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Research Article

Thymomas: Analysis of Histological Subtypes and Staging in Patients with Surgical Treatment in Two Reference Centers in Argentina

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ARTICLE INFO

Article history:
Received: 5 July, 2021
Accepted: 21 July, 2021
Published: 2 Aug, 2021

Keywords:
Thymomas
TNM staging
histologic subtype

ABSTRACT

Background: Thymomas are a heterogeneous group of tumors which represent the most frequent tumor of the anterior mediastinum.

Aims: To describe the clinical, histological, surgical and oncological characteristics of a cohort of patients with a diagnosis of thymoma surgically treated in two centers in Argentina and to evaluate the possibility of retrospectively implementing the 8th edition of TNM staging.

Materials and Methods: 180 patients with thymoma surgically treated over a period of 41 years were studied. The following variables were analysed: age, sex, presence of myasthenia gravis at diagnosis, Masaoka staging (1994), TNM staging of thymus tumors, Histological classification (WHO 2015), neoadjuvant treatment with chemotherapy, post-operative radiation treatment and clinical evolution of myasthenia gravis defined according to the modified Osserman classification.

Results: 96 men and 84 women were analysed. Median age 51 years (range 13-85). 85% of the patients analysed came from the public sphere. When analysing the institutional distribution by Masaoaka-Koga stage and TNM, a higher proportion of stages I was observed for both staging systems. Most myasthenic patients belonged to the WHO B2 histological classification (49%, p=0.04) and 15 patients received neoadjuvant treatment prior to surgery to improve the chances of resection, most of them classified as stages III of Masaoka (p=0.002) or IIIa of the TNM stage (p=0.001). 74 (46%) cases received post-operative RT when they presented Masaoka Koga stages II (p=0.000) and IIIa or more advanced TNM staging (p=0.000). 76% of the patients presented remission or stability of symptoms after surgical treatment and only 3/6 died due to myasthenic crisis in the immediate post-operative period.

Conclusion: As reported in the literature, we have observed a higher frequency of B2 thymomas and their association with Myasthenia gravis. The histological criteria of the WHO 2015 classification, based on the ITMIG recommendations, favour precision in the definition of subtypes. The retrospective implementation of the 8th edition of TNM staging highlights the need to standardize protocols for pathological and surgical studies.

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Introduction

Thymomas are thymic epithelial neoplasm characterized by thymus-like organoid differentiation. According to the morphology of the epithelial cells, the proportion of non-neoplastic lymphocytes and similarity with the normal thymus, they are classified into histological subtypes A, AB, B1, B2 and B3 [1]. Thymomas represent the most common tumor of the anterior mediastinum, contribute with 21-50% of all anterior mediastinal masses in the adult population, have low incidence and, the age at the time of diagnosis is 40 to 60 years, with the same distribution by gender.

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http://dx.doi.org/10.31487/j.COR.2021.08.01

An initial review of our casuistry published in 2006 revealed that in a period of 30 years, 482 mediastinal lesions were surgically treated, of which 174 were malignant [2]. Of these, 102 had a thymoma diagnosis, 74% of which had associated myasthenia gravis at the time of diagnosis. Myasthenia gravis is the paraneoplastic syndrome most frequently associated with Thymic epithelial tumors (TET), followed by red cell aplasia and hypogammaglobulinemia. However, there is a significantly larger group of autoimmune diseases linked to this pathology that should not be underestimated.

Aims

To describe the clinical, histological, surgical, and oncological characteristics of a cohort of patients with thymoma surgically treated in two centers specialized in thoracic malignant diseases in Argentina and to evaluate the possibility of retrospectively implementing the 8th edition of TNM staging.

Material and Methods

A retrospective, descriptive study was conducted on 180 patients surgically treated from January 1972 to November 2019. In all of them, the presence of subclinical myasthenia gravis was investigated, if symptoms were not manifested at the time of diagnosis. Whenever the thymoma was resectable, associated or not with myasthenia gravis, upfront surgery was performed by sternotomy in the first years, followed by the minimally invasive approach (Videothoracoscopy or subxiphoid) in the last 10 years. In those cases, in which the mediastinal masses were large and simulated invading surrounding structures, a surgical biopsy was chosen, and when the diagnosis of thymoma was confirmed, neoadjuvant treatment was started to improve the possibility of complete resection. The schemes of chemotherapy were based on cisplatin plus cyclophosphamide, adriamycin and corticosteroids. The indication of post-operative radiotherapy has been based on capsular invasion and, therefore, indicated in Masaoka stages II onwards. The following variables were analysed: age, gender, presence of myasthenia gravis at the time of diagnosis, Masaoka-Koga staging of the original tumor, TNM Staging according to the proposal of the IASLC 8th edition, WHO Histological Classification 4th edition, oncological treatment and clinical evaluation of Myasthenia according to the modified Osserman classification.

Because the interval of time is wide, TET had to be staged retrospectively according to the data recorded in the pathological reports, adjusting by the information provided by the Masaoka Koga post-surgical staging system. There is no record of lymph node sampling, because historically no lymph node survey was indicated in this pathology. Therefore, the progression by stages was to be determined by the progression in the T-descriptor or the presence of local or distant metastases. Since the cases were treated in both: public and private health systems, both were compared for each of the variables analysed.

Statistical Analysis

The continuous variables were compared with the student's test or the Wilcoxon test according to their distribution and chi square test for categorical variables, establishing a value of $p \leq 0.05$ as statistically significant for a two-tailed test.

Results

Ninety-six male and 84 female patients were analysed. Median age 51 (range 13-85) There was no difference in age, presence of Myasthenia Gravis, Masaoka Koga stage or health care system by gender. Eighty-five percent of the cases were treated in the public health care versus 15% that were treated in the private setting. Because the Hospital de Rehabilitación Respiratoria Maria Ferrer is a Myasthenia Gravis reference center, there is selection bias in the analysed cohort (Tables 1 & 2).

Table 1: Clinical features of 180 patients who underwent thymoma treatment.

Variable	Male	Female	Total	p
Gender	96	84	180	-
Age(median and rank)	53 (20-85)	49.5 (13-80)	180	0.64
MG				
-Yes	54 (57%)	54 (65%)		
-No	41 (43%)	29 (35%)	180	0.322
-N/D	1	1		
Institution				
-HRRMF	85	69	180	0.210
-IAF	11	15		
Masaoka-Koga				
-I	39	40		
-II	19	29	180	0.56
-III	24	16		
-IV	13	7		
-N/D	1	.		

MG: Myasthenia Gravis; HRRMF: Hospital de Rehabilitación Respiratoria Maria Ferrer; IAF: Instituto Alexander Fleming; N/D: No Data.

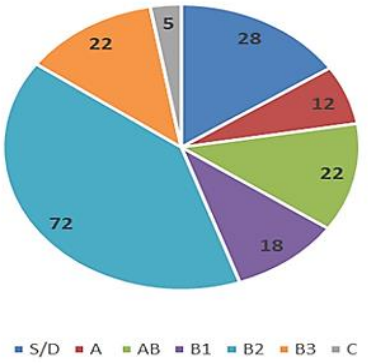
Table 2: Institutional distribution by Masaoka-Koga and TNM stages.

	HRRMF (n, %)	IAF (n, %)	P
Masaoka-Koga			
-I	69(45%)	10(39%)	
-II	34(22%)	5(19%)	**0.388**
-III	35(23%)	5(19%)	
-IV	14(9%)	6(23%)	
-N/D	1(1%)	0	
T.N.M			
- E I	89(58%)	15(57%)	
- E II	0	0	
- E IIIa	19(12%)	2(8%)	**0.005**
- E IIIb	1(1%)	0	
- E IV	0	3(12%)	
- N/D	44(29%)	6(23%)	
Subtotal	154(85%)	26(15%)	
Total	**180(100%)**		

HRRMF: Hospital de Rehabilitación Respiratoria Maria Ferrer; IAF: Instituto Alexander Fleming; N/D: No Data.

I Institutional Distribution by Stage and WHO Histological Classification

The analysis of the distribution by stages of Masaoka Koga shows a polarization towards the early stages, concentrating stages I and II more than 50% of the treated cases. However, in the comparative analysis, no significant differences were found by stage, for each institutional category analysed (p=0.388). Although the distribution by stages according to TNM staging system, shows the same trend, there is a significant difference in distribution by stages, with zero cases in stage II and a large percentage of cases with undetermined stage for both institutions (p=0.005) (Table 2). According to the 2015 WHO classification, the most frequent histological subtype diagnosed was B2, with 72 cases (40.22%). The rest of the histological spectrum account between 6% and 12% of the cases, and the type C (thymic carcinoma poorly differentiated) was diagnosed in 5 patients (less than 3% of the total) (Figure 1).



A

Histologic Type	Frecuency	%
N/D	29	15.64
A	12	6.70
AB	22	12.29
B1	18	10.06
B2	72	40.22
B3	22	12.29
C	**5**	**2.79**
Total	180	100.00

B

Figure 1: Histologic subtypes and frequency. **A)** WHO histologic Subtype. **B)** Distribution frequency.

Table 3: The relationship between World Health Organization histological type and Masaoka-Koga and TNM clinical stage.

Histological Subtype	Masaoka-Koga P=0.204						8° Ed. TNM P=0.000						
	n	**I**	**II**	**III**	**IV**	**N/D**	**n**	**I**	**II**	**IIIa**	**IIIb**	**IV**	**N/D**
A	**12**	7	3	1	1	0	12	7	0	0	0	0	5
AB	**22**	10	7	4	1	0	22	18	0	1	0	0	3
B1	**18**	11	2	4	1	0	18	18	0	0	0	0	0
B2	**72**	29	22	16	5	0	72	38	0	11	1	0	21
B3	**22**	6	3	8	5	0	22	14	0	4	0	1	3
C	**5**	2	1	2	0	0	5	3	0	1	0	1	0
N/D	**28**	14	1	5	7	1	28	0	0	4	0	0	18

Although the histological classification system and the staging systems evaluate different aspects of TET, when comparing them, it is observed that B2 thymomas are more frequently associated with early stages of both staging systems, and that association reached statistical significance in the proposal of the 8th edition of the TNM (Table 3). In addition, 108 patients had myasthenia gravis at the time of diagnosis. Of these, 52 (49%) belonged to the WHO B2 histological subtype.

II Chemotherapy, Radiotherapy and Clinical Response of Myasthenia Gravis after Treatment

Twenty-one patients received chemotherapy prior to surgery, 85% of whom belonged to Masaoka Koga stages III and IV, and 39% to stages III and IV of the TNM staging system. On the other hand, 79 (45%) of the patients received post-operative radiotherapy (RT). Ninety-six belonged to Masaoka stages II onwards, while this percentage reached 27% among the advanced stages of TNM. Nevertheless, a high number of patients with Stage I of the TNM staging system received post-operative RT.

Of the 108 patients with myasthenia gravis, information about the clinical course of this disease after the surgery was obtained in 101 cases. Thirty-eight patients (48%) presented complete clinical remission of the symptoms during six years after surgery, while 22 (28%) showed stability of the symptoms, defined as no need to increase the medication dose. Thirteen patients (16%) presented progression of symptoms, which caused death in one of them and six presented myasthenic crisis; all of them dying from this cause (3 in the immediate post-operative period). No overall survival or disease survival analysis was done in this case series, and the interest was focus on the demographic characteristics of the population analysis.

Discussion

Thymic neoplasms are the most common tumors of the anterior mediastinum, generally have an indolent course, and most patients survive for many years [3]. Historically, the Masaoka staging, modified by Koga, has been used to define the local or distant extension of these tumors. On the other hand, ITMIG, in an attempt to establish a common language for staging these tumors, and, with the aim to defining more accurately the prognosis of the different descriptors, proposed in 2014 the use of a staging system that based on the T, N, and M descriptors that are commonly used for lung cancer staging [4, 5]. The highlight of this new classification is that the T1 descriptor encompasses Masaoka stages I and II and is only sub classified into T1a or T1b according to the mediastinal pleura invasion, since the latter has produced a drop in survival curves. On the other hand, it incorporates a concept that was overlooked in the previous staging system: the lymph node involvement, in two anatomical levels: N1 (stations 1, 3a, 5 and supradiaphragmatic/phrenic of the IASLC map) and N2 (stations 2,4, 5, 7,10, internal mammary lymph node map of the IASLC). Based on this, a systematic lymph node survey is proposed at one level or another, according to the stage of the tumor. Finally, the concept of N3 is not incorporated, instead the concept of loco-regional (M1a) or distant (M1b) metastasis. The result, after the distribution by stages, is a clear definition of the overall survival curves and the recurrence-free survival, both for patients with complete resection, and for those with any type of resection status [5, 6].

The implementation of TNM staging system in this cohort of patients has forced the retrospective reclassification of more than 130 patients, and this explains that between 23-29% of the patients could not be reclassified. Our work has been able to establish the T and M descriptor retrospectively, with the histopathology records, but not the N descriptor because in most cases we did not perform a systematic lymph node sample. Because the Hospital de Rehabilitación Respiratoria María Ferrer is a reference center for the diagnosis and treatment of Myasthenia gravis, it has concentrated a greater number of cases in general (85% vs 15% in private practice). This fact has made it possible to diagnose thymomas in early stages due to its systematic screening in patients with this pathology. Although this trend has not reached a significant difference in the distribution by Masaoka-Koga stages according to the institution of care, it was observed that the distribution frequency reached a statistically significant difference when considering the TNM staging. However, it is important to note the absence of stages II in the retrospective classification, as well as the significant number of unclassified cases, which may affect the observed results.

WHO Classification of thoracic tumors was updated recently, but no changes were done in classification, nomenclature and defining criteria of thymoma and thymic carcinoma [1]. So, the analysis of histopathological findings in this study are still valid. The most frequent histological subtype was B2, of the WHO histological classification. It was also the most frequently associated with the presence of Myasthenia gravis. This finding, as well as its association with early stages, as previously explained, agrees with previously reported by Girard *et al.* [3]. Weis *et al*. have shown in a retrospective analysis of 4221 cases that the importance of the histological subtype as an independent variable of poor prognosis, adjusted for stage and resection status, observing a sustained increase in the percentage of recurrences as it progresses from subtype A to B3 [7].

Lesions with spread to mediastinal structures were referred to neoadjuvant treatment with chemotherapy. Although the time analysis is more than 40 years, the treatment has not differed significantly, based on cisplatin schemes. In our series, 21 of 180 patients underwent neoadjuvant treatment, the majority with advanced Masaoka Koga stages. Radiation treatment decision is based on stage, resection status (R0 vs R1) and TET histological subtype: stages IIb onwards, RO and WHO subtypes B2 and B3 should be considered for adjuvant treatment. Patients with incomplete resections, regardless of the above variables, should also be considered for post-operative RT. In the case of thymic carcinomas, once surgical resection has been performed, regardless of the stage, treatment with chemo and radiotherapy should be considered, due to their more aggressive biological behaviour [3].

A small percentage of these tumors are thymic carcinomas (TC), which are generally diagnosed in advanced stages, and present aggressive behaviour, with 5-year survival rates ranging from 28-67% [8, 9]. Its exact incidence is unknown, but it can be estimated at around 1 to 3 cases per 10 million inhabitants [10-15]. Hsu *et al.* studied the incidence of thymic epithelial tumors (TETs) in the United States, using the database of the National Cancer Institute (SEER) and the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Control Disease Prevention. Of the 13,586 patients diagnosed with TET, 2772 (20.4%) had a diagnosis of TC [16]. According to epidemiological data published by Ahmad *et al.*, the average age of the population with this condition is 56 years and 39% of cases are women [17]. CTs have a more aggressive biological behaviour and must be clearly differentiated from thymomas. Therefore, in most series, at the time of diagnosis, they present advanced stages, which represents a therapeutic challenge. Kondo analysed 1,320 patients with thymic epithelial tumors (TTS), of whom 111 had a diagnosis of CT. Of these, 10 patients (5.3%) were in Masaoka-Koga stage I, 11 in stage II (5.9%), 74 in stage III (39%), 26 (13.9%) in stage IVa and 61 (32.6%) in stage IVb [9]. In our series, only 5 cases presented a post-operative diagnosis of thymic carcinoma. None required neoadjuvant treatment, although due to the pathological finding, they were referred to radiation treatment.

The present work compares the casuistry of two centers: Hospital de Rehabilitación Respiratoria Maria Ferer, which belongs to public health care, and IAF where the same team develops its private practice. Our first publication on 482 mediastinal tumors when the cases treated in private practice were not included-revealed that 102 of them were thymic epithelial tumors of which 74% had myasthenia gravis associated (higher than 30% described in the literature) [3]. In the current work, it is important to highlight the vast majority of cases treated at the public health center, which far exceeds the private practice with 85% of cases. This data comes from the fact that the María Ferrer Hospital is a reference center in the diagnosis and treatment of Myasthenia gravis and this has allowed a significant number of thymomas in early stages to be diagnosed. Thymomas diagnosed in private practice were an incidental finding in a tomographic study for another cause and most of them presented in advanced stages, requiring multimodal treatment. The importance of focusing the attention of certain pathologies in referral centers has shown greater diagnostic effectiveness and a reduction in the

mortality rate and complications [18]. Although this has not been a reason for study in the present work, it is important to conclude that the particular specialization of the hospital has been of benefit to patients since it has allowed a timelier diagnosis and treatment.

Conclusion

In the series of patients with a diagnosis of thymoma presented, we found similar results to those already described: a higher frequency of B2 thymomas and their association with Myasthenia gravis. The histological criteria of the WHO 2015 classification, based on the ITMIG recommendations, favour precision in the definition of subtypes. The retrospective implementation of the 8th edition of TNM staging highlights the need to standardize protocols for pathological and surgical studies. The care of this pathology in referral centers allows an early diagnosis and adequate treatment.

Conflicts of Interest

None.

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