 DOI: 10.5958/2394-6792.2015.00006.X

# Mediastinal lymphomas – A clinicopathologic study

**Fatima Shamsuddin[1,*], Urmila N Khadilkar[2], Debarshi Saha[3], Sily Sreedharan[4]**

[1,4]Assistant Professor, Dept. of Pathology, Malabar Medical College Modakkallur, PO Atholi, Kozhikode, Kerala – 673315
[2]Professor, [3]Associate Professor, Dept. of Pathology, Kasturba Medical College, Manglore, Karnataka

***Corresponding Author:**
E-mail: fatimahaneeshkhanie@gmail.com

## ABSTRACT

**Background:** *Mediastinal lymphomas are relatively uncommon lesions that sometimes pose an interesting diagnostic and therapeutic problem for the clinician. A multifaceted approach to both disease definition and diagnosis, as proposed by the Revised European and American Lymphoma (REAL) classification and updated in the WHO classification is now considered the state of the art.*

**Objective:** *To classify and evaluate the histomorphology of mediastinal lymphomas and correlate the clinical findings with radiological, immunohistologic and other laboratory parameters.*

**Method:** *A 5 year study was done in Dept. of Pathology, of a private Medical College on mediastinal lesions. Total number of cases studied was 66, with lymphomas making up 8 cases. Histopathology sections taken were stained with routine Hematoxylin and Eosin stains. Immunohistochemistry was done as required.*

**Results:** *The age range of patients with mediastinal lymphomas were 12 to 80 years with a mean of 41 years. All non-Hodgkin's lymphomas (NHL) were NHL-B cell type and were in the older age group. Three out of the four cases of Hodgkin lymphoma (HL) were mixed cellularity type and the fourth was nodular sclerosing type. The HLs were seen in a younger age group. Immunohistochemistry was done in all cases to confirm the diagnosis.*

**Conclusion:** *Mediastinal lymphomas are rare & interesting neoplasms, usually located in all compartments of mediastinum. A histomorphological analysis aided by immunohistochemistry and radiology permits an exact diagnosis in many cases.*

**Keywords:** *Hodgkin lymphoma, Mediastinum, Non-Hodgkin lymphoma*

## INTRODUCTION

The mediastinum is a space demarcated by the pleural cavities laterally, the thoracic inlet superiorly, and the diaphragm inferiorly. It is further compartmentalized into anterior, middle and posterior divisions based on several structural landmarks. The mediastinum may be affected by a wide variety of pathological processes. Nearly half the patients are asymptomatic at the time of diagnosis. When present, symptoms usually relate to the location of mass.[1] The classification of hematological malignancies has undergone significant reappraisal in recent years. These changes have resulted from insights gained through the application of immunological and genetic techniques, as well a better understanding of the clinical aspects of lymphoid and myeloid neoplasms through advances in diagnosis, staging and treatment. A multifaceted approach to both disease definition and diagnosis, as proposed by the Revised European and American Lymphoma (REAL) classification and updated in the WHO classification is now considered the state of the art.[2]

Classical Hodgkin lymphoma, nodular sclerosis type (HLNS) can arise in the thymus gland, and is genotypically of B-cell origin. Fechner reports 3 such cases presenting as anterior mediastinal masses with attached thymic remnants.[3] A study of 97 cases of malignant lymphoma of the mediastinum shows the influence of clinical and histopathologic features and therapeutic modalities with regard to prognosis. Patients with Hodgkin disease and stage I disease were found to have better prognosis than patients with lymphosarcomas. Mature lymphocytic predominance of lymphomas and nodularity were also associated with increased survival. Radical surgery was found to have a distinct advantage.[4] Mediastinal large B-cell lymphoma and nodular sclerosis Hodgkin lymphoma share many epidemiological features, including prevalence in young adult females, and propensity to present with localized disease.[5]

## AIMS & OBJECTIVES

- To study the clinical presentations of mediastinal lymphomas and the various physical attributes like age incidence and gender incidence.
- To correlate the pathological findings with radiology, serology and other laboratory findings.
- To classify mediastinal lymphomas and type the conditions with the help of immunostains.

## MATERIALS & METHODS

The present study was conducted in the Department of Pathology of a private medical college. The specimens were received from attached District Hospital, and other hospitals in and around Mangalore and North Kerala.

**Duration of sample collection**:
Study involves samples of all mediastinal lesions received in the department for 5 years from January 2006 to June 2011.

**Methodology**
The patient's name, age, sex, detailed clinical history, laboratory investigations, Fine Needle Aspiration Cytology (FNAC) reports and radiological findings were recorded as per Data Proforma. The gross specimens obtained after surgery were examined in detail. Tissue was fixed in 10% buffered formalin, and processed by paraffin embedding. The blocks were serially cut, each of 3-5µ thickness and the sections counterstained with H & E. The histopathological findings were studied. Special stains and immunostains were done wherever necessary for evaluation and confirmation.

**RESULTS**

The present study is an analysis of 66 cases of mediastinal lesions received over a period of 5 years in Kasturba Medical College, Mangalore. The specimens consisted of 52 surgical resections and 13 tru-cut biopsies. The types of lesions are as depicted in figure 1. In the present study, the second most common lesion was of lymph nodes (28.8%) with lymphoma forming 12% of the lesions. The cases were seen in all three compartments of the mediastinum. Among the 19 cases involving the mediastinal lymph nodes, 11 (58%) were non-neoplastic and the remaining 8 (42%) were malignant neoplasms (Figure 2). Tuberculous lymphadenitis (37%) was the commonest non-neoplastic lesion, followed by granulomatous and sarcoid lymphadenitis (15.7%) and one case of reactive lymph node hyperplasia (5.3%). Among the malignant neoplasms, both Hodgkin lymphoma (21%) and Non-Hodgkin lymphoma (21%) were present in equal frequency (Table 1). Lymphomas constituted 12.1% of mediastinal lesions and 42% of lymph node lesions in the present study (Figure 3). Lymphomas were found in a wide age group ranging from 12 years to 80 years of age with a mean age of 41 years. Overall, males were more commonly affected with a male: female ratio of 7:1 (Figure 4)

All the Non-Hodgkin lymphoma's (NHL) were NHL-B cell type. NHL's were found in the older age group with the youngest patient being 30 years and the oldest patient 80 years of age. (Mean age = 60 years). Among the four patients, only one was female. Three out of the four cases of Hodgkin lymphoma (HL) were mixed cellularity type and the fourth was nodular sclerosing type. The HLs were seen in a younger age group compared to the NHL with the youngest patient being 12 years of age and oldest being 32 years with a mean age of 22.5 years. All the 4 cases were seen in male patients. Immunohistochemistry was done in all the cases to confirm the diagnosis (Table 2).

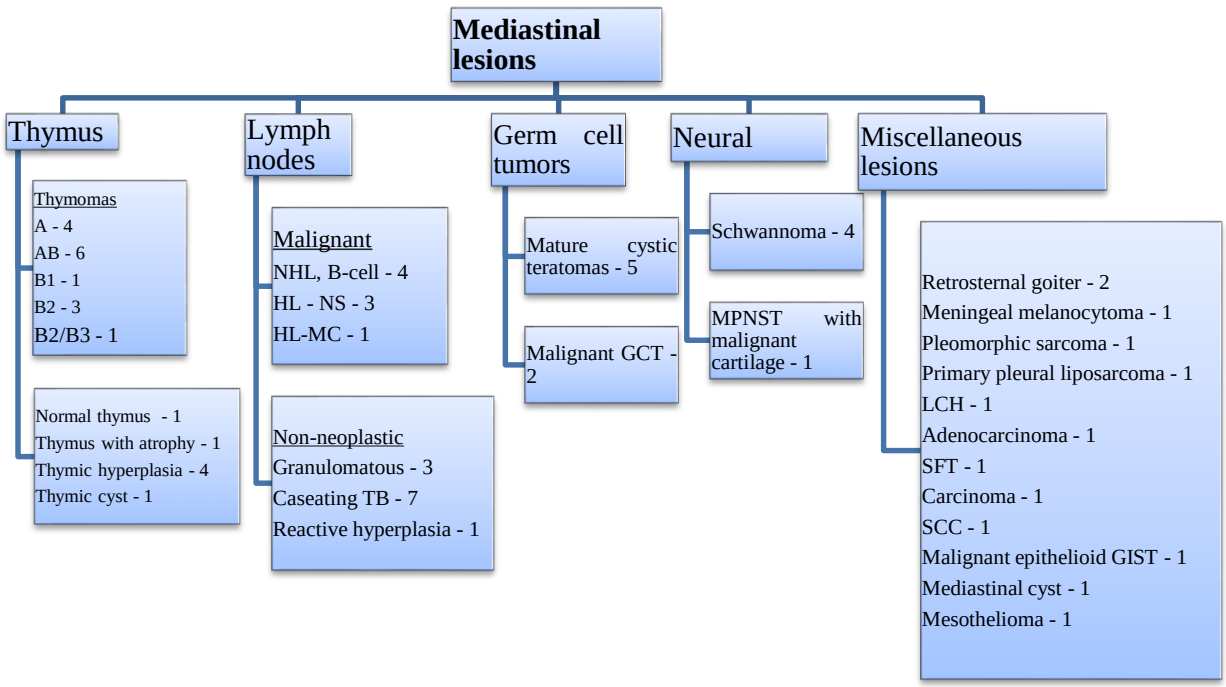


**Figure 1: Types of mediastinal lesions**

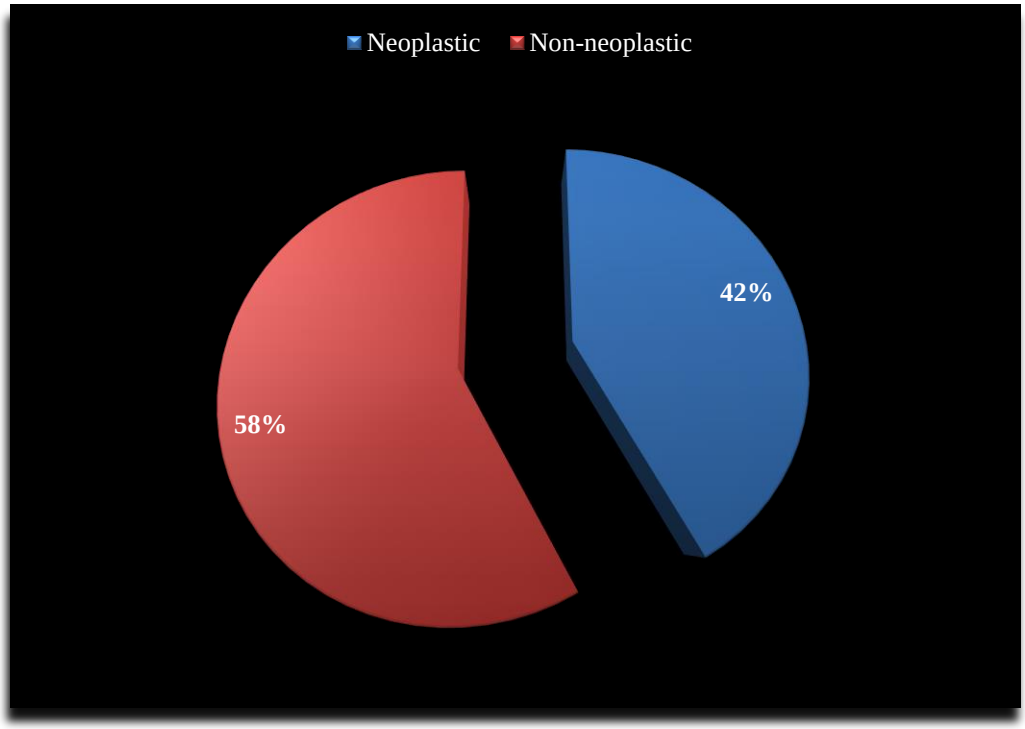


**Figure 2: Neoplastic vs. non-neoplastic lesions of lymph node**

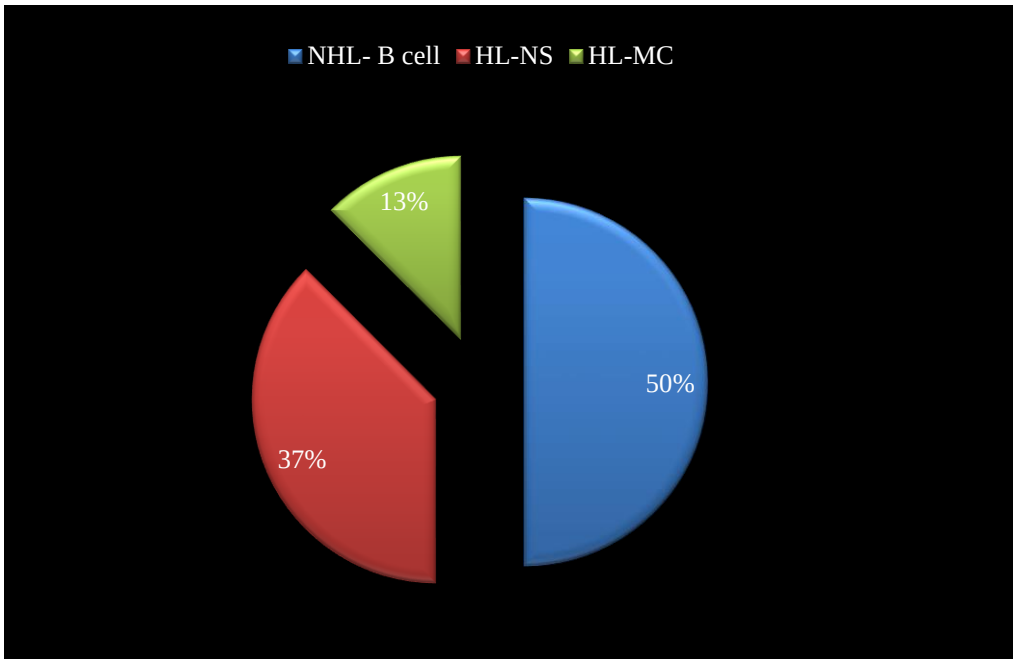


**Figure 3: Distribution of mediastinal lymphomas**

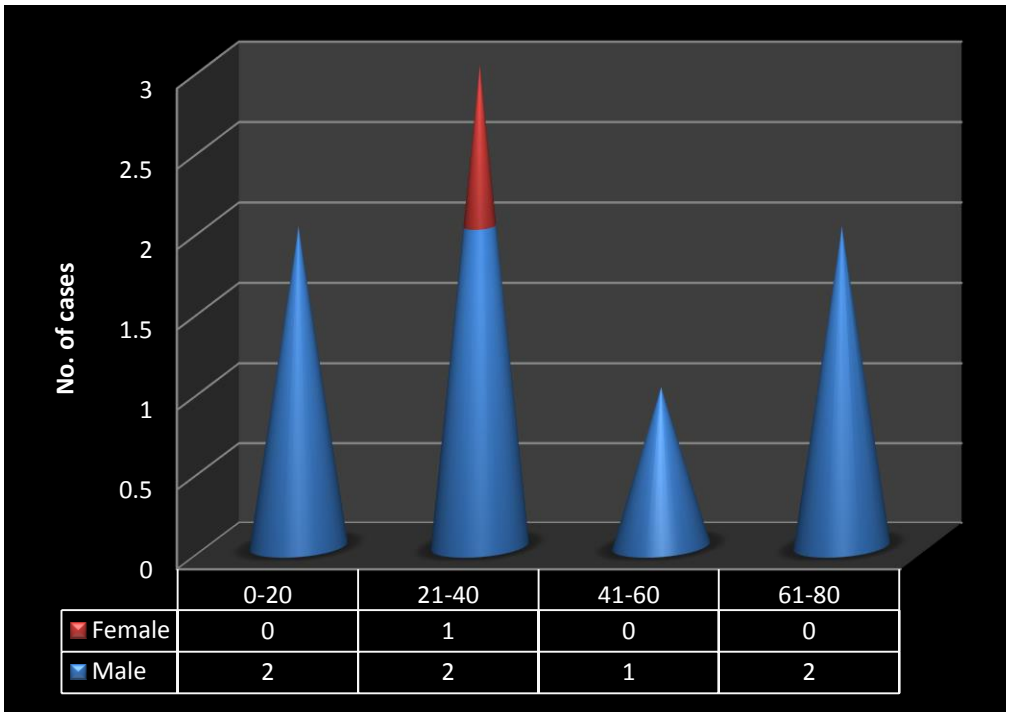


**Figure 4: Age and sex distribution of mediastinal lymphomas**

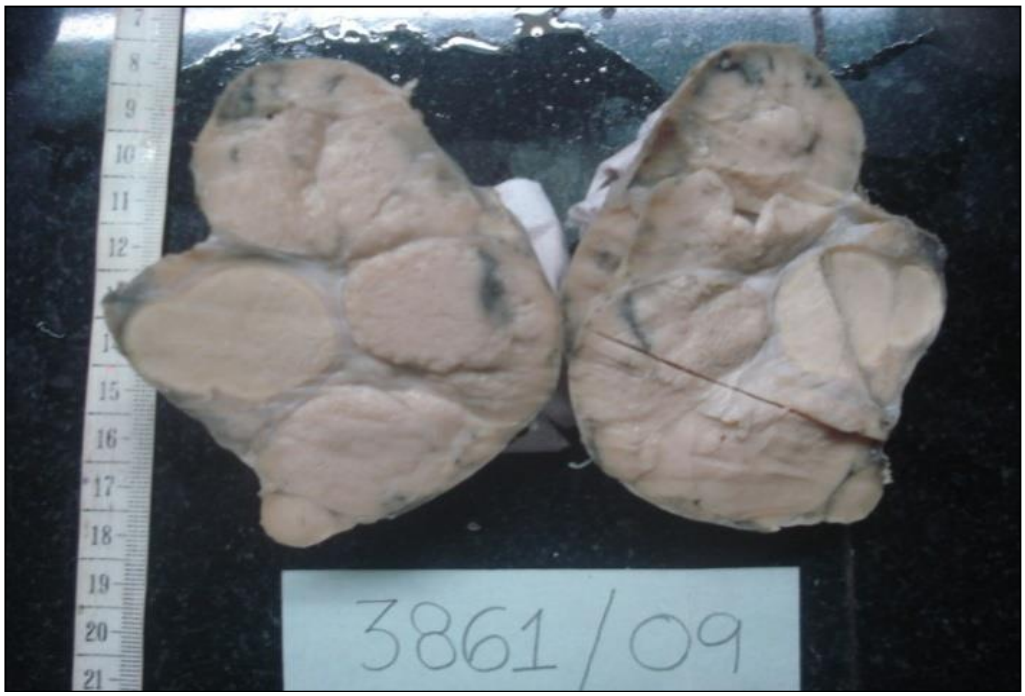


**Figure 5: Matted group of lymph nodes having homogenous, fleshy, cut surface**.

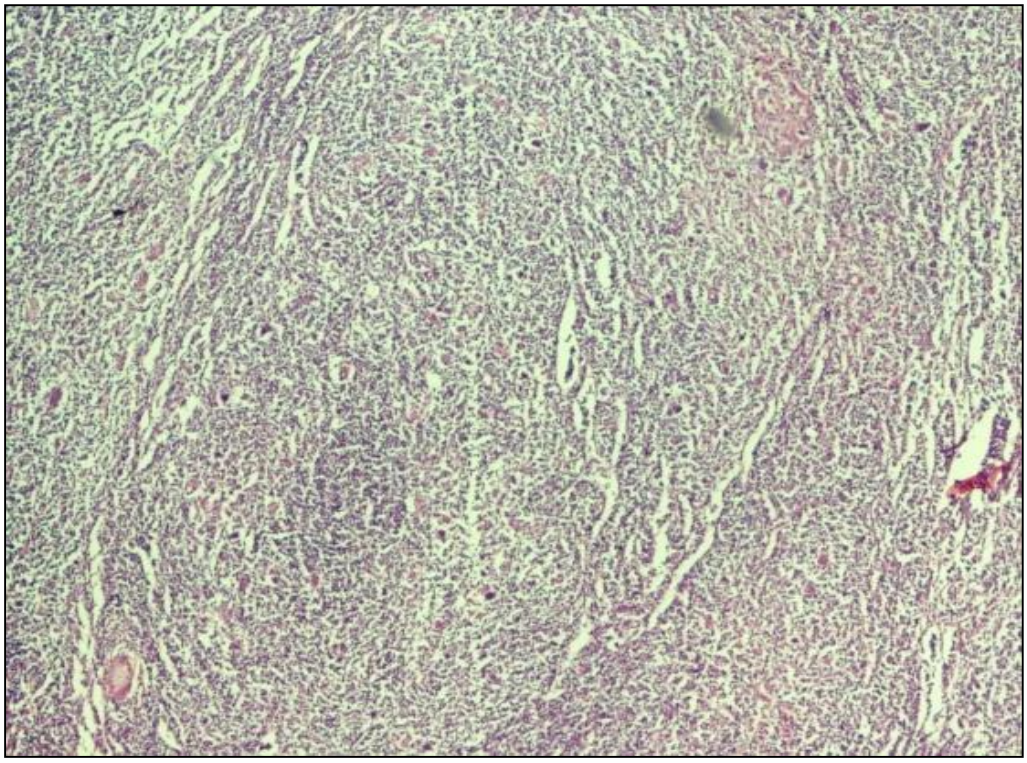

**Figure 6: Microscopy of nodular sclerosing Hodgkin lymphoma [H&E x40].**

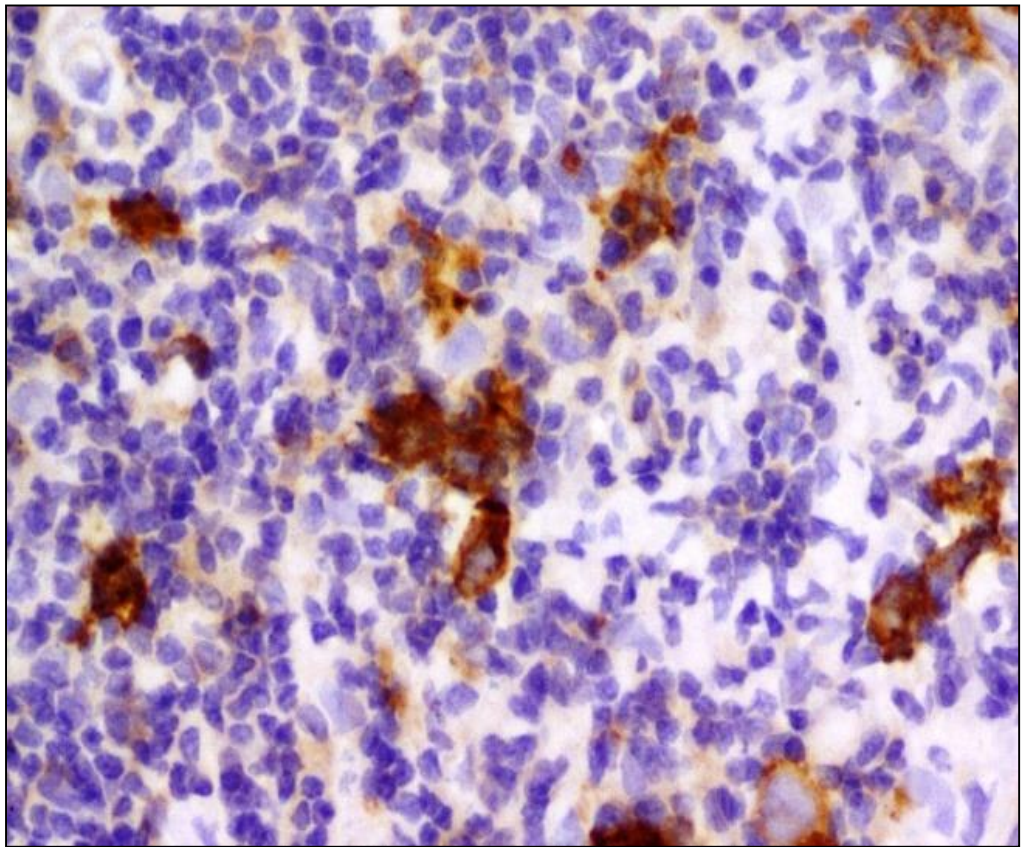

**Figure 7: CD30 positivity in RS cells [IHC x400].**

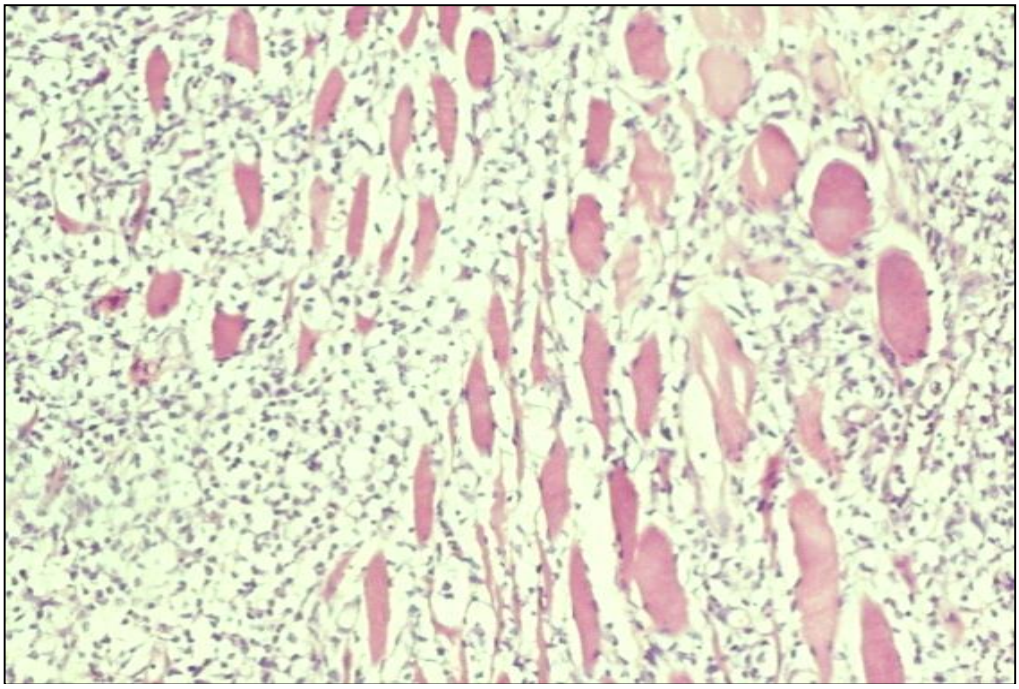

**Figure 8: NHL infiltrating skeletal muscle [H&E x100]**

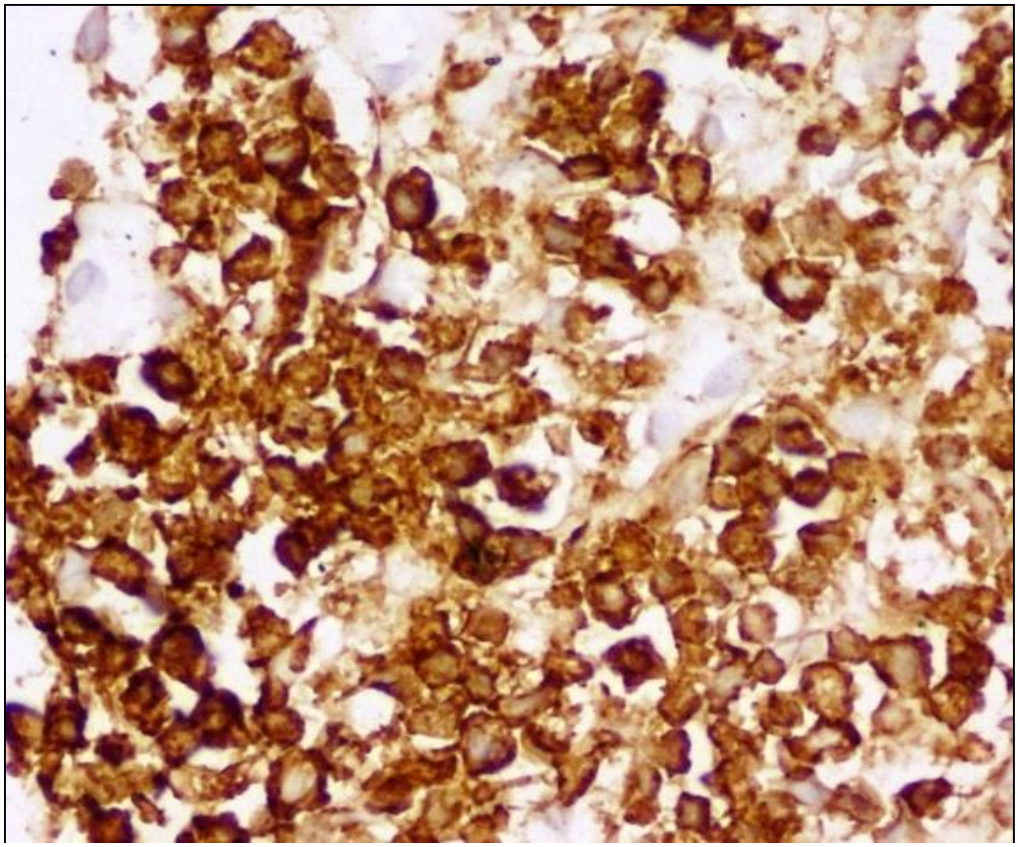

**Figure 9: NHL with lymphoid cells immunoreactive for CD20 [IHC x400]**

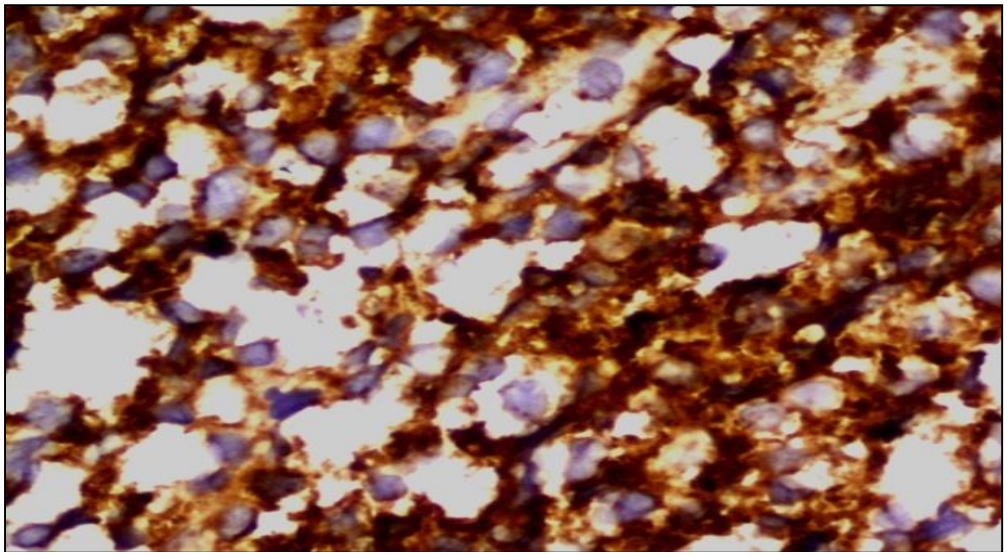

**Figure – 10: NHL with lymphoid cells immunoreactive for LCA [IHC x400]**

**Table 1: Distribution of lymph node lesions.**

| Type of lymph node lesion | Total number (19) | 100 % |
|---|---|---|
| Non Hodgkin Lymphoma-B cell | 4 | 21% |
| Hodgkin Lymphoma – Nodular Sclerosis | 3 | 15.7% |
| Hodgkin Lymphoma – Mixed cellularity | 1 | 5.3% |
| Tuberculous lymphadenitis | 7 | 37% |
| Granulomatous sarcoidlymphadenitis | 3 | 15.7% |
| Reactive hyperplasia | 1 | 5.3% |

**Table 2: IHC in Lymphomas**

| Sl No | HP Number | Diagnosis | Immunoprofile |
|---|---|---|---|
| **1** | 933/09 | NHL-B cell type | LCA: strongly +ve<br>CD20: strongly +ve<br>CD3:+ve in background cells. |
| **2** | 7557/09 | NHL-B cell type | CD20:+ve in follicles and large cell nodules<br>CD3:focally +ve<br>BCL2-+ve focally around the follicles<br>CD10:+ve in follicular cells<br>CD30:negative in tumor cells |
| **3** | 4936/10 | NHL-B cell type | LCA: +ve<br>CD20:+ve |
| **4** | 8167/10 | NHL-B cell type | LCA: strongly +ve.<br>CD20: strong cytoplasmic +vity<br>CD30: +ve in few tumor cells(background)<br>CD3: -ve in tumor cells. |
| **5** | 2977/07 | Hodgkin lymphoma-Mixed Cellularity | CD30: +ve in Hodgkinsand RS cells<br>CD15: equivocal |
| **6** | 2955/09 | Hodgkin lymphoma-Nodular Sclerosis | LCA: strongly +ve<br>CD20: +ve<br>CD3:+ve in background cells<br>CD15:+ in few mono andbinucleate RS cells<br>CD30:+ in majority of mono andbinucleate RS cells |
| **7** | 3861/09 | Hodgkin lymphoma-Nodular sclerosis | LCA: +ve<br>CD20:+ve<br>CD3:+ve in the background<br>CD15: equivocal<br>CD30:strongly +ve in RS cells |
| **8** | 4430/10 | Hodgkin lymphoma-Nodular sclerosis | CD30:+ve in RS cells<br>CD20:+ve in residual normal B lymphocytes |

**Table 3. Distribution of lymphoma, HL and NHL among mediastinal lesions**

| | Nelson, Shefts, Bowers[97] (1957) | Davis, Oldham, Sabiston[2] (1987) | Cohen et al,[32] (1991) | Shabb[10] (1998) | Temes et al, [116] (1999) | Shrivastava, Devgarha, Ahlawat[7] (2006) | Dubashi, Cyriac, Tenali[95] (2009) | Present study (2012) |
|---|---|---|---|---|---|---|---|---|
| % of Lymphoma | 20.5% | 15.5% | 15.7% | 31% | 55% | 29% | 30.6% | 12% |
| % of HL | 10% | 6% | 9.6% | 16.7% | 18% | 24% | 6.5% | 6% |
| % of NHL | 11% | 9.5% | 6.1% | 14% | 37% | 5% | 24.1% | 6% |

**Table 4: Literature summary of Mediastinal HL**

| | Van Heerden et al[83] (1970) | Davis, Oldham, Sabiston[2](1987) | Shabb et al[10] (1998) | Present study (2012) |
|---|---|---|---|---|
| **% of HL in lymphomas** | 58% | 37% | 54% | 50% |
| **Age group of HL** | 35.4 yrs. | 3rd and 4th decade | 30 years. | 12 to 32 years with a mean of 22.5 years |
| **Most common type of HL** | NSHL | NSHL | | MCHL |
| **Male: Female** | 1:1.3 | | 1:1.3 | All males |

## DISCUSSION

Mediastinal lymphomas arise in either mediastinal lymph nodes or the thymus gland. Thymic lymphomas are unique in many respects, as they reflect the function of the thymus gland as an organ involved in T-cell generation and differentiation.[6]

Studies by Davis et al,[7] Shrivastava et al,[8] Conkle et al,[9] and Dubashi et al[10] found that lymphomas were the second most common mediastinal lesion which was corroborating with the present study. Lymphomas constituted 15% to 55% of mediastinal lesions in various studies, while in the present study they formed only 12% of the mediastinal lesions. The relative frequency of HL and NHL varied in different studies. In the present study they were seen in equal frequency (Table 3).

## HODGKIN LYMPHOMA

Classic Hodgkin lymphoma is divided into four subtypes, including nodular sclerosing, lymphocyte-rich, mixed cellularity, and lymphocyte depleted HD, with the nodular sclerosing subtype representing more than two thirds of cases.[11] For mediastinal-predominant disease, prevalence peaks in young women during the third decade of life, while it is unaffected by age in men. Most patients experience constitutional symptoms (B symptoms), including fevers, night sweats, and weight loss. For patients with mediastinal involvement, cough, dyspnea, chest pain, pleural effusions, and superior vena cava syndrome may occur.[12]

The classic immunohistochemical profile is biomarker positivity for CD15 and CD30 cells.[1] In the present study, all 4 cases of HL were immunoreactive for CD30. Similar to the studies done by Shabb& co-workers[13] and Van Heerden& co-workers,[4] the present study also revealed a 50% incidence of HL among lymphomas. The previous studies show a predominance of HL in the 3rd decade and an age group lower than that of NHL. In the present study too, the age group of patients affected with HL was less compared to NHL with a mean of 22.5 years. While other studies showed a slight female predominance, the present study had an absolute male predominance. In contrast to studies by Davis, Oldham, Sabiston[7] and Van Heerden& co-workers,[4] in the present study, mixed cellularity HL was commoner than the nodular sclerosing variant (Table 4).

A tumor of the thymus gland characterized by a polymorphic infiltrate similar or identical to Hodgkin's disease has often been diagnosed as granulomatous thymoma. Fechner describes three such cases.[3] Both the clinical course and the morphologic changes suggest that these patients have nodular sclerosing Hodgkin's disease in which diagnostic Reed-Sternberg cells are present but extremely sparse. The chance of extrathoracic involvement is extremely high in comparison with all other types of thymomas. For prognostic and therapeutic purposes, these cases should be designated as "Hodgkin's disease of the thymus" and not "granulomatous" thymoma.

## NON-HODGKIN LYMPHOMA

Although there are many classes and grades of NHL, lymphoblastic lymphoma and large B-cell lymphoma are the most common subtypes to affect the mediastinum. The mean ages of presentation for lymphoblastic lymphoma and primary large B-cell lymphoma are 28 and 30 to 35 years, respectively.[14]

In the study by Davis et al,[7] NHL was more common than HL among the lymphomas and they

were equally dispersed throughout the first five decades of life. In contrast, Hodgkin's lymphomas occurred predominantly in the third and fourth decades of life. Lymphoblastic, diffuse lymphocytic, and diffuse histiocytic lymphomas were the most common cell types among the non-Hodgkin's lymphomas. In the present study, NHL's were seen in an older age group compared to HL with a mean age of 60 years; all the NHL's were B-cell type and there was a male preponderance. The study by Shabb& co-workers[13] showed a male majority while the study by Van Heerden& co-workers[4] showed a female predominance for mediastinal NHL. In the present study, a male predominance was seen (M:F = 3:1). Primary mediastinal B-cell lymphoma is a diffuse large B-cell lymphoma derived from the thymus. Common symptoms at presentation include chest pain, cough, dysphagia, superior vena cava syndrome, phrenic nerve palsy, and hoarseness.[15] The involvement of extrathoracic structures and bone marrow is less common at presentation than for lymphoblastic lymphoma. However, on the recurrence of disease, involvement of the liver, kidneys, and brain can occur.[16] Studies have concluded that Primary mediastinal large B-cell lymphoma represents a distinct entity with unique clinicopathologic features and a molecular gene-expression signature reminiscent of nodular sclerosis subtype of classical Hodgkin's lymphoma. Recent studies, including those using a refined molecular signature, suggest that the outcome is more favorable than that of diffuse large B-cell lymphoma. [17]

Computer tomography scanning is used to characterize the lesion and to determine the extent of invasion. The middle and posterior mediastinal nodes are involved more often than the anterior ones.[18] Treatment for mediastinal Non-Hodgkin lymphoma depends on the stage, histologic subtype, and extent of the disease. Patients with primary mediastinal B-cell lymphoma can be treated with conventional chemotherapy. Currently, if patients fail to have a full response to standard chemotherapy, high-dose chemotherapy and/or radiation therapy are considered. After relapse, many patients are treated with high-dose chemotherapy and autologous bone marrow transplant.[15] In a multi center study of 106 patients, they concluded that mediastinal B-cell lymphoma is an aggressive NHL with unique clinicopathologic aspects, often refractory to current chemotherapy designed for high-grade NHL. Poor performance status and pericardial effusion predict non-response and poor survival.[19] A prospective multi-center trial on 44 patients with primary mediastinal large cell lymphomas have also concluded that treatment of mediastinal large cell lymphoma should focus on intensification of methotrexate treatment along with radiotherapy and gene profiling.[20]

## CONCLUSION

Lymphomas constituted the second common primary malignant mediastinal lesion (15%) with equal number of HL and NHL. The mean age of patients with HL (22.5 yrs) was less compared to patients with NHL (60 yrs). The most common subtype of HL was mixed cellularity HL while all the NHLs were NHL-B cell type. Mediastinal lymphomas are rare & interesting neoplasms, usually located in all compartments of mediastinum. A histomorphological analysis aided by immunohistochemistry and radiology permits an exact diagnosis in many cases.

## REFERENCES


1. Kornstein MJ, deBlois GG. Pathology of the Thymus and Mediastinum. 1st edition. Philadelphia(PA): Saunders; 1995.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. 1st ed. Lyon: IARC Press; 2008
3. Fechner RE. Hodgkin's disease of the thymus. *Cancer* 1969;23(1):16-23.
4. Van Heerden JA, Harrison EG, Bematz PE, Kiely JM. Mediastinal malignant lymphoma. *Chest* 1970;57(6):518-29.
5. Perrone T, Frizzera G, Rosai J. Mediastinal diffuse large-cell lymphoma with sclerosis. A clinicopathologic study of 60 cases. *Am J Surg Pathol* 1986;10(3):176-91.
6. Müller-Hermelink HK, Engel P, Kuo TT, Ströbel P, Marx A, Harris NL. Tumors of The Thymus: Introduction. In: Travis WD, Brambilla E, Müller-Hermelink HK and Harris CC. World Health Organization Classification of Tumours. Pathology and Genetics of Tumors of the Lung Pleura Thymus and Heart. Lyon: IARC; 2004.
7. Davis RD, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. *Ann Thorac Surg* 1987;44(3):229–37.
8. Shrivastava CP, Devgarha S, Ahlawat V. Mediastinal tumors: A clinicopathological analysis. *Asian Cardiovasc Thorac Ann* 2006;14(2):102-4.
9. Conkle DM, Adkins RB Jr. Primary malignant tumors of the mediastinum. *Ann Thorac Surg* 1972;14(5):533-67.
10. Dubashi B, Cyriac S, Tenali SG. Clinicopathological analysis and outcome of primary mediastinal malignancies – A report of 91 cases from a single institute. *Ann Thorac Med* 2009;4(3):140-2.
11. Yung L, Linch D. Hodgkin's lymphoma. *Lancet* 2003;361(9361):943-51.
12. Vaeth JM, Moskowitz SA, Green JP. Mediastinal Hodgkin's disease [abstract]. *Am J Roentgenol* 1976;126(1):123-6.
13. Shabb NS, Fahl M, Shabb B, Haswani P, Zaatari G. Fine-needle aspiration of the mediastinum: A clinical, radiologic, cytologic and histologic study of 42 cases. *Diagn cytopathol* 1998;19(6):428-36.
14. Sutcliffe SB. Primary mediastinal malignant lymphoma. *Semin Thorac Cardiovasc Surg* 1992;4(1):55–67.

15. van Besien K, Kelta M, Bahaguna P. Primary mediastinal B-cell lymphoma: a review of pathology and management. *J Clin Oncol* 2001;19(6):1855-64.
16. Kirn D, Mauch P, Shaffer K, et al. Large-cell and immunoblastic lymphoma of the mediastinum: prognostic features and treatment outcome in 57 patients. *J Clin Oncol* 1993;11(7):1336–43.
17. Savage. K.J Primary Mediastinal Large B-cell lymphoma. The Oncologist. 2006;11:488–495).
18. Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: Tumors of the anterior mediastinum. *Chest* 1997; 112(2):511-22.
19. Lazzarino M, Orlandi E, PaulliM, Strater J, Klersy C, Gianelli U et al. Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell lymphoma: a multicenter study of 106 patients. J Clin Oncol 1991;15:1646-1653.
20. Fietz T et al. Treatment of primary mediastinal large B cell lymphoma with an alternating chemotherapy regimen based on high-dose methotrexate. Annals of hematology 2009;88.5:433-439.