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Research Article

PREDOMINANT EXTRANODAL PRESENTATION OF PTCL::AN EFFORT TO UNDERSTAND RARE CLINICOMORPHOLOGIC PATTERNS

***Gayatri Gogoi and Mondita Borgohain**
Department of Pathology, Assam Medical College
**Author for Correspondence*

ABSTRACT

Peripheral t-cell lymphomas (ptcl) are rare and heterogenous group of non-hodgkin's lymphoma associated with poor clinical outcome. Ptcl represents 12% of lymphoid neoplasm worldwide. It is roughly subdivided into specified and not otherwise specified (nos). Nos represent commonest subtype, while anaplastic large cell lymphoma (alcl) falls under specified category. Ptcl commonly have nodal presentation whereas predominant extranodal involvement is very rare, we are presenting two cases of ptcl-nos and one case of anaplastic large cell lymphoma presenting mainly with extranodal features and diverse clincopathological manifestation leading to a diagnostic dilemma.case reports: case-1: a 45 year lady presented with swelling in the scalp (vertex) with severe headache and diplopia (5-8 months), which showed extra and intracranial extension with sclerosis of skull vault. Case-2: one 52year male with a swelling over the clavicle and skin involvement for 6 months. Initial diagnosis were reactive diseases in two and non-lymphoid malignancy in one. Integrated workup involving cyto-histopathology. Case-3: a 38year male, presented with a non-healing ulcer in the lower end of femur, followed by generalised lymphadenopathy. Biopsy followed by immunohistochemistry led to the final diagnosis of two cases of ptcl-nos and one case of alcl. In case1&2, fine needle aspiration cytology (fnac) were non-contributory and h&e sections showed mostly medium sized and few large cells with irregular, pleomorphic, hyperchromatic or vesicular nuclei, prominent nucleoli in a background of small lymphocyte and high endothelial venule fna of case 3 showed large multinucleated cells, in a polymorphous background which in h& e revealed large pleomorphic cells along with hallmark cells, having eccentric horseshoe shaped nuclei. Immunohistochemistry helped to arrived at the diagnosis of case 1&2 as ptclnos and case 3 as alcl. Discussion: ptcl with predominant extranodal involvement are rare entities which can lead to sufficient diagnostic confusion with reactive disease and/or non-lymphoid malignancy. Overall prognosis is poor, as diagnosis is late in stage iii /iv requiring prompt treatment alcl has better prognosis than ptclnos and important to differentiate from b cell nhl where immunohistochemistry is crucial. There is a need to understand rare types of nhl and its clinicopathologic behaviour for prompt diagnosis and treatment.

Key Words: *PTCLNOS, ALCL, Hallmark cells, Extranodal and Immunohistochemistry*

INTRUDUCTION

Case Report 1

A 45 years female presented with swelling in the scalp (vertex) with severe headache for 8 months and diplopia for 5 months. On X-ray showed a shadow in the vertex and focal calvarial thickening with sclerosis. CT and MRI revealed sclerosis of skull vault with adjacent enhancing soft tissue mass in intracranial and extracranial regions. Intracranially the lesion extends through superior parafalcine region with encasement to superior sagittal sinus (Figure 1.A). The radiologic features suggestive of Haemangiopericytoma/Atypical meningioma. No other lymphadenopathy and bone involvement was detected. Routine haematological examination was normal except with mild anaemia with Haemoglobin level 9.5gm/dl. Routine biochemical examination was normal. Biopsy from scalp, showed diffuse infiltrate of round to spindle shaped mostly medium size lymphoid cells and atypical irregular nuclei and mostly inconspicuous nucleoli with moderate amount of cytoplasm. There are high endothelial venule and

prominent sclerosis. The neoplastic cells often form clusters. Some reactive cells like lymphocytes, eosinophil and plasma cell in background (Figure-1.B). The provisional histological diagnosis Extra Nodal- Non Hodgkin's lymphoma most likely DLBCL and a private laboratory reported as haemangioendothelioma. Immunohistochemical profile as follows (Figure-1.C) - CD3 strongly positive in the neoplastic cells, CD20, CD15, CD30, CD 5, CD10, CD23, CD56 and EMA all were negative. CD4 showed positive 70% of cells. The proliferative marker Mib1 was reactive in 45% of cells indicating a high proliferative index. So, the final diagnosis was PTCL-NOS.

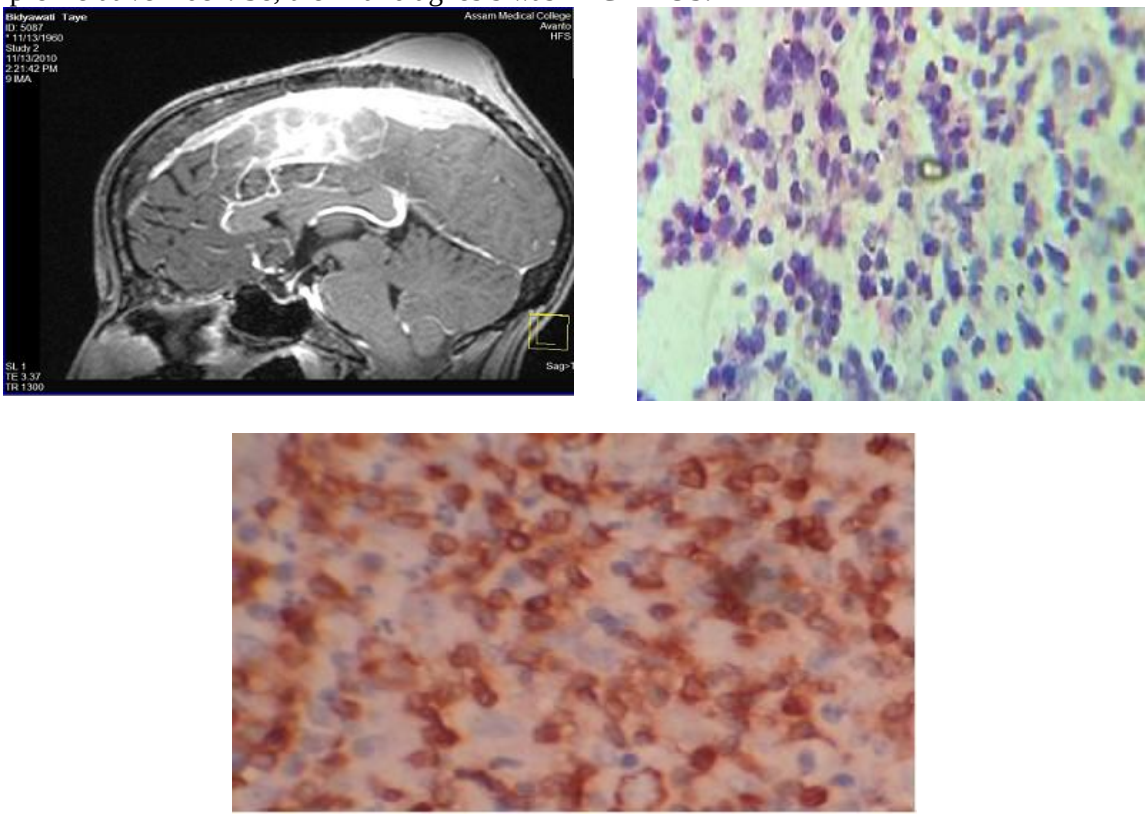

Figure-1: A- MRI of brain revealed sclerosis of skull vault with adjacent enhancing soft tissue mass in intracranial and extracranial regions. Intracranially the lesions extend through superior parafalcine region with encasement to superior sagittal sinus. Minimal perilesional odema noted in left parietal.There is evidence of extradural plaque lesion with an extracranial soft tissue extension with an smooth margin of subcutaneous plane. The multiple plial vessels and cortical draining vessels are seen to interpose between the mass lesions on and brain parenchyma. B- Hematoxylin and Eosin staining showsmostly intermediate size tumour cells with some reactive cells like eosinophil and plasma cell and high endothelial venule in background. C- Immunohistochemistry staining shows CD 3 staining by all intermediate size tumour cells indicating T cell phenotype.

Case Report 2

A 52 years male with a swelling measuring 3×3.5×3.5 over the clavicle which developed with a period of 2 months which gradually ulcerated leading to skin involvement and biopsy was taken when the lesion was 6 month duration. The x-ray shows an intramedullary osteolytic lesion with breakdown of cortex and soft tissue enhanchment over the clavicle. The x-ray suggestive of a malignant tumour. No other radiologic findings from other parts of the body detected. Routine blood shows mild anaemia with relative polymorphonuclear leucocytosis (TC-12000, P-80%). Bone marrow aspiration findings were normal with

slight increased in myeloid precursor. Biopsy from nodulo-ulcerative lesion over the clavicle. H/E shows diffuse infiltrate of mostly medium size lymphoid like cells round to elongated, having pleomorphic hyperchromatic nuclei, inconspicuous nucleoli .The cytoplasm is scanty and eosinophilic. The mitosis is moderate. There are occasional large cells. The background was polymorphic with scattering of eosinophils and reactive lymphocytes and numerous vessels (Figure-2.A). The Provisional diagnosis was Non Hodgkin's Lymphoma and small round cell tumour with a prominent inflammatory component. Immunohostochemistry profile excluded small cell tumour further lymphoma profile helped to final diagnosis of PTCL-NOS (Figure-2.B).

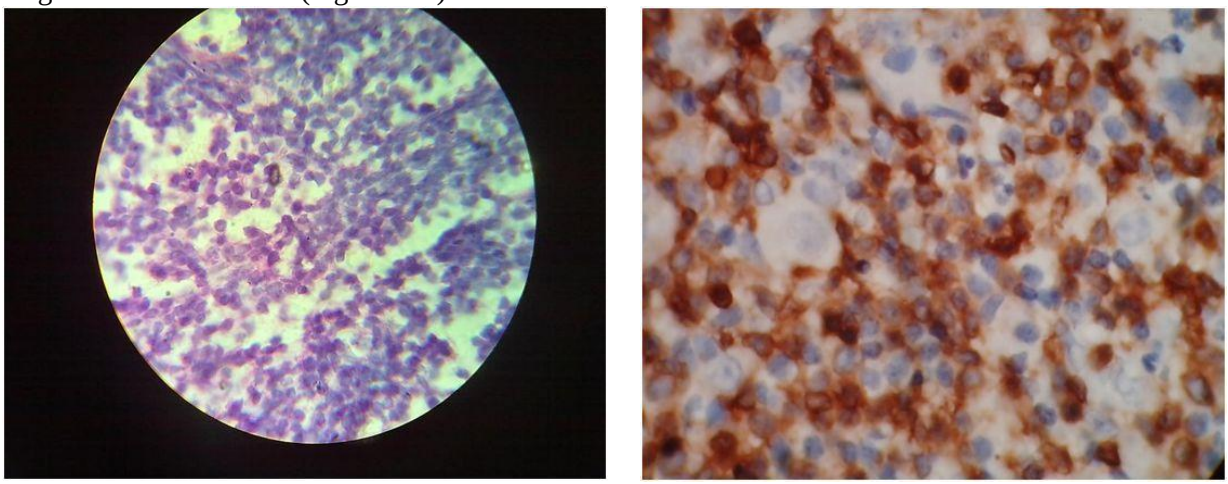

Figure-2: A- Round to elongated intermediate size cells hyper chromatic nuclei, indistinct nucleoli scanty eosinophillic cytoplasm. B- CD4 positive in least 65% of cells.

Case Report 3

A 38 years male, presented with a deep non-healing ulcer of soft tissue in the lower end of femur involoving the bone itself for which he was admitted in orthopaedic ward and, followed by generalised lymphadenopathy involving huge inguinal, axillary, supraclavicular, cervical groups of lymph nodes. His

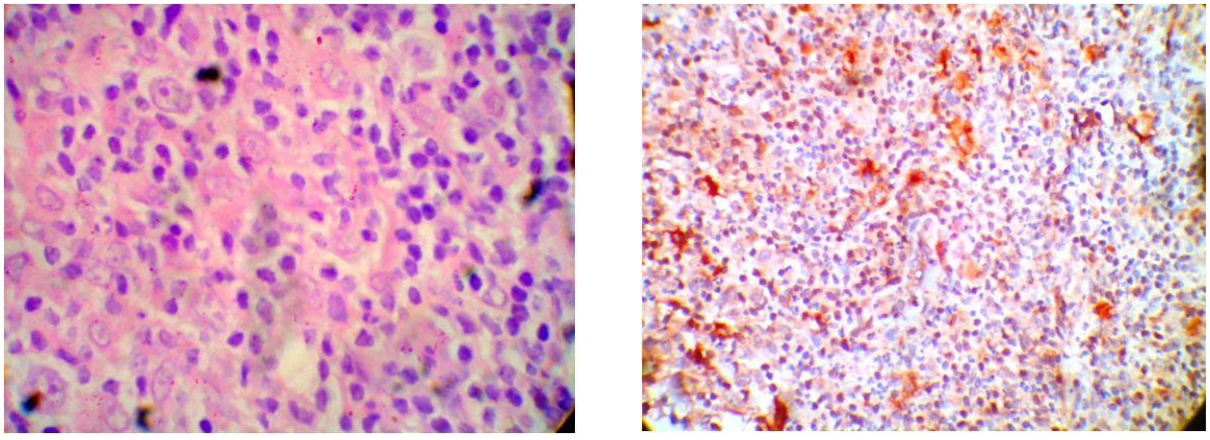

Figure-3: A- Hematoxylin and Eosin staining section showing distinct population of large lymphoid cells, having single or multiple nuclei, distinct nucleoli , moderate to abundant cytoplasm. Some scattered cells with bean or kidney shaped nuclei also noticed. The background was polymorphic rich in small lymphocytes, eosinophil and plasma cells. B- IHC of case 3 showed CD 30 staining by large cells, Hallmark cells with horseshoe shaped nuclei, strong in membrane and golgi region in large cells.

Table 1: General Profiles

S. No.	Age	Sex	Site	Lymphadenopathy	Radio- Diagnosis	Final Diagnosis
Case 1	45	F	Scalp (vertex)	Nil	Meningioma/ Hemangiopericytoma	PTCL-NOS
Case 2	52	M	Clavicle	Nil	Malignant lesion	PTCL-NOS
Case 3	38	M	Lower end femur	Yes	TB/Mycotic lesion	ALCL- ALK 1-ve

first complains started as fever and ulcer over femur almost year ago.The inguinal groups are very large, size of 3.5×3.5 cm with ulceration and irregular margins superficially. X-ray of femur suggestive of chronic osteomyelitis. The USG abdomen shows, multiple hypoechoic lesions in liver and with mild spleenomegaly, enlarged preaortic, paraaortic, groups of lymph nodes. USG diagnosis was tuberculosis/mycotic lesions. He had history of receiving anti tubercular drugs for 3 months. The biopsy from bone and large ulcerative inguinal node showed a distinct population of large lymphoid cells, having single or multiple nuclei, distinct nucleoli , moderate to abundant cytoplasm. Some scattered cells with bean or kidney shaped nuclei also noticed. The background was polymorphic rich in small lymphocytes, eosinophil and plasma cells (Figure-3). So provisional histological differential diagnosis was diffuse large cell lymphoma and Hodgkin's lymphoma. Further work up by immunohistochemistry confirmed the diagnosis of ALCL, Alk-1 negative type

DISCUSSION

Peripheral t-cell lymphomas (PTCL) are rare and heterogenous group of non-hodgkin's lymphoma associated with poor clinical outcome. PTCL represents 12% of lymphoid neoplasm worldwide, *Dennis D et.al (2008)*. One of the most common subtypes of PTCL is a heterogeneous group of nodal and extranodal mature T-cell lymphomas that do not correspond to any of the specifically defined T-cell entities in theWorld Health Organization classification,1 and are)therefore called PTCL, not otherwise specified (NOS) , *Dennis D et.al (2008)*

Peripheral T cell lymphomas (PTCL) are defined by their post thymic origin, in comparison to precursor or pre-thymic lymphomas. It is generally occurs in older individuals and with slight male preponderance. PTCL represents 12% of lymphoid neoplasm worldwide and it is subdivided into specified and non specified category (NOS) , *Dennis D et.al (2008)*The commonest type of PTCL is PTCL-NOS 30%[(2)]followed by angioimmunoblastic type(AITL) and anaplastic large cell lymphoma type(ALCL). The commonest extranodal presentation is by specified category of PTCL. In western countries, PTCL accounts for 15% - 20% of aggressive lymphomas and 5% - 10% of all Non Hodgkin's Lymphoma. In Asian continent this number is higher 15% - 20% of all lymphomas classified as PTCL or NK/T cell lymphoma.

PTCL-NOS is defined as heterogenous category of nodal and extranodal mature T cell Lymohma which donot correspond to any of the specific entities of mature T cell Lymphoma in current classification[(2)].Most patients present with peripheral lymph node involvement, though any site may be affected. Generalized disease is often encountered with infiltrates in bone marrow, liver spleen, extranodal tissues (*WHO 2008*)

The morphological spectrum is very broad from highly polymorphous to monomorphous , *(WHO-2008)* Most cases consist of numerous medium sized and /or large cells, with irregular hyperchromatic or vesicular nuclei, prominent nucleoli and many mitotic figures. Rare cases have predominance of small lymphoid cells with atypical irregular nuclei. High endothelial venules may be increased. An

Table 2: IHC Profiles

Case No.	Markers	Result
1	LCA or CD 45	Strongly positive in diffuse proliferating clusters of cells.
	Vimentin	Shows staining of the endothelial lining, thus enhancing prominent high endothelial venule.
	CD31	Negative
	Cytokeratin	Negative
	Desmin	Negative
	S100	Negative
	CD3	Strongly positive in the neoplastic cells.
	CD20	Negative
	CD 15	Negative
	CD30	Negative
	CD4	Positive in 70% cells.
	CD8	Negative
	CD23	Negative
	CD 5	Negative
	CD56	Negative
	CD10	Negative
	EMA	Negative
	Mib1	Positive in 45% cells.
2	LCA or CD 45	Strongly positive in proliferating clusters of cells.
	Vimentin	Shows staining of the endothelial lining signifying a vascular component.
	CD31	
	Cytokeratin	Negative
	Desmin	Negative
	S100	Negative
	CD3	Negative
	CD20	Strongly positive by neoplastic cells.
	CD 15	Negative
	CD30	Negative
	CD4	Occasional weak positivity in few cells.
	CD8	Positive in 65% cells.
	CD23	Negative
	CD 5	Negative
	CD56	Negative
	CD10	Negative
	EMA	Negative
	Mib1	Negative
		Positive in 65% cells.
3	CD3	Positive in all large cells.
	CD20	Negative
	CD15	Negative
	CD30	Strong and diffusely positive in membrane and golgi region.
	Alk-1	Negative
	EMA	Moderately Positive.

inflammatory background is often present, which includes small lymphocytes, eosinophil, plasma cells, large B cells, and clusters of epithelioid histiocytes.

ALCL is a T cell Lymphoma consisting of lymphoid cells that are usually large with abundant cytoplasm, pleomorphic often horseshoe shaped nuclei with a translocation involving Alk gene and expression of Alk protein and expression of CD30.ALCL frequently involved lymph nodes and extranodal sites like skin, bone , soft tissue, lung and liver.The hall mark cells may look like Reed Sternberg cells like very large, abundant cytoplasm, multiple nuclei and prominent eosinophic nucleoli(WHO 2008) This picture has be differentiated from Hodgkin lymphoma in lymph node to pleomorphic sarcoma or carcinoma in extranodal sites.

Extranodal involvement takes the form of diffuse infiltrate composed of similar cells in PTCL-NOS (WHO 2008). So, all these inherent diversity of morphological features and in situation of extranodal involvement, the diagnosis become more challenging. The pleomorphic cytomorphology of ALCL leads to confusion with the more frequent bone and soft tissue sarcomas affecting the musculoskeletal *system, Pant V et.al(2007).With* the exception of a few subgroups, the prognosis of PTCL is poor, partly due to a limited understanding of their pathophysiological features. There is considerable variability in clinical presentation, which may greatly prolong the time taken to reach an accurate diagnosis in an individual patient. Additionally, treatment standards in PTCL have not yet been established, *Weidmann E et.al (2004)* and *The Lymphomas (WB Saunders 1998).*

In our both the cases of PTCL-NOS initial clinical suspicion were inflammatory conditions of bone or soft tissue tumour. Radioimaging and Fine needle aspiration cytology reports were inconclusive in both the cases of PTCL-NOS and the case of ALCL. Histological picture lead to differential diagnosis of lymphoma with intermediate sized moderately pleomorphic lymphoid cells and high endothelial venule were few clues to lymphoma from non lymphoid malignancy. In case of ALCL, histological diagnosis was of primary malignant lymphoma though subtype was not in the differential list. The most useful ancillary technique was application of immunohistochemistry in diagnosis. Beside primary lymphoma panel, an extended panel of T cell markers were used for diagnosis of PTCL-NOS.The case of ALCL was somewhat easier with a primary panel of lymphoma maker where CD 30 and ALK 1 is most specific.The PTCL-NOS cases were required to go for extended T cell lymphoma panel markers CD4, CD8(Table 2) and proliferating score with Mib 1 also high, indicating tumours of poor prognostic as cited by many authors, Rüdiger T et al (2002)

There is needed to be familiar with the extra-nodal presentations such as in case 1 involvement of brain with symptoms of diplopia and intense headache etc. A high index of suspicion is necessary to initiate the correct panel of immunohistochemical markers to first confirm the lymphomatous nature of this tumour and to subsequently subclassify , *Pant V et al(2007*). However, within the PTCL 'not otherwise specified' category, but not angioimmunoblastic lymphoma, the number of transformed blasts was prognostically relevant, ·Currently; all types of PTCL should be considered high-grade lymphomas. An increased ability to distinguish T-lymphocyte subsets is needed in order to better subclassify the PTCLs for therapeutic and prognostic purposes· , Rüdiger T et al (2002). We also evaluated a variety of pathologic features as possible prognostic factors in PTCL-NOS. In our study, Ki67 proliferation (_ 25%) was an adverse predictor of survival. Ki67 proliferation (_ 80%) was also reported by Went et al to predict for poor survival and was incorporated into their prognostic model(1).The study of the these 3 cases helped us to understand the heterogeneous nature , varied clinical diagnosis due to unusual extra-nodal presentation and application of crucial immunohistochemical markers for diagnosis of this rare NHL.

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