

Clinicopathological Spectrum of Mediastinal Mass Lesions - A Cross-Sectional Study of 58 Cases in Kolkata, West Bengal

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ABSTRACT

BACKGROUND

Mediastinal masses, an enigma to surgical pathologist are among the most complicated lesions explored and relatively inaccessible. They often connote a process with mass effect presenting with superior mediastinal syndrome. This is a challenging area faced by surgical pathologist as varied lesions are found here and often biopsies obtained are tiny and crushed. Appropriate therapy of various mediastinal tumours differs considerably and may significantly impact survival. We wanted to evaluate the various lesions in different compartments of mediastinum and categorise them according to anatomical location, and histopathology.

METHODS

Patients with mediastinal masses attending outpatient department were selected, history taken and relevant investigations done with radiological evaluation for proper anatomical location of lesion. Histopathological study done on tissues obtained by ultrasound / CT guided biopsy, open surgical biopsy were categorized according to histologic types. Immunohistochemistry was done wherever applicable.

RESULTS

A total of 58 cases of mediastinal lesions were studied where males predominated and age of patients ranged from 11 months to 68 yrs. All patients were symptomatic. Shortness of breath, superior vena cava syndrome was dominant in anterior and superior mediastinal lesions, middle and posterior mediastinal masses presented with chest pain. Most lesions were neoplastic. Germ cell tumours were found in (24.14 %) followed by lymphoma in (20.69 %) and thymic lesions in (18.97 %) of patients. Neurogenic tumours found in (13.79 %) were located in posterior mediastinum whereas, germ cell tumours and lymphomas were located in anterior mediastinum. Non neoplastic lesions included tuberculosis, sarcoidosis. Unsuspected lesion was metastatic deposit of adenoid cystic carcinoma.

CONCLUSIONS

A wide variety of non-neoplastic and neoplastic lesions can be found in different compartments of mediastinum and accurate diagnosis is considered necessary to formulate management strategies.

KEYWORDS

Mediastinum, Biopsy, Radiology, Histopathology

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BACKGROUND

Mediastinal masses are always an enigma to surgical pathologist as they are among the most complicated lesions explored and are relatively inaccessible. There are various lesions occurring here but biopsies obtained are often scanty and crushed. Moreover, few pathologists have remarkable knowledge about mediastinal pathology since these specimens are rare.¹ Thorough evaluation and exact diagnosis of various undifferentiated mediastinal tumours with overlapping histology are needed because their suitable treatment schedule differs considerably and may significantly impact survival.²

A benign lesion in mediastinum is usually asymptomatic and a malignant lesion is symptomatic.³ Imaging studies help immensely in their initial evaluation.⁴ Computed tomography (CT) scan reveals the exact site and to some extent the nature of the masses. Surgical biopsy (Tru-cut / open surgery) remains the gold standard for final conclusive opinion. CT-guided needle biopsies now are the first diagnostic procedures used in these cases.⁵

This prospective study deals with the evaluation and clinicopathological spectrum of mediastinal masses. The objective of the study was to analyse the epidemiologic profile, clinical features, histopathological findings and treatment in patients presenting with a mediastinal mass. Various common and rare tumours were identified with the help of histopathology. Immunohistochemistry (IHC) was done wherever required because treatment and outcome depends on the histologic subtypes. This study shows that symptoms can sometimes provide clues enabling the timely order of investigations.

METHODS

Patients with mediastinal masses, who got admitted to R.G. Kar Medical College & Hospital, Kolkata, West Bengal for a period of one year from April 2011 to March 2012, were included in the study. The cross sectional study was carried out following permission from institutional ethics committee and informed consent of patients. Those with acute inflammation and moribund patients were excluded. The anatomical location of the mediastinal mass was determined by chest radiographs (posteroanterior and lateral views).

CT scan was performed to assess operability. Neurologic evaluation was carried out in suspected cases of myasthenia gravis. Histopathological study was done by ultrasound or CT guided Tru-cut biopsy and open surgical biopsy from mediastinal lesions. Tru-cut biopsy was done in 29 cases & open surgical biopsies in 29 cases. The surgical approach was planned according to anatomical location of the lesion. Specimens from cardiothoracic vascular surgery (CTVS) department were properly grossed in the pathology department. Tru-cut biopsies mainly consisted of 1.5 - 2 cm linear tissue pieces.

The formalin fixed surgical biopsy tissue post grossing was dehydrated using 90 % and 100 % alcohol followed by acetone I and II. The dehydrated tissue was then cleared by xylene I and II and kept in paraffin I and II. The paraffinised

section embedded in blocks were cut in 3 - 4 μ m thickness. The sections floated in warm water, teased, and mounted on glass slides coated with egg albumin. The sections were deparaffinised with xylene I and II for ten minutes each. The air dried sections were dipped in graded alcohol for five minutes each followed by placing under running tap water. The sections were then stained with Harris haematoxylin for 10 minutes and washed in running tap water for 5 minutes. Decolourization done by dipping in 1% acid alcohol; blueing done by placing under running tap water for thirty minutes.

Rinsing done by quick dip in 1 % eosin and in 90 % alcohol for 5 minutes. The section was then placed in absolute alcohol for 5 minutes, air dried, followed by subsequent clearing in xylene and mounted in DPX with coverslip.

For immunostaining technique, slides were cleaned with spirit and coated with poly 2 lysine by dipping for 5 minutes. The tissue was then embedded on the air dried slide and incubated at 37°C overnight followed by 65°C for 30 minutes. Dipping in xylene I and II was done for 10 minutes each, and then in graded alcohol for 5 minutes each. The slide was placed in deionised water and in (hydroxymethyl) - amnomethane (TRIS) buffer for 5 minutes. The slide was taken out from TRIS buffer, wiped, peroxidase block added and placed in humid chamber for 5 - 8 minutes. Slide in slide holder placed in pressure cooker containing Citrate buffer. After three whistles, cooker was cooled, and slide taken out and dipped in TRIS buffer for 5 minutes. The slide was wiped, protein block added and kept in humid chamber for 5 - 8 minutes. Primary antibody was then added for 1 hour, washed with TRIS buffer by syringe and dipped in two changes of TRIS buffer for five minutes each. The slide was again wiped and post primary antibody added for 30 minutes followed by same washing procedure. Polymer was added to wiped slide for 30 minutes, washed and diluted with DAB chromogen in DAB buffer in ratio of 1: 20. Slide dipped in DAB solution for 3 - 4 minutes and washed in tap water. Haematoxylin was added to wiped slide for 5 minutes followed by tap water wash.

Then, dipped in graded alcohol for 5 minutes each and wiped, dipped in xylene I, II for 10 minutes each with subsequent DPX mounting. The immunohistochemical markers used in the study were cytokeratin, vimentin, EMA, CD 3, 5, 15, 19, 20, 30, 68, 117, TdT, MIC2, calponin, bcl2. Etiological diagnosis of all mediastinal cases ascertained with the help of non-invasive and invasive procedures. They were then classified as per mediastinal topography.

Statistical Analysis

All the available information's were recorded meticulously and a database created. The different parameters like age, sex, addictive habits, presenting complaints, clinical features were noted to delineate distribution of mediastinal diseases in the population. Different radiological features of mediastinal lesions were studied. A grand chart was prepared. Statistical analysis performed by chi square test, Fisher exact tests and ANOVA was applied. Calculation of P value was done wherever applicable.

RESULTS

The study comprised of 58 patients. 34 patients (58.62 %) were male and 24 patients (41.38 %) female with a male to female ratio of 1.42: 1. The age of patients was from 6 months to 68 years with mean age of 35.72 years. Most common age group with mediastinal lesions was 21 - 40 years (46.55 %). Tobacco smoking was the most common sort of addiction found and was common among males (50 %) in the study population. All patients in the present study were symptomatic. Shortness of breath (72.41 %) was the leading symptom followed by cough (67.24 %), fever (55.17 %) and chest pain (39.66 %). (Table - 2). Clinical features were present according to particular topographical position. Superior venacava syndrome (SVCS) was seen in cases where lesion was located in anterior mediastinum with or without simultaneous involvement of the superior mediastinum.

Chest pain was most commonly found in patients with posterior mediastinal involvement. Diabetes was present in 15.52 % patients, 17.24 % had hypertension and 10.34 % had hypothyroidism in cases with comorbidities. Three patients (5.17 %) had dilated cardiomyopathy, ischemic heart disease was found in 15.52 % cases and myasthenia gravis in two females (3.45 %). One isolated compartment of mediastinum was involved in 65.52 % of total cases. It was observed that a single tumour can involve more than one compartment. Anterior mediastinum was the most common site (43.1 %) when the lesion was confined to one isolated compartment of mediastinum.

All cases of superior mediastinal lesions were seen to have simultaneous involvement of anterior mediastinum which comprised 70.69 % of total cases. (Table: 1) The surgical approach was decided on the basis of anatomical location of the tumour. Thoracotomy was most commonly tried in 70.42 % of the patients who underwent surgery. Among the open biopsy specimens, solid homogenous cut surface was found only in 9 patients.

Solid lesions as large as 22 x 12 x 8 cm and as small as 5 x 4 x 3 cm were found. Eighteen patients showed cystic components and calcification was evident in four patients. Left posterolateral approach was the most common applied approach and sternotomy was done in 16.9 % of patients. Most of the masses in the study were found neoplastic (94.83 %) of which 48.3 % were malignant. Three patients (5.17 %) presented with non-neoplastic lesions. Germ cell tumours were the most common lesions in the study and of them 10 were benign, 4 malignant. The location of the tumours were confined to anterior mediastinum in (64.29 %) cases followed by simultaneous involvement of superior compartment in 35.71 % of cases (Table : 1). A middle mediastinal mass was diagnosed as malignant mixed germ cell tumour comprising of seminomatous and yolk sac tumour components.

The range of age group affected by lymphomas was from 12 years to 60 years. Males and females showed a 1: 1 ratio. Three adolescent and teenaged males were diagnosed with lymphoma. A 42-year old female with anterior mediastinal mass and SVCS was diagnosed as thymic lymphoma (non-

Hodgkin lymphoma, diffuse cell type, intermediate grade of thymic origin). Anterior mediastinum involving superior compartment was found to be the most common site for lymphoma (41.7 %) (Fig. 1 & 2) in the study followed by thymic tumours (18.97 %).

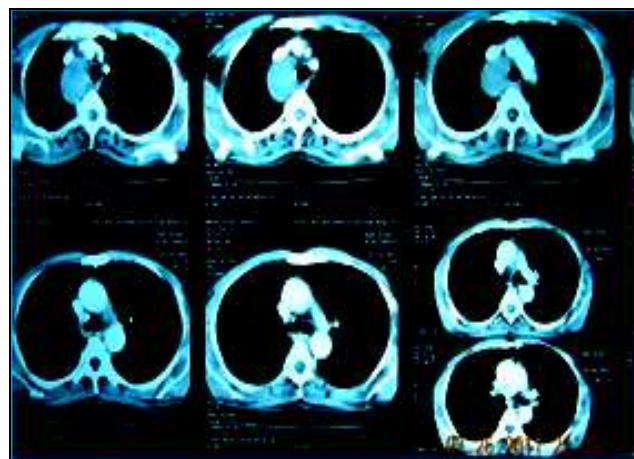


Figure 1. CT Scan of Non-Hodgkin Lymphoma (NHL) Presenting as Anterior Mediastinal Mass

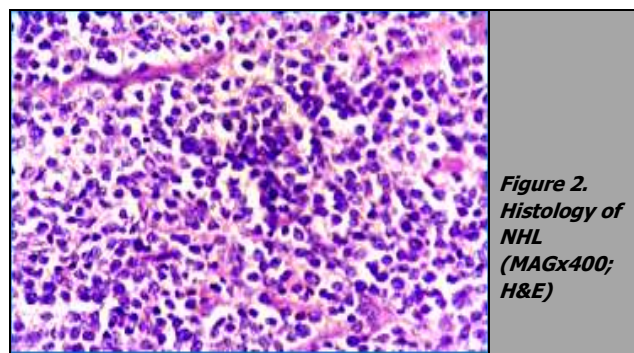


Figure 2. Histology of NHL (MAGx400; H&E)

Among the thymic lesions, 54.55 % were found located in anterior mediastinum and 36.36 % in superior mediastinum with simultaneous involvement of anterior compartment. Age group affected ranged from 11 months to 60 yrs. Tumours comprised of nine benign and two malignant tumours. (Table: 1).

Benign tumours were dominant in males but no gender dominance was found in malignant group. Youngest one with thymoma was reported in a 13-year-old girl. (Fig. 3 & 4) Incidentally, a huge mediastinal mass weighing 75 gm in a 11-month-old child was reported on histopathology as true thymic hyperplasia.

Follicular thymic hyperplasia was reported in a boy of 16 yrs. An anterior mediastinal mass showing lacy pattern of strong cytokeratin positivity was diagnosed as spindle cell thymoma. Thymic carcinoma was reported in a male aged 47 years and a 37-year-old female.

Neurogenic tumour was reported in 13.79 % of total cases and their anatomical location was in posterior mediastinum. Male to female ratio was 1.67: 1. Malignant tumours did not show any gender dominance. The age group affected was from 6 years to 52 years. The benign tumours comprised of schwannoma, neurofibroma and ganglioneuroma. Ganglioneuroma was reported in a six-year-old boy. The malignant tumours included malignant

peripheral nerve sheath tumour (MPNST) in a male of 35 years and ganglioneuroblastoma in a female aged 39 years.



Figure 3.
Thymoma in
Anterior
Mediastinum
(X-Ray) and CT
Scan

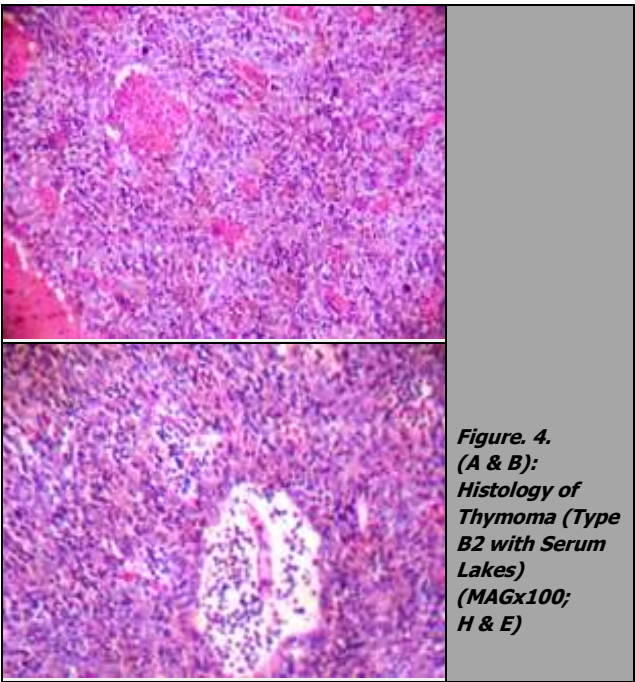


Figure 4.
(A & B):
Histology of
Thymoma (Type
B2 with Serum
Lakes)
(MAGx100;
H & E)

The age of the patients suffering from germ cell tumours was between 13 years and 52 years. Females predominated in the benign category but there was no gender dominance in the malignant group. The male to female ratio in benign teratomas and immature teratomas was 1: 2. Malignant mixed germ cell tumour was reported in a male patient of 30 years. The youngest girl in this group (13 years) presented with benign teratoma and immature teratoma was reported in a boy of 13 years.

The paediatric and teen age group (below 16 years) presented with five benign and four malignant tumours with male to female ratio of 3.5: 1. Lymphoma and thymic lesions were reported in three cases each. Benign teratoma and thymoma were reported in females, both in age group of 13 years. Immature teratoma and lymphoma were reported in 12 to 16-year-old boys. The other benign tumours found in the age group of 6 months to 16 years comprised of true thymic hyperplasia, ganglioneuroma, follicular thymic hyperplasia.

IHC was done in a few cases. A huge mediastinal mass occupying the left hemithorax provisionally diagnosed as primitive neuroectodermal tumour (PNET) demonstrated MIC2 positivity with CK and synaptophysin negativity. CK, EMA and p63 positivity was demonstrated in a middle mediastinal mass diagnosed histologically as metastatic deposit of poorly differentiated squamous cell carcinoma. A case of monophasic synovial sarcoma showed EMA, MIC2, bcl2 & calponin positivity. Positive CD68 was demonstrated in a giant cell tumour of soft part. The spindle cell thymoma showed CK +, CD3 +, TdT + but CD20 -. Diffuse large B cell lymphoma was CD20 +, CD3 -, CD15 -, CD30-.

Aetiological Diagnosis	Mediastinal Involvement					
	Involvement of Single Compartment			Involvement of 2 Compartments		
	Anterior (N1 = 25)	Middle (N2 = 05)	Posterior (N3 = 08)	Superior + Anterior (N4 = 16)	Middle + Posterior (N5 = 03)	Involvement of > 2 Compartment (N 6 = 1)
Thymic Tumour (N1=11) - Benign - 9;Malignant-2	06	00	00	04	00	01
Germ Cell Tumour (N2 = 14) Benign – 10; Malignant- 4	09	00	00	05	00	00
Neurogenic Tumour (N3 = 8) Benign - 6; Malignant-2	00	00	08	00	00	00
Oesophageal Lesion (N 4 = 1) (Malignant)	00	00	00	00	01	00
Lymphoma (N4 = 12)	07	00	00	05	00	00
Infective(N5 = 2) - TB lymph node	00	02	00	00	00	00
Cyst(N6 = 1) bronchogenic cyst	01	00	00	00	00	00
Others (N7 = 9)-Mediastinal lipoma, Sarcoidosis, Biphasic synovial sarcoma, monophasic synovial sarcoma, Primitive neuroectodermal tumour, metastatic adenocarcinoma of lung & adenoid cystic carcinoma of lung, Malignant spindle cell tumour, Giant cell tumour of soft parts	02	03	00	02	02	00
Table 1. Topographical Distribution of Mediastinal Lesions						

Table 1. Topographical Distribution of Mediastinal Lesions

The patients presenting with lymph node enlargement were diagnosed with Hodgkin's disease in two cases, one with metastatic deposit of squamous cell carcinoma of oesophagus, three with sarcoidosis (stage1) and tubercular lymphadenitis. Widening of neural foramina of thoracic vertebra in schwannoma and ganglioneuroblastoma cases

were evident on radiology. Dumbell shaped posterior paravertebral lesion was seen in neurofibroma. Left upper lobar parenchymal infiltration was evident in a case of tubercular lymphadenitis. Postoperative morbidity was encountered in six cases and preoperative mortality in one. Among the postoperative morbidity cases, 2 cases were reopened on the day of surgery for bleeding, 4 cases had postoperative wound dehiscence which were treated accordingly.

Nine cases were referred for radiotherapy and chemotherapy for further management. Two thymic tumour cases associated with myasthenia gravis were treated preoperatively with four cycles of plasmapheresis followed by surgery and postoperatively by four cycles of plasmapheresis and tablet pyridostigmine. Patients were followed up in the neuro-medicine department.

Parameter		Anterior & Superior Mediastinal Mass	Middle & Posterior Mediastinal Mass	P Value
SVC Obstruction	Yes	34	1	$\chi^2 = 18.63$ df = 1 P = .0000159 4.11 < or < 132.44
	No	8	15	
SOB	Yes	38	4	Fisher exact 2 tailed P value = 0.0000026
	No	4	12	
Chest pain	Yes	8	15	$\chi^2 = 23.99$ df = 1 P = .000 0.00 < OR < 0.15
	No	34	1	
Anterior D'espine sign	Yes	30	1	$\chi^2 = 19.78$, df = 1, P = 0.0000087 OR = 37.5 (4.25 < OR < 848.44)
	No	12	15	
Cystic change	Yes	35	3	$\chi^2 = 23.99$ df = 1 P = .000 6.81 < OR < 1498.44

Table 2. Distribution of Cases by Location of Mediastinal Mass and SVCO, SOB Chest Pain, Anterior D'espine Sign and Cystic Change

DISCUSSION

Mediastinal masses are relatively uncommon lesions producing an interesting diagnostic and therapeutic dilemma for the clinician.⁶ Shrivastava et al. found thymic pathology in (39 %) patients, lymphoma in (29 %), germ cell tumours in (13 %) patients.⁶ Vaziri et al. observed SVCS as the most common complication with dyspnoea in (41 %) patients and cough in (40 %). Twelve percent of patients were asymptomatic. The most common site was anterior mediastinum (65 %). Malignant lymphoma was the most common malignancy during the first four decades of life.⁷

Shrivastava PC et al. analysed 106 cases of mediastinal diseases and found male to female ratio of 1.9 : 1 and the peak age group was from 3rd to 4th decade of life which included (56 %) of patients. Chest pain was found in 84 % and shortness of breath in 59 % patients. Anterior with superior mediastinum was involved in 72 %, middle mediastinum in 12 %, and posterior mediastinum in 16 % cases. Anterior with superior mediastinum showed thymic neoplasms in (54 %) patients followed by lymphomas. All germ cell tumours were located in anterior mediastinum. Neurogenic tumours comprising neurilemmomas,

neurofibromas, and ganglioneuromas were found in the posterior mediastinum except for one neurilemmoma.⁶

Present study shows similar anatomic location of neurogenic tumours. Giant cell tumours were found confined to anterior mediastinum and also in anterior involving superior compartment of mediastinum. However, incidences of thymic tumour and lymphoma were lower in the present study. This can be explained by low study population of present study. In this study, thoracotomy was done in most patients. 68 % patients underwent complete excision but only biopsy and debulking was performed in 32 %.

Dubashi et al. showed male preponderance with mean age of 37.48 ± 17.04 years. 97 % patients were symptomatic; 28 % patients presented with SVCO. Most of the lesions were located in anterior mediastinum.⁸ Thymoma (39 %), lymphoma (30 %) and germ cell tumours (15 %) were the common tumours in the adult population whereas lymphoma, PNET and neuroblastoma were common in paediatric group.⁸ The ratio of adult-to-paediatric patients in the study by Azarow *et al.* was 3.1: 1.⁹ A similar study in the black African population included 75 males and 30 females with mean age of 34 ± 20.4 years. Most patients were symptomatic. Thymic tumour was the most common neoplasm located in the anterior and superior mediastinum. Most of the lesions were located in anterior and superior mediastinum (63.8 %), lymphoma being the most common lesion (21.9 %) resembling present study.¹⁰ This study found mature cystic teratoma, thymic and neurogenic lesions in the benign group. The malignant tumours were commonly lymphomas followed by immature teratomas and metastatic deposits.

Davis et al. established that 85 % of malignant patients were symptomatic in their study population, compared to 46 % of patients with benign neoplasms.¹¹ Crausman RS found that specific clinical features strongly indicated mediastinal pathology.¹²

In a study by Singh et al. the anterior with superior mediastinum was the most frequent location.¹³ Saad R Jr et al. found lymphoma as the most common malignancy (13.1 %).¹⁴ Rubush et al. observed thymoma in 59 % patients.¹⁵ The small sample size coupled with constrained lack of infrastructure and finance was a hindrance in the present study. IHC was not undertaken in all the cases of present study which is also a limitation.

Masses located in anterior and superior mediastinum presented with SVC, shortness of breath, positive anterior D'espine with cystic change while chest pain was the presentation in middle and posterior mediastinal masses which was found to be statistically significant. (Table: 2) The difference in proportion of mediastinal masses with or without SVC obstruction was statistically significant. Even, the difference in proportion of mediastinal masses with or without shortness of breath was statistically significant. Statistical significance was also found in mediastinal masses with or without chest pain. Lesions with or without anterior D'espine sign were found statistically significant. (Table: 2)

Deficiency in exact incident data lies on varied causes of mediastinal tumours. They are infrequent, representing about 3 % of intrathoracic tumours.^{15,16} About 25 % to 49 % of these lesions are malignant.¹⁵ Present study reported

48.3 % malignant cases. Dixit R et al. found two lymphoma cases in the age group less than 20 years in a study population of 125 cases.¹⁷ A study conducted on 188 children in a children's hospital found lymphoma in 87 children and ganglioneuroma in 17 children.¹⁸ Chien-Ho et al. found lymphomas in (47.5 %) followed by germ cell tumour (12.5 %), neuroblastoma (12.5 %) and thymoma in 12.5 % patients in a study population of 40 patients below age of 18 years.

65 % of them presented with dyspnoea and 35 % with SVC.¹⁹ Temes R et al. noted lymphoma presentation in 55 % of cases in a study population of 22 patients below age of 18 years compared to 197 adults.²⁰ Jerrold L found lymphomas in 45 % of tumours followed by germ cell tumours in (24 %) and thymoma in 17 % children in a study on children presenting with anterior mediastinal mass.²¹ The population of children (including paediatric and teenaged group below 16 years) in the present study was low as compared to the adult population with a ratio of 0.18:1. However, lymphoma was the predominant malignant tumour in the present study similar to the findings of previous studies.

A more elaborate study is necessary to determine the incidence and prevalence of mediastinal masses. A proper evaluation should be done to determine location and extension of the lesion. Since compression of the vital organs can be a significant risk, early diagnosis and proper surgical removal are considered mandatory. Nevertheless, mortality and morbidity rates have improved with novel approaches in anaesthesia, surgical techniques, postoperative care, chemotherapy, immunotherapy and radiotherapy. Excision can be done in operable cases. Exploratory thoracotomy may be done for diagnosing the mediastinal lesions with help of histopathology where cases are beyond operability.

CONCLUSIONS

Mediastinum remains an uncharted territory for anatomists, surgical pathologists, and cardio-vascular surgeons. A wide variety of non-neoplastic and neoplastic lesions are found in different compartments of mediastinum and accurate diagnosis is necessary to formulate management strategies.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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