Primary mediastinal lymphomas, their morphological features and comparative evaluation

Riti Aggarwal, Seema Rao, Shashi Dhawan, Sunita Bhalla, Arvind Kumar¹, Prem Chopra

Department of Pathology, Sir Ganga Ram Hospital, ¹Department of Thoracic Surgery, Sir Ganga Ram Hospital, New Delhi, India

ABSTRACT

Background: Primary mediastinal lymphoma is an uncommon tumor. Hodgkin's lymphoma (HL), primary mediastinal B-cell lymphoma (PMBCL), and T-lymphoblastic lymphoma are the most common primary mediastinal lymphomas. Key morphological and immunohistochemistry (IHC) features play a very crucial role in diagnosis as well as further categorization. **Materials and Methods:** In this study, the morphological spectrum and histological features of 32 cases of primary mediastinal lymphomas diagnosed over 5 years were studied and morphological and IHC features of PMBCL versus HL were compared. Features of PMBCL were also compared against a control group of systemic diffuse large B-cell lymphoma. **Results:** Although PMBCL and HL are known to show overlapping morphological features, it was observed that presence of clear cells and compartmentalizing fibrosis in PMBCL; and classical Reed–Sternberg cells and dense inflammatory background in HL are important morphological clues while evaluating the biopsies. PMBCL showed diffuse, strong and uniform CD20 positivity; whereas CD30 showed focal/patchy, weak to moderate and heterogeneous expression, wherever found positive. As against this, HL showed diffuse, strong and uniform CD30 positivity; and focal/patchy, weak to moderate and heterogeneous CD20 expression, if found positive. CD20, CD3, and CD30 were sufficient in most of the cases while diagnosing PMBCL and HL. **Conclusion:** This study emphasizes the critical examination of IHC markers. Only positive expression in neoplastic cells is not sufficient to make a diagnosis, equal importance should be given to percentage, intensity, pattern, and type of positivity. Apart from basic IHC described above; CD15, leukocyte common antigen and fascin played an important role in differentiating HL and PMBCL in select doubtful cases.

KEY WORDS: CD20, CD30, immunohistochemistry, lymphoma, mediastinum, morphology, primary mediastinal B-cell lymphoma

Address for correspondence: Dr. Seema Rao, Department of Pathology, Sir Ganga Ram Hospital, New Delhi - 110 060, India.
E-mail: seemarao1974@yahoo.co.in

INTRODUCTION

Lymphoma can involve almost any organ and any chain of lymph nodes in the body. Mediastinal lymphoma is uncommon and may be primary or secondary. Mediastinal lymph nodes are usually involved secondarily as a part of the systemic disease.[1] Only 10% of lymphomas which involve the mediastinum are primary.[2] Hodgkin's lymphoma (HL), primary mediastinal B-cell lymphoma (PMBCL) and T-lymphoblastic lymphoma (TLL) are the most common primary mediastinal lymphomas.[3] This study aims to detail the histological features of mediastinal lymphomas diagnosed in our Institute, to discuss the close differentials and to compare the morphological and immunohistochemistry (IHC) features of mediastinal HL versus PMBCL as well as PMBCL versus systemic diffuse large B-cell lymphoma (DLBL).

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MATERIALS AND METHODS

This was a hospital-based retrospective study conducted in the Department of Pathology. A total of 205 mediastinal lesions, obtained through nonsurgical (ultrasonography or computed tomography-guided tru-cut biopsy) and surgical approach (excisional and incisional biopsy) were received over a period of 5 years (January 2010 - December 2014). Of these, 36 cases of diagnosed lymphoma category were retrieved from the archives and evaluated further. The criteria to categorize a case as primary mediastinal lymphoma was taken as - "a bulky mediastinal mass (>5 cm in largest diameter) with the absence of any other large mass at the extramediastinal site." Three cases failed to meet this criterion and were excluded. The diagnostic material of remaining 33 biopsies included nonexcisional small biopsies in 24 cases (14 guided, 10 incisional) and the excisional specimen in 5 cases. In 4 cases though it was possible to categorize the lymphoma as HL or non-HL (NHL), however, a repeat biopsy was done as further subtyping could not be done on the first biopsy due to the presence of scant material and crushing artefact. In addition, of the 14 guided biopsies, one biopsy was a case of TLL showed extensive (postchemotherapy) necrosis and was inadequate for opinion, thus was excluded. Hence, a total of 32 cases of primary mediastinal lymphoma were studied. The slides (hematoxylin and eosin and IHC stained) were analyzed. An equal number (same as PMBCL cases) of diagnosed cases of systemic DLBL were taken as controls.

All these cases were reviewed independently by two experienced pathologists with special emphasis on architectural and cytological details. The following morphological features were evaluated in each case: Partial or complete effacement of architecture by diffuse or nodular growth pattern of cells; type of neoplastic cell (small/medium/large sized, irregular/monomorphic/vesicular nuclei, conspicuous/inconspicuous nucleoli, absence/presence of classical Reed–Sternberg [RS] or RS-like cells, clear cells); background cells (lymphocytes, plasma cells, eosinophils, histiocytes, neutrophils, or polymorphous); necrosis; and extent and type of fibrosis (compartmentalising, polarising). The presence of additional feature such as granulomas was also noted.

The panel of IHC markers included CD45 (leukocyte common antigen [LCA]), CD3, CD20, CD30, CD15, CD5, CD23, CD10, terminal deoxynucleotidyl transferase (Tdt), Epstein–Barr virus (EBV), Fascin, and PAX5.

The IHC expression of neoplastic cells was evaluated based on following features:
- Percentage positivity of cells (diffuse, focal [either positively and negatively stained cells are intermingled] or patchy [positive cells have zonal distribution])
- Intensity of staining (weak, moderate, strong)
- Pattern of positivity (membranous, cytoplasmic, nuclear, Golgi-zone)
- Type of positivity (uniform or heterogeneous [i.e. variation in intensity and pattern of positive staining cells]).

Since wide range of IHC is not available in every center, one has to rely on the most commonly available markers. Thus, in this study, CD20 and CD30 were the two basic markers which were evaluated in detail. Additional IHC panel included CK, LCA, placental alkaline phosphatase, fascin, PAX5, CD15, and EBV that helped to reach the final diagnosis in certain cases. For CD20, complete membranous staining was considered positive and for CD30, complete membranous with or without Golgi zone staining was taken as positive. Incomplete membranous or nonspecific cytoplasmic staining was taken as negative thus was disregarded.

Relevant clinical information were recorded from the patients' files.

RESULTS

A total of 32 cases of primary mediastinal lymphoma were diagnosed over a period of 5 years (January 2010 - December 2014). The age range was 5–77 years (median, mean 44.5 years). Overall, the most common age group to be involved was between 21 and 30 years. Twenty-four were men and 8 were women (M: F ratio, 3:1). All the cases had bulky mediastinal mass (6–13 cm). None of these cases had generalized lymphadenopathy although 6 cases had direct extension to contiguous lymph nodes (supraclavicular) in addition to mediastinal mass. Bone marrow involvement was noted in a single case of TLL. In this study, the procurement rate (percentage adequacy for guided and incisional biopsies) for 28 biopsies (24 + 4 repeat) was 97% (27/28) with a diagnostic accuracy of 100% (27/27). Even in the 4 cases where a repeat biopsy was done for further sub-categorization of lymphoma, the primary diagnosis of HL or NHL provided on the first biopsy corroborated with the final diagnosis.

NHL and HL constituted 18 and 14 cases, respectively. Of the 18 NHL cases, there were 8 cases each of TLL and PMBCL. Remaining were the single case each of NK cell lymphoma and histiocytic lymphoma. No case of mediastinal gray zone lymphoma (MGZL) was encountered in our study.

TLL cases had a wide age range with the most common age group being 41–50 years, and M: F ratio of 7:1. Although bone marrow was involved in a single case, leukemia was not present. On microscopy, the tumor showed diffuse sheets of medium-sized cells having round to irregular nuclei, inconspicuous to small nucleoli and scant cytoplasm. In addition, focal vague nodular pattern was seen in 2/8 cases. Prominent endothelial venules were present within the tumor. Four cases showed large number of scattered tingible body macrophages giving a starry-sky appearance [Figure 1a]. On IHC, the tumor cells were

positive for LCA, CD3, CD5, Tdt [Figure 1b], and CD10 and were negative for CD20.

Most of the PMBCL cases were in 20–30 years age group with M: F ratio of 3:1. Microscopic evaluation showed complete effacement of architecture by medium sized tumor cells arranged in diffuse sheets revealing large nuclei with irregular contours and conspicuous nucleoli [Figure 2a and b]. No definite thymic tissue was identified in any of the case. Remaining features are discussed in Table 1. All the cases were strongly, diffusely, and uniformly positive for CD20. CD30 expression was seen in 4/8 cases, however, type of expression was weak to moderate, focal/patchy, and heterogeneous [Figure 2c and d].

Morphological and IHC features of PMBCL were compared with an equal number of diagnosed cases of systemic DLBL. In the control category, the most common age group involved was 61–70 with M: F ratio of 1.7:1. Microscopic features and IHC findings are discussed in Table 1. All the cases were strongly, diffusely and uniformly positive for CD20. CD30 expression was seen 2 out of 8 cases that was weak, focal/patchy and heterogeneous.

HL cases were mostly seen in 20–30 age group with M: F ratio of 1.8:1. With 9/14 cases, the most common variant was nodular sclerosis type (NScHL), followed by 3 cases of mixed cellularity type. One case showed marked chemotherapy-related changes and another showed diffuse
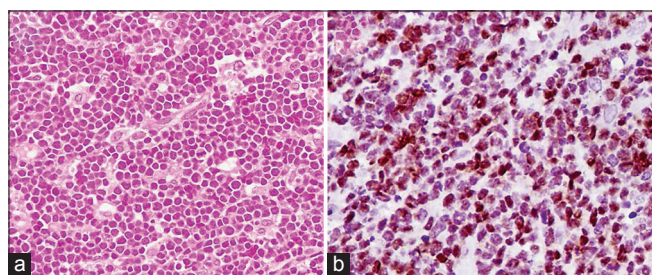
crushing artefacts thereby rendering the tumor unsuitable for further categorization and subtyping. Microscopic features and IHC findings [Figure 3a and b] are discussed in Table 1. Granulomas were not seen in any of the PMBCL or HL case.

DISCUSSION

Mediastinum can play host to a wide spectrum of lesions including thymic epithelial lesions, germ cell tumors, sarcomas, and lymphoma. Diagnosis of mediastinal lesions can be very challenging. First, mediastinum is a difficult site to approach and most pathologists do not have enough experience in interpreting mediastinal lesions including lymphoma. Second, guided biopsy even though regarded as a sensitive and reliable diagnostic tool for mediastinal lesions,[4] can sometimes pose difficulty due to paucity of diagnostic material, limited architectural details, sclerosis, and marked crushing artefacts. In latter cases, on IHC there is marked diffusion of the antigen leading to nonspecific background staining and thereby difficulty in interpretation.
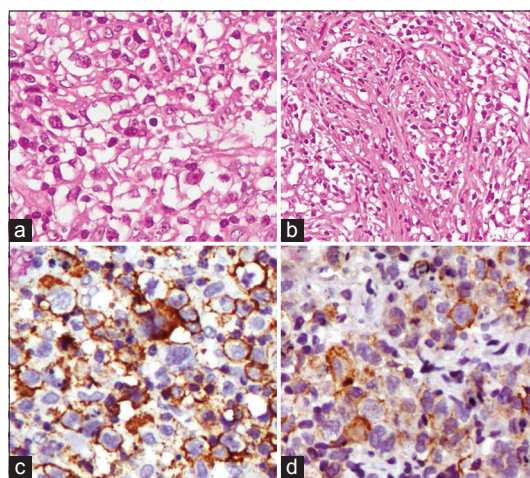

Figure 2: Primary mediastinal B cell lymphoma - (a) tumor cells are round to ovoid with abundant clear cytoplasm (b) compartmentalizing fibrosis (c) diffuse and strong CD20 positivity (d) and heterogenous CD30 positivity

Figure 1: T-lymphoblastic lymphoma - (a) diffuse sheets of monomorphic lymphoid cells with a starry-sky pattern (b) immunohistochemisty for terminal deoxynucleotidyl transferase shows diffuse and strong nuclear positivity

Table 1: Clinicopathological findings of cases of primary mediastinal B cell lymphoma, diffuse large B cell lymphoma and Hodgkin's lymphoma

	PMBCL	DLBL	HL
Age (years) range	22-52 (21-30)	34-65 (61-70)	8-53 (21-30)
Sex ratio, male: female	3:1	1.7:1	1.8:1
Clear cells	5/8	2/8	0/14
RS/RS-like cells	2/8	2/8	14/14
Inflammatory background cells	5/8 (mild)	2/8 (mild)	14/14 (moderate to dense)
Fibrosis and type	Compartmentalizing - 5/8	Compartmentalizing - 3/8	Compartmentalizing - 0/14
	Band-like - 2/8	Band-like - 0/8	Band-like - 9/14
CD20	8/8*	8/8*	7/14#
CD30	4/8#	2/8#	14/14*

*Diffuse, strong and uniform, #Focal, weak to moderate and heterogenous. Other IHC markers like EBV, PAX-5, CD15, CK were applied in individual cases as and when required. PMBCL: Primary mediastinal B cell lymphoma, DLBL: Diffuse large B cell lymphoma, HL: Hodgkin's lymphoma, RS: Reed-Sternberg, EBV: Epstein-Barr virus
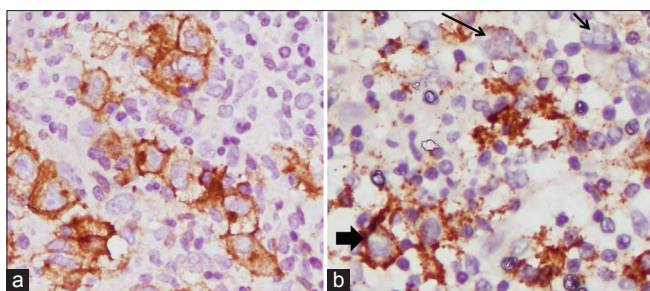
Figure 3: Hodgkin's lymphoma - (a) the tumor cells are strongly and diffusely positive for CD30 (membranous and Golgi-zone positivity). (b) CD20 shows heterogenous expression (small arrow - negative, long arrow - weak, bold arrow - strong)

The diagnosis of lymphoma involves a multimodal approach and includes a meticulous histological examination followed by IHC evaluation. Rare cases may require even cytogenetics and molecular diagnostics. Other important parameters include clinical history and laboratory findings such as complete blood count and peripheral smear examination. Bone marrow examination along with radiological investigations are crucial in reaching the diagnosis and in further staging of the disease. Lymphoma of almost any histological type can occur in the mediastinum. The most common lymphomas include PMBCL and classical HL.

PMBCL and classical HL are the most common type of mediastinal lymphomas. PMBCL is a unique subtype of DLBL arising from medullary B lymphocytes of the thymus.[5] It accounts for 2–3% of all cases of NHL.[6] Most of these cases typically present as "bulky" rapidly enlarging anterior mediastinal mass invading the thoracic structures. The patients usually have a short clinical history and show signs and symptoms related to local invasion or compression as the disease progresses, extrathoracic organs are involved. In recurrent cases, hematogenous spread to parenchymal organs may occur but bone marrow involvement is extremely rare.[7]

PMBCL has been considered a distinct entity from DLBL that has specific clinical and histological features. Although many studies suggest that PMBCL has favorable prognosis than DLBL with secondary mediastinal involvement[8,9] but conflicting studies reporting overall survival rate either poor[10] or similar to DLBL[11] are also present. Its prognosis is still a matter of debate. In this study, we tried to evaluate morphological features and the expression of basic IHC markers (CD20 and CD30) in PMBCL cases and compare them with DLBL control group.

PMBCL is characteristically seen in the young adult population and has a slight female predominance. In this study, most of the PMBCL cases were in 20–30 years age group but with a male predominance. Other studies also have shown contrasting gender predilection with some reporting male preponderance like ours[12,13] and others reporting a female predominance.[7,14,15]

Histologically, PMBCL shows a diffuse proliferation of medium to large sized lymphoid cells having moderate cytoplasm, irregular round or ovoid nuclei and conspicuous nucleoli. A frequently reported feature is prominent cytoplasmic clearing present in this group of lymphomas.[7,16] In our study, focal or diffuse clearing of the cytoplasm of neoplastic cells was noted in more than half cases (5/8 cases). A very useful feature commonly documented in various studies is a distinctive fibrosis made up of irregular collagen bands that compartmentalizes the cellular areas.[15,17,18] Varying degree of compartmentalizing fibrosis was a common feature (4/8 cases) in this study also. However, some studies also observed that it is difficult to assess sclerosis in many cases because of the small size of biopsy and extensive crush artefact.[14,18] The distinctive cytoplasmic cellular clearing and diffuse compartmentalizing fibrosis may impart a "seminoma-like" picture to PMBCL.[5] RS-like cells may also be present in a polymorphous background in some PMBCL cases.[12,19,20] In this study, few cases showed scattered RS-like cells (2/8 cases) and mixed inflammatory cells were present in the background in 5 out of 8 cases.

DLBL control cases were usually seen in sixth decade in contrast to PMBCL. Morphologically, features such as clear cells, compartmentalizing fibrosis, and background inflammatory cells were present in less number of DLBL cases [Table 1]. RS-like cells were present in equal number of cases (2/8 cases) in PMBCL and DLBL control group.

The neoplastic cells of PMBCL are derived from activated germinal center or postgerminal center cells and are frequently positive for CD20, CD79a, CD23, BCL2, BCL6, and MUM1.[21] However, it differs from other aggressive B-cell lymphomas in that it invariably lacks expression of surface immunoglobulin protein despite the expression of B-cell transcriptional factors (BOB.1, OCT-2, and PU.1).[21] CD30 expression is also commonly reported in PMBCL, thereby resulting in it being misdiagnosed as HL.[22] In our study, all the cases were strongly, diffusely, and uniformly positive for CD20. Four cases showed additional CD30 positivity, however the expression was weak to moderate, focal/patchy and heterogeneous. In DLBL control group, CD20 was positive in all cases but CD30 expression was seen in lesser number of cases and was usually weak and focal.

Despite these characteristic features thus described in PMBCL, it may not be prudent to differentiate it from conventional DLBL with secondary involvement of mediastinal lymph nodes depending on morphology and IHC alone. The corner-stone is clinico-radiological features, size of mediastinal mass, and extent of extrathoracic involvement.

HL presenting as isolated primary mediastinal disease is uncommon and has a distinct histology and biological behavior. NScHL is the most common variant.[3]

Table 2: Key morphological and immunohistochemisty features

	Typical cell	Background	CD30	CD15	CD20	CD45	PAX-5	Fascin (%)	BOB.1	OCT 2	PU.1
PMBCL	Cell with pale cytoplasm	Polymorphous, compartmentalizing alveolar fibrosis	±	−	+	+	+	± (10-15)	+	+	+
NScHL	Lacunar cell	Polymorphous, polarizing fibrosis	+	+	±	−	+	+	−	−	−
DLBL		Polymorphous	±	−	+	+	+	±	+	+	+
MGZL	Indeterminate	Polymorphous	±	±	±	±	+	±	±	±	±

PMBCL: Primary mediastinal B cell lymphoma, NScHL: Nodular sclerosis classic Hodgkin's lymphoma, DLBL: Diffuse large B cell lymphoma, MGZL: Mediastinal gray zone lymphoma

Necrosis and massive neutrophilic infiltrates can occur spontaneously and can be prominent findings in patients with HL, especially the NScHL.[23-25] it is important to consider the possibility of primary HL in the presence of abscessified suppurative mass in anterior mediastinum apart from the more common causes such as tuberculosis and fungal infection, especially when the patient does not respond to treatment. A detailed search for the characteristic neoplastic cells of HL supported by IHC is crucial in such cases.

PMBCL and HL demonstrate overlapping clinical and histomorphological features.[20] In fact, gene expression profiling studies have suggested that the signature of PMBCL is closer to HL than to DLBL.[9,26]

In this study, all HL cases characteristically had RS cells and dense inflammatory background but complete absence of clear cells and compartmentalizing fibrosis. The neoplastic cells strongly expressed CD30 with either negative or variable/weak expression of B-cell markers. Details of IHC markers differentiating the two is discussed further in detail in Table 2.

Since, PMBCL and HL carry distinct prognostic and therapeutic implications, it is important for pathologists to segregate these two entities.[27] Although many cases are resolved such, there exists an intermediate category, which cannot be assigned categorically as HL or NHL. Such lesions show the considerable overlap of morphological and immunophenotypic features and have been described as MGZL.[28] cases of composite lymphomas with PMBCL and HL occurring as synchronous/metachronous tumors have been reported.[29] We did not encounter any case of MGZL or composite lymphoma in our study.

Precursor TLL/precursor T-acute lymphoblastic leukemia (T-ALL) is the most common T-cell lymphoma presenting as a mediastinal mass in young adults.[5] Patients with <25% bone marrow involvement are classified as TLL while patients with 25% or more bone marrow blasts are diagnosed as T-ALL.[30] In this study, BM was involved in a single case but the blasts were <25%.

Apart from the mediastinal lymphomas discussed so far, the other common differentials are thymic epithelial neoplasm, germ cell tumor, metastatic malignancy, and sarcoma. It is difficult to differentiate these without IHC maneuvres particularly on small biopsy. However, discussion on this matter is beyond the scope of this article and will not be undertaken.

CONCLUSION

Needle biopsy is commonly the initial diagnostic procedure in a patient with an undiagnosed mediastinal mass. In this study, the procurement rate was 97.0% with a diagnostic accuracy of 100.0%. The common mediastinal lymphomas are TLL, PMBCL and HL. Since a wide range of IHC is not available in every center, one has to rely on the most commonly available markers. In the present study, CD20 and CD30 were the two important IHC markers that helped to reach the diagnosis in most of the cases. This study also emphasizes the critical examination of IHC markers (CD20 and CD30). A positive expression in neoplastic cells alone is not sufficient to make a diagnosis, equal importance should be given to percentage, intensity, pattern, and type of positivity.

Conflicts of interest
There are no conflicts of interest.

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