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Epidemiological, Clinical, Therapeutic and Evolutionary Aspects of Thymic Epithelial Tumors: Experience of the National Institute of Oncology, Rabat

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Abstract— **Background: Thymic epithelial tumors are rare mediastinal tumors with an annual incidence of 0.15 cases per 100.000. The basis of treatment depends on the stage and histological subtype. The aim of our study is to shed light on the epidemiological, clinical, therapeutic and evolutionary aspects of thymic epithelial tumors.**

Methods: This is a retrospective study of a series of thymomas and thymic carcinomas collected over a period of 4 years from January 2019 to December 2022, involving 35 cases of thymic epithelial tumors (TET) listed and managed within: Medical Oncology Department, National Institute of Oncology (INO), Rabat; Thoracic Surgery Department, Ibn Sina University Hospital, Rabat; Radiotherapy Department, Mohammed V Military Hospital, Rabat.

Results: Thymic epithelial tumors represent an annual incidence of 8.75 cases per year in our department. Of the 35 patients in our series, 16 were male (45.7%) and 19 female (54.3%), giving a sex ratio (M/F) of 0.84. The age of patients on admission ranged from 20 to 72 years, with a median age of 53. The disease was discovered in 10 patients (28.57% of cases) during the etiological workup for myasthenia gravis. (54.28%) had one or more symptoms suggestive of mediastinal involvement.

The predominant histological type in our patients was B2 thymoma (29% of cases) and there was a significant positive correlation between histological type and Masaoka stage. Indeed, invasion according to Masaoka stage was significantly greater in cases of increasingly aggressive histology.

28 cases (80%) in our series underwent surgery and negative resection margins with pathologically confirmed (R0) were achieved in 14 (50%) patients. 6 patients received radiotherapy as an adjuvant to surgical resection. Besides, induction chemotherapy was performed in 10 patients (28.5%), eight of which used triple therapy (CAP): Cyclophosphamide, Adriamycin, Cisplatin, and one patient received neoadjuvant CAP-based chemotherapy in the first line, and only one patient received Carboplatin and Paclitaxel regimen.

Conclusion: Thymic tumors are rare mediastinal tumors. Thymomas are mixed epithelial and lymphocytic tumors of complex histological classification, which may be associated with autoimmune manifestations. Pre-therapeutic workup and tumor staging help determine treatment strategy. Surgical resection is the cornerstone of treatment for resectable thymic tumours and interesting therapeutic possibilities are ongoing particularly with the advent of targeted therapies and immunotherapy.

***Index Term*- Thymic tumour, Thymoma, Thoracic oncology, Clinical characteristics, Chemotherapy, Therapeutic strategy.**

I. INTRODUCTION

Thymic epithelial tumors (TETs) are rare tumors, encompassing a heterogeneous group of tumors with variable evolution and prognosis. No single risk factor is clearly implicated in the development of TETs, particularly infectious or environmental. Often discovered incidentally, TETs are associated with autoimmune diseases.

Annual incidence rate ranging between 0.9 and 2.3 per million [1].TETs are classified into thymomas (TMs) and thymic carcinomas (TCs) based on the World Health Organization (WHO) histologic classification [2–4], and 4 molecular subtypes of TETs has been identified based on a specific molecular aberrations rather than histological properties according to The Cancer Genome Atlas (TGCA) [5].Thymomas are categorized into five distinct subtypes (A, AB, B1, B2, B3), a classification based on the morphological characteristics of the epithelial cells and the prevalence of non-neoplastic lymphocytes[6,7]. The prognosis of patients with thymomas (TMs) declines progressively from type A to type B3 TMs [8]. Thymic carcinomas constitute about 10-12% of thymic malignancies, with more aggressive disease, high invasion and worse prognosis [5,9–12].

The important role of thymus in the development of the immune system explains the high rate of autoimmune disease in TETs. Regardless of the disease's stage, around 40% of thymomas have an associated autoimmune disease[13] , and the most common paraneoplasic syndrome is myasthenia gravidis (MG) which develops in 30% of thymomas cases [14,15]. The incidence of myasthenia gravidis (MG) varies according to histological subtype [16,17]. About 10% to 15% of Tms patients have paraneoplasic conditions rather than myasthenia, and 4-7 % of myasthenic patients with thymoma have more than one paraneoplasic syndrome[14–16,18,19].

The primary therapeutic approach for TETs is upfront surgery, and the most significant prognostic factor is complete resection (R0) [18]. After radical surgery, the 5-year overall survival rate for TETs is 90% for stages I and II, 60% for stages III, and less than 25% for stages IV[16,20,21].

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Chemotherapy, radiotherapy or concomitant chemoradiotherapy as an adjuvant strategy can be utilized based on stage, margin infiltration and histology subtype[16,19–22].

Their therapeutic management, still poorly codified, is the subject of growing interest. The aim of this study is to review the experience of the oncology department at the Rabat National Institute of Oncology with TETs, to report on their main epidemiological, pathophysiological, clinical and evolutionary features, and to describe the different therapeutic modalities administered and their efficacy.

II. MATERIALS AND METHODS

This study is carried out retrospectively over a period of 4 Years from January 2019 to December 2022, involving 35 cases of thymic epithelial tumors (TET) listed and managed within: Medical Oncology Department, National Institute of Oncology (INO), Rabat; Thoracic Surgery Department, Ibn Sina University Hospital, Rabat; Radiotherapy Department, Mohammed V Military Hospital, Rabat.

A. Eligibility

Inclusion criteria for our study were: diagnosis of thymic epithelial tumour (either thymoma or thymic carcinoma), histological diagnosis was confirmed on a scan-guided biopsy or surgical excision specimen, adult individuals (>18-year-old) at the time of diagnosis, and patients who have benefited from additional examinations to establish tumour classification and staging.

B. Collected Data

We collected epidemiological, clinical, paraclinical and anatomopathological data, as well as therapeutic and evolutionary modalities, either from the electronic files of the "Enova Santé" software in the INO medical oncology department and the "Green Cube" software in the CHUIS thoracic surgery department, or from archived paper files in the HMIMV radiotherapy department.

C. Statistical analysis

Data were entered and statistically analyzed using Microsoft Office Excel for descriptive data analysis and SPSS for survival calculations.

Survival was calculated from the date of diagnosis to death or the end of follow-up, and was estimated using the Kaplan-Meier method. Differences in survival between groups were compared using the log rank test.

Categorical variables were compared using the Chi-2 test. Statistical significance was set at $P = 0.05$.

D. Results

Patients' characteristics

In our series, most patients were female, younger than 65 years old, and the most frequent paraneoplasic syndrome was MG found in 31% of cases.19 patients in our series (54.28%) had one or more symptoms suggestive of mediastinal involvement, and in 10 patients (28.57%), the disease was discovered during the etiological work-up for myasthenia gravis. Incidental findings were noted in 6 patients (17.14%) on thoracic CT scans as part of a pre-therapeutic work-up, or during covid-19 infection.

Histological diagnosis was made after surgical excision in 24 patients (68.57%) or transparietal biopsy under computer tomography CT in 11 cases (31.43%) as a part of patients who presented with tumors requiring pre-therapeutic histology and neoadjuvant treatment prior to curative surgery.

Histological analysis of the 35 TETs according to WHO 2015 recommendations established the distribution shown in Table 1. There were 30 thymomas and 5 thymic carcinomas and the predominant histological type in our patients was B2 thymoma (29% of cases). The classification commonly used in our patients was that of Masaoka. Twenty-eight TETs could be classified with certainty according to Masaoka's classification, integrating scanographic and histological data. Seven others, corresponding to tumors for which exact staging was not available. Of the 28 definite TETs, 7 were stage I (20%), 10 stage II (28.5%), 7 stage III (20%), 3 stage IVa (8.6%) and 1 stage IVb (2.9%).

There was a significant positive correlation between histological type and Masaoka stage. Indeed, invasion according to Masaoka stage was significantly greater in cases of increasingly aggressive histology (P value = 0.001 < 0.05).

Table I: *Epidemiological, clinical and anathomopathological characteristics*

Characteristics	n	%	Characteristics	n	%
Sex			Incidentally	6	17
Male	16	46	**Intrathoracic extension**		
Female	19	54	Pulmonary invasion	1	3
Age at diagnosis			Pericardial invasion	2	6
20-35 y	6	17	Pleural invasion	2	6
35-50 y	10	29	Major blood vessels invasion	5	14
50-65 y	17	48	Mediastinal adenopathy	4	11
65-80 y	2	6	**General signs**		
Median age by histological type			Altered general condition	2	6
Thymoma	48.8		Asthenia	2	6
Thymic carcinoma	50.4		**Histological diagnosis**		
Background			Surgical excision	24	68.57
Myasthenia	11	31	Transparietal biopsy puncture	11	31.43
Smoking	7	20	**Histological type OMS 2015**		
Familiar Cancer	1	3	Thymoma A	2	6%
Thyroidectomy	2	6	Thymoma AB	4	12%
Arterial hypertension	5	14	Thymoma B1	7	20%
Diabetes mellitus	4	11	Thymoma B2	10	29%
Asthma	2	6	Thymoma B3	6	18%
Circumstances of discovery			Thymic carcinoma	5	15%
Mediastinal involvement(s)	19	54	**Masaoka staging**		
Chest pain	9	26	I	7	20%
Dyspnea	6	17	II	10	28.5%
Cough	5	14	III	7	20%
Dysphonia/Dysphagia	2	6	Iva	3	8.6%
SVC	1	3	IVb	1	2.9%
Etiological assessment of myasthenia	10	29	Undetermined	7	20%

SVC: superior vena cava

Therapeutic modalities

Therapeutic characteristics for the entire series are shown in Table 2.

28 cases (80%) in our series underwent surgery. 21 patients (60%) underwent immediate surgery, while 7 patients (20%) underwent surgery after neoadjuvant chemotherapy.

The vast majority of patients underwent median sternotomy (n = 21, 75%). Six patients were operated on by videothoracoscopy (VATS), including 2 converted to median manubritomy due to the adherent nature of the tumor. Only one patient underwent thoracotomy.

All patients underwent surgical resection with curative intent. Negative resection margins with pathologically confirmed (R0) were achieved in 14 (50%) patients. Otherwise, 10 (36%) and 4 (14%) patients had microscopic residual disease (R1) and macroscopically incomplete resection (R2) respectively.

A total of eight patients received radiotherapy. It was indicated as an adjuvant to surgical resection in 6 patients. The average dose delivered to the target tumour volume was 55.5 Gy, with a total dose of between 50 and 60 Gy and a fractionation of 2 Gy at a rate of 5 fractions per week. In only one case radiation was given concomitantly with chemotherapy. Another patient with a thymoma deemed unresectable underwent radiotherapy after neoadjuvant chemotherapy.

Chemotherapy was administered to a total of 13 patients (37.1%). Induction chemotherapy with the aim of achieving tumor response and secondary surgical resection was performed in 10 patients (28.5%). The protocol used in 8 cases was based on triple therapy (CAP): Cyclophosphamide, Adriamycin, Cisplatin, and one patient received neoadjuvant CAP-based chemotherapy in the first line, followed by PC-based chemotherapy in the second line after progression. Only one patient with cardiovascular comorbidities received double therapy (DBT) comprising Carboplatin and Paclitaxel.

Palliative chemotherapy was chosen in 2 cases (5.7%) of our series. Both were thymic carcinomas.

One patient received exclusive Carboplatin and Paclitaxel PC-based chemotherapy and one patient received Vincristine.

Otherwise, only one case of thymic carcinoma (2.9%) deemed unresectable after neoadjuvant chemotherapy received concomitant chemotherapy with radiotherapy of 3 courses of Carboplatin and Paclitaxel (PC).

Table II: **Therapeutic characteristics in our hospital series**

Characteristics	*n*	%	Characteristics	*n*	%
Modality			Stage III B3 thymoma	1	
Surgery	28	80	Stage I B3 thymoma	1	
Radiotherapy	8	22.8	Stage III B2 thymoma	2	
Chemotherapy	13	37.1	Stage II B2 thymomas	2	
Surgery type			Stage II B1 thymoma	1	
Sternotomy	21	75	**Chemotherapy**		
VATS	6	21	Neoadjuvant	10	28.5
Thoracotomy	1	4	Adjuvant	0	0
Surgical margins			Palliative	2	5.7
RO	14	50	Concomitant	1	2.9
R1	10	36	**Protocoles**		
R2	4	14	CAP	8	22.8
Radiotherapy indications			PC	3	8.6
Stage III thymic carcinoma	1		CAP+PC	1	2.9

Table III: *Chemotherapy modalities and their therapeutic response*

Chemotherapy indications	Protocoles	*n*	Radiologic response
Neoadjuvant	CAP	8	6 regression
			2 progression
	PC	1	progression
	CAP+PC	1	progression
Palliative	PC exclusive	1	progression
	Vincristine	1	Stability
Concomitant	PC	1	progression

Overall survival and progression-free survival

Survival analysis was interrupted due to the low median follow-up and the large number of patients lost to follow-up. Overall survival and progression-free survival data were analyzed for 26 patients (74%), while 26% could not be followed up.

Median progression-free survival was 38 months, with a maximum of 48 months and a minimum of 3 months. In our series, five deaths occurred (3 thymomas and 2 thymic carcinomas), corresponding to an overall survival rate of 80.8% at 4 years. The median overall survival was not reached (overall survival data not yet mature).

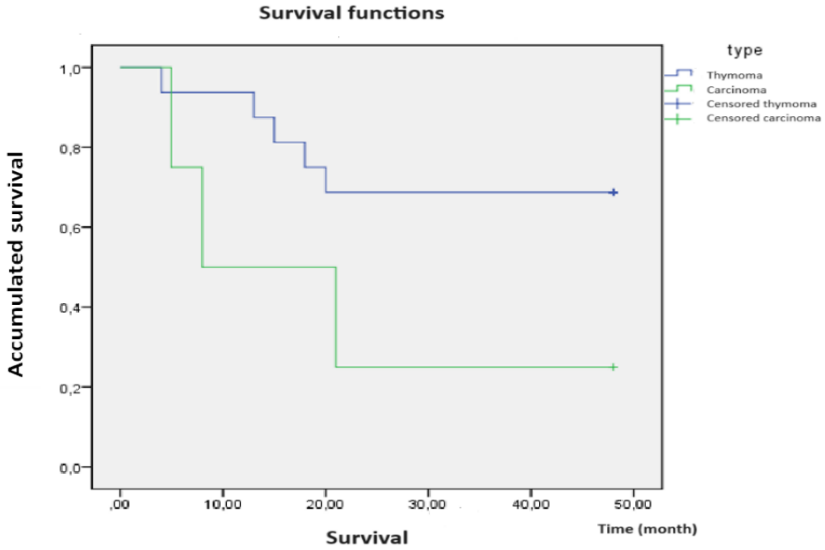

Figure1: *Progression-free survival by histological type*

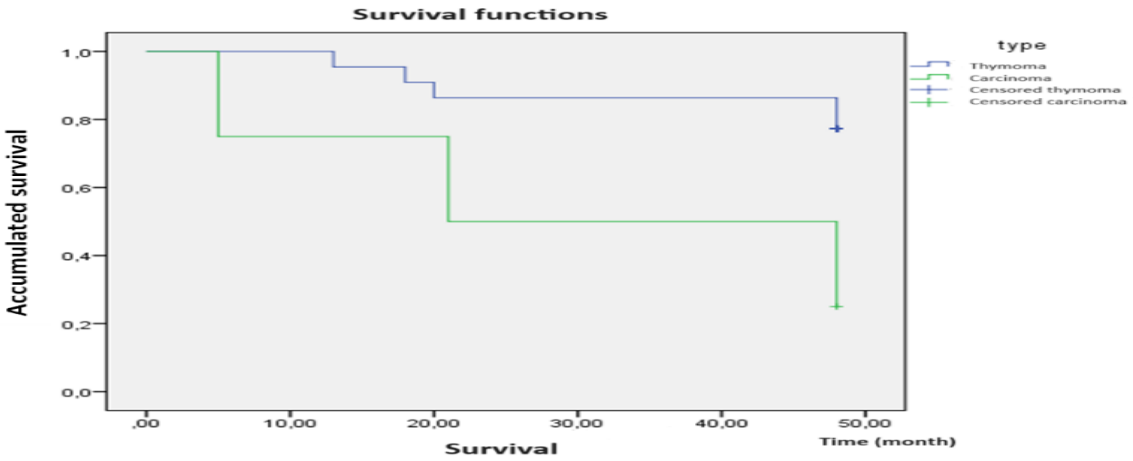

Figure2: *Overall survival by histological type*

III. DISCUSSION

Over a four-year period, 35 cases of thymic epithelial tumors were recorded, divided into 30 thymomas and 5 thymic carcinomas. This represents an annual prevalence of 8.75 cases per year, a figure that testifies to the rarity of this tumour pathology.

In our sample, we had 16 men (45.7%) and 19 women (54.3%), i.e. a sex ratio F/M = 1.19. This slight female predominance was also noted in a recent study in France[23].

Among the patients studied, the age group most affected was between 50 and 65 years of age, with 17 patients (48.6%). The mean age was 53 years. The same age range was found in a study of 1,470 thymomas[24]. It is certain that this is a pathology of the young adult.

Myasthenia gravis was found in 11 patients, corresponding to almost a third of our series. According to Pert Martinovsky, between a third and a half of patients with thymoma have myasthenia, but only 10% of myasthenics have thymoma[25]. No patient had presented with other autoimmune manifestations.

Our series was marked by a delay in diagnosis, with a mean delay between onset of symptoms and consultation of 10.37 months. This may be explained by the slow evolution of this type of tumor.

The predominant histological type in our patients was B2 thymoma. Histological type was correlated with Masaoka stage in our study. Thus, type A or AB thymomas are more frequently stage I or II at diagnosis, whereas B3 thymomas and thymic carcinomas are more frequently stage III or IV. This correlation has already been mentioned in the literature[26].

The therapeutic management of our TETs was broadly in line with the international recommendations, with surgical management in 80% of cases, most often R0, the main prognostic factor for the disease. With regard to radiotherapy, doses were not always standard. As with the treating centers, chemotherapy regimens varied, but in most cases were based on a platinum regimen. Based on retrospective and prospective phase II studies, platinum-based chemotherapy remains the gold standard in first-line treatment, with ORR for thymomas (Tms) ranging from 75 to 92% for CAP and CAP-vincristine chemotherapy[27–29]. The Paclitaxel-carboplatin regimen is considered an option for TETs, with an ORR of 43% for Tms and 22% for Tcs [30,31].

No patient benefited from immunotherapy. The high expression of PDL1 encourages the use of immunotherapy in TETs[32], pembrolizumab showed an ORR of 23% in thymic carcinomas with stable disease in 53% of cases [33].

Other studies were testing immunotherapy alone for which data is not yet available (MSB0010718C, NCT04321330).

Combinations of anti PD1-PDL1 with anti CTLA4 or antiangiogenic agents are being evaluated in several clinical trials (NCT03134118, NCT03463460, NCT03583086, CAVEATT [34], NCT04710628). New drugs are emerging such as selinexor, XPO-1 inhibitor, (NCT03193437, NCT03466827), and epacadostat or SO-C101 in monotherapy or in association to pembrolizumab (NCT02364076, NCT04234113).

Survival was influenced by histological type. There was a trend towards better survival in thymoma versus thymic carcinoma. This was clear in several studies[35].

All in all, the 35 TETs making up our series covering the period 2019 to 2022 present clinical, histological and prognostic features superposable to those of the TETs making up currently published series.

Given the rarity of these tumors, further collaborative studies are essential to better understand the epidemio-clinical profile in Morocco, and the importance of establishing a national registry for the disease.

IV. CONCLUSION

Thymic tumors are rare mediastinal tumors. Thymomas are mixed epithelial and lymphocytic tumors of complex histological classification, which may be associated with autoimmune manifestations. Pre-therapeutic workup and tumor staging help determine treatment strategy. Surgical resection is the cornerstone of treatment for resectable thymic

tumours. The absence of invasion of resection margins is an essential prognostic factor. Post-operative radiotherapy is usually performed in cases of incomplete resection, invasive tumors (stage III) and histologically aggressive tumors (B3 thymoma or thymic carcinoma). Adjuvant chemotherapy has little place.

The prognosis of thymic epithelial tumors is poor in cases of thymic carcinoma. This was also the case in our study. At present, there are interesting therapeutic possibilities, particularly with the advent of targeted therapies and immunotherapy.

Finally, to improve the therapeutic and prognostic results of these patients, we propose to establish prospective studies of thymic tumors and more codified management by a network of expert centers within the framework of multidisciplinary coordination.

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