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Original Article

Pathology Section

Histomorphological Spectrum of Mediastinal Masses with Special Emphasis on Rare Lesions

SAKTHISANKARI SHANMUGA SUNDARAM[1], S VIDHYALAKSHMI[2]

ABSTRACT

Introduction: Mediastinal lesions are not frequently observed in routine clinical practice. A wide variety of disease process can occur within the mediastinum. Tissue from needle biopsies forms the major diagnostic material. There is need for detailed studies to make pathologists aware of the wide histological spectrum and to know the unusual lesions that can be encountered during diagnosis.

Aim: To describe the histomorphological spectrum of various mediastinal lesions and to highlight the rare lesions that posed a diagnostic challenge.

Materials and Methods: This was a retrospective study done on all mediastinal masses over a period of two years from January 2016 to December 2018. The clinical data and imaging findings were collected from the test request forms and patients' files for all the cases. Haematoxylin and eosin stained slides of all cases and immunohistochemistry markers and cytochemical stains wherever done were reviewed and analysed. Mean, median and percentage were used for statistical analysis.

Results: Thirty-four cases of mediastinal lesions were included in the study. Of these, 28 cases (82.4%) presented as anterior mediastinal masses, three cases (8.8%) each in the middle and posterior mediastinum. Thymoma (n=15) followed by lymphoma (n=4) were the most frequent neoplasms reported. There were five lesions which were rare in the mediastinum with unusual presentation that posed diagnostic difficulties. These lesions included Primitive neuroectodermal tumour in an adult, Primary Mediastinal B Cell Lymphoma (PMBCL), Malignant Peripheral Nerve Sheath Tumour (MPNST) with nodal metastasis, Seminoma deposits in mediastinal node occurring as late relapse and dedifferentiation of thyroid carcinoma in mediastinal node metastasis without an obvious primary.

Conclusion: Primary mediastinal tumours were more frequent than metastasis. Although thymomas and lymphomas are dealt extensively in literature, this article highlights the fact that pathologists must be aware of those lesions that don't display the classical histological and/or clinical features as observed in this study.

Keywords: Malignant peripheral nerve sheath tumour, Mediastinum, Mediastinal B cell lymphoma, Morphological spectrum, Primitive neuroectodermal tumour

INTRODUCTION

Primary mediastinal tumours are rare. Anterior mediastinal masses constitute >50% of mediastinal lesions and majority of them involve thymus. Middle mediastinal lesions include congenital cyst, (pericardial and bronchogenic cyst) while neurogenic tumours form the majority of posterior mediastinal masses [1-3]. Lymphomas can arise in any of these three compartments [4]. Aggarwal R et al., in their study of mediastinal lesions have reported 70% of lesions confined to anterior mediastinum, of which thymic lesions were the most frequent, constituting to 45.7% [1]. Posterior, superior and middle mediastinal lesions were reported to be 19, 6 and 4%, respectively. Lymphomas were the second most common tumour (11.2%) after thymoma. Sarcoma was seen in 6.9% cases and showed random compartment localisation. In their study, primary lesions were more common when compared to secondary deposits.

Dixit R et al., in their evaluation of 144 cases of mediastinal lesions have reported metastasis to be the most common, contributing to 37.4% of malignant lesions followed by lymphoma [5]. The clinical findings with radiological findings can narrow the differential diagnosis. However, advent of new techniques has made it easier to obtain tissue material from this site [5,6]. Hence, it is important for a pathologist to be familiar with the wide variety of lesions in the mediastinum since an accurate early tissue diagnosis directs therapy. There are variations in the existing literature regarding the frequency of individual lesions encountered in mediastinum. Hence, the study was undertaken to analyse the histopathological spectrum of mediastinal lesions in the population and to highlight the rare lesions.

MATERIALS AND METHODS

This was a retrospective study done on all mediastinal masses over a period of two years from January 2016 to December 2018. The data was retrieved from the archives of Pathology department of PSG Institute of Medical Sciences and Research. Institutional Human ethics committee clearance was obtained before conducting the study (vide letter 20/108).

Needle biopsies and surgical resections were included in the study. A total of 36 cases were received during the study period. Of these cases, two cases showed necrosis and hence were excluded from the study. The remaining 34 cases were included.

Relevant demographic and clinical data including the presenting symptoms, past history relevant to the lesions and examination findings was collected from patient files in all the cases. Laboratory investigations such as serum markers like carcinoembryonic antigen, CA125, alpha fetoprotein wherever available were obtained from test request forms and hospital information system. Computed Tomography findings including the location, size and solid or cystic nature of the lesion were recorded. Haematoxylin and eosin stained slides of all cases and Immunohistochemistry (IHC) markers and cytochemical stains like periodic acid, Ziehl Neelsen wherever done were reviewed and analysed. Immunohistochemical markers included cytokeratin (Mouse, polyclonal, AE1/AE3), CD99 (Mouse, 12E7) S100 (rabbit, polyclonal, 504), Thyroid transcription factor (Mouse, 056), napsin (EP205), CD45 (Mouse, EP273), CD3 (rabbit, polyclonal, 503), CD20 (Mouse, L26), CD15 (Mouse, 273), CD30 (Mouse, BER-H2), CD117 (IB 077) and PLAP (mouse, 376). IHC was done on paraffin embedded tissue sections using heat induced

antigen retrieval. Diaminobenzidene was the chromogen used. The cases which posed diagnostic challenge or had an unusual presentation were extensively studied.

STATISTICAL ANALYSIS

Mean, median and percentage were used for statistical analysis. The analysis was done using Statistical Package for the Social Sciences (SPSS) software version 20.0.

RESULTS

Thirty four cases of mediastinal lesions were included in the study. Age of the patients ranged from 14 to 75 years. Majority of the lesions were females with male to female ratio being 1:1.5. The presenting symptoms included chest pain, cough and breathlessness in 26 cases. A total of 24 cases were the Primary mediastinal tumours while metastatic lesions were two in number. About Twenty eight (82.4%) cases presented as anterior mediastinal masses, and three cases each in the middle and posterior mediastinum. The majority of lesions were involving the thymus (n=21) constituting to 67.8% [Table/Fig-1]. The frequency of malignancy was higher in females (6 cases).

S. No.	Diagnostic category	Anterior 82.4% (n=28)	Middle 8.8% (n=3)	Posterior 8.8% (n=3)	Total % (n)
1	Non-neoplastic				
	Retrosternal goitre	1		1	23.5 (8)
	Sarcoidosis	1	1		
	Thymic cyst	2			
	Thymolipoma	2			
2	Neoplastic, Benign				
	Thymoma	15			47 (16)
	Teratoma		1		
3	Neoplastic, Malignant				
	Thymic carcinoma	2			
	Lymphoma	3	1		23.5 (8)
	Primitive neuroectodermal tumour			1	
	Malignant peripheral nerve sheath tumour			1	
4	Neoplastic, metastatic	2			6 (2)

[Table/Fig-1]: Distribution of mediastinal lesions.

The variants of thymoma included four cases each of type A, B1 and B2 and three cases of type AB thymoma. Both the cases of thymic carcinoma occurred in females, one of which occurred in a young female (age 28 years).

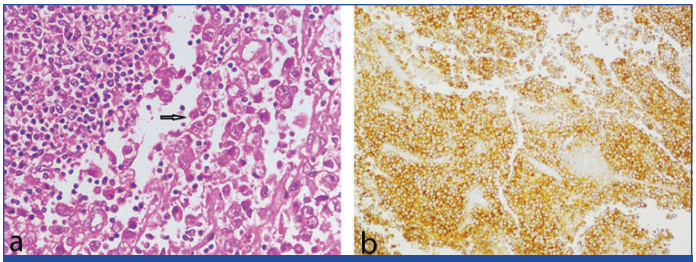
The two cases of Non-Hodgkin Lymphoma (NHL) reported were precursor T-lymphoblastic lymphoma in adolescent patients. The other NHL was Primary Mediastinal B Cell Lymphoma (PMBCL). The two cases of Hodgkin Lymphoma (HL) included one case each of Nodular Sclerosis and Mixed cellularity HL.

Of the 34 cases, 13 (38.2%) were diagnosed on guided biopsies and 21 (61.8%) on excision biopsies. In all the guided biopsies, a confirmatory diagnosis was made only after immunohistochemistry.

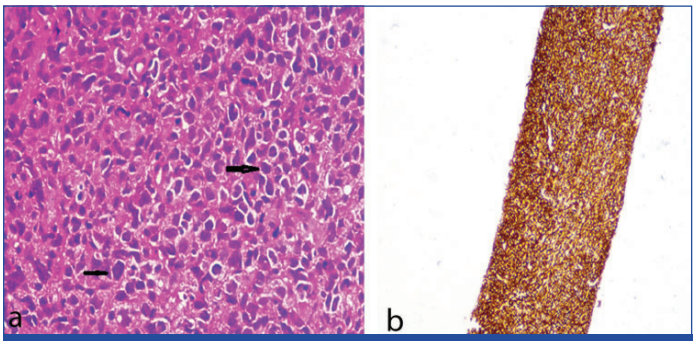
The rare tumours encountered are described below [Table/Fig-2]. Case 1 presented with multiple lymph nodes involvement suggesting the possibility of lymphoma. Seminoma relapse was not initially considered for this case. The diagnosis of seminoma metastasizing to lymph node was made only with the help of immunohistochemistry [Table/Fig-3]. Case 2 (PMBCL) was a rare lesion occurring in a young male, but had the typical presentation. Differential diagnosis entertained in this case were PNET and thymoma based on the morphology [Table/Fig-4]. Case 3 (MPNST) occurred in a patient with Neurofibromatosis. Cytology of pleural fluid also showed atypical cells. Based on the morphology, a provisional diagnosis of high-grade sarcoma was made. The diagnosis of MPNST with nodal metastasis was made with immunohistochemistry (S100 positive and Ki67 90%) [Table/Fig-5]. Case 4 (PNET/Ewing's sarcoma) occurred in an adult female (65 years) which is rare [Table/Fig-6]. Case 5 (dedifferentiated thyroid carcinoma in mediastinal nodes) occurred in an adult female who did not have any history of thyroidectomy. Histopathological examination showed an anaplastic tumour suggesting the possibility of sarcoma/carcinoma. Extensive sampling revealed tiny foci of conventional papillary thyroid carcinoma which was supported by IHC markers (Thyroid transcription factor positive, Napsin negative, Cytokeratin positive in anaplastic areas). Lung carcinoma was ruled

Case No.	Clinical details	Imaging findings (CT Scan)	Histology and IHC	Diagnosis and unusual finding
1	48/M, operated for testicular seminoma 5 years back and had defaulted surveillance	Hypodense, soft tissue mass of size 5.5×2.9 cm in anterior mediastinum. Mediastinal lymphadenopathy +. Beta HCG-420 mIU/mL LDH-1820IU/L	Lymph node with sheets of large cells having pleomorphic vesicular nuclei and prominent nucleoli separated by fibrous septa rich in lymphocytes. There was no other germ cell tumour elements. CD117 and PLAP positive.	Seminoma metastasing to mediastinal lymph nodes. Late relapse presenting with generalised lymphadenopathy
2.	21/M, anorexia, night sweats, significant loss of weight for two months. No organomegaly or superficial lymphadenopathy	large anterior mediastinal mass of size 6×7 cm invading superior vena cava.	Monomorphous population of blue round cells separated by thick fibrous septa. CD20 and CD45 positive Neuron Specific enolase, Cytokeratin negative	Primary Mediastinal B Cell Lymphoma (PMBCL). Rare lesion (incidence-2 to 3% of NHL) [1]
3.	35/M, known case of Neurofibromatosis presented with a complaint of dry cough associated with breathlessness	Multiple nodules in both lungs and pleura. Multiple enlarged mediastinal, para-aortic, celiac lymph nodes suggesting metastasis	Oval to spindle neoplastic cells exhibiting marked pleomorphism arranged in sheets. Vimentin, S100 positive. Ki67 index-90% Desmin and CD34 negative	MPNST with nodal metastasis. Rare presentation
4	65/F, chest pain, breathlessness and fever	intrathoracic mass measuring 15×12 cm extending into posterior mediastinum, encasing and lifting aorta, inferior vena cava and causing diaphragmatic inversion.	Small round cells with scant cytoplasm, uniform hyperchromatic nuclei with perivascular accentuation and surrounded by fibrous septa. Differential diagnoses entertained were lymphoma, Ewing's sarcoma and rhabdomyosarcoma. CD99 positive, CD45, Tdt and Myogenin negative	PNET/Extraskeletal Ewing's sarcoma in adult. (incidence -1.8%) [27]
5	69/F, chest pain, breathlessness and intermittent fever and inspiratory stridor	Large heterogeneously enhancing mass measuring 5×4×5 cm in the right upper posterior mediastinum encasing the esophagus in the left lateral aspect. Few small nodules in the right lung suggestive of metastasis were seen. A small nodule was noted in the thyroid. Thyroidectomy could not be done in this patient.	An anaplastic tumour composed of multinucleated giant cells and highly pleomorphic cells with extensive areas of coagulative necrosis. Tiny foci of conventional papillary thyroid carcinoma. No normal thyroid tissue identified. (strong nuclear expression of TTF1 in conventional papillary thyroid carcinoma. The anaplastic component was positive for Cytokeratin and lacked TTF 1 expression. Napsin-negative (rules out lung carcinoma)	Dedifferentiated thyroid carcinoma metastasis with no obvious lesion in thyroid.

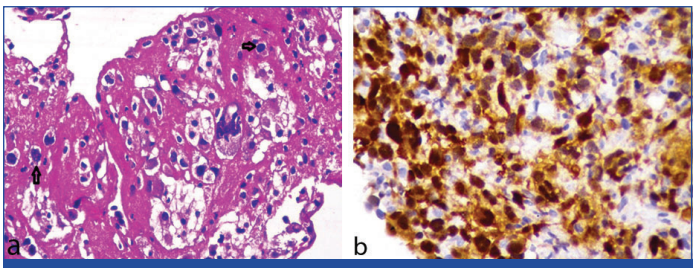
[Table/Fig-2]: Unusual features of the reported rare cases.
MPNST: Malignant peripheral nerve sheath tumour; PNET: Primitive neuroectodermal tumour; CT: Computed tomography; IHC: Immunohistochemistry



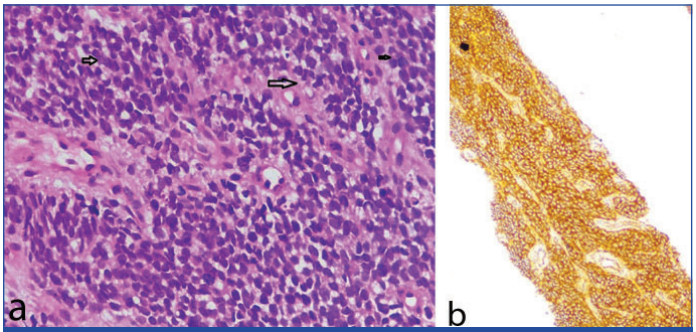
[Table/Fig-3]: a) Large neoplastic cells separated by fibrous septa rich in lymphocytes, Seminoma (H&E,40X). b) Neoplastic cells with strong membranous expression of PLAP (IHC-40X).



[Table/Fig-4]: a) Discohesive pleomorphic large round cells (arrow), PMBCL (H&E, 40X).b) Neoplastic cells with strong membranous CD20 expression (IHC, 10X).



[Table/Fig-5]: a) Pleomorphic tumour cells, MPNST (H&E, 40X). b) Tumour cells expressing S100 (IHC 40X).



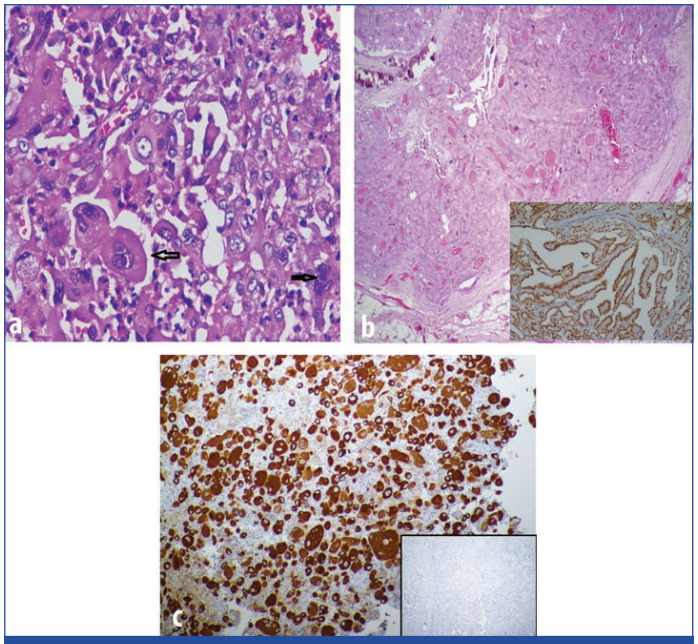
[Table/Fig-6]: a) Small round cell tumour, PNET (H&E, 10X). b) Tumour cells expressing membranous staining for CD99 (IHC 10X).

out by napsin negativity [Table/Fig-7]. Normal thyroid parenchyma was not identified in the tissue and thus the possibility of aberrant thyroid and retrosternal extension were ruled out. Small nodule identified in thyroid by Computed Tomography of neck could not be evaluated, since thyroidectomy could not be done on this patient.

DISCUSSION

In the present study, the majority of the tumours were primary in origin except for two cases. Literature review also showed that primary mediastinal lesions are more common than metastatic malignancies [3,4,6-9]. There was a female predominance in the current study which contrasts with the previous studies [5-9].

In keeping with other studies [3-10], most of the lesions were in the anterior compartment (82.4%) and benign lesions (47%) were more frequent than malignant tumours (23.5%). However, there are studies reporting malignant lesions to be more commoner constituting about 60% of lesions [11,12].



[Table/Fig-7]: a) Sheets of pleomorphic cells with multinuleation and hyperchromatic nuclei (H&E- 40X).b) Conventional papillary carcinoma component. (IHC-10X). Inset TTF1 expression (IHC 10X). c) Anaplastic carcinoma with CK expression (IHC-40X). Inset TTF 1 negative (IHC 10X).

Thymoma was the most frequent neoplasm in the present study which is similar to other studies [3-9]. However, Vaziri M et al., in their study had reported lymphomas to be more common than thymoma in a series of 105 cases [11]. In the current study, thymic lesions constituted 61.7% of anterior mediastinal masses which is higher when compared to the studies by Aggarwal R et al., and Dasgupta S et al., [1,3].

Thymic carcinomas are reported to be rare malignancies occurring in the age group of 30 to 60 years. Suster S, in his study have reported a slight male predilection (1.5:1) [13]. In the present study, both the cases of thymic carcinoma occurred in females.

Retrosternal goitres are usually located anteriorly, in the superior or anterior mediastinum. Posterior mediastinum is rarely involved. Their incidence in the general population is about 1:5000 [14]. The case described in the study also occurred in posterior mediastinum. In the present study, there were five cases which were either rare or had unusual presentations that posed diagnostic difficulties [Table/Fig-2].

Primary mediastinal Seminomas originating from extragonadal germ cells are rare [15]. In general, the relapse occurs within 2 to 3 years. It has been reported in inguinal lymph nodes, contralateral testis, retroperitoneum, mediastinum and lung [16-18]. The case described here presented with seminoma deposits in mediastinal lymph nodes along with multiple abdominal lymphadenopathy 5 years after orchidectomy. Hence, the possibility of any mediastinal germ cell tumour representing a metastasis from testicular primary should always be investigated. Considering the above facts, this case is unusual, since it presented as a late relapse.

PMBCL is a subtype of Diffuse Large B Cell Lymphoma (DLBCL) of thymic B cell origin affecting adolescents and young adults and having a slight female preponderance. Of the cases reported, 75% present with bulky anterior mediastinal mass greater than 10 cm that grows rapidly and nearly always present with superior vena cava obstruction [19]. Bone marrow involvement is reported to be extremely rare. It shares the biological and clinical characteristics with Nodular Sclerosis type of Hodgkin Lymphoma (NSHL) [19]. The characteristic histologic findings include clearing of cytoplasm of cells and alveolar fibrosis. Because of the presence of compartmentalisation of

cells divided by fibrous septa, it mimics thymoma, NSHL and germ cell tumours. Hence, immunohistochemistry becomes an essential aid in diagnosis. All the cases of PMBCL express CD20 and a proportion of cases express CD30. PMBCL has been reported to have better prognosis when compared to DLBCL with secondary mediastinal lymph node involvement [19,20]. The case presented here had the typical presentation of PMBCL with superior vena cava obstruction and absence of superficial lymphadenopathy and organomegaly but its occurrence in a young male is rare.

Intrathoracic presentation of MPNST is rare. There are nearly 20 such cases reported in literature, majority of them in the posterior mediastinum [21]. A 20 -30% of MPNST occur in the setting of Neurofibromatosis. Those cases show an increased recurrence and risk of distant metastasis [22,23]. Lung, bone and pleura are the most common sites of metastasis. Metastasis to lymph nodes is reported in less than 10% of patients and is usually seen as a part of widespread metastasis. In the case presented here, there was mediastinal lymph node metastasis from MPNST. Since these tumours show a weak expression of S100 in majority of cases, it becomes difficult in cases of unusual presentation like nodal metastasis, especially in small biopsies to diagnose [24]. The challenge faced in this case was that the presence of neurofibromatosis in this patient was not available at the time of diagnosis.

PNET is a rare and aggressive tumour of neuroectodermal origin most frequently occurring in children and young adults. There are only a few published series of PNET in adults [25]. Primary mediastinal PNET is very rare constituting 1.8% of mediastinal tumours. In a study by Applebaum MA et al., it was found that Extraskeletal Ewing sarcoma had a higher mean age when compared to those with skeletal tumours [26,27]. Metastasis was frequent in the cases with extraskelatal Ewings sarcoma/PNET [25,28]. The case presented here also occurred in an adult female (65 years).

PTCs are known for anaplastic transformation at the metastatic sites [29] and have been reported in retroperitoneum, liver and lungs. This has been proven even with papillary microcarcinoma [29,30]. The cases reported previously were postsurgery for papillary carcinoma which occurred as a recurrence, many years after treatment for papillary carcinoma [29]. The case presented here did not have any history of proven PTC nor did the patient present with thyroid mass. This could probably represent an occult papillary microcarcinoma in thyroid with mediastinal metastasis of papillary thyroid carcinoma that has undergone dedifferentiation. The diagnosis of dedifferentiated thyroid carcinoma was not made on the initial sections. This case re-emphasises the need for extensive sampling in a case of anaplastic tumour to look for a well differentiated tumour to accurately diagnose even a remote possibility.

Limitation(s)

The smaller sample size in this study precludes generalisation of study results considering the frequency and distribution of mediastinal tumours. Further studies including larger sample size and studies aiming at analysing correlation with clinical and radiological findings are needed to estimate the subtype distribution of mediastinal lesions.

CONCLUSION(S)

To summarise, benign tumours were more common than malignant ones. Primary mediastinal tumours were more frequent than metastasis. Although thymomas and lymphomas are dealt extensively in literature, this article highlights the fact that pathologists must be aware of those lesions that don't display the classical histological and/or clinical features as observed in this study.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.
2. Associate Professor, Department of Pathology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. S Vidhyalakshmi,
Associate Professor, Department of Pathology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.
E-mail: dr.vidhyalakshmi07@gmail.com

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