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Research Article

A clinicopathologic study of mediastinal lesions with special emphasis on thymomas

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

[1]Department of Pathology, Malabar Medical College and Research Centre, Modakkallur, Calicut, Kerala, India
[2]Department of Pathology, Kasturba Medical College, Mangalore, Manipal University, Karnataka, India

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***Correspondence:**
Dr. Fatima Shamsuddin,
E-mail: fatimahaneeshkhanie@gmail.com

ABSTRACT

Background: Mediastinal masses are relatively uncommon lesions that sometimes pose an interesting diagnostic and therapeutic problem for the clinician. Thymomas are one of the common mediastinal neoplasms and exhibit a wide spectrum of morphologic features and an unrivalled frequency of other autoimmune diseases. The great morphologic variability and heterogeneity in thymomas has rendered their histological classification difficult and highly controversial.
Methods: This retrospective and descriptive study on thymoma was done in the department of pathology, Kasturba Medical College Mangalore (Manipal University), India over a period of five years from January 2006 to June 2011. Histopathology sections taken were stained with routine Hematoxylin and Eosin stains in every case. Additional stains and immunohistochemistry were done as required.
Results: Total number of mediastinal lesions studied was 66, with thymomas making up 15 cases. The age range of patients with thymomas was 22 to 65 years with a mean of 48 years. The most common histologic sub-type of thymoma was B2. Type AB thymoma was associated with bad prognosis. Five cases of thymomas were associated with Myasthenia Gravis. All thymomas showed cytokeratin positivity. Reticulin fibers were seen around individual tumor cells in Type A thymoma while Type B2 showed around tumor nests.
Conclusion: Thymomas are rare & interesting neoplasm located in the mediastinum. A histomorphological analysis aided by immunohistochemistry and radiology permits an exact diagnosis and also allows for differentiation between benign and malignant neoplasms.

Keywords: Mediastinum, Thymomas, Myasthenia Gravis

INTRODUCTION

The mediastinum is a space demarcated by the pleural cavities laterally, the thoracic inlet superiorly, and the diaphragm inferiorly. It is further compartmentalized into anterior, middle and posterior divisions based on several structural landmarks. The mediastinum may be affected by a wide variety of pathological processes. Nearly half the patients are asymptomatic at the time of diagnosis. When present, symptoms usually relate to the location of mass.[1]

The thymus is an organ of antero-superior mediastinum and is a lymphoepithelial structure critical for development of cell-mediated immunity. It can be affected by, or contribute to, immunologic disorders. It can also be involved by neoplastic processes, usually of an epithelial or lymphoid nature. The thymus is the subject of an extensive medical literature with considerable controversy.

Thymomas are thymic epithelial tumors. They are the most frequent tumors in the anterior part of mediastinum. They exhibit a wide spectrum of morphologic features

and an unrivaled frequency of other autoimmune diseases, especially myasthenia gravis. The great morphologic variability and heterogeneity in thymomas has rendered their histological classification difficult and highly controversial.[2-6]

In this study we try to classify thymomas according to the current WHO classification and study their relation to prognosis. The age and sex incidence of thymomas and their relation to myasthenia gravis is also analysed.

METHODS

The present study was conducted in the Department of Pathology of Kasturba Medical College, Mangalore over a period of five years from January 2006 to June 2011. This study is a retrospective and descriptive study. The specimens were received from attached District Hospital, and other hospitals in and around Mangalore and North Kerala.

The patient's name, age, sex, detailed clinical history, laboratory investigations, Fine Needle Aspiration Cytology (FNAC) reports and radiological findings were recorded as per Data Proforma from the hospital records. The gross specimens obtained after surgery were examined in detail. The specimens consisted of both excision and tru-cut biopsies. Tissue was fixed in 10% buffered formalin, and processed by paraffin embedding. The blocks were serially cut, each of 3-5µ thickness and the sections stained with Hematoxylin and Eosin. The histopathological findings were studied. In addition to conventional light microscopic studies, immunohistochemistry was performed on paraffin sections using a two-step process; first, the binding of primary antibody to the antigen of interest and second the detection of bound antigen by a chromogen. Appropriate positive and negative controls were used. The various antibody markers utilized to substantiate a diagnosis of thymoma and sub-classify it included CD99 (monoclonal, Biogenex San Ramon CA USA) and Cytokeratin (AE1 + AE3, monoclonal, Biogenex). Immunohistochemical staining was done with Envision detection kit from Dako Corporation and DAB as chromogen.

All the tumors were classified according to the WHO classification of tumors of the thymus and mediastinum.

RESULTS

In the present study on mediastinal lesions, the most common lesion was thymic in origin (33.3%) of which thymoma (22.7%) was predominant. All cases were located in the anterior mediastinum.

The age range of patients with thymomas was 22 to 65 years with a mean age of 47.8 years. Maximum number of thymomas (8 cases) was seen in the age group of 40-60 years. However, no thymomas were encountered in less than 20 years of age group. Overall, there was a male predominance with a male:female ratio of 2.7:1 (Figure 1). Patients with myasthenia gravis with co-existing thymoma showed a slight female preponderance with a male:female ratio of 1:1.5.

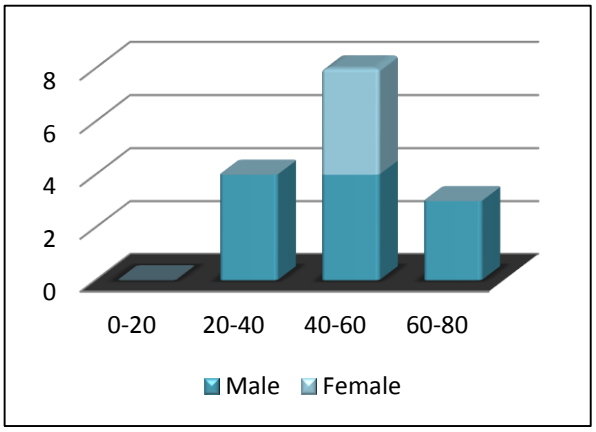

Figure 1: Age and sex distribution of thymomas.

Staging of thymomas were done according to the WHO modification (TNM staging) of Masaoka staging system. In one case, the initial diagnosis on tru-cut was spindle cell/type A thymoma and the final diagnosis after excision biopsy was type AB thymoma with focal invasion of capsule. Two cases had only tru-cut biopsies, so the histology and capsular invasion could not be assessed adequately.

The relation between histologic type of thymomas and age, sex, myasthenia gravis, as well as clinical outcome is summarized in Table 1.

In the present study, 33.3% cases of thymomas were seen to be associated with myasthenia gravis (MG). A statistical analysis using Chi square test showed that the highest degree of association was seen in B1 thymoma, followed by B2 thymoma and then type Athymoma (Table 2).

A varying degree of invasiveness was seen with different histologic type of thymomas. There was only one case of thymoma B3 which was invasive and showed areas of squamous differentiation, necrosis and moderate nuclear atypia. The one case of B1 thymoma encountered in this study did not show any invasion. In two cases where only tru-cut biopsies were received, invasiveness could not be assessed. A statistical analysis using t-test showed that the highest degree of invasiveness was seen with thymoma B3, followed by AB and then B2 (Table 3).

An attempt was made to correlate outcome with invasion, presence or absence of MG and histologic type of thymomas. Statistical analysis using Chi-square test showed that none of the cases without invasion had an adverse prognosis whereas 25% of the cases associated with invasion had an adverse outcome (Table 4).

A positive association was seen between thymoma cases associated with MG and adverse outcome, in that 20% of thymoma cases with co-existing MG patients died compared to only 12.5% of thymoma cases without co-existing MG (Table 5).

Table 1: Clinicopathologic features of patients with Thymoma.

Sl No	Age	Sex	Presenting complaints	Associated Myasthenia Gravis	Size of tumor	Thymoma subtype	Invasion	Stage	Surgery	Outcome
1	22	M	Respiratory distress	No	15x8x8	B2	No	I	Excision	Alive and well
2	60	M	Cough	No	16x9x5	AB	Yes	II(IIB)	Excision	Expired 2 months later
3	51	M	Respiratory distress, limb weakness	Yes	9x6x2	A	No	II(IIB)	Excision	Alive and well
4	42	F	Features of MG	Yes	5x5x2	B2	No	I	Excision	MG improved
5	64	M	Cough	No	8x8x4	A	Yes	II(IIB)	Excision	Alive and well
6	65	M	Dysphagia	No	18x12x8	B2	Yes	III	Partial excision	Alive and well
7	42	M	Features of MG	Yes	3x2x2	B1	No	I	Excision	MG improved
8	52	F	MG	Yes	4x3x2	AB	No	I	Excision	MG improved
9	48	F	MG	Yes	11x6x4	B2	Yes	II (IIB)	Excision	Passed away next year
10	62	M	Chest pain	No	7x7x6	AB	Yes	I	Excision	Alive and well
11	33	M	Cough	No	NA	A			Tru-cut	NA
12	45	M	Chest pain	No	8x4x3	B3	Yes	II(B)	Excision	Received RT. Alive and well
13	56	F	Dysphagia	No	7x6x4	AB	Yes	II(B)	Excision	Alive. Received chemo
14	38	M	Cough	No	10x7x6	B2	Yes	II(B)	Excision	Alive. Received chemo
15	37	M	Chest pain	No	8x7x7	AB			Tru-cut	NA

Table 2: Association between histology of thymoma and MG.

		No MG	MG	Total	Chi square	P value
A	Count	2	1	3	3.000	0.558
	% within stage	66.7%	33.3%	100.0%		
AB	Count	4	1	5		
	% within stage	80.0%	20.0%	100.0%		
B1	Count	0	1	1		
	% within stage	.0%	100.0%	100.0%		
B2	Count	3	2	5		

		% within stage	60.0%	40.0%	100.0%
	B3	Count	1	0	1
		% within stage	100.0%	.0%	100.0%
Total		Count	10	5	15
		% within stage	66.7%	33.3%	100.0%

Table 3: Association between histology of thymoma and invasion.

			No invasion	Invasion	Total
	A	Count	1	1	2
		% within stage	50.0%	50.0%	100.0%
	AB	Count	1	3	4
		% within stage	25.0%	75.0%	100.0%
	B1	Count	1	0	1
		% within stage	100.0%	.0%	100.0%
	B2	Count	2	3	5
		% within stage	40.0%	60.0%	100.0%
	B3	Count	0	1	1
		% within stage	.0%	100.0%	100.0%
Total		Count	5	8	13
		% within stage	38.5%	61.5%	100.0%

	Thymoma	N	Mean	Std. Deviation	Std. Error Mean	t	P value
Maximum size	No invasion	5	7.0000	5.14782	2.30217	-1.391	0.192
	Invasion	8	10.625	4.20671	1.48730		

Table 4: Association between invasion and outcome.

		Outcome/ Prognosis		Total
		Alive	Dead	
	No invasion	Count	5	0	5
		% within invasion	100.0%	.0%	100.0%
	Invasion	Count	6	2	8
		% within invasion	75.0%	25.0%	100.0%
		Count	11	2	13
		% within invasion	84.6%	15.4%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.477[a]	1	0.224

Table 5: Association between thymoma with MG and outcome.

			Outcome/ Prognosis		Total
			Alive	Dead	
	No MG	Count	7	1	8
		% within MG	87.5%	12.5%	100.0%
	MG	Count	4	1	5
		% within MG	80.0%	20.0%	100.0%
Total		Count	11	2	13
		% within MG	84.6%	15.4%	100.0%

	Value	df	Asymp. Sig.
Pearson Chi-Square	0.133[a]	1	0.715

Table 6: Age and gender distribution of thymomas.

	Bernatz, Harrison, Clagett[20] (1961)	Salyer, Eggleston[21] (1976)	Suster, Rosai[22] (1992)	Gripp et al,[23] (1998)	Moran, Suster[24] (2001)	Okumura et al,[9] (2002)	Present study (2012)
Male: Female	1:1	1:1.2	1:1	1:1	1.1:1	1:1.1	2.7:1
Age range (years)		32-77	23 to 81	15-71	18-73	17 to 78	22 to 65
Mean	48 yrs	50 yrs		46.5 yrs	45.5 yrs	49 yrs	47.8

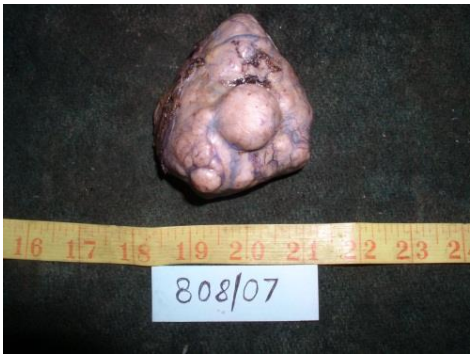

Figure 2: Well-encapsulated tumor with lobulated appearance.

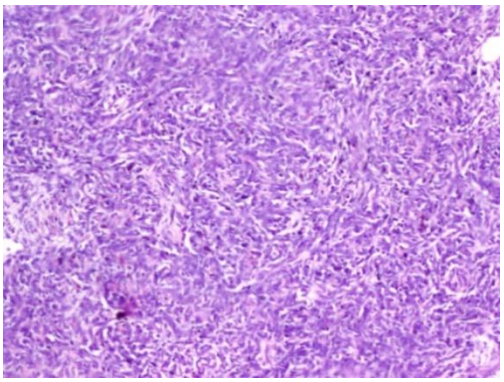

Figure 3: Type A thymoma composed of oval to spindly cells arranged in a storiform pattern (H&E x100).

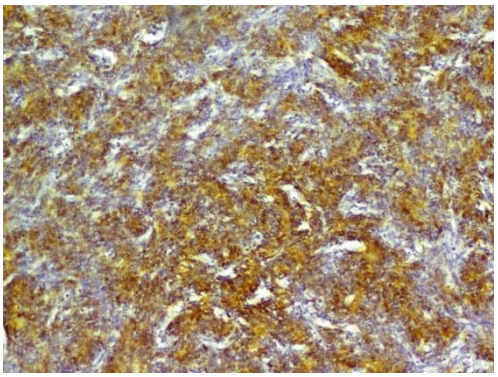

Figure 4: Type A thymoma showing cytokeratin positivity (IHC x100).

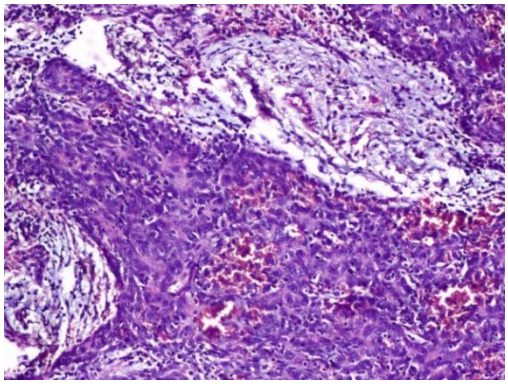

Figure 5: B3 thymoma showing large tumor cell sheets with a vaguely epidermoid appearance (H&E x100).

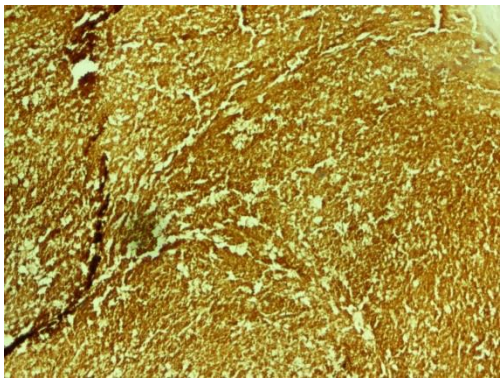

Figure 6: Strong and uniform cytokeratin positivity (IHC x100).

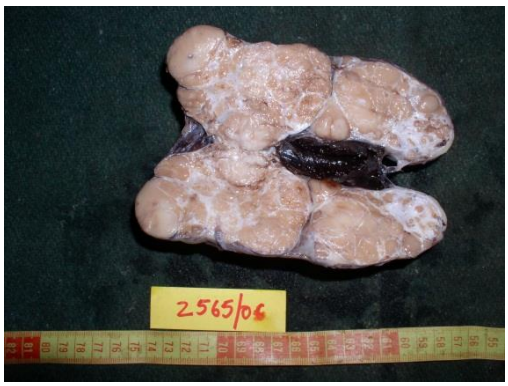

Figure 7: AB thymoma showing multiple nodules separated by fibrous bands.

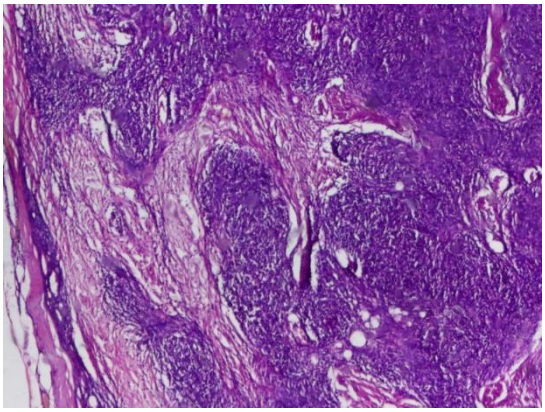

Figure 8:AB thymoma showing nodular growth pattern with diffuse areas (H&E x40).

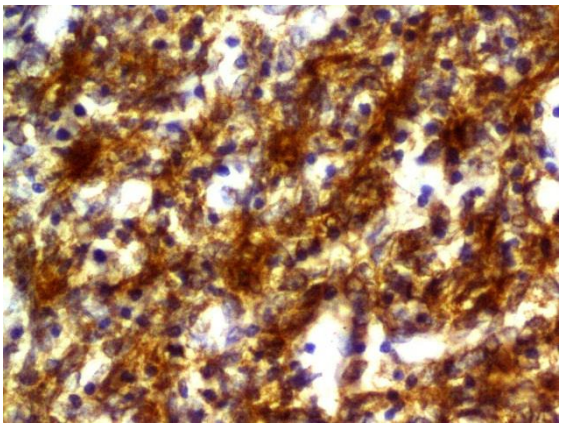

Figure 9: AB thymoma with diffuse and strong cytokeratin positivity (H&E x400).

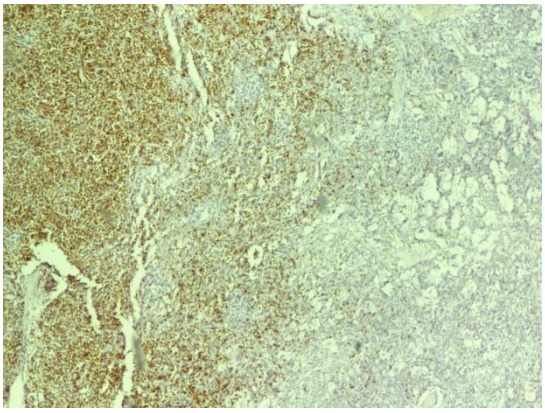

Figure 10: AB thymoma showing CD99 positivity only in the B area on the left side (IHC x40).

DISCUSSION

Thymomas are the most common neoplasm of anterior mediastinum with an incidence of 0.15 cases per 1,00,000.[7] Thymomas as a group have a wide spectrum of histologic diversity and are classified based on cell type of predominance as lymphocytic, epithelial, or spindle cell variants. There is a strong association between histologic subtype and invasiveness as well as prognosis.[8-10]

Thymoma formed the predominant group and was the commonest anterior mediastinal lesion in the present study. This was in agreement with the studies done by Shrivastava et al.,[11] Conkle and Adkins,[12] Rubush & colleagues,[13] Dubashi et al.[14] and Azarow & colleagues[15] who found that thymomas were the most common mediastinal lesions. Studies done by Davis et al.,[16] Cohen & colleagues,[17] Mullen & Richardson,[18] and Gara et al.[19] found that thymomas were the most common anterior mediastinal lesions lending support to similar findings in the present study.

Studies show that gender ratio for the occurrence of thymoma is almost equal, whereas in the present study, there was a distinct male preponderance (2.7:1). The age of the patients with thymomas in most studies ranged from 23 to 78 years with the mean age of 47.8 years. A similar finding was seen in the present study also, where thymomas were seen in an age ranging from 22 to 65 yrs with a mean age of 48 years (Table 6).

Studies on histologic type of thymomas by Lewis & co-workers,[25] Masaoka & co-workers,[26] and Chen & co-workers[27] found that epithelial and lymphoepithelial types of thymomas (AB, B1, B2, B3) were more common that spindle cell thymomas (A). In the present study also, the most common type of thymoma was B2, followed by AB and then type A.

In a clinicopathological study of 65 cases of thymoma, Salyer, Eggleston[21] stated that "Any thymoma may invade locally, give rise to implants or metastasize, and this behavior cannot be predicted on histologic grounds". This was confirmed by Moran and Suster[28] who studied a total of 630 cases of thymoma and found that invasive tumors could be identified in all histologic types. Fifteen percent of thymomas were invasive regardless of their histologic subtype. They concluded that all thymomas should be considered potentially malignant with a potential for recurrence and metastases if left untreated.

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, it was seen that none of the cases without invasion had an adverse effect on prognosis whereas 25% of the cases associated with invasion had an adverse outcome.

As for the association of histologic type to outcome and invasion in thymomas, there have been conflicting opinions. Studies by Bernatz et al.,[20] Lewis & colleagues,[25] Masaoka & colleagues,[26] LeGolvan, Abell,[29] Okumura & colleagues,[9] Gripp & colleagues,[23] Chen & colleagues,[27] and Verley, Hollmann,[30] has shown that WHO histologic classification reflected the invasive nature of thymomas. Type B2 and B3 tumors seemed to be more invasive than type A, AB, and B1 tumors. The study by Okumura & co-workers[9] also showed that the 20- year survival rates progressively decreased from type A to type B3 thymomas. Thus, type B2 and B3 tumors

were supposed to have an oncologically more aggressive nature compared with type A, AB, and B1 tumors. As opposed to these findings, studies by Salyer, Eggleston[21] and Legg, Brady[31] found no association of histology with either invasion or outcome in thymoma. In the present study type AB thymoma followed by type B2, was associated with bad prognosis.

Pan & colleagues[32] studied 192 patients with thymoma and found that thymoma is associated with an increased risk of second malignancy. However, in the present study no such association was seen.

MG is associated with thymoma and is more frequent in women. Symptoms include diplopia, ptosis, dysphagia, weakness, and fatigue. Thirty to 50% of patients with thymoma have MG, compared to 10-15% of patients with MG who have a thymoma.[33,34]

A clinicopathologic study of 200 cases of thymoma by Chen & co-workers[27] showed that although MG had an adverse prognostic significance among patients with type B2 or B3 thymomas on univariate analysis (log rank test: $P< 0.03$), there was no difference in survival between thymoma patients with and without MG on multivariate analysis. MG was more frequent in type B2 and B3 than in type A, AB and B1. Most of the studies show a 35% to 52% association of MG with thymoma. In the present study, a 33.3% association was seen and MG was the most frequent presenting symptom along with a marginal female predominance as was seen in other studies.

There are contradicting views as regards to the association of MG with any particular histologic type of thymoma. WHO and studies by Lattes,[7] LeGolvan, Abell,[29] and Verley, Hollmann[30] showed a definite association with lymphoepithelial or epithelial type of thymomas. In the present study, MG was associated mainly with epithelial type of thymoma with only one case of spindle cell thymoma with MG.

In the study by Seybold & colleagues,[35] it has been contended that surgeons could not hope to influence the course of patients with MG by excising a thymoma, and surgical indications, therefore, were primarily based on the lethal potential of the neoplasm itself. But the course of patients with MG in another case series by the same author[20] showed that 28% had definitely benefited from the operation. Wilkins, Edmunds, Castleman[36] reported five-year survival rates of 45.1% for thymoma with MG and 77.3% for thymoma without MG, and ten-year survival rates of 32% and 67% respectively. Salyer, Eggleston[21] showed a five-year survival rate of 30% for thymomas with associated diseases including MG or pure red cell aplasia (PRCA) and 61% rate for those without them. On the other hand, Bernatz, Harrison, Clagett,[20] reported a five-year survival rate of 63.8% for thymoma with MG and a 62.5% rate for those without MG. A follow-up study of thymomas by Masaoka & colleagues[26] found no difference in five-year survival rates, but a poorer prognosis for those with MG in ten years. This was because of death from MG rather than due to thymoma.

In the present study, a decreased rate of survival was seen in thymomas associated with MG. However, the beneficial effect of excision is highlighted with 60% patients showing improvement in the symptoms of MG.

MG was associated with 10 thymic lesions in the present study. These lesions were thymoma (5 cases), TTH (4 cases) and 1 normal thymus which was resected as a part of treatment for myasthenia gravis. The thymus showed features of physiological involution with islands of epithelial cells devoid of lymphocytes, partly cystic Hassall's corpuscles and abundant intervening adipose tissue.

The differential diagnosis of thymoma ranges from small-cell malignant lymphoma with respect to predominantly lymphocytic tumors, to large-cell lymphoma or carcinoma in regard to predominantly epithelial tumors. However, neoplasms with obviously malignant cytologic characteristics should be excluded from consideration as true thymomas. Spindle cell variants with a vascular stroma or storiform pattern may be confused with hemangiopericytoma or fibrous histiocytoma. The latter possibilities are unlikely diagnoses because most spindle cell tumors of the anterior-superior mediastinum are found to be of thymic epithelial origin. Predominantly lymphocytic tumors generally contain small, regular lymphocytes that occasionally assume an "activated" appearance. The enlarged nuclei in the latter, with slightly folded nuclear membranes, should not be mistaken for the highly convoluted nuclear contours of lymphoblasts. The presence of characteristic histologic features such as medullary differentiation, perivascular serous lakes, and microcystic change will help to distinguish predominantly lymphocytic thymoma from lymphoma. Differentiation from angiofollicular lymph node hyperplasia (Castleman's disease) may be based on the absence of a concentric arrangement of lymphoid cells and of eosinophilic intercellular material in thymoma. Predominantly epithelial tumors may show histologic patterns that lead to confusion with a number of other neoplasms. The epithelial cells in such thymomas may form rosettes or pseudorosettes, similar to the cellular arrangements encountered in neuroendocrine tumors. A chloroacetate esterase stain in these cases may demonstrate the presence of scattered mast cells, a feature that is absent in carcinoid tumors. Squamous metaplasia and keratin pearls may be seen in predominantly epithelial thymomas, but the absence of cytologic malignancy should exclude the diagnosis of thymic squamous cell carcinoma. The presence of gland-like spaces can lead to confusion with metastatic adenocarcinoma; however, the overall cellular composition and benign nuclear characteristics of thymoma should again suggest the correct diagnosis. In some cases, electron microscopic and

immunohistochemical studies are useful in differential diagnosis and may be necessary.[25]

CONCLUSION

This series highlights clinicopathological features of 15 cases of thymomas and its association with myasthenia gravis (MG). The mean age of patients with thymomas was 47.8 years with a male predominance (M:F = 2.7:1). But for patients with thymoma co-existing with MG there was a slight female predominance (M:F = 1:1.5).There was no association between histologic type and invasion in thymoma. Analysis showed that all cases of thymoma without invasion remained disease-free on follow-up whereas 25% of cases associated with invasion succumbed to the disease.MG was associated with thymoma in 33.3% cases. Highest degree of association was seen with B1 thymoma, followed by B2 and Type A thymoma.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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