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SILENT AND VIOLENT SINISTROUS MEDIASTINAL MASSES: A CLINICO HISTOMORPHOLOGICAL STUDY

Pathomorphology

Dr. Meghashree V Assistant Professor, Department of Pathology, ACS Medical College & Hospital Velappanchavadi , Chennai -600077

Dr. Prajna K.S. Assistant Professor, Department of Pathology, KLE JGMMC, Near Gabbur Cross Hubballi – 580024

Dr Purnima S Rao* Professor, Department of Pathology, A.J. Institute of Medical Sciences & Research Centre Mangalore-575004 *Corresponding Author

Dr. Zulfikar Ahmed Senior Consultant, Department of Immunohematology & Transfusion Medicine, Wenlock District Hospital Mangalore - 575001

Dr. Muktha Pai Consultant Pathologist, Mangalore Institute of Oncology, Pumpwell, Mangalore -575002

ABSTRACT

Background: Mediastinal masses remain an interesting diagnostic and therapeutic problem for the clinician. **Objectives:** To understand the tissue diversity of lesions in mediastinum and analyse the histomorphology of the same **Methods:** Resection specimens and core needle biopsies of mediastinal lesions submitted to the Department of Pathology in a tertiary care hospital for a duration of 3 years **Results:** The lesions were encountered in a wide age group from 10 months to 73 years. The study unwinded a plethora of findings with thymoma being the most common type of lesion **Conclusion:** Recent advances in radiographic techniques, including CT, MRI and radioisotope scanning, have improved the ability to delineate the nature and extent of a mediastinal mass preoperatively .Management strategies of mediastinal lesions are diverse and depend strongly on the pathological diagnosis and the extent of the disease

KEYWORDS

Germ cell tumour, lymphoma, Mediastinum, thymoma, thymus

INTRODUCTION

Mediastinum is an area of the body where wide range of tissue variability exists . The numerous structures within the mediastinum make it prone for development of variety of lesions ranging from inflammatory to neoplastic, benign to malignant, primary to metastatic, many of which present as mediastinal masses.

Lesions that occur in this area therefore can represent many different clinical entities and pathological processes. Although clinical data, location in the mediastinum and radiological findings all aid in narrowing the differential diagnosis, a tissue diagnosis helps in management of mediastinal lesions.

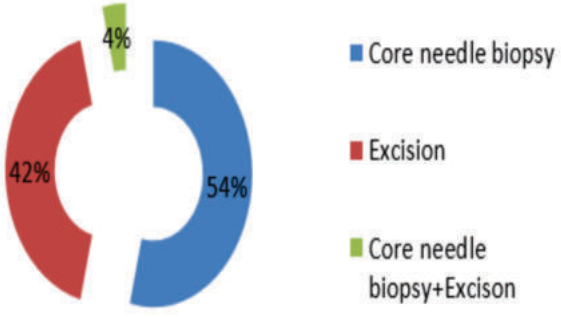
METHODS

All the resection specimens and core needle biopsies of mediastinal lesion submitted to the Department of Pathology in a tertiary care hospital for a duration of 3 years were enrolled. Clearance from Institutional Ethical committee was obtained.

A total of 52 cases were included in this study. H&E sections from the tumour were analysed for histomorphology and corresponding tumour section was used for immunohistochemistry analysis wherever required.

RESULTS

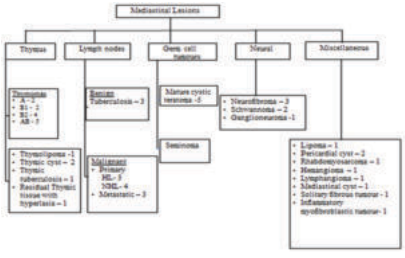
1) ***Type of sample analysed***



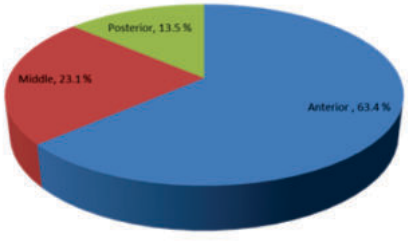
Graph 1 : Pie chart showing type of specimen studied

2) Bird's eye view of different lesions encountered in the study

Table 1 : Flow chart showing the distribution of different lesions in mediastinum



3) ***Distribution of lesions in various compartments of mediastinum***



Graph 2 : Pie chart showing the distribution of lesions in different compartments of mediastinum

4) ***Various lesions of mediastinum***

Thymomas formed the major bulk of anterior mediastinal lesions while the lymph node lesions constituted most of middle mediastinal lesions. Posterior mediastinum was the home of neural tumours (Table 2)

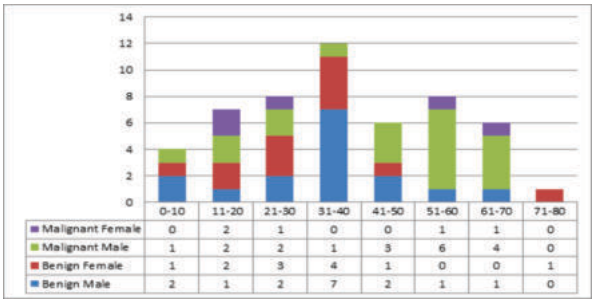
Table 2 : Table showing various mediastinal lesions

ANTERIOR MEDIASTINUM	Total number (33)	100%
Thymomas	13	39.4
Other thymic lesions	5	15.2
Lymphomas	5	15.2
Germ cell tumours	5	15.2

Hemangioma	1	3.0
Solitary fibrous tumour	1	3.0
Lipoma	1	3.0
Mediastinal cyst (Bronchogenic cyst)	1	3.0
Inflammatory myofibroblastic tumour	1	3.0
MIDDLE MEDIASTINUM	Total number (12)	100%
Non neoplastic lesions of lymph nodes	3	25
Lymphomas	2	16.7
Germ cell tumours	1	8.3
Metastatic Squamous cell carcinoma	2	16.7
Metastatic Adenocarcinoma	1	8.3
Pericardial cyst	2	16.7
Lymphangioma	1	8.3
POSTERIOR MEDIASTINUM	Total number (7)	100%
Neurofibroma	3	42.8
Schwannoma	2	28.6
Ganglioneuroma	1	14.3
Rhabdomyosarcoma	1	14.3

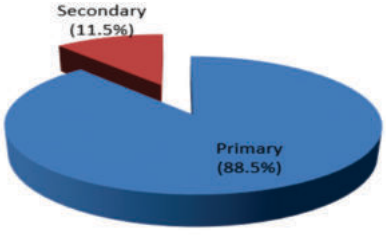
5) *Distribution of mediastinal lesions with respect to age and gender*

Mediastinal lesions were distributed over a wide age group ranging from 10 months to 73 years with mean age of 38.2 years. Maximum number of lesions (25%) was in the age group of 31to 40 years . The mediastinal lesions showed a slight male predominance with male:female ratio of 1.7:1. (Graph 3) In the present study , both benign and malignant lesions were common in males. Among benign lesions, 57.2% was seen in males while females constituted 42.8% of benign lesions. Among the malignant lesions, 79.2% was seen in males and 20.8% was seen in females. (Graph 3)



Graph 3: Distribution of mediastinal lesions with respect to age and gender

6) *Primary vs. Secondary lesions of mediastinum*



Graph 4 : Pie chart showing the frequency of primary & secondary of lesions in mediastinum.

7) *Different types of primary lesions*

Table 3 : Table showing the distribution of various benign & malignant primary mediastinal lesions

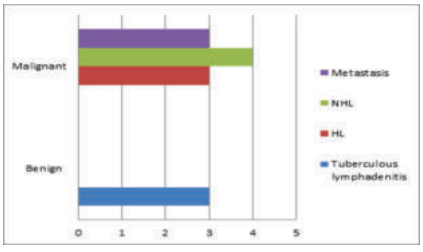
TYPE OF PRIMARY LESION	TOTAL NUMBER	PERCENTAGE
Malignant	22	47.8
Thymoma	13	28.2
Non-Hodgkin's lymphoma(NHL)	4	8.7
Hodgkin's lymphoma(HL)	3	6.5
Seminoma	1	2.2
Rhabdomyosarcoma	1	2.2
Benign	24	52.2
Mature cystic teratoma	5	10.8
Neurofibroma	3	6.5
Schwannoma	2	4.3
Pericardial cyst	2	4.3
Thymic cyst	2	4.3
Thymic tuberculosis	1	2.2
Thymic hyperplasia	1	2.2
Ganglioneuroma	1	2.2
Lipoma	1	2.2
Hemangioma	1	2.2
Lymphangioma	1	2.2
Mediastinal cyst	1	2.2
Inflammatory myofibroblastic tumour	1	2.2
Solitary fibrous tumour	1	2.2
Thymolipoma	1	2.2

8) *Secondary lesions of mediastinum*

Table 4 : Table showing the distribution of various neoplastic & non-neoplastic secondary lesions in Mediastinum

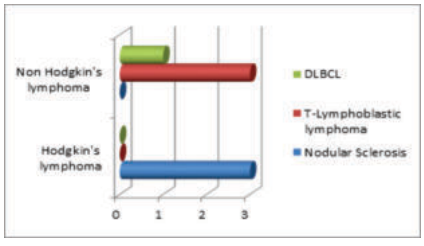
TYPE OF SECONDARY LESION	TOTAL NUMBER	PERCENTAGE
Non-neoplastic	3	50
Tuberculous lymphadenitis	3	50
Neoplastic	3	50
Squamous cell carcinoma	2	33.3
Adenocarcinoma	1	16.7

9) *Neoplastic vs. non neoplastic lesions of mediastinal lymph nodes*



Graph 5: Bar graph showing the distribution of various benign & malignant lesions in Mediastinal lymph nodes

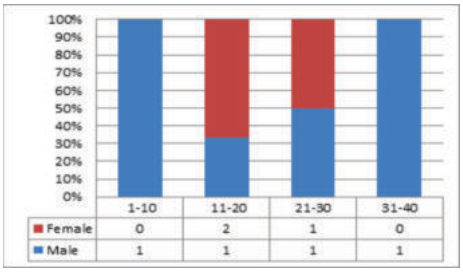
10) *Distribution of mediastinal lymphomas*



Graph 6: Bargraph showing different types of Mediastinal lymphomas

11) *Age and sex distribution of mediastinal lymphomas*

Lymphomas were found in the age group ranging from 7 years to 32 years with a mean age of 19.7 years. There was a slight male preponderance with a male: female ratio of 1.3:1.

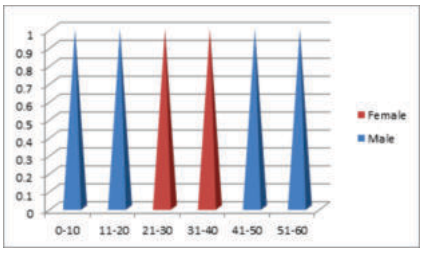


Graph 7 : Bar graph showing age and sex distribution in lymphomas of mediastinum

12) *Age and sex distribution of germ cell tumours (GCT)*

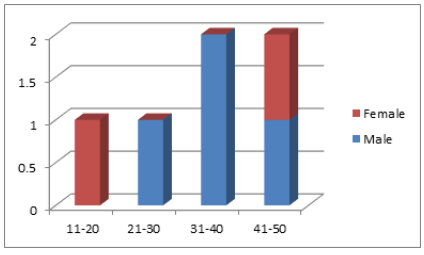
The age of patients with GCT ranged from 4 years to 60 years with a mean age of 32.8 years. There was a single case of malignant GCT

seen in a male. Mature cystic teratoma was the benign GCT encountered in the study and was seen both in males and females. There was a male predominance of mediastinal GCTs with a male to female ratio of 2:11



Graph 8 : Bar graph showing age and sex distribution in mediastinal germ cell tumours

13) ***Distribution of neural tumours in posterior mediastinum***



Graph 9 : Bar graph showing age and sex distribution of neural tumours in mediastinum

14) ***Spectrum of mediastinal lesions in children (<15years)***

Table 5 : Table showing paediatric mediastinal lesions

Age	Gender	Type of lesion
10 months	M	Pericardial cyst
2 years	F	Lipoma
4 years	M	Mature cystic teratoma
7 years	M	NHL - T lymphoblastic type
11 years	F	NHL - T lymphoblastic type
12 years	F	HL - Nodular Sclerosis
14 years	F	Thymic tuberculosis

DISCUSSION

Mediastinal masses remain an interesting diagnostic and therapeutic problem for the Clinician. Recent advances in radiographic techniques, including CT, MRI and radioisotope scanning, have improved the ability to delineate the nature and extent of a mediastinal mass preoperatively . Application of monoclonal antibody techniques to immunohistochemistry has led to more accurate clinical histological diagnosis In the study, histomorphology of 52 cases of mediastinal lesions were studied using H and E with few cases having special stains and immunohistochemistry.

Of these, 28 were core needle biopsies and 22 were surgical resections. In the case of lymphomas, core needle biopsies proved adequate for diagnosis while in the case of thymomas, capsular invasion could not be assessed in majority of the cases. This was a disadvantage because capsular invasion is the single most important factor in determining prognosis in thymomas[1]. In the present study, it was found that majority of the lesions were located in the anterior mediastinum (AM) followed by middle (MM) and the posterior mediastinum (PM). Studies by Dubashi et al.,[2] Karki et al.,[3] Bagheri et al.,[4] and Gadingan et al.[5] also had majority of tumours in the anterior mediastinum. But this was followed by posterior mediastinum and then the middle mediastinum , in contrast to the present study.(Table 6)

Table 6 : Table comparing the distribution of lesions in different studies

S.No	Study	AM	MM	PM
1	Present study	63.4	23.1	13.5
2	Dubashi et al[2]	93.6%	0	6.4%
3	Karki et al[3]	70.3	3.8	25.9
4	Bagheri et al[4]	69.5	10.5	20
5	Gadingan et al[5]	94.9	1.3	3.8

Distribution of Lesions In Anterior Mediastinum

It is seen that the distribution of anterior mediastinal lesions in the present study corresponds closely with the various studies done previously and thymoma was the commonest lesion in the anterior mediastinum (Table 7)

Table 7 : Table showing comparative distribution of lesions in anterior mediastinum in different studies

Gara, Horn, Enterline[6]	Mullen, Richardson[7	Davis, Oldham, Sabiston[8]	Cohen et al,[9]	Present study
Thymic lesions (45%)	Thymic lesions (47%)	Thymic lesions (40%)	Thymomas	Thymic lesions (54.4%)
Lymphomas (20%)	Lymphomas (23%)	Lymphomas (24%)	lymphomas	Lymphomas (15.2%)
Teratomas (20%)	Endocrine (16%)	Germ cell tumours (19%)	Germ cell tumours	Germ cell tumours(15.2%)
Miscellaneous (15%)	Germ cell tumours (14%)	Carcinoma (17%)		Miscellaneous (15.2%)

Distribution of Lesions In Middle Mediastinum

In the present study, lesions of the lymph node formed the majority of the middle mediastinal lesions. This was in contrast to the other studies in which benign primary cysts were the most common lesion of the middle mediastinum. However, the present study is in concordance with Boyd's statement that majority of the lesions of the middle mediastinum are primary and secondary malignant tumours of the lymph nodes.[10] (Table 8)

Table 8 : Table showing comparative distribution of lesions in middle mediastinum in different studies

Davis, Oldham, Sabiston[8]	Cohen et al, [9]	Present study
Primary cysts (60%)	Primary cysts	Lymph node lesions (66%)
Lymphomas (21%)	Lymphomas	Pericardial cyst (16.7)
Benign mesenchymal lesions (9%)		GCT(9%)
Primary carcinoma (7%)		Solitary fibrous tumour (8.3)

Distribution of Lesions In Posterior Mediastinum

Neurogenic tumours were the most common lesions in the posterior mediastinum in the below mentioned previous studies (Table 9) and study by Karki et al[3], which corroborated with the present study. Blades, Harrington and Laipply's reviews that 90% of posterior mediastinal tumours are neural in origin[10] is in concordance with the present study

Table 9: Table showing comparative distribution of lesions in posterior mediastinum in different studies

Davis, Oldham, Sabiston[8]	Cohen et al, [9]	Present study
Neurogenic tumours (53%)	Neurogenic tumours	Neurogenic tumours(85.7%)
Cysts (34%)	Cysts	Mesenchymal tumour (Rhabdomyosarcoma)14.3 %
Mesenchymal tumours (13%)	Mesenchymal tumours	

Age And Gender Distribution of Mediastinal Lesions

Previous studies on mediastinal lesions showed a slight male preponderance and an age range from new-born to 83 years with a peak between third to fourth decades, which was similarly reflected in the present study (Table 10)

Table 10 : Table showing comparative distribution of age and gender in mediastinal lesions from different studies

	Davis, Oldham, Sabiston[8]	Cohen et al,[9]	Shabb et al[11]	Shrivastava, Devgarha , Ahlawat[12]	Dubashi, Cyriac, Tenali[2]	Present study

Male:Female	1.1:1	1.5:1	1.5:1	1.9:1	2.8:1	1.7:1
Age range	7days to 83 years	Newborn to 69 years	10 to 72 years	6 months to 62 years	1to 76 years	10 months to 73 years
Mean age	35.4 years	28.8 years	41 years	35 years	37 years	38.2 years

Distribution of Benign And Malignant Neoplasms

In the present study, benign neoplasms were more common than malignant neoplasms.This is in comparison with the various below mentioned studies. While lymphoma was the commonest in other studies, thymoma was the predominant lesion in the present study, which compared well with the study by Shrivastava et al[12]. The most common benign lesion in the present study was mature cystic teratoma which was not seen in any other study.

Table 11: Table showing comparative distribution of benign and malignant mediastinal lesions in different studies

	Nelson, Shefts, Bowers[13]	Davis, Oldham, Sabiston[8]	Cohen et al,[9]	Present study
Malignant	32%	42%	36%	48%
Benign	68%	58%	64%	52%
MC malignant lesion	Lymphoma	Lymphoma	Lymphoma	Thymoma
MC benign lesion	Neurogenic	Cysts	Cysts	Mature cystic teratoma

Thymic lesions

Thymomas

Thymomas composed the most common mediastinal lesion in the study with type AB being the most common form (Fig 1). Studies show that gender ratio for the occurrence of thymoma is almost equal, whereas in the present study , there was a distinct male preponderance (Table 12). Invasion/stage is the single most important factor predicting outcome in thymomas as evidenced by the extensive case studies done in this subject. In the present study, since majority of cases (76.9%) of thymomas were core needle biopsies, capsular invasion could not be assessed and analysed.

Table 12 : Table showing comparative distribution of age and gender in thymomas from different studies

	Bernatz et al[14] (1961)	Salyer et al[15] (1976)	Suster et al[16] (1992)	Gripp et al[17] (1998)	Moran et al[18] (2001)	Okumura et al[19] (2002)	Present study (2017)
M:F	1:1	1:1.2	1:1	1:1	1.1:1	1:1.1	3.3:1
Age range	26-75	32-77	23-81	15-71	18-73	17-78	26-69
Mean age	48	50	49	46.5	45.5	49	55.1

Thymic hyperplasia

Ricci & co-workers,[20] in a study of 4 cases with thymic hyperplasia concluded that true thymic hyperplasia has a well-defined clinicopathological profile with prevalence in children or young males, absence of associated autoimmune diseases and often presence of respiratory distress or peripheral blood lymphocytosis or both. In the present study a case of residual thymic tissue with nodular thymic hyperplasia was encountered in an elderly lady of 73 years who presented with respiratory distress.

Thymic tuberculosis

The involvement of the mediastinum by tuberculosis is very rare.[21] There are Only fifteen cases of thymic tuberculosis that has been reported in literature in the past seven decades, worldwide.[22] One such rare case was seen in the present study in a 14 year old girl who presented with cough, right sided neck swelling and matted cervical lymph nodes.

On microscopy, the thymic tissue was studded with numerous large, confluent, caseating and non caseating epithelioid granulomas with dispersed Langhans giant cells Dispersed foci of dystrophic calcification, haemorrhage surrounded by reactive lymphoid tissue and thymic parenchyma with Hassalls corpuscles were also noted. Acid fast bacilli was demonstrated on Ziehl Neelsen staining.

Lymphomas

Lymphomas constituted 15% to 55% of mediastinal lesions in various studies, while in the present study they formed only 13.5% of the mediastinal lesions. The relative frequency of HL and NHL varied in different studies and so was with the present study (Table 13) .

Table 13: Table showing literature summary of lymphomas in mediastinum

	Nelson, Shefts, Bowers [13]	Davis, Oldham, Sabiston[8]	Cohen et al,[9]	Shabb et al[11]	Temes at al[23]	Shrivastava, Devgarha, Ahlawat[12]	Dubashi, Cyriac, Tenali[2]	Present study
Lymphoma (%)	20.5	15.5	15.7	31	55	29	30.6	13.5
HL (%)	10	6	9.6	16.7	18	24	6.5	5.8
NHL (%)	10.5	9.5	6.1	14.3	37	5	24.1	7.7

The most common type of Mediastinal HL in the present study was in comparison with the studies by Davis et al[8] and Van Heerden at al.[24] In the study by Davis et al,[8] Dubashi et al[2] and Temes at al[23] NHL was more common than HL , the present study too showed a higher incidence of NHL than HL. In the present study it was seen that mediastinal NHL occurred in an younger age group with a mean age of 16.5 years while study by Davis et al[8] showed an equal distribution of NHL throughout the first five decades of life

Germ cell tumours

Mediastinal GCTs are derived from primitive germ cells that fail to migrate completely during early embryonic development . In one the largest studies done to date, 322 cases of primary mediastinal GCTs were studied histologically an immunohistochemically by Moran, Suster[25] in 1997. The present study was in concordance with Morans study in having teratomatous (Fig 2) lesions as the most common GCT and a male predominance. A mediastinal GCT should prompt a search for a primary gonadal malignancy. In the present study, there was only one case of malignant GCT and it was seminoma (Fig 3) in a male of 20 years without any prior history of gonadal or retroperitoneal tumour.

Neural tumours

In all studies of neurogenic tumors of mediastinum, an age range from very young to elderly is seen. Tumours of sympathetic nervous system is seen in the younger age group[26] and the present study was in concordance as it included a case of ganglioneuroma (Fig 4) in a 16 year old female. It is also seen that neurogenic tumours of the mediastinum has a slight female predominance while in the present study, a male preponderance was seen (Table14)

Table 14 : Table showing literature summary of neurogenic tumours in mediastinum

	Ackerman,Taylor[27]	Patcher, Lattes[26]	Davidson et al[28]	Present study
Age range	3rd to 4th decade	6 months to 77 years	7 months to 63 years	16 years to 46 years
M:F	1:1.08	1:2	1:1.3	2:1
% in posterior mediastinum	100%	94%	94.5%	100%
% of tumours of nerve sheath origin	65%	52%	70%	83.3%
MC tumour	Schwannoma	Schwannoma	Neurofibroma	Neurofibroma
% of malignant nerve sheath tumour	8.3%	4%	0	0

Mediastinal lesions in children

Table 15 : Table showing literature summary of paediatric mediastinal lesions

	Heimburger et al158 (1965)	Haller et al159 (1969)	Pokorny et al160 (1974)	Bower et al 161 (1977)	Present study (<15 years)(2017)
Neurogenic tumours	9	18	35	41	0

Lymphomas	3	9	27	12	3
GCTs	4	8	4	5	1
Thymic lesions	6	8	13	6	1
Bronchogenic cysts	8	2	11	6	0
Other tumours	2	13	6	3	1 (Lipoma)
Duplications	3	6	3	11	0
Angiomatous tumours	4	4	7	5	0
LN infection	3	9	3	1	0
Pericardial cyst	0	1	0	1	1
Other	0	2	0	2	0
Total	42	80	109	93	7

The various studies concluded that paediatric mediastinal malignancies occurred with a frequency of 1 per 5,013 patients with malignant tumours. Lymphomas, GCTs and neurogenic tumours predominated. Compared to adults, children had more neurogenic tumours and fewer thymomas.[23] In the present study, there were no cases of neurogenic tumours or thymomas in the paediatric age group. The most common lesion was lymphoma with 2 cases of NHL and one case of HL . A rare case of thymic tuberculosis was seen in the study in a 14 year old girl.

CONCLUSION

The compartmentalisation of mediastinum into anterior, middle and posterior divisions based on structural landmarks on radiology has important implications for diagnosing suspected masses. CT and MRI have greatly aided in the evaluation and anatomical divisions of mediastinal lesions. However, a histomorphologic analysis of either a tru-cut or excision biopsy sample permits not only an exact diagnosis but also allows for differentiation between benign and malignant neoplasms. Histomorphologic analysis ofmediastinal lesion is a strong determinant for the treatment options ranging from medication and surgery to irradiation and chemotherapy.

Acknowledgement

Sincere thanks to all technicians, teachers and friends who helped me complete the study

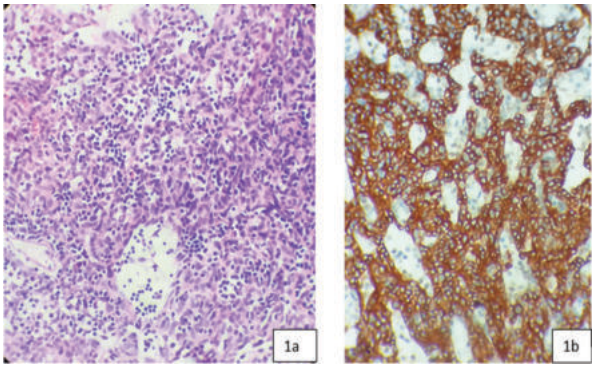


Fig 1a: Type AB thymoma showing spindle cells admixed with lymphocytes (H & E X 400). Fig 1b : Cytoplasmic positivity of Cytokeratin in type AB thymoma (IHC-Cytokeratin X400)

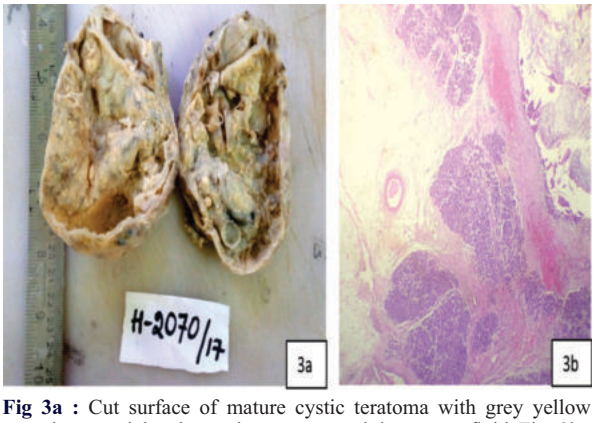


Fig 3a : Cut surface of mature cystic teratoma with grey yellow granular material and cystic spaces containing serous fluid. Fig 3b : Microscopy showing cyst wall lined by stratified squamous epithelium with underling adipose tissue, pancreatic tissue and lumen containing keratin flakes (H & E X 100)

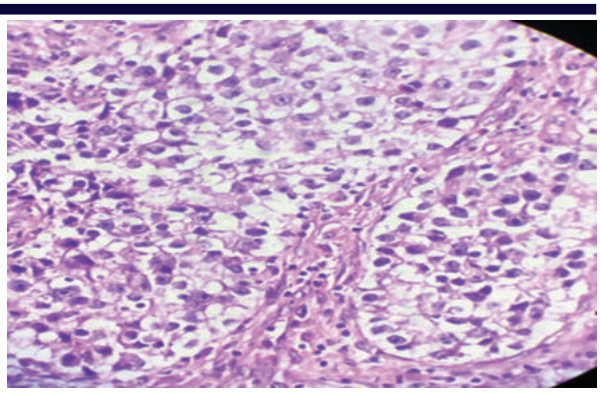


Fig 3 : Seminoma showing lobules of tumour cells separated by fibrous septae infiltrated by lymphocytes. (H & E X 400)

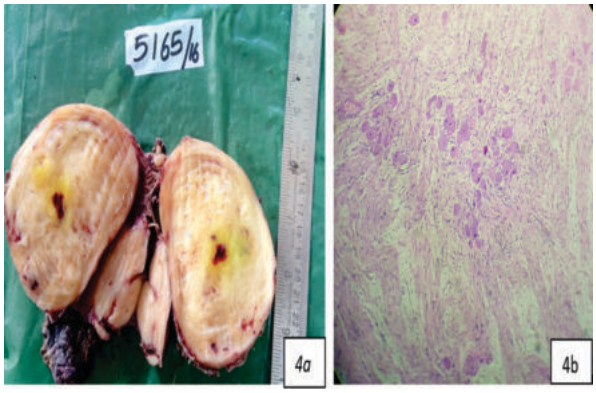


Fig 4a : Cut surface of ganglioneuroma showing circumscribed grey yellow tumour with a trabeculated appearance. Fig 4b: Microscopy showing clusters of ganglion cells deposited in a neuromatous stroma (H&E X 100)

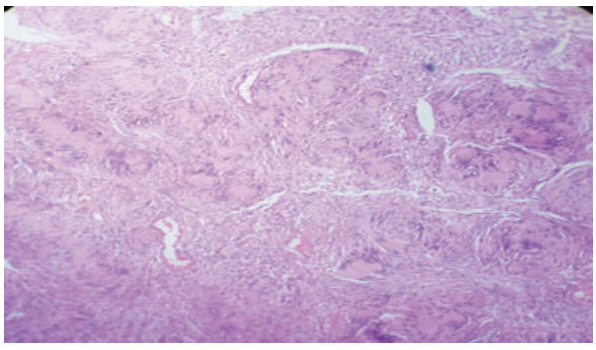


Fig 5 : Schwannoma showing Antoni A areas with Verocay bodies and thick walled hyalinised blood vessels (H & E X 400)

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