

ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES

SCHOOL OF GRADUATE STUDIES

DEPARTMENT OF PATHOLOGY



**Histomorphologic Patterns of Primary Mediastinal Masses at Tikur Anbessa Hospital: A
Retrospective Cross-Sectional Study**

For Partial Fulfillment of the Post Graduate Program in Pathology

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This thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature, and acknowledgement of collaborative research and discussions.

The work was done under the guidance of Dr. Yonas BekureTsion (Associate Professor of Pathology) at Addis Ababa University college of Health Sciences.

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Signature_____ Date _____

In my capacity as supervisor of the candidate's thesis, I certify that the above statements are true to the best of my knowledge.

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List of Acronyms and Abbreviations

cHL	Classic Hodgkin lymphoma
CT	Computed tomography scan
GCT.....	Germ cell tumors
ITMIG.....	International Thymic Malignancy Interest Group
NHL	Non-Hodgkin lymphoma
NT	Neurogenic tumors
PMN	Primary mediastinal neoplasms
SPSS	Statistical Package for the Social Sciences
SRBCT	Malignant small round blue cell tumor
SVCO	Superior venacaval obstruction
TC/TNET.....	Thymic carcinomas/ thymic neuroendocrine tumors
WD.....	Well differentiated

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Abstract

Background: The mediastinum is a complex anatomic division of the thorax, housing numerous organs and harboring many histologically diverse tumors and cysts affecting people of all ages. Data regarding to their true incidence, symptomatology, age distribution and incidence trends of particular histologic types is lacking due to their heterogeneity and rarity.

Aims: The aim of this study is to assess epidemiologic profile and histomorphologic patterns of primary mediastinal masses in Tikur Anbessa Specialized Hospital, Addis Ababa University over a five years' period from August, 2015 to 2020.

Methods: This is a retrospective cross-sectional study in which we collected, compiled and analyzed documents of patients with biopsy diagnosis of primary mediastinal tumor from the archives of Department of pathology, Addis Ababa University from August 2015 to 2020. Data were entered, cleared, and analyzed using SPSS statistical software package.

Result: Among 102 patients with primary diagnosis of mediastinal tumors, 52 (51.0 %) were males. The mean age of the patients was 33.6 ± 18.9 years. Seventy-two (70.6%) of the masses were in the anterior, 5 (4.9%) were in the middle, and 20 (19.6%) were in the posterior mediastinum. The most common neoplasms seen most frequently were thymomas (37.3%), neurogenic tumors (12.7%) and lymphomas (10.8%). Sixty-five (63.7%) of cases were malignant, benign tumors accounted for thirty-seven cases (36.3%). Compartment localization and age group (pediatric (<15) vs adult) had significant association with the presence of malignancy ($P < 0.01$).

Chest pain (58.5%) and shortness of breath (52.8%) were the two most common symptoms.

Conclusion: In our study malignant tumors were more common than benign tumors. Thymomas and neurogenic tumors were the most common mediastinal tumors. The anterior mediastinum was the most common location of tumors. The frequency of malignancy was significantly higher in male population as compared to females. Compartment localization and age group (pediatric (<15) vs adult) had significant association with the presence of malignancy ($P < 0.01$).

Key words: Mediastinum, compartment, Tikur Anbessa, Addis Ababa

1. Introduction

1.1. Background

The mediastinum is a complex anatomic division of the thorax, extending from the thoracic inlet superiorly to the diaphragm inferiorly. It is anatomically bound on the lateral side by the parietal pleural reflections along the medial aspects of both lungs, anteriorly by the sternum, and posteriorly by the anterior surfaces of the thoracic vertebral bodies (1). It has been traditionally divided into superior, anterior, middle, and posterior compartments based upon arbitrary landmarks on the lateral chest radiograph. A new scheme based on cross-sectional imaging, principally multidetector computed tomography, has been developed by the International Thymic Malignancy Interest Group (ITMIG) and accepted as a new standard (2,3).

According to ITMIG, the three compartments of the mediastinum are prevascular (anterior), visceral (middle), and paravertebral (posterior) compartment. The prevascular (anterior) compartment is bounded superiorly, by thoracic inlet; inferiorly, by the diaphragm; anteriorly, by the posterior border/cortex of the sternum; laterally, by the parietal mediastinal pleura; and posteriorly, by the anterior aspect of the pericardium. Its major contents include thymus, fat, lymph nodes, and the left brachiocephalic vein. The visceral (middle) compartment is defined superiorly, by the thoracic inlet; inferiorly, by the diaphragm; anteriorly, by the posterior boundaries of the prevascular compartment; and posteriorly, by vertical line connecting a point on each thoracic vertebral body 1 cm posterior to its anterior margin. The visceral (middle) compartment contains heart, major blood vessels and thoracic duct, trachea, carina, esophagus, and lymph nodes. The paravertebral (posterior) compartment is defined superiorly, by the thoracic inlet; inferiorly, by the diaphragm; anteriorly, by the posterior boundaries of the visceral compartment; and posterolaterally, by a vertical line along the posterior margin of the chest wall at the lateral aspect of the transverse processes. The paravertebral (posterior) compartment houses the thoracic spine and paravertebral soft tissues (2,3).

Many histologically different tumors and cysts that affect people of all ages arise from the multiple anatomic structures present in the mediastinum. They may be congenital or acquired, which can be primary or secondary tumours. Secondary mediastinal tumours are more common

than the primary tumours, and most frequently represent lymphatic involvement from primary tumours of lung or infradiaphragmatic organs such as pancreatic, gastro-oesophageal and testicular cancer. The likelihood of malignancy is influenced primarily by location of the mass, patient age; and the presence or absence of symptoms. Age is an important predictor of malignancy as well with many of the lymphomas and germ cell tumors (GCTs) presenting between the second and fourth decade of life (4,5).

The most common tumors encountered in the prevascular (anterior) compartment include thymic lesions, germ cell neoplasms, lymphoma, metastatic lymphadenopathy and intrathoracic goiter. Masses in this area are more likely to be malignant than those in other compartments. Masses of the middle mediastinum include lymphadenopathy (related to lymphoma or metastatic disease), duplication cysts, tracheal lesions, and esophageal neoplasms. Additionally, vascular lesions arising from the heart, pericardium, and great vessels may also be present. The posterior mediastinum is the location of most neurogenic tumors arising from the dorsal root ganglia. Other potential lesions in this compartment are of infectious (discitis/osteomyelitis) or traumatic (hematoma) origin, or miscellaneous lesions related to other underlying conditions (such as extramedullary hematopoiesis) (2,3).

Most mediastinal tumors in adults are either asymptomatic (found on plain chest radiographs or computed tomographic (CT) scans obtained for other reasons) or are associated with vague complaints such as aching pain or cough. By comparison, tumors in children are more often symptomatic and may cause respiratory difficulty and recurrent pulmonary infection. They can present as an oncological emergency in the form of superior vena caval obstruction (SVCO) syndrome and stridor warranting thoracotomy for diagnosis. Symptoms are either due to compression or direct invasion of surrounding structures or due to paraneoplastic syndromes. Common localizing symptoms include respiratory compromise; dysphagia; paralysis of the limbs, diaphragm, and vocal cords; Horner syndrome; and superior vena cava syndrome. Systemic symptoms are typically due to the release of excess hormones, antibodies, or cytokines. Some mediastinal tumors are associated with systemic diseases such as thymoma with myasthenia gravis, immune deficiencies, and red cell aplastic anemia. Thymic neuroendocrine

tumors are associated with Cushing syndrome, goiter with thyrotoxicosis, and parathyroid adenoma with hypercalcemia and osteoporosis (3,4).

The initial workup of a suspected mediastinal mass involves obtaining posteroanterior and lateral chest radiographs. This can provide information pertaining to the size, anatomic location, density, and composition of the mass. CT scanning is used to further characterize mediastinal masses and their relationship to surrounding structures as well as to identify cystic, vascular, and soft-tissue structures (4).

Although the number of diagnostic possibilities can be narrowed by considering the patient's clinical profile, tumor location, and radiographic findings, pathologic diagnosis is almost always required to confirm a presumed diagnosis and to select the optimal treatment modality. A variety of biopsy techniques for obtaining tissue from the mediastinum have been described, including ultrasound-guided endoscopic biopsy, percutaneous image-guided needle biopsy, parasternal anterior mediastinotomy, cervical mediastinoscopy, and video-assisted thoracoscopic surgery. The choice of biopsy technique depends on the localization of the lesion, clinical factors such as the age and the condition of the patient, and the availability of special techniques with the required expert and the equipment (5).

In our setting, Tikur Anbessa Specialized Referral hospital (TASH) in Addis Ababa, Ethiopia, the combination of imaging, transthoracic or transbronchial needle aspiration, imaging guided tissue biopsies and open biopsies are being used to diagnose mediastinal lesions.

1.2. Statement of the problem

The most frequent lesions encountered in the mediastinum are thymomas, neurogenic tumors and benign cysts, altogether representing 60% of patients with mediastinal masses. Age related differences of tumor biology, host characteristics, or treatment protocol exist in mediastinal lesions. Histopathological distribution, location, symptomatology and prevalence of malignancy are different between adult and pediatric populations (6).

The most commonly encountered tumors in children include neurogenic tumors, germ cell neoplasms and foregut cysts accounting for nearly 80% of childhood neoplasms. In adults, primary thymic neoplasms, thyroid masses and lymphomas take the highest toll. Anterior

mediastinal masses account 50% of mediastinal masses including thymoma, teratoma, thyroid lesions and lymphomas. Lesions most commonly found in the middle mediastinum are developmental cysts. Neurogenic tumors are most common in the posterior compartment (7). Mediastinal masses create significant diagnostic dilemma for the clinicians, radiologists and histopathologists. Age distribution and clinical features, together with their anatomic location from the mediastinum provide important diagnostic information for mediastinal lesions. Because of the heterogeneity of mediastinal lesions, descriptive data on age patterns and incidence trends of particular histopathological type are limited (5,6).

This study highlighted the epidemiological profile and histomorphologic patterns in patients presenting with mediastinal masses over 6 years' period from August 2015 to August 2020.

1.3. Significance of the study

Understanding epidemiologic profile of patients and location of the tumor has paramount importance to correct diagnosing the histologic type of primary mediastinal masses. The purpose of this study was to assess our institutional experience on histomorphologic patterns of primary mediastinal masses over six years. As descriptive studies on epidemiologic and histomorphologic patterns of primary mediastinal tumors are lacking in our setup as well as nationwide, this study will help as a bench mark for further large-scale studies in our hospital and the country at large.

1.4. Literature review

In a study done in 867, (676 adults and 130 children) patients over a period of fifty years in Osaka university, Japan; 244 cases were thymomas (36%), 106 germ cell tumors (16%), 95 congenital cysts (14%), 82 lymphomas (12%), 76 neurogenic tumors (11%), and 24 thyroid tumors (4%) in adult patients. There were 60 neurogenic tumors (46%), 24 germ cell tumors (19%), 17 lymphomas (13%), 10 congenital cysts (8%), and 5 thymomas (4%) in the pediatric patients. There was a significant higher incidence of neurogenic tumors and a lower incidence of thymomas and thyroid tumors in children. The most common location was the anterior compartment (68%) in adults and the posterior compartment in children (52%). The prevalence of malignancy in pediatric patients was lower than adults (37% vs.47%) (8).

In a retrospective study conducted in a series of 400 consecutive patients with primary lesions of the mediastinum seen at Duke University Medical Center, 99 (25%) had a primary cystic lesion.

The primary tumors included thymic neoplasms (17%), neurogenic tumors (14%), lymphoma (16%), germ cell tumors (11%), and a miscellaneous group. Malignant neoplasms were present in 166 patients (42%). The anterosuperior mediastinum was the most commonly involved site by a primary cyst or neoplasm (54%), followed by the posterior mediastinum (26%) and the middle mediastinum (20%). Symptoms were present in 62% of the patients and included chest pain (30%), dyspnea (16%), fever and chills (20%), and cough (16%). Of the lesions found on routine chest roentgenograms, 83% were benign. In contrast, 57% of the lesions in symptomatic patients were malignant (9).

In a study done on childhood mediastinal masses in the Department of Pathology, Royal Children's Hospital, Melbourne in 121 children, the commonest cause of a mediastinal mass was NHL (36 cases). This was followed by Hodgkin lymphoma (24 cases), then neuroblastoma and ganglioneuroma (16 and 9 cases respectively), duplication cysts (10 cases), teratomas (7 cases), neurofibroma (4 cases) and lymphangiomas (3 cases). Other rare conditions included mediastinal abscess, thymic cyst, pericardial cyst, accessory lobe of lung, plasma cell granuloma, fibromatosis, paravertebral Ewing's tumor, carcinoid tumor and neurofibrosarcoma. The presentation of the children with NHL was often acute with respiratory distress, while the child with Hodgkin disease was usually older and symptoms were more often systemic than local (10).

In a study conducted in 91 patients in the period 1993-2006 in Department of Medical Oncology, Cancer Institute (WIA), Chennai, India; primary mediastinal tumors were seen commonly in males with mean age of 37.48 ± 17.04 years. As many as 97% of patients were symptomatic at presentation. Superior venacaval obstruction (SVCO) was seen in 28% of the patients. As many as 50% of the patients were diagnosed by a fine-needle aspiration or trucut biopsy, while 28% of the patients required thoracotomy for a diagnosis. Majority of the tumors had anterior mediastinal presentation. Pleural effusion was seen in 20% of the patients, but diagnosis was obtained in only 1%. In adults, thymoma (39%), lymphoma (30%) and germ cell tumor (15%) were the common tumors. In the pediatric population, lymphoma, PNET and neuroblastoma were the common tumors. The 5-year disease free survival and overall survival are 50% and 55%, respectively (11).

In a study done in Department of Pulmonary and Mediastinal Pathology, Armed Forces Institute of Pathology, Washington, DC; of the 322 cases of primary mediastinal germ cell tumors, the overwhelming majority of patients were men (320); only 2 were women (both had teratomatous lesions with additional malignant components). The patients' ages ranged from 1 to 79 years (mean, 40 years). Histologically, all types of germ cell tumors were represented, including 138 teratomas (87 mature teratomas, 6 immature teratomas, and 45 teratomas with additional malignant components); 120 seminomas; 52 nonseminomatous, nonteratomatous germ cell tumors (38 yolk sac tumors, 6 embryonal carcinomas, and 8 choriocarcinomas); and 12 mixed germ cell tumors without teratomatous components (12).

In a study done in a total of 29 adult patients with mediastinal masses in Department of Surgery, Government Medical College & Hospital, Chandigarh, India, 29 patients 15 (51.7%) were males and 14 (49.3%) were females. Age range was from 18 to 75 years with a mean age of 33.6 years and median of 30 years. Most mediastinal masses were identified in the 3rd decade of life. Benign pathologies dominated the study with 28 out of 29 being benign masses (96.5%), and only a single case turned out to be malignant (3.5%), 17 masses (58.6%) were localized to anterior mediastinum and 9 (31%) were localized to posterior mediastinum. Only 3 cases (10.3%) were localized to the middle mediastinum, 4 patients (13.7%) were asymptomatic at the time of diagnosis (13).

In another retrospective study in Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India, in 60 patients with mediastinal masses, 22 were anterior, 20 middle and 18 posterior mediastinal masses. The most common pathology was thymoma (12 cases) followed by ten cases of lymphoma, eight cases each of tubercular lymphadenopathy and schwannoma, six cases of neurofibroma, four cases of extragonadal germ cell tumours, two cases each of thymic cyst, bronchogenic cyst, retrosternal goiter, ganglioneuroma and neuroblastoma, and one case each of lipoma and thymolipoma. The most common presenting complaint was cough, seen in 54 patients (87.0%), followed by chest pain (50; 80.6%), weight loss (36; 58.0%), dyspnea (26; 41.9%) and hoarseness (14; 22.5%). Myasthenic symptoms were seen in four patients with thymoma. Two patients each of thymic cyst and lipoma were diagnosed incidentally (5).

In a retrospective study conducted in the National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; 3,691 primary mediastinal lesions were found, including 1,005 (19%) primary mediastinal neoplasms: lymphomas (533, 53%), thymomas (215, 21%), neurogenic tumors (NTs) (100, 10%), germ cell tumors (GCTs) (62, 6%), soft tissue tumors (STTs) (47, 5%) and thymic carcinomas/ thymic neuroendocrine tumors (TCs/TNETs) (37 in total, 4%). The most frequent lymphomas were classical Hodgkin lymphomas (256) and primary mediastinal large B-cell lymphomas (163). Type AB (73) predominated in thymomas and squamous cell carcinomas (9) and carcinoids (10) in TCs/TNETs. Lymphomas, thymomas and neurogenic tumors were more often in women, TCs/TNETs in men ($P<0.001$). Lymphomas predominated between the 2nd and 4th decade of life, neurogenic tumors under the 3rd decade and thymic epithelial tumors between the 6th and 8th decade ($p<0.001$). There was no correlation between thymoma subtypes and patients' gender ($p=0.389$) but it was found between histology and patients' age: in patients <30 years of age type B2 and B3 thymomas and >70 years of age AB type and micronodular thymomas with lymphoid stroma ($P<0.001$) predominated. In the group of germ cell tumors, half of them were malignant and these were noted exclusively in men (14).

In a retrospective observational study done in Cardiac Center, Bahrain Defense Force - Royal Medical Services Hospital (BDF-RMS), Bahrain in Fifty-five patients; 19 (34.5%) were non-neoplastic lesions including cystic lesions and retrosternal goiters; 36 (65.5%) were neoplastic lesions, 10 (18.2%) were benign tumors, and 26 (47.3%) were malignant, 15 (27.3%) primary and 11 (20%) secondary. Thirty-eight (69.1%) masses were in the anterior mediastinum, 9 (16.4%) in the middle mediastinum and 8 (14.5%) in the posterior mediastinum. The mean age of presentation was 46.6 years (range: 14-74); male to female ratio was 1.3:1. The mean age of males was 48.1 years compared to 44.7 years in females (15).

In a study done in Guilan University of sciences, Rasht City, Iran; in a series of 101 patients, the mean age was 35.84 ± 1.71 years and 56.4% of them were male. The most common mediastinal tumors were Non-Hodgkin lymphoma (30.7%), thymoma (13.8%) and Hodgkin lymphoma (12.9%) respectively. 78.2% of tumors was in the anterior mediastinum. The most common symptoms were cough and dyspnea. There were seen significant differences between type of tumor and location of them ($P<0.001$). In addition, no significant differences were seen between different location of tumor and age ($P=0.4$) and gender ($P=0.82$) (16).

In a study done in 105 patients in University College Hospital, Ibadan, Nigeria, the mean age was 34.0 ± 20.4 years. There were 75 males and 30 females. Eighty-one (77.1%) were symptomatic, 24 (22.9%) were asymptomatic. Thirty-seven (45.7%) of the symptomatic patients had malignant disease while 44 (54.3%) had benign disease. Forty-five patients (43%) and 60 patients (57%) had malignant and benign diseases respectively. Incidence of symptoms, was 82.2% for malignant and 73.3% for benign diseases. Majority of asymptomatic patients (70.8%) had benign disease whereas 29.2% of patients with malignancy were asymptomatic. The frequency of mediastinal masses was anterosuperior, in 67 patients (63.8%), posterior mediastinal, 24 patients (22.9%) and middle mediastinal in 14 patients (13.3%). Lymphoma 23 (21.9%), thymic tumours 19 (18.1%) and endocrine tumours (goiters) 18 (17.1%) were the commonest types of primary mediastinal masses (17).

In study done on 73 patients in department of surgery on patterns of mediastinal tumors operated at the Tikur Anbessa Hospital, Addis Ababa, Ethiopia from August 2005-2011, in a six years' period, forty-nine (67.1%) were males. The mean age of patients was 35.9 ± 10.5 years (range 14 to 74). Forty-five (61.6%) had lesions of the anterior, 23 (31.5%) posterior and 5 (6.8%) the middle mediastinum. The commonest anterior mediastinal tumors were thymic origin and thymic lesions were found more common in females (17:7 ratio). From the 23 patients with posterior mediastinal tumors, 18 had benign neurogenic tumors (4 of which were dumbbell tumors). Chest pain and shortness of breath (dyspnea) were the two most common symptoms in 31 (42.4%) of the patients. Twenty-three patients (31.5%) were asymptomatic, and all had benign lesions. None of the malignant lesions were asymptomatic. The rate of malignancy in the study was 24 (32.8%), of which 19 (79.1%) were in the anterior compartment (18).

1.5. Objectives

1.5.1. General objectives

The objective of this study was to assess histomorphologic patterns of primary mediastinal masses in five years' period from August 2015 to August 2020.

1.5.2. Specific objectives

To assess histopathologic distribution of mediastinal tumors across anatomic compartments.

To identify the differences in morphologic pattern of mediastinal tumors across age spectrum.

To evaluate epidemiologic and clinical profile of patients with mediastinal masses.

To evaluate adequacy of tissues obtained by guided biopsies for providing a definite diagnosis.

To highlight our institutional experience and compare results with different studies.

2. Methods

2.1. Study design, area, period and subjects

In this retrospective descriptive cross-sectional study, 102 documents of patients with primary mediastinal masses were reviewed to assess the epidemiologic data and histomorphologic pattern of primary mediastinal tumors from August 2015 to August 2020 in the department of pathology at Tikur Anbessa specialized Hospital which is the largest referral and teaching hospital located in the nation's capital, Addis Ababa, Ethiopia.

Department of pathology, in Tikur Anbessa Specialized Hospital is the oldest pathology department in Ethiopia which is established in 1974. Currently the department has twelve senior staff pathologists with a rank of assistant professor to associate professors, eight histotechnologists and three laboratory assistants. The department gives surgical pathology, cytopathology, hematology and neonatal autopsy services.

All complete data registered during the study period were taken from archives of the department of pathology for analysis. Biopsy specimens fixed in 10% formalin were processed and stained with hematoxylin and eosin stain and were evaluated by a pathologist. No ancillary special stain, immunohistochemical, molecular or cytogenetic study were used in this study.

2.2. Data collection and analysis

The data was collected by retrospective examination of patient records using data extraction sheet. Patient's records were reviewed for age, sex, clinical presentation, anatomic location of tumor by imaging, type of biopsies and histologic type of tumor. Primary esophageal, pleural, pulmonary, pericardial and tumors from chest wall structures were excluded.

All data were entered, cleared, and analyzed using SPSS version 26. Descriptive statistics was used to present data and Chi square test was employed to assess association between relevant variables. Level of statistical significance was set at p value less than 0.05.

3. Ethical considerations

Institutional ethical permission was obtained from the Research and Publication Committee Ethical Review Board of Addis Ababa University, and ethical committee at Tikur Anbessa Hospital. All data for statistical analysis were handled anonymously.

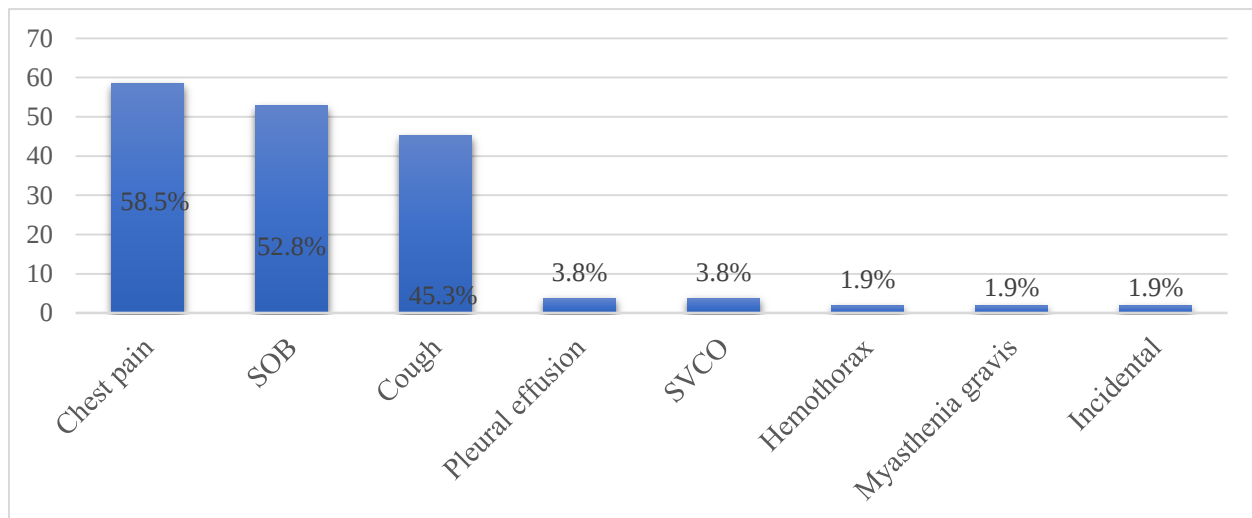
4. Result and analysis

4.1. Demographic and clinical profile of patients

There were 125 patients with mediastinal abnormalities in the database of Department of Pathology between August, 2015 and August, 2020. In 23 cases, the diagnosis could not be established due to the unrepresentative nature of the sample. A total of 102 cases of mediastinal masses, confirmed by biopsy were included in the study constituting 81.6% of all mediastinal disorders. Forty eight (47.1%) were diagnosed on CT guided biopsy, 5 (4.9%) on open biopsy and 49 (48%) on excised specimens. Of the registered study subjects, 52 (51%) were males and 50 (49%) were females with a male to female ratio of 1.04:1. The mean age of the patients was 33.6 ± 18.9 years with ages ranging from newborns to 70 years. The mean age of presentation for males was 33.37 ± 19.2 years and 33.8 ± 18.7 years for females. Sixteen (15.7%) of patients were pediatric (age < 15) and 86 (84.3%) were adults.

Retrospective analysis of the clinical signs and symptoms was done. Clinical symptoms were documented in 52 (51%) of patients. Chest pain and shortness of breath were the two most common presenting symptoms, seen in 31 (58.5%) and 28 (52.8%) of patients respectively. Cough occurred in 24 (45.3%) of patients. One patient with type B1 thymoma was diagnosed incidentally. Other less common symptoms included, pleural effusion, superior venacaval obstruction, hemothorax and myasthenia gravis (Figure 1).

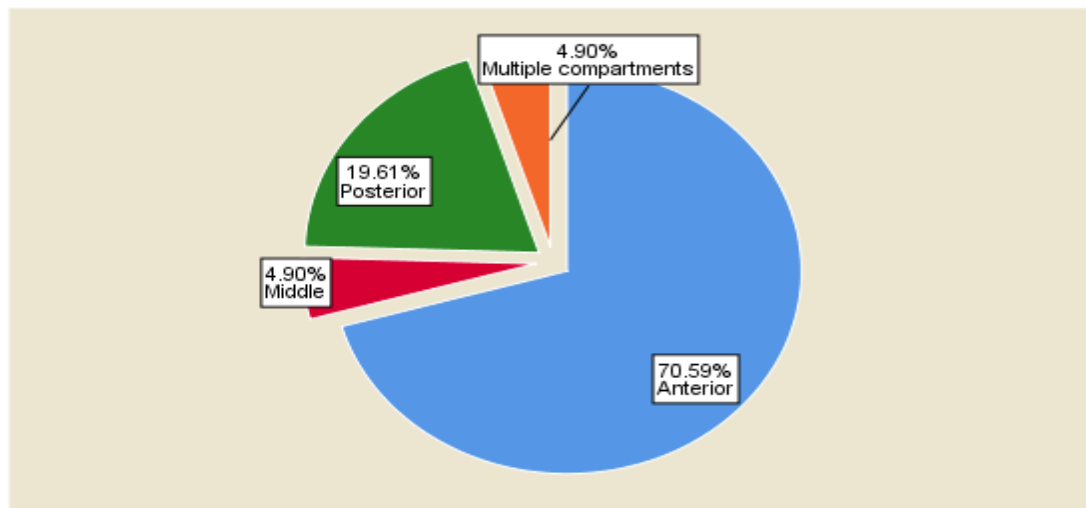
Figure 1. Clinical presentation of patients with mediastinal masses at Tikur Anbessa specialized Hospital, Addis Ababa, 2020.



4.2. Anatomical location

Based on the subdivision of the mediastinum reported by ITMIG, 72 (70.6%) of the masses were in the anterior mediastinum, 5 (4.9%) were in the middle mediastinum, 20 (19.6%) were in the posterior mediastinum and 5 (4.9%) span multiple compartments (Figure 2).

Figure 2. Anatomic distribution of primary mediastinal masses at Tikur Anbessa Specialized Hospital, Addis Ababa, 2020.



The most common location was the anterior compartment (79.1%) in adults and the posterior compartment in children (50%). A significantly greater number of anterior mediastinal masses were diagnosed in second to fourth decade. Compartment localization had significant association with the presence of malignancy ($P < 0.01$). The relative incidence of the various histological diagnoses in the different anatomical subdivisions is illustrated in Table 1.

The most common neoplasms seen most frequently in the anterior mediastinum were thymomas (47.2%), lymphomas (13.9%), germ cell tumors (13.9%), and carcinomas (8.3%). Bronchogenic cysts were the most common lesion in the middle mediastinum (80%). Neurogenic tumors (60%) and neuroenteric cysts (15%), were the most frequent posterior mediastinal masses. Thymoma constitutes the largest (60%) among mediastinal masses involving the multiple compartments.

Table 1. The relative incidence of the various histomorphologic types of mediastinal masses in the different anatomical compartments in Tikur Anbessa Hospital, Addis Ababa, 2020.

Mediastinal mass	Anterior mediastinum	Middle mediastinum	Posterior mediastinum	Multiple compartments
Thymic lesions				
Thymomas	34	1	0	3
Carcinomas	6	0	0	0
Thymic carcinoid	1	0	0	0
Lymphomas				
Non-Hodgkin	6	0	1	0
Hodgkin, (cHL)	4	0	0	0
Germ cell tumors				
Mature cystic teratoma	9	0	1	0
Immature teratoma	1	0	0	0
Neurogenic tumors				
Benign	0	0	12	0
Malignant	0	0	0	1
Developmental cysts				
Thymic cyst	3	0	0	0
Neuroenteric cyst	0	0	3	0
Bronchogenic cyst	1	4	0	0
Thyroid lesions				
Colloid goiter	2	0	1	0
Thyroid carcinomas	2	0	1	0
Mesenchymal tumors				
Benign	1	0	0	1
Sarcomas	1	0	0	0
SRBCT	1	0	1	0

4.3. Histomorphologic diagnosis

Mediastinal lesions displayed a wide histomorphological spectrum. In this study, 65 (63.7%) of cases were malignant, benign tumors accounted for thirty-seven cases (36.3%). Thymic epithelial neoplasms were the most frequent constituting a total of 45 (40.2%) cases, of which 38 were of thymomas and six were of thymic carcinoma and one thymic carcinoid. The most common histologic type of thymoma was of type B1. In two cases of thymoma, further subtyping and categorization was not possible on needle biopsy.

The mean age of patients with thymomas was 45.41 ± 16.08 years (range, 13 to 70). Thymic pathologies were more commonly seen in males, (M: F ratio of 2.2:1). No correlation between histologic types of thymomas and patients' age and gender were found ($p > 0.05$). Primary thymic carcinomas, occurring predominantly in fifth and sixth decades represented 5.9% of the lesions. Three (50%) were undifferentiated carcinomas, 2 (33.3%) squamous cell carcinomas and 1 (16.7%) of sarcomatoid carcinoma. The incidence of benign and malignant neoplasms with respect to age group is shown in Figure 3.

Neurogenic tumors were the second most frequent lesion representing 12.7% of mediastinum masses, with 11 benign and two malignant tumors. Benign neurogenic tumors include schwannomas 4 (30.8%), ganglioneuromas 4 (30.8%), paraganglioma 2 (15.4%), neurofibroma 1 (7.7%). Malignant tumors were well differentiated ganglioneuroblastoma, and malignant peripheral nerve sheath tumor accounting 1 (7.7%) each. The mean age at diagnosis was 23.92 ± 18 years (range, 3 to 68 years).

Lymphoma was diagnosed in 11 (10.8%) of cases. Six (54.5%) were high grade Non-Hodgkin lymphomas, 4 (36.4%) classic Hodgkin lymphomas and 1 (9.1%) case was Low grade non-Hodgkin lymphoma. All Hodgkin lymphomas were diagnosed in the 2nd to 3rd decade and the mean age for high grade NHLs were 27.33 ± 17.5 years (range, 6 to 62 years).

Germ cell tumors accounted for 10.8% of the masses and were mostly benign. These tumours included 10 mature teratomas and one immature teratoma. The mean age of patients with germ cell tumor was 20.2 ± 14.46 years (range, 1 to 50 years).

Eleven (10.8%) developmental cysts of the mediastinum were recorded. These cysts were bronchogenic 5 (45.5%), thymic 3 (27.3%) and neuroenteric 3 (27.3%).

Table 2. Histomorphologic patterns of primary mediastinal tumors in 102 patients at Tikur Anbessa Hospital, Addis Ababa, 2020.

Histopathologic subtype		Frequency (n=102)
Thymomas	Unclassified ^a	2
	A	6
	AB	5
	B1	11
	B2	8
	B3	6
Carcinomas/NETs	Squamous cell	2
	Undifferentiated	3
	Sarcomatoid	1
	Thymic carcinoid	1
Lymphomas	High grade, NHL	6
	Hodgkin, (cHL)	4
	Low grade, NHL	1
Germ cell tumors	Mature cystic teratoma	10
	Immature teratoma	1
Neurogenic tumors	Schwannoma	4
	Paraganglioma	2
	Neurofibroma	1
	Ganglioneuroblastoma, WD	1
	MPNST	1
	Ganglioneuroma	4
Developmental cysts	Thymic cyst	3
	Neuroenteric cyst	3
	Bronchogenic cyst	5
Thyroid lesions	Colloid goiter	3
	Papillary carcinoma	1
	Follicular carcinoma	1
	Poorly differentiated carcinoma	1
Mesenchymal tumors	Solitary fibrous tumor	1
	Desmoid Fibromatosis	1
	Rhabdomyosarcoma	1
Miscellaneous	SRBCT	2

^a Further subtyping and categorization were not possible on needle biopsy.

Intrathoracic goiters and thyroid tumors comprised 6 (5.9%) of mediastinal masses in adults, but were not found in the pediatric population. Three (50%) were intrathoracic colloid goiters and one case each of follicular, papillary and poorly differentiated thyroid carcinoma.

There were also 3 (2.9%) mesenchymal tumors one case each of solitary fibrous tumor, desmoid fibromatosis and rhabdomyosarcoma. Two core needle biopsies were diagnosed with malignant small round blue cell tumor with a recommendation of ancillary studies for further subtyping.

5. Discussion

Primary mediastinal tumours are rare, accounting for 3% of tumours occurring within the chest (5). In this study, a total of 102 cases of mediastinal masses were reviewed across a period of 5 years. The mean patient age was 33.6 ± 18.9 years with a slight male preponderance. These demographic profile of the patients in the study were comparable to a previous study done in our institution and other published literatures (16–18).

In Bekele study, the mean patient age was 35.9 ± 10.5 years (range, 14 to 70) and 67.1% of patients were males. In the Adegboye study, in a series of 105 patients, the mean age was 34.0 ± 20.4 years and 73% of patients were male and in Hemmati study in 101 patients the mean age was 35.84 ± 1.71 years and 56.4% of them were male (16–18).

In our study, the most common clinical findings in order of decreasing frequency were chest pain (58.5%), shortness of breath (52.8%) and cough (45.3%) which were approximately similar to past studies. In Bekele study, chest pain and shortness of breath were the commonest presenting symptoms (42.4%) followed by cough (31.5%). Our study was also in line with a comparable case series done in Ibadan, Nigeria by Adegboye et al., in which 67% presented with chest pain and fullness, 49.4% dyspnea and 27.2% with cough (17). In study done by Davis et al., (1987), Duke University Medical Center in 400 consecutive patients, symptoms were present in 62% of the patients with chest pain (30%), dyspnea (16%) and cough (16%) of patients (9).

In our study, the most common locations of mediastinal tumors in order of decreasing frequency were anterior mediastinum (70.6%), posterior mediastinum (19.6%) and middle mediastinum (4.9%). This was in line with other studies where anterior mediastinal masses were more common than middle and posterior mediastinal masses. In Bekele study, 61.7% of patients has

lesions of anterior mediastinum, 31.5% in the posterior mediastinum and 6.8% in middle mediastinum (18). Davis reported that most common location of mediastinal tumors was anterior mediastinum (54%) and Takeda et al., reported anterior mediastinum was the most common location of mediastinal tumors (67.8%) (8,9).

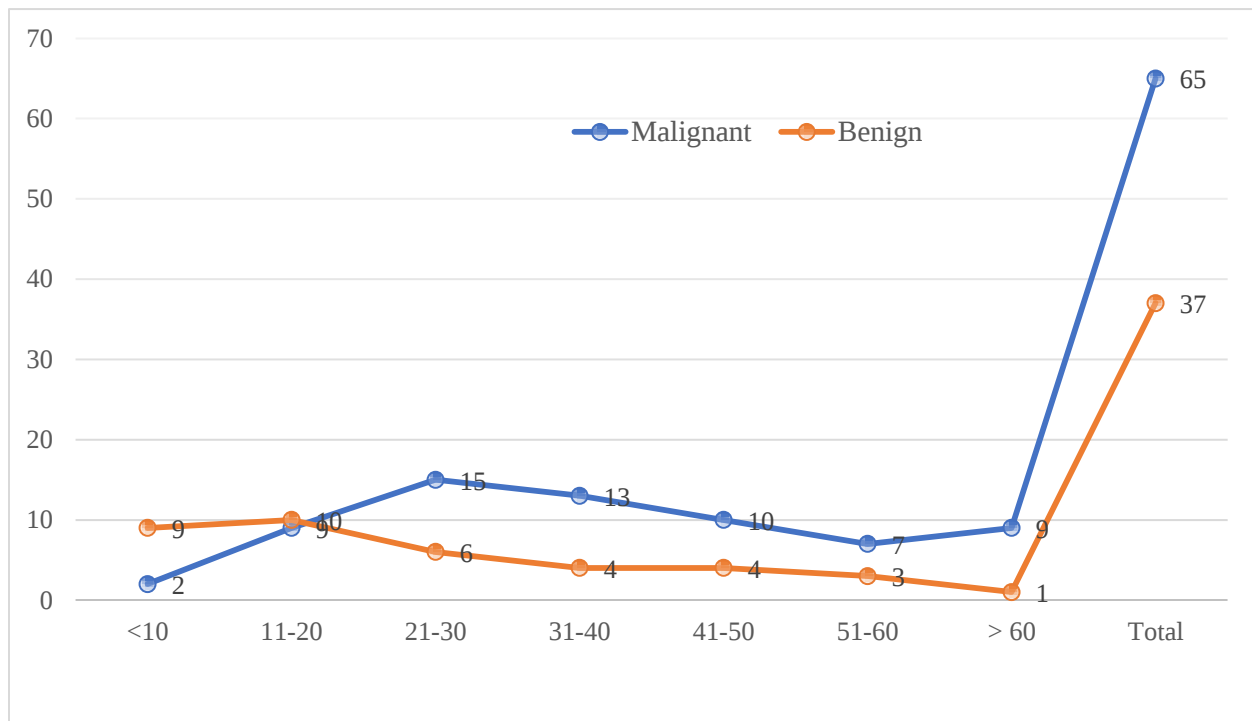
The most common tumor in our series was thymoma, which constituted 37.3%, followed by neurogenic tumors (12.7%) and lymphomas, germ cell tumors and developmental cysts each accounting 10.8% of cases. Thymomas were the most commonly found in the anterior mediastinum (52.8%), followed by lymphomas and germ cell tumors constituting (13.9%) of cases each. In various studies, thymoma was found to be the most common mediastinal tumor reported to occur (8,9,11,18). While studies by Adegboye, Hemmati and Aroor reported lymphoma as the most common histology seen in 21.9% to 50% of patients (16,17,19).

In our study, the most common histologic subtype of thymoma was type B1 followed by type B2 and the mean age of presentation was 43 years with peaks between the third and fifth decades. In studies done by Dasgupta, Sharma and Kumar et al., type AB thymoma was the commonest subtype (5,7,22). In our study thymoma was found in one case of pediatric patient (age<15). In other studies, thymoma was not reported in the pediatric population (9,11,20).

According to International Thymic Malignancy Interest Group created worldwide retrospective database, from analyzed 4221 thymomas diagnosed between 1983 and 2012 with World Health Organization histotype information type B2 thymoma was the most common (28%) and type A the least common (12%) histotypes and differences in gender distribution was not noted (21).

Thymic carcinomas are a heterogeneous group of aggressive, invasive epithelial malignancies. Their incidence is rare, occurring predominantly in middle-aged men (4). We found six (5.9%) cases of thymic carcinoma diagnosed in patients 35 to 62 years old; 3 cases of undifferentiated carcinoma, 2 cases of squamous cell carcinoma and one case of sarcomatoid carcinoma. This was in line with the Davis Study, in which primary thymic carcinomas occurred predominantly in patients 40 to 60 years old accounting 9% of lesions and undifferentiated carcinoma as the most common histomorphologic subtype (9). In a retrospective multicenter cohort study done jointly by European Society of Thoracic Surgeons and the International Thymic Malignancy Interest group squamous cell carcinoma was the most common histological subtype (79%), followed by lymphoepithelioma-like and basaloid ones (22).

Figure 3. Distribution of benign and malignant mediastinal masses across different age groups seen at Tikur Anbessa Hospital, Addis Ababa, 2020.



Lymphoma was diagnosed in 11 (10.8%) of cases. Six (54.5%) were high grade NHL, 4 (36.4%) classic Hodgkin lymphomas and 1 (9.1%) case was low grade NHL. These results are in accordance with results obtained in previous studies, non-Hodgkin lymphomas (NHL) followed by Hodgkin lymphoma being the commonest histologies(7,11,23).

Germ cell tumors are found in young adults and represent 15% of anterior mediastinal masses found in adults. Malignant GCTs are more common (90%) in men (4). In our study, germ cell tumors accounted for 10.8% of the masses and were all mature teratomas except one case of malignant teratoma in 17-year male patient.

Neurogenic tumors are derived from tissue of the neural crest, including cells of the peripheral, autonomic, and paraganglionic nervous systems. Ninety-five percent of posterior mediastinal masses arise in the intercostal nerve rami or the sympathetic chain region. Seventy percent to 80% of neurogenic tumors are benign, and nearly half are asymptomatic (4). In our study, 85% were benign and 2 (15%) were malignant.

In a study by Al-Khalifa, retrosternal goiters accounted for 23.6% of mediastinal masses. Two resected retrosternal goiters in this series consisted of an incidental finding of papillary thyroid carcinoma (15). In our study, retrosternal thyroid masses accounted 5.9% of mediastinal lesions. Three cases were substernal colloid goiter and one case each of undifferentiated, follicular, papillary thyroid carcinomas. All cases were diagnosed in adults.

According to Liu et al., mesenchymal tumors commonly presented with benign tumors, 78.7%, followed by malignant tumors, 21.3% (6). The results in our study were comparable with 66.7% benign and 33.3% malignant mesenchymal tumors.

Developmental cysts of various sorts comprise 10% to 20% of all mediastinal masses. Most can be identified as bronchogenic, enteric, or pericardial. Cysts in the mediastinum could occur at any age and they are usually asymptomatic (24). Thymic cysts account for 3% of anterior mediastinal masses (15). We found that bronchogenic cysts account 5% of mediastinal masses and were mostly in the middle mediastinum. Thymic cysts account 4.2% of anterior mediastinal tumors and neuroenteric cysts accounted for 3% of mediastinal masses and were found in the posterior compartment which is comparable to most of previous studies (9,25,26).

6. Conclusion

The mediastinum is a complex anatomic area playing host to a wide range of neoplastic and non-neoplastic lesions. In our study malignant tumors were more common than benign tumors. The frequency of malignancy was significantly higher in male population as compared to females. Compartment localization and age group (pediatric (<15) vs adult) had significant association with the presence of malignancy ($P < 0.05$). Thymomas and neurogenic tumors were the most common mediastinal tumors and the anterior mediastinum was the most common location of mediastinal tumors.

Awareness of basic epidemiology, incidence and radiological findings may be very helpful for the pathologist to conduct the diagnosis in the proper direction.

7. Limitation of the Study

Considerable proportion of tissues obtained by core needle biopsies were unrepresentative and we were unable to achieve large sample size.

In significant proportion of patients, clinical data and exact location of the lesion was lacking making it difficult to compare with histomorphologic patterns.

It was difficult to achieve estimated number of reports due to poor data keeping methods in our archives and needs to be improved.

Histologic diagnosis was made in core biopsies in about half of study subjects. Due to the heterogenous growth pattern of mediastinal tumors, it may not match with the actual histologic type in resected specimens.

8. Recommendations

Primary mediastinal lesions are not uncommon in our setting and further studies with large sample sizes are required to understand the histomorphologic patterns regarding mediastinal masses. Biopsy request forms should be provided with relevant clinical data and imaging findings.

It is crucial to improve our data keeping methods and sort out the archives systematically.

Significant proportion of tissues obtained by core needle biopsies are not representative and needs to be discussed with thoracic surgery unit.

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10. Annex

Data Extraction Format

Age: -----, Sex: M ☐ F ☐

Clinical presentation: -----.

Imaging: CT ☐ X-ray ☐ MRI ☐

Location of Mass: Anterior mediastinum ☐ Middle mediastinum ☐

Posterior mediastinum ☐ Multiple compartments ☐

Type of biopsy: Core needle ☐ Incisional biopsy ☐ Resection ☐

Specimen Adequacy: Diagnostic ☐ Non-diagnostic ☐

Histologic Diagnosis: -----.