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Thymic Epithelial Tumors : A Clinicopathologic Study

Wasan Fadhel Abbas[1*], Aseel Abd Al-Zahra Alqzweni [2], Sara Raad Taha[3], Salam Salah Jumaah[4]

Author's Information
1.M.B.Ch.B, Candidate of the Arab, Board of Medical Specialties, Department of Histopathology, Al-Sadr medical City, Al-Najaf, Iraq
2.M.B.CH.B, F.I.C.M.S (path), Consultant Pathologist, Department of Histopathology, Al-Sadr medical City, Al-Najaf, Iraq
3.M.B.CH.B CABMS Pathology ,DIP \ RCPATH, Department of Histopathology, Al-Sadr medical City, Al-Najaf, Iraq.
4.Department of Oncology, Euphrates Cancer Hospital, Najaf, Iraq

Corresponding author:
Wasan Fadhel Abbas
wasanfadhel9@gmail.com

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ABSTRACT

Background: *Thymic epithelial tumors (TETs) include thymo¬mas and thymic carcinomas. Despite their rarity TETs are the most frequent tumors of the anterior part of the mediastinum; some of them are associated with autoimmune diseases. thymic epithelial tumors (TETs) have attracted much interest over the years, leading to an impressive number of histological and staging classifications.*
Objectives: *Study the clinic-pathological features of thymic epithelial tumors in a sample of Iraqi patients.*
Methods: *This is retrospective study for forty-eight cases of thymic epithelial tumors diagnosed between January 2015 and October 2023 , collected from Middle Euphrates Cancer Center , Al-Sadr Medical City and three private labs ,Najaf ,Iraq. Paraffin blocks were collected, and 4 micrometers sections were stained with Hematoxyline & Eosin stain. Thymoma was classified according to the most recent WHO histopathological classification(2021) and staged according to 8th edition of AJGG/TNM staging system(2017).*
Results: *A total of 48 patients were enrolled in this study with a mean age of 47.1 ± 16.3 (range: 18 – 100) year. Males were dominant, contributed for 58.3% with a male to female ratio of 1.4 .Regarding to the WHO types, B3 was the more frequent (31.3%).Staging was available in only 26 patients , most cases (69.3%) were at Stage 3 A or higher. Type A patients were the younger compared to those with other types(P. value < 0.05, significant). No significant association between age and staging. With regard to the MG, only 8 cases were reported*
Conclusion: *In our study ,the most frequent WHO type was B3 thymoma .There was significant correlation between patients age and WHO types . Most cases presented at high stages .Myasthenia gravis was the only paraneoplastic syndrome included in this study . Patients with MG presented at younger age and most were females.*

Keywords: ***Thymic epithelial tumors, Epidemiology, Clinicopathologic features***

1. INTRODUCTION

Thymic epithelial tumors are the most frequent tumors of the anterosuperior mediastinum (1).Thymoma and thymic carcinomas (TC) are rare tumor entities that present mostly in the fourth to sixth decade of life (2,3) affects males and females in roughly equal proportions (4,5).According to Iraqi cancer registry 2021 the incidence rate is 0.07/100.000 Population (0.05 /100.000 for male, 0.02/100.000 for female) (6). In the US overall incidence rate is 0.13–0.15 per 100,000 population at risk .In Europe, is 0.17 per 100,000 population at risk (7). Thymoma is associated with a variety of autoimmune diseases, such as hyperthyroidism, pure red cell aplastic anemia, myasthenia gravis (MG), and endocrine disorders (8). Myasthenia gravis is most frequent paraneoplastic syndrome proved to have no effect on prognosis (9–11). According to the World Health Organization 2021 pathological classification (12). Thymoma classified histologically into (A,B1,B2,B3,AB) subtypes, Letters based on shape of neoplastic cells (A spindled, B polygonal). Numbers in type B thymoma (B1 → B3) according on the ratio of neoplastic epithelial cells to thymocytes and the degree of cytologic atypia in malignant cells. Medullary islands more in B1; less in B2; absent in B3. Type AB (AB1,AB2): morphology of mixed spindle and polygonal neoplastic cells components can be mixed or separated (13). Rare thymoma: micronodular thymoma, metaplastic thymoma and lipofibroadenoma. Thymic carcinoma also arise from thymic epithelial cells, but they have both a malignant cellular appearance and behavior , squamous variant (the most common), basaloid, adenocarcinoma, lymphoepithelioma-like carcinoma and others (14). As with other malignant tumors , the extent and spreading of thymic malignancies play important role in terms of the patients' prognosis (15). Masaoka-Koga staging system previously used .Yamakawa et al. first introduced an adaption of the Masaoka-Koga classification into a TNM system (16).The 8th edition of the TNM Classification of Malignant Tumors published in 2017 is now used for staging of thymic epithelial tumors (17,18). Prognosis depends on multiple factors such as histology, stage and surgical radicality, with an overall 5-year survival rate of 78% for thymoma and 30% for thymic carcinoma (19).

2. METHODOLOGY

This is retrospective study based on forty-eight cases of thymic epithelial tumors diagnosed between January 2015 and October 2023 , collected from Middle Euphrates Cancer Center , Al-Sadr Medical City and three private labs ,Najaf ,Iraq. Age, Sex, Histological type, Stage , Association with myasthenia gravis , were obtained from medical records. twenty-sex of cases received as resection biopsies ,twenty-two of cases were tru-cut biopsies . H&E sections were re-examined and classified according to WHO classification (12) into subtypes A, AB ,B1,B2,B3 and Thymic Carcinoma. .Staging of twenty-six of cases according to AJCC/TNM staging system (17) using radiological data of CT ,PET scan and resection biopsy data.

3. RESULTS

A total of 48 patients were enrolled in this study with a mean age of 47.1 ± 16.3 (range: 18 – 100) year. Males were dominant, contributed for 58.3% with a male to female ratio of 1.4:1.0 (**Table 1 & Figure 1**). Regarding to the WHO types, B3 was the more frequent , where 15 of our patients with this type contributed for 31.3% of the studied group, followed by type AB1 in 8 patients, thymic carcinoma and type A in 7 patients type B2 in 5 (**H&E picture 1**) , and the least frequent type was AB2 in only 2 patients, (**Table 2**). Staging was available in only 26 patients and were distributed in (**Table 3**), however, most cases, (69.3%), were at Stage 3 A or higher. The comparison of patients age according to the WHO types and stage, revealed that patients with type A were the younger, (mean age = 30.6 ± 7.4), while patients with type B2, Thymic Ca and type AB were the older with a mean age of 56.2 ± 12.8, 56.1 ± 19.7 and 55.3 ± 17.4 years, respectively, (P. value < 0.05, significant), (**Table 4 and Figure 2**). Elderly patient with mean age of 56 years presented with stage 4 , However No significant association was reported between age and staging, (P>0.05), (**Table 4**). Regarding the association between gender with each of WHO types and staging ,most type A thymoma and thymic carcinoma in male while type B3 in female. Most male patients were in stage 3A while high percent of females were in stage1 and 3A. However no significant differences were found in gender across types or stages, in both comparisons, (P>0.05), (**Tables 5 & 6**). Furthermore, cross-tabulation was performed to assess the relationship between types and

stage of Thymic epithelial tumors using Fisher's exact test which revealed no significant association, (P. value = 0.976 not significant), (**Table 7**) With regard to the MG, only 8 cases were reported, their descriptive characteristics are shown in (**Table 8 & 9**), their age ranged between 32 and 45 years, they were 5 females and 3 males, one of them had type AB1, 5 cases with B3 and 2 cases with AB2 type , most cases presented in young females and type B3 thymoma . staging was available for only 4 patients of them 3 patients with stage 3 and one patient with stage 1.

Table 1. Age and gender distribution of the studied group (N=48)

Variable		No.	%
Age (year)	≤ 30	7	14.6
	31 - 40	14	29.2
	41 - 50	8	16.7
	51 - 60	10	20.8
	> 60	9	18.8
	Total	48	100.0
	Mean (± SD)	47.1 ± 16.3	-
Gender	Male	28	58.3
	Female	20	41.7
Total		48	100.0

SD: standard deviation

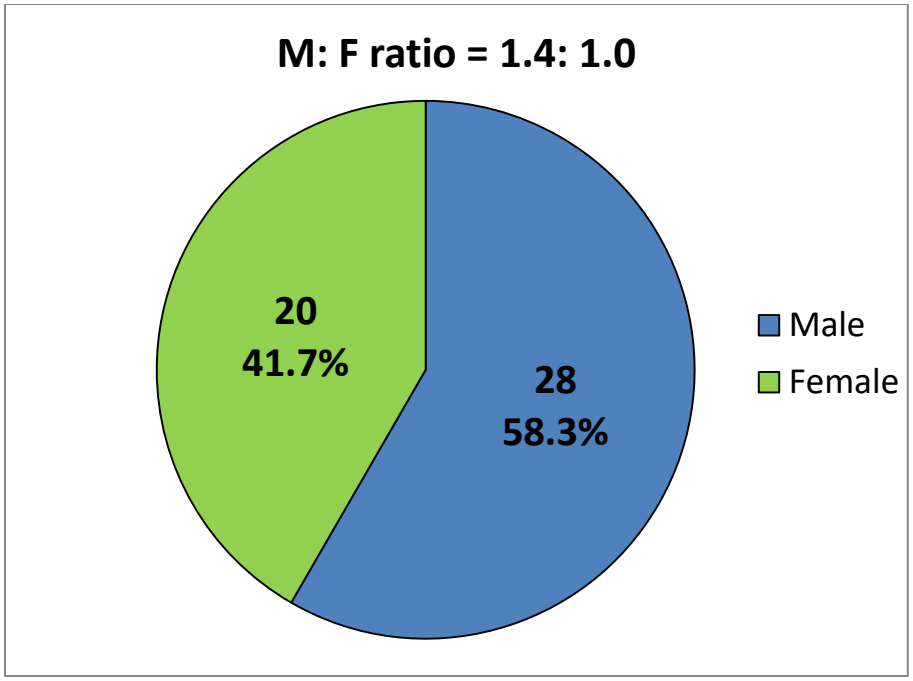
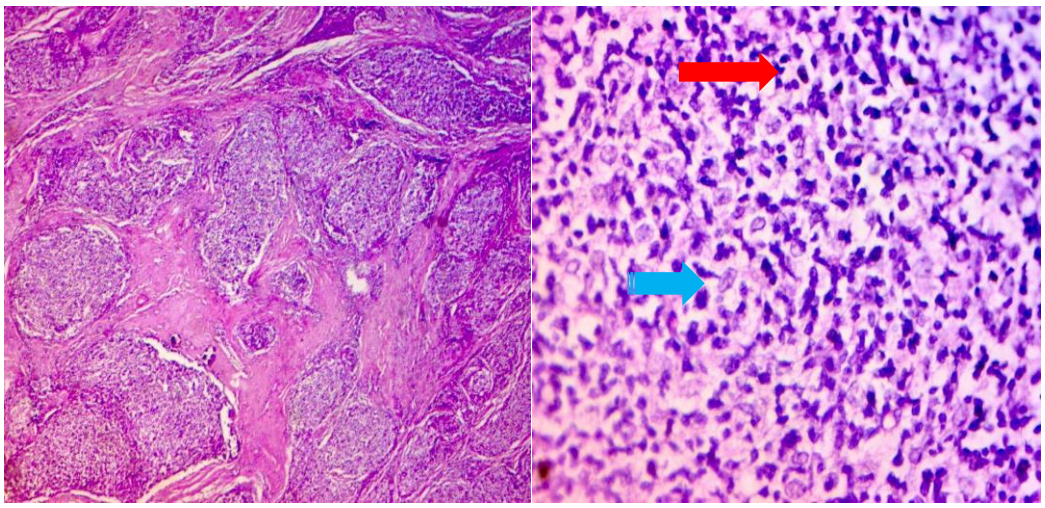


Figure 1. Gender distribution with male to female ratio (N=48)

Table 2. Distribution of types among the studied group

Types	No.	%
A	7	14.6
AB1	8	16.7
AB2	2	4.2
B1	4	8.3
B2	5	10.4
B3	15	31.3
Thymic Ca	7	14.6
Total	48	100.0



Picture1: WHO Type B2 thymoma ,A: Lobulated architecture comprised of cellular lobules intersected by sharply demarcated fibrous bands H&E, magnification (10X) .B: Mixture of small lymphocytes (thymocytes)(red arrow) and large, polygonal epithelial cells(blue arrow) H&E ,magnification (40X).

Table 3. Distribution of Stages among the studied group

Stages	No.	%
Stage 1	7	26.9
Stage 2	1	3.8
Stage 3 A	9	34.6
Stage 3B	4	15.4
Stage 4 A	5	19.2
Total	26	100.0

Table 4. Comparison of mean age of different types and stages

Variable		Age		P. value
		Mean	SD	
Types	A	30.6	7.4	0.018 sig
	AB	55.3	17.4	
	AB2	41.5	2.1	
	B1	40.0	18.4	
	B2	56.2	12.8	
	B3	45.8	12.7	
	Thymic Ca	56.1	19.7	
Stages	Stage 1	48.0	15.1	0.955 ns
	Stage 2	48.0	0.0	
	Stage 3 A	52.8	22.5	
	Stage 3B	50.0	19.1	
	Stage 4 A	56.0	13.0	

SD: standard deviation, sig: significant, ns not significant

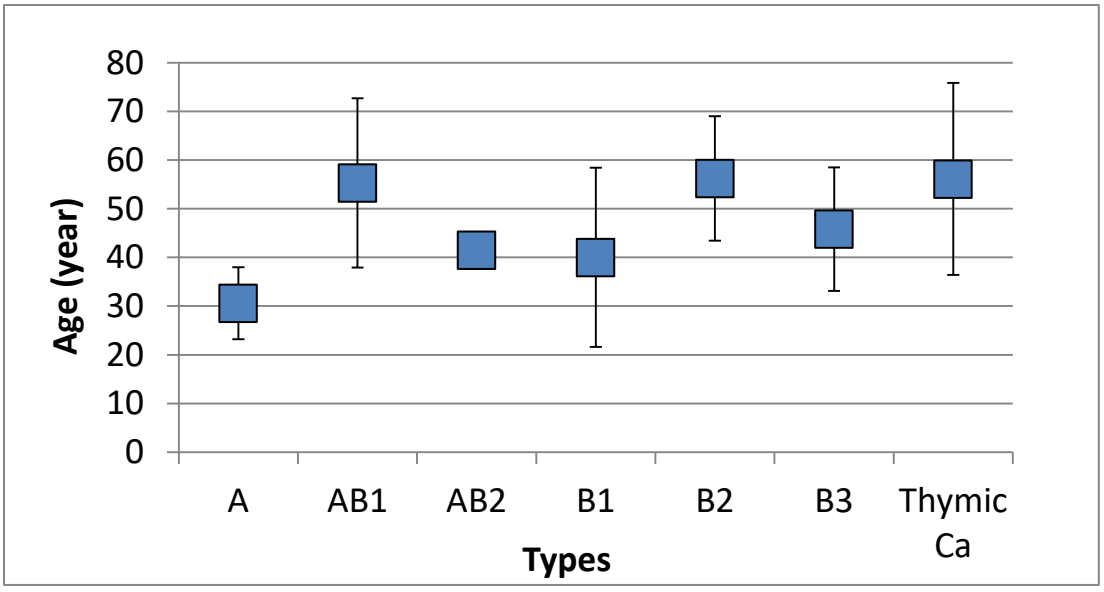


Figure 2. Line-marker graph showing the significant variation in age across different types

Table 5. Distribution of types according to gender

Types	Male		Female	
	No.	%	No.	%
A	6	21.4	1	5.0
AB1	3	10.7	5	25.0
AB2	2	7.1	0	0.0
B1	2	7.1	2	10.0
B2	3	10.7	2	10.0
B3	6	21.4	9	45.0
Thymic Ca	6	21.4	1	5.0
Total	28	100.0	20	100.0

P. value = 0.158 not significant

Table 6. Distribution of stages according to gender

Stages*	Gender			
	Male		Female	
	No.	%	No.	%
Stage 1	3	20.0	4	36.4
Stage 2	0	0.0	1	9.1
Stage 3 A	5	33.3	4	36.4
Stage 3B	3	20.0	1	9.1
Stage 4 A	4	26.7	1	9.1
Total	15	100.0	11	100.0

P. value = 0.475 not significant. Staging was available for only 26 cases

Table 7. Cross-tabulation for the relationship between types and stage of Thymic epithelial tumors

Stage	Types							Total
	A	AB	AB2	B1	B2	B3	Thymic Ca	
Stage 1	1	2	0	1	1	2	0	7
Stage 2	0	0	0	1	0	0	0	1
Stage 3 A	1	2	1	1	1	2	1	9
Stage 3B	1	1	0	0	0	1	1	4
Stage 4 A	0	1	0	0	0	2	2	5
NA	4	2	1	1	3	8	3	22
Total	7	8	2	4	5	15	7	48

Fisher's exact test used in comparison, P. value = 0.976 not significant

Table 8. Descriptive characteristics of 8 MG cases

Patient No.	Age	Gender	Type	Stage
1	38	Female	AB1	Stage 1
2	38	Female	B3	NA
3	40	Female	B3	NA
4	32	Female	B3	Stage 3 A
5	45	Female	B3	Stage 3B
6	43	Male	AB2	NA
7	40	Male	AB2	Stage 3 A
8	35	Male	B3	NA

NA: not available

Table 9. Summary of characteristics of the 8 MG patients

Variable		No.	%
Age (year) mean (SD)		38.9 (4.2)	-
Gender	Male	3	37.5
	Female	5	62.5
Types	B3	5	62.5
	AB	3	37.5
Stages	Stage 1	1	12.5
	Stage 3	3	37.5
	NA	4	50.0

SD: standard deviation of mean , NA: not available

4. DISCUSSION

Thymic epithelial tumors are rare neoplasms orginate from epithelial component of thymus ,thymoma is most common but thymic carcinoma is less frequent (20).Therefore the current study included a total of 48 patients of thymic epithelial tumors, the mean age of the studied group was 47.1 ± 16.3 (range: 18 – 100) year, however, the distribution of patients across age groups revealed no much variation across these age groups, nonetheless, majority of the patients (85.4%%) were older than 30 years, these findings were not unexpected due to the fact that incidence of thymoma increases with the age; Anna L. Rich from United Kingdom reported that the peak incidence of thymoma is in the age between 45 and 55 years (5). An earlier study conducted by Engel et al. (4) reported that the peak incidence was in the age of 70 years. The presentation of malignant processes in older patients is consistent with the age-related accumulation of genetic destruction. However, it is notable that despite the noticeable decrease in the size of the thymus gland with advancing age, the situation like almost most other malignancies (5). In a large recent study conducted in 2023, Gerber et al. (21) documented that thymoma was less frequent in patients younger than 20 years and the incidence increased with advanced age in those older than 20 years and the higher incidence rates reported in those aged 45 – 79 years,which consistent with our findings. It is worth mentioned that age still an important factors associated with the survival and prognosis of this disease where it has been proved that younger patients on time of diagnosis had better

survival and prognosis compared to older patients (22). In our study, males were dominant, contributed for 58.3% with a male to female ratio of 1.4:1.0 ; our findings agreed that reported in previous studies that documented a predominance of males; Yen et al. from Taiwan documented in 2011 a male to female ratio of 1.42 to 1.0 (23), conversely, Alqaidy et al. suggested relatively higher incidence in females (24). Furthermore, Gerber et al. stated that only minor differences are found between both genders in diagnosed thymomas (21). However, it has been generally suggested that sex does not have an impact on the development of the disease (5). In the present study we used World Health Organization (WHO) histologic classification for typing of thymoma, this classification nowadays is the most widely used for histologic classification of thymic epithelial tumors because it provides a beneficial clinical guidance for most surgeons, oncology therapist and clinically helps oncologists in making decision (25,26). The distribution of our patients according to the WHO histologic classification revealed that B3 type was the more frequent type compared to other types. We found that patients with type A, AB, B1,B2, B3 and thymic carcinoma contributed for 14.6%, 20.8%, 8.3%, 10.4%, 31.3%, 14.6%, respectively. In a study conducted by Naji et al. (27), the proportion of patients with type A, Ab, B1, B2 and B3 was 15.7%, 7.8%, 19.6%, 35.3% and 21.6%, respectively. Like our study, Wang et al. reported higher rate of type B3 (23.7%) among 873 patients with different types of thymoma, followed by type B, B1, B2 and A, respectively (22). Rioja et al. (28) found that among 83 patients with thymic epithelial tumors, thymoma contributed for almost 64% while thymic carcinoma for 36%, the histological typing by Rioja et al. revealed that type AB was the more frequent type followed by type A (14.4%), B1 (12%), B2 (3.6%) and B3 in 7.4%. This variation in the proportional distribution of types was not unexpected where no homogenous and fixed distribution of these types in different studies and literatures due to different factors that may contribute to the incidence of the disease and its types like ethnicity, genetic factors and survival rates in different populations in addition to the variation in the number of enrolled population. Moreover, some diagnostic pitfalls may be attributed to the wide variety of histologic growth patterns of thymoma, patient presented with an unusual histological subtype, or faulty diagnosed as other neoplasms (24). Therefore, differential diagnosis must be considered with caution on needle biopsy of an anterior mediastinal

masses. For instance, in types AB, B1& B2 thymomas, which are lymphocyte rich they may be misdiagnosed with thymic hyperplasia and non-Hodgkin lymphomas. In particular, differentiating type B1 thymomas and type AB with dense lymphocytic population, from thymic hyperplasia is too difficult on biopsy (26). Unfortunately, in our study, staging was not available for all patients, however, we analyzed the available data for staging in 26 patients, we found that more than two thirds (69.2%) of these cases with stage 3 A or higher, these findings indicated that most cases presented with more advanced stages. Our findings close to that reported by Rioja et al. (28) who found that 65% of patients had advanced stage (III and IV) at diagnosis. The higher proportion of advanced stages could possibly be due to difficulty in accessing the imaging and biopsy for early detection of the disease or due to late presentation of patients particularly in asymptomatic cases where it has been reported that almost 30% of thymomas are asymptomatic or have non-specific symptoms that mislead the early diagnosis. Additionally, the clinical diagnosis of thymoma is not always easy and hence it must be supported by accurate imaging (25). In our study we analyzed the association between types and stages of thymoma from one side against other variables from the other side; with regard to the association with age, we significantly found that type A was associated with younger age where the mean age of patients with this type was 30.6 ± 7.4 years compared to those with other types with a mean age ranged between 40 and 56.2 years. In our study, patients with type B2, Thymic Carcinoma and those with type AB were the older patients with a mean age of 56.2, 56.1 and 55.3 years, respectively, with a significant difference compared to patients with other types, ($P<0.05$). Conversely, Nam et al. (29) found that patients with type A was older than those with other types and thymic carcinoma, where Nam et al found that patients with type A thymoma had a mean age of 63 years , however, the mean age of patients in other groups in Nam's study was close to our findings where they found that the mean age of patients with type AB was 54 years, in type B1 was 49 years, and in type B3 it was 50 years, while the oldest group was thymic carcinoma patients(>60 years). (29). Another study conducted by Weis et al. found that patients with type A had a mean age of 64 years and those with type AB a mean age of 57 years, that study concluded that Type A and AB were significantly occurred in older age than other thymomas (1). The lower mean age of patients with type A in our study compared to

other studies may be attributed to the differences in the sample size and variation in the diagnostic facilities of different institutions where these studies were performed in addition to the longer duration of these studies. However, our findings regarding other histologic types according to age are close to that of previous studies (1,29). In our study we did not find a significant difference in the mean age of patients across different stages of thymoma which reflected that stage of disease mainly related to other factors other than age of the patients such as time of detection and diagnosis of diseases where the late detection lead to more advanced stage at time of diagnosis. Our findings agreed the findings of Guleria et al. who found no significant differences in the mean age of patients across the different stages (30). In the present study the association of sex was neither significant with types nor staging of thymoma. Despite that our finding consistent with multiple previous studies, however, some earlier studies documented that females more likely to have thymic carcinoma than other types of thymic epithelial tumors compared to males (21,28–30). In contrast to our study, Guleria et al. found that men were more likely to have more advanced stages than women (30). With regard to the association between types and stage of disease we performed a cross-tabulation and found no significant variation in the staging of disease across the different types. Similar findings also reported in previous studies, however, Guleria et al. (30) found that patients with type B thymoma had more advanced stages than those with type A and AB. So as, Weis et al. found lower stage in type A and AB and higher stage in type B thymomas (1). In the present study we have 8 patients with MG and most of them were females with type B3 thymoma, this reflected that type B3 thymoma associated with MG, however, we could not statistically proved this association because we have only 8 patients and could not be statistically analyzed. Nonetheless, Okumura et al. documented that MG often associated with type B3 thymoma (31). Velasco et al.(32) found higher rate of MG in patients with type B thymoma . However, all types of thymoma can be accompanied by MG (33). The discrepancy in some findings among different studies and ours, could be attributed to smaller sample size in our study where we were unable to include larger sample size due to shortage in the duration of our study and rarity of the disease under study; thymoma is one of the rare malignancies that contributed for only 0.2-1.5% with an estimated annual incidence of only 0.13 – 0.32 per 100,000 population (25). Therefore we

suggest further studies with large sample size and include large number of resection specimen for proper typing.

5. CONCLUSIONS

In our study ,the most frequent WHO type was B3 thymoma .There was significant correlation between patients age and WHO types . most cases presented at high stages .myasthenia gravis was the only paraneoplastic syndrome included in this study

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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