Case Series

DOI: 10.7860/NJLM/2017/25288:2213

T-Cell/Histiocyte Rich Large B-Cell Lymphoma –A Case Series with Review of Literature

Pathology Section

PRIAVADHANA RAJAN PRASAAD, BHAWANA ASHOK BADHE

ABSTRACT

T-Cell/Histiocyte Rich Large B-Cell Lymphoma (THRLBCL) is a rare variant of Diffuse Large B Cell Lymphoma (DLBCL). This entity differs from the classical DLBCL in the morphology as well as immunohistochemical expression of various CD markers. This lymphoma is characterized by paucity of large, atypical B-cells and surrounded in the background by a dense population of reactive T-cells and histiocytes. This lymphoma gains importance in differentiation from the classical DLBCL in that it is morphologically very similar to the Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL). THRBCL is often refractory to the current line of treatment available. Hence, identification of this entity with the help of immuohistochemical and molecular studies is essential for the correct diagnosis and management. Here in this study, we report a series of four cases which are diagnosed as THRLBCL along with review of the literature.

Keywords: Hodgkin lymphoma, Lymphadenopathy, Non-Hodgkin lymphoma

T Cell/Histiocyte Rich Large B Cell Lymphoma (THRLBCL) is classified as a subset of the classical DLBCL according to the WHO classification of hematolymphoid neoplasms 2008. It is a high grade, aggressive non-Hodgkin lymphoma, affecting mainly middle aged men [1,2]. Most of the patients present with lymphadenopathy as the predominant manifestation with frequent infiltration of the bone marrow and reticulo-endothelial organs like spleen and liver.

Case Report-1

A 26-year-old male presented to the Medicine out patient Department with complaints of fever and left Inguinal lymphadenopathy for a period of 18 months. There was no history of enlargement of any other group of nodes. No history of evening rise of temperature, sweating and contact with known case of tuberculosis. On examination, there was left inguinal lymphnode enlargement measuring 10X6 cm, mobile, firm, not warm. No other node enlargement noted. There was no hepatosplenomegaly at the time of presentation. The patient underwent fine needle aspiration cytology of the inguinal node which was reported as reactive lymphoid hyperplasia. There was no decrease or clinical improvement with a course of antibiotics and anti-inflammatory agents and hence a lymphnode biopsy was performed.

Case Report-2

A 60-year-old male presented to the surgical Outpatient Department with complaints of right sided neck mass for the past one month. No history of fever, sweating or loss of weight. On examination, the patient had right cervical lymphnode enlargement measuring 3X3cm, mobile, firm to hard, not fixed to the underlying structures. On systemic examination, no other group of lymphnode enlargement noted. No hepatosplenomegaly noted at the time of presentation. Bilateral testes examination was within normal limits. Fine needle aspiration cytology of the node revealed scanty cellular smears with increase in histiocytes. Eventually, a lymphnode biopsy was performed to arrive at a diagnosis.

Case Report-3

A 41-year-old male patient presented to the Medicine Outpatient Department with complaints of swelling in the left side of the neck for the past 3 months. No history of loss of weight, contact with tuberculosis and fever was present. On examination, the patient had left cervical lymphadenopathy measuring 4X2.5cm, mobile, not warm. Systemic examination did not reveal any other group of lymphnodes and hepatosplenomegaly was absent. Chest X-ray and USG abdomen were within normal limits. Subsequently, a lymphnode excision biopsy was performed.

Case Report-4

A 35-year-old male presented to the Medicine Outpatient Department with history of right neck swelling for the past 5 months duration. No history of B symptoms, contact with tuberculosis noted. On examination, right cervical lymphnode was enlarged measuring 3X2cm, mobile, firm. No evidence of lymphadenopathy of the other groups and hepatosplenomegaly noted. FNAC of the lymphnodes showed paucicellular smears with occasional atypical

large cells in a background of histiocytes and lymphocytes suggestive of lymphoproliferative disorder. Lymphnode biopsy was performed to arrive at a diagnosis. The lymphnodes excised were received in the Department of Pathology. These were routinely processed (formalin fixed and paraffin embedded) and 3 microns sections were taken and stained with Hematoxylin and Eosin (H&E) and examined.

After the initial examination with H&E stain, appropriate special stains like the Reticulin stain, Periodic Acid Schiff stain and the Ziehl-Neelsen stains are performed along with the specific Immunohistochemical markers.

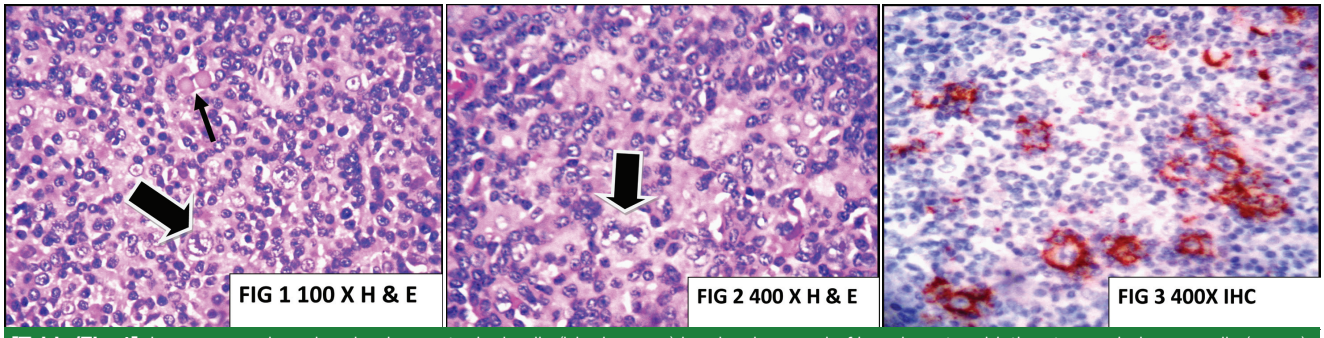
Immunohistochemistry was carried out according to the standard protocol in the formalin fixed and paraffin embedded sections after treatment with series of xylene and alcohols [3]. Subsequently, these sections are treated with 3% H_2O_2 solution for blocking the endogenous peroxidase activity. After this, the antigens are retrieved by incubating the sections in the citrate buffer at a pH of 6 using the Heat Epitope Antigen Retrieval method (HEAR) by pressure cooking. Once the antigens are retrieved the sections are incubated for 60 minutes in the primary antibody solutions and the streptavidin – biotin polymer complex is used to label these antibodies. The final colour reaction product is brown with the use of the chromogen Diamino Benzidine (DAB) and the results are interpreted as either positive or negative and specified as cytoplasmic, membranous or nuclear staining in the tumor cells.

After a morphological diagnosis is made, the following panel of markers were used – CD3, CD4, CD8, CD20, CD10, CD15, CD30, EMA, ALK protein, EBV LMP, BCL-2 and Ki-67 (MIB-1) for the differential diagnosis and sub-categorisation of lymphomas.

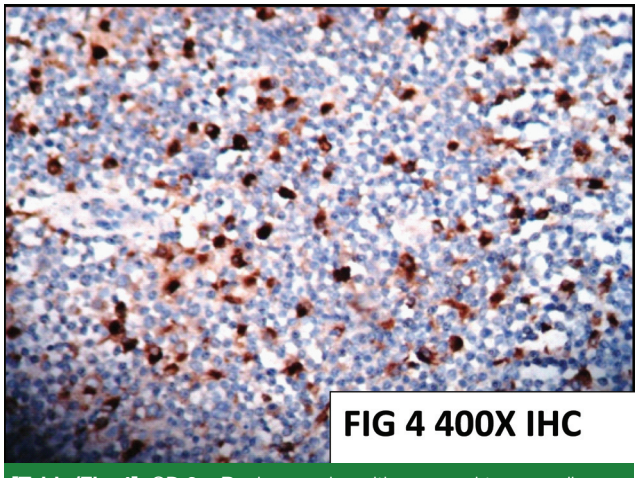
Histopathology of the lymphnodes in all the cases showed diffuse effacement of architecture. These were composed of large atypical cells and the background population consisted of a dense infiltration by lymphocytes and histiocytes [Table/Fig-1,2]. These large tumor cells shows a very low mitotic activity. Background vascularity and high endothelial vessels were within normal limits.

Immunohistochemistry findings show these large tumor cells to be positive for CD20 (B-cell marker) [Table/Fig-3], CD3 strong positivity in the background around the tumor cells in all the cases [Table/Fig-4].

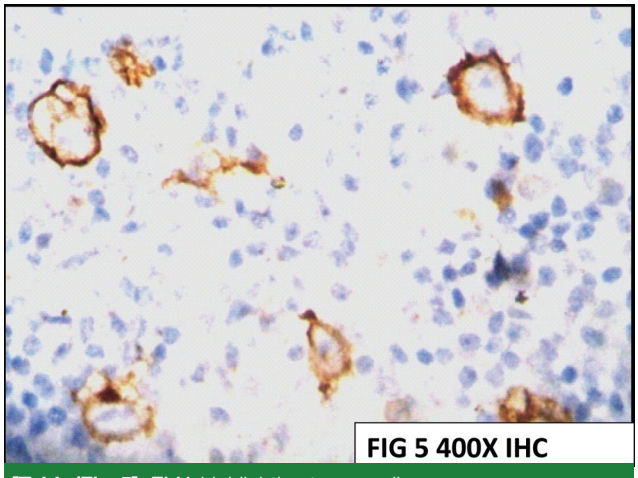
The germinal center marker CD10 was not expressed in these cases. 100% strong positivity was seen for Epithelial Membrane Antigen (EMA) [Table/Fig-5]. Also, the anti-apoptotic marker BCL-2 showed 100% strong expression in all the cases.



[Table/Fig-1]: Low power view showing large atypical cells (block arrow) in a background of lymphocytes, histiocytes and plasma cells (arrow). **[Table/Fig-2]:** High power view showing large atypical cells mimicking reed-sternberg cells (block arrow). **[Table/Fig-3]:** CD 20 positive in atypical cells.



[Table/Fig-4]: CD 3 – Background positive around tumor cells.



[Table/Fig-5]: EMA highlighting tumor cells.

EBV-LMP (Ebstein Barr virus- Latent Membrane Protein) was found to be strongly positive in all the cases.

CD 30 and ALK protein expression was absent in these cases. CD68 showed a strong positivity in the background histiocytes. Ki 67 showed a mean value of 28%. With the above morphological findings and the immunohistochemical characteristics, a diagnosis of THRLBCL was made in all these four cases.

DISCUSSION

THRLBCL is considered as an uncommon morphologic variant of DLBCL (3-4% of all DLBCLs) with a distinct clinical profile affecting middle age population, with frequent involvement of liver, spleen and bone marrow and hence a worser prognosis compared to the traditional DLBCL [1,2]. This has gained importance morphologically since it mimics the NLPHL and the Classic Hodgkin Lymphoma (cHL). This tumor is defined by the paucity of the neoplastic B-cells which are CD20 positive (constituting < 10% of the tumor) and an abundance of the background population of the non-neoplastic CD3 positive T-cells and CD68 positive histiocytes [3-5]. The characteristic features which distinguishes the NLPHL from THRLBCL is the CD57 rosettes which are absent in the latter entity. There is also a hypothesis that the NLPHL progress to this subtype of DLBCL [6]. But, the morphology and immunohistochemical expression is similar to THRLBCL even in these cases. If spleen is involved, a multifocal or micronodular involvement of the white pulp is noted. In cases of liver involvement, the lymphoma cells are localized in the portal tracts [1].

There are also cases mimicking THRLBCL but with lack of histiocytes. These have been categorized as Classical DLBCL rather than THRLBCL.

Immunophenotyping of THRLBCL shows, the large atypical cells to be positive for pan B-cell markers and BCL-6. Few cases also show a variable expression for BCL-2 and EMA. These lymphomas do not show positivity for CD15, CD30 and CD138 [7,8]. Strong background positivity of CD3 and CD5 is observed in the background reactive T-cells. Lack of T-cell rosettes around the large atypical cells, lack of IgD positive cells in the mantle zone and lack of follicular dendritic cell meshwork differentiate THRLBCL from NLPHL [9,10].

Morphologically, THRLBCL had a differential diagnosis of the NLPHL. With the paucity of the malignant cells(<10%), diffuse architecture and absence of the rosettes by the CD3+ and CD57+ cells along with an abundance of the background lymphocytes and histiocytes, a consistent expression of BCL-2 favour a diagnosis of THRLBCL than a Hodgkin lymphoma. This category has its importance among the high grade B NHLs since it poses a diagnostic difficulty between the Hodgkin lymphoma [9,11].

Rets V and Gottesman S in their case report have said that both THRLBCL and NLPHL are morphologically difficult entities and pose diagnostic problems [9]. Immunohistochemically, they have identified the background population to be distinct in THRLBCL and NLPHL. They have studied that THRLBCL shows a strong positivity of reactive T-cells in the background whereas the reactive cells are of B-cell type in NLPHL.

Hartmann S et al., in their study have studied the three entities of NLPHL, THRLBCL and THRLBCL like NLPHL [12]. They analysed the gene expression profiling of these three entities and found BAT 3/BAG 6, HIGD1A AND FAT10/UBD were expressed in all the three lymphomas. Only studies on the background histiocytic and T-cell population differed in these entities. They have concluded in their study that THRLBCL like NLPHL behaves more like THRLBCL rather than NLPHL.

Franke S et al., have analyzed 17 cases of THRLBCL using comparative genomic hybridization and concluded that THRLBCL is a distinct subset of DLBCL, possibly originating from the same precursor cell of NLPHL [13].

Chang C et al., have reported a CD 5 positive THRLBCL. They have also documented that CD 5positive cases have a better response to treatment and hence prognosis [14].

Rare sites of involvement of THRLBCL have been documented in the literature. Mangal Pandure et al., have reported a case of THRLBCL presenting as a spinal mass [15].

Advani P et al., have reported a rare case of Primary Central Nervous system lymphoma presenting with THRLBCL morphology [16].

Turkoz HK et al., have reported a case of splenic THRLBCL presenting in a micronodular pattern in a previously diagnosed case of small lymphocytic lymphoma of the spleen [17]. They

Characteristics	NLPHL	THRLBCL
Morphology	Paucity of large atypical cells of B-type (LP cells)	Paucity of large atypical cells of B-type
Neoplastic Cell Nucleus	One or multilobed nuclei	Pleomorphic often multilobed
Nucleoli	Prominent basophilic	Many eosinophilic
Cytoplasm	Scant	Scant
CD45	Positive (tumor cells)	Positive (background)
CD20	Positive (tumor cells and background cells)	Positive (tumor cells)
CD3	Rosettes around tumor cells	Positive (background)
CD68	Negative	Positive (background)
CD15	Negative	Negative
CD30	Negative	Negative
EMA	Negative	Positive (tumor cells)
BCL-2	Positive	Positive
BCL-6	Positive	Positive
IgD	Positive	Negative
FDC Mesh	Positive	Negative

[Table/Fig-6]: Differentiating features of NLPHL and THRLBCL.

have concluded that this occurrence is a part of Richter's transformation of the lymphoma.

The identification of these two morphologically is important since NLPHL in its early stages is managed by limited field radiation therapy in contrast to THRLBCL which is treated primarily by chemotherapy. [Table/Fig-6] highlights the features distinguishing both these entities.

CONCLUSION

THRLBCL is a distinct high grade non-Hodgkin lymphoma which can be diagnosed appropriately with the help of ancillary studies like Immunohistochemistry and molecular diagnostics. Identification of this entity is crucial for the management since it very closely mimics NLPHL.

ACKNOWLEDGEMENTS

I sincerely acknowledge the Department of Pathology, JIPMER and Professor Dr.Bhawana Ashok Badhe for helping me in acquiring the required material and for helping me in the diagnosis of these cases.

REFERENCES

[1] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA and Stein H, Thiele J, Vardiman JW Editors. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. IARC: Lyon 2008.
[2] Ioachim HL, Ratech H. Nomenclature and classification of lymphomas. In: Ioachim's Lymphnode Pathology. 3rd ed. Philadelphia. Lippincott Williams and Wilkins; 2002. p. 315-24.
[3] Gocke CD, Non Hodgkin's lymphoma. In: Dabbs DJ. Diagnostic Immunohistochemistry. Philadelphia: Churchill Livingstone; 2002. p. 113-34.
[4] Abramson J. T-cell/histiocyte-rich B-cell lymphoma: biology, diagnosis, and management. The Oncologist. 2006;11(4):384-92.
[5] Aki H, Tuzuner N, Ongoren S, Baslar Z, Soysal T, Ferhanoglu B, et al. T-cell-rich B-cell lymphoma: a clinicopathologic study of 21 cases and comparison with 43 cases of diffuse large B-cell lymphoma. Leukemia Research. 2004;28(3):229-36.
[6] Zhao FX. Nodular lymphocyte predominant hodgkin lymphoma or T cell/histiocyte rich large B cell lymphoma: The problem in "Grey Zone" lymphomas. Int J Clin Exp Pathol. 2008;1:300-05
[7] Jaffe E, Harris N, Stein H, Isaacson P. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008;112(12):4384-99.
[8] Maes B, Anastasopoulou A, Kluin-Nelemans JC, Teodorovic I, Achten A and Carbone A. Among diffuse large B cell lymphomas, T cell/Histiocyte rich B cell lymphoma and CD 30 + anaplastic B cell subtypes exhibit distinct clinical features. Ann Oncol. 2001; 12:853-58.
[9] Rets A Gottesman S. Nodular lymphocyte predominant hodgkin lymphoma versus T-cell/histiocyte-rich large B-cell lymphoma: a diagnostic challenge. Case Reports in Pathology. 2014;2014:01-05.
[10] Pittaluga S, Jaffe E. T-cell/histiocyte-rich large B-cell lymphoma. Haematologica. 2010;95(3):352-56.
[11] Tirado C, Chen W, García R, Kohlman K, Rao N. Genomic profiling using array comparative genomic hybridization define distinct subtypes of diffuse large b-cell lymphoma: a review of the literature. Journal of Hematology & Oncology. 2012;5(1):54.
[12] Hartmann S, Döring C, Jakobus C, Rengstl B, Newrzela S, Tousseyn T, et al. Nodular lymphocyte predominant hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma - endpoints of a spectrum of one disease? PLoS ONE. 2013;8(11):e78812.
[13] Franke S, Wlodarska I, Maes B, Vandenberghe P, Achten R, Hagemeijer A et al. Comparative genomic hybridization pattern distinguishes T-cell/histiocyte-rich B-cell lymphoma from nodular lymphocyte predominance hodgkin's lymphoma. The American Journal of Pathology. 2002;161(5):1861-67.
[14] Chang C, Bunyi-Teopengco E, Eshoa C, Chitambar C, Kampalath B. CD5+ T-cell/histiocyte-rich large B-cell lymphoma. Modern Pathology. 2002;15(10):1051-57.
[15] Pandure M, Karle R, Dongre S, Deshpande V. T-cell rich large B-cell lymphoma: a rare variant of diffuse large b cell lymphoma. Annals of Pathology and Laboratory Medicine. 2016;3(1):27-31.
[16] Advani P, Starr J, Swaika A, Jiang L, Qiu Y, Li Z, et al. T-cell/histiocyte-rich large B-cell lymphoma presenting as a primary central nervous system lymphoma. Rare Tumors. 2015; 7(4):6084.
[17] Türköz H, Polat N, Akin I, Özcan D. Micronodular T-cell/histiocyte-rich B-cell lymphoma of the spleen in a case of small lymphocytic lymphoma: A Richter's transformation. Upsala Journal of Medical Sciences. 2010;115(3):217-19.

AUTHOR(S):
1. Dr. Priavadhana Rajan Prasaad
2. Dr. Bhawana Ashok Badhe

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Sree Balaji Medical College and Hospital, Chennai, Tamilnadu, India.
2. Professor, Department of Pathology, JIPMER, Pondicherry, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Priavadhana Rajan Prasaad,
NO.7, CLC Works Road, Chromepet,
Chennai-600044, Tamil Nadu, India.
E-mail: rajankpondy@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Online Ahead of Print: **Feb 24, 2017**
Date of Publishing: **Apr 01, 2017**