evident in one case. CD 23 staining confirmed the presence of this follicular dendritic cell meshwork. In the other case, where extrafollicular dendritic cell network was not evident on H & E staining, immunostaining with CD23 showed the presence of these cells.

Hepatosplenic T cell lymphoma is a rare and aggressive subtype of extranodal peripheral T cell lymphoma. HSTL accounts for less than 1% of NHL and about 3% of T cell lymphoma [11]. It occurs more frequently in immunocompromised patients. It occurs predominantly in adolescents and young adults. However in this study, the patient was a 4 year old female who presented with abdominal distension and fever without any history of immunosuppression. The diagnosis was made based on morphology and immunohistochemistry (CD 3 positivity). TCR rearrangement analysis could have helped in analyzing the variant.

We acknowledge that the sample size was small to generalize our results, but in view of rarity of this Peripheral T Cell lymphoma, our study will help in differentiating PTCL from its mimics like Hodgkin lymphoma and thus by itself may guide further treatment modalities.

Conclusion

In our study, the frequency of Peripheral T cell lymphomas is higher when compared to other Indian studies. Knowledge about the various morphological patterns and cellular composition of PTCL is essential to select the panel of immunohistochemistry markers. In our study we found that morphology when combined with immunohistochemistry is more effective in differentiating PTCL from Hodgkin lymphoma and T cell rich B cell lymphoma and also to classify various PTCLs. We by this study, conclude that immunohistochemistry becomes essential in the diagnosis of PTCL.

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