Clinicopathologic and prognostic factors of thymoma in Tunisia

Particularités clinico-pathologiques et facteurs pronostiques des thymomes en Tunisie

Emna Braham[1], Tarek Kilani[2], Faouzi El Mezni[1].

1- Department of Pathology, Abderrahmen Mami Hospital,
2- Department of Thoracic Surgery, Abderrahmen Mami Hospital. Ariana, Tunisia.

RÉSUMÉ

Prérequis: bien que rares, les thymomes sont les plus fréquentes des tumeurs du thymus de l'adulte représentant environ 20% de l'ensemble des tumeurs médiastinales.

But: présenter les caractéristiques clinico-pathologiques et d'analyser les facteurs pronostiques des thymomes en Tunisie.

Méthodes: de 1993 à 2004, les données cliniques de 40 cas de thymomes ont été compilées et les lames microscopiques reclassées selon la classification de l'OMS des tumeurs thymiques 2004. Le stade clinique adopté était celui de Masaoka. L'analyse de la survie a été déterminée selon la méthode de Kaplan-Meier et le log-rank test a été utilisé pour comparer les courbes de survie. Ces analyses statistiques ont été effectuées par SPSS.

Résultats: il s'agissait de 23 femmes et de 17 hommes âgés entre 14 et 76 ans (âge moyen 51 ans). Histologiquement, ils étaient répartis en: 1 type A, 7 type AB, 6 type B1, 17 type B2, 6 type B3, 2 thymomes micronodulaires à stroma lymphoïde et un métaplasique. Selon le système de masaoka, 10 patients étaient stade I, 11 stade II, 9 stade IIIA, 4 stade IIIb, 5 stade IVa et 1 stade IVb. La survie globale moyenne était de 56 mois. En analyse
univariée, le stade de Masaoka, la résection chirurgicale complète et l'âge étaient des facteurs pronostiques tandis qu'en l'analyse multivariée, l'âge était le seul facteur pronostique. Ni la myasthénie, ni le type histologique n'avaient d'effet sur la survie.

Conclusion : le stade de Masaoka, la résection chirurgicale complète et l'âge sont des facteurs pronostiques prédictifs de la survie.

Mots-clés

Thymome-classification-histologie-pronostic

SUMMARY

Background: although rare, thymomas are the most common tumors of the thymus in adults. They represent about 20% of all mediastinal tumors.

Aim: the aim of this study is to present clinicopathological features of thymomas in Tunisia and analyse the prognostic factors.

Methods: From 1993 to 2004, clinical data of 40 cases of thymomas were compiled retrospectively. Microscopic slides were reviewed and reclassified according to the WHO classification of thymic tumors 2004. Clinical staging adopted was Masaoka system. Analysis of survival was determined by Kaplan-Meier method and log-rank test was used to compare survival curves. These statistical analyses were performed by SPSS.

Results: they were 23 women and 17 males of ages ranging from 14 to 76 years (mean age 51 years). The distribution of histological WHO types was: 1 type A, 7 type AB, 6 type B1, 17 type B2, 6 type B3, 2 cases of micronodular thymoma with lymphoid stroma and 1 case of metaplastic thymoma. According to Masaoka stage, 10 patients were in stage I, 11 stage II, 9 stage IIIa, 4 stage IIIb, 5 stage Iva and 1 stage IVb. The average overall survival was 56 months. Univariate analyses showed that Masaoka stage, completeness surgical resection and age were prognostic factors whereas in multivariate analysis, age was the only prognostic factor. Neither myasthenia gravis nor histological WHO subtypes had effect in survival.

Conclusion: masaoka stage, completeness surgical resection and age are the prognostic factors predicting survival in our series.

Key-words

Thymoma- Classification- Histology- Prognosis.

Although rare, thymomas are the most common tumors of the anterior mediastinum. They are histologically characterized, by a mixture of neoplastic epithelial cells with nonneoplastic lymphocytes, and clinically by indolent growth pattern and variable behaviour.
The aim of this retrospective study is to present clinicopathological features and prognostic factors of thymomas in Tunisia.

METHODS

From October 1993 to October 2004, clinical, radiological data and surgical findings of 40 cases of thymomas were compiled retrospectively from hospital records of the thoracic surgery department. Follow-up continued until January 2005. All patients have chest Roentenogram and thoracic computed tomography scan. All microscopic slides were reviewed and reclassified according to the new World Health Organization histological classification (WHO) of thymic tumors 2004. Immunohistochemical study was available for 28 cases. It was achieved using cytokeratin, epithelial antigen membrane (EMA), CD3, CD20 and CD99. Clinical staging adopted was Masaoka system and was retrospectively performed, based on the review of the pathology and operative notes of the surgeons.
Analysis of survival was determined by Kaplan-Meier method and log-rank test was used to compare survival curves. To determinate prognostic factors, a univariate analysis was performed with a Log Rank test and a multivariate analysis with Cox's proportional hazards regression model was performed. These statistical analyses were performed by SPSS. A *p* value <0.05 was considered to represent statistical significance.

RESULTS

Clinical findings

The tumours occurred in 23 women and 17 males of ages ranging from 14 to 76 years (mean age 51 years). At presentation 4 patients were asymptomatic, incidental finding on chest X-ray and 7 presented with myasthenia gravis (17.5%). Respiratory symptoms were predominant: dyspnea (n =22), chest pain (n=18), cough (n=15) and haemoptysis (n=3). Superior vena cava syndrome was found in 5 cases and general weakness in 11 cases.

Radiological findings

Thirty nine patients had a mediastinal abnormality on chest X-ray: mediastinal opacity (n= 30) and mediastinal enlargement (n=8). A pleural opacity was noted in one case. Chest X-ray was normal in another case.
Chest computed tomography showed an anterior mediastinal mass (n=39), a parietal mass (n=1). The tumour had homogeneous density (n=33) and was heterogeneous (n=6). A vena cava invasion was reported in 5 cases, a pleural effusion in 2 cases and pericardial effusion in one case.

Diagnostic methods

The diagnosis was done on surgical specimen (n= 29). The preferred surgical approach was through median sternotomy (n=17) followed by thoracotomy (n=12).
Biopsy was achieved in inoperable tumours (n=11) through mediastinostomy (n=5) and thoracoscopy (n=6).

Treatment and follow-up

Complete surgical resection was performed in 25 cases. Seven of them received postoperative radiotherapy. Twenty three patients feel well (1 to 4 years). A recurrence was noted in one case, 4 years after diagnosis and one patient was lost for follow-up.
An incomplete surgical resection was achieved in 4 cases (stage III of Masaoka). Two of them received postresection radiotherapy; they feel well 25 and 26 months after; the two other patients had a radio-chemotherapy and were lost of view.
Eleven patients underwent only biopsy because they presented with advanced invasive nonresectable disease. Two of them received radiotherapy (stage IIIa and IIIb), they feel well one year after. Two other patients had radio-chemotherapy (stage IVa and IVb) and one patient had chemotherapy (stage IVa); they were alive 6 months, 6 months and 15 months after retrospectively. For the six other cases who didn't receive adjuvant therapy: two died for respiratory failure and suicide and 4 were lost for follow-up after biopsy (table n°1).

Table 1: Patient's clinical, pathological and treatment characteristics

Characteristic	N
Sex (M vs F)	17 vs 23
Age	51 years (Range 14-76)
Myasthenia gravis	7 (17.5%)
Masaoka stage	
I	10 (25%)
II	11 (28%)
III	13 (32%)
IV	16 (15%)
Histologic type	
A	1 (2.5%)
AB	7 (17%)
B1	6 (15%)
B2	17 (43%)
B3	6 (15%)
MNLS	2 (5%)
Metaplastic thymoma	1 (2.5%)
Surgical treatment	
Complete	25
Incomplete	4
Biopsy	11
Adjuvant therapy	
Radiotherapy	11
Chemotherapy	1
RT+CT	4

MNLS: Micronodular thymoma with lymphoid stroma; RT: Radiotherapy; CT: Chemotherapy

Masaoka staging system

According to Masaoka system, 10 patients were in stage I (25%), stage II (28%), stage IIIa (22%), stage IIIb (10%), stage IVa (13%) and stage IVb (2%) (table n°1).

Pathological features

The tumour size ranged from 4 to with a mean of . Lobulation was found in 26 cases and cystic changes in 8 cases.

The distribution of histological WHO subtypes was: 1 type A (2.5%), 7 type AB (17%), 6 type B1 (15%), 17 type B2 (43%), 6 type B3 (15%), 2 cases of micronodular thymoma with lymphoid stroma (5%) and 1 case of metaplastic thymoma (2.5%) (table n°1).

Correlation myasthenia/Histological subtypes

Myasthenia was associated with 3/7 thymomas type AB, 1/6 type B1, 2/17 type B2, and 1/6 type B3. Thus myasthenia was commonly associated with type AB and B2.

Survival and prognostic factors

The average overall survival was 56 months (figure 1). Univariate analyses showed that Masaoka stage, completeness surgical resection and age were prognostic factors. In fact, patients with stage I and II have a better survival than patients with stage III and IV with a difference statistically significant (*p=0.01*) (figure 2). Patients who had complete resection have a better survival than those with incomplete resection or biopsy with a difference statistically significant (*p=0.001)* (figure 3). Finally, a young age (<30 years) is correlated with a worse prognosis *(p=0.0001)* (figure 4)*.).* In multivariate analysis, age was the only prognostic factor *(p=0,04)*. Histological type and myasthenia showed no effect on survival in uni and multivariate analyses.

Figure 1: overall patient's survival

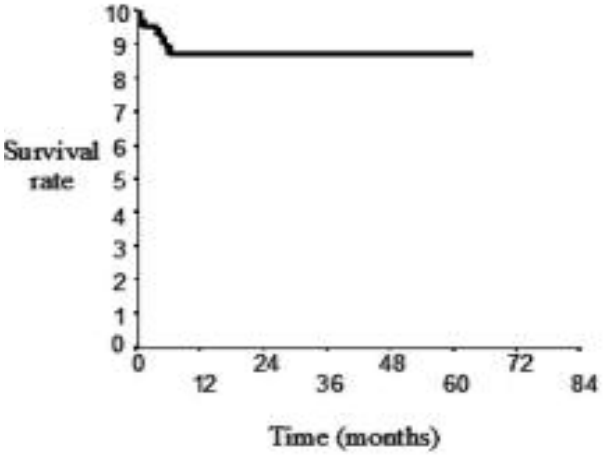


Figure 2: survival curves according type of surgical resection

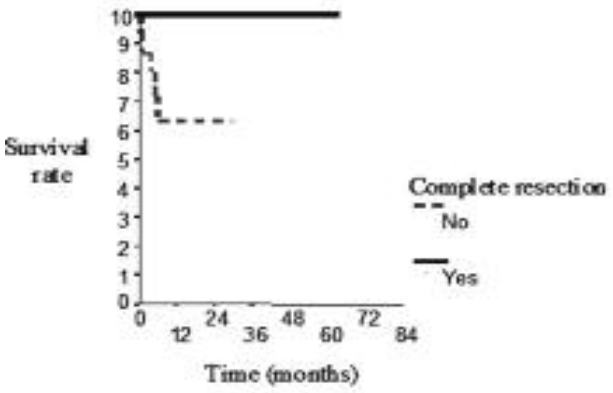


Figure 3 : survival curves according Masaoka stage

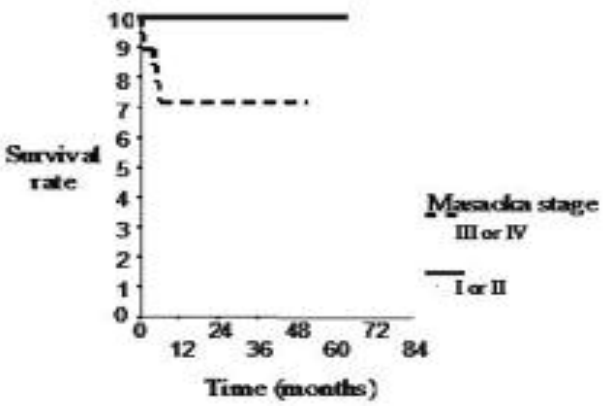
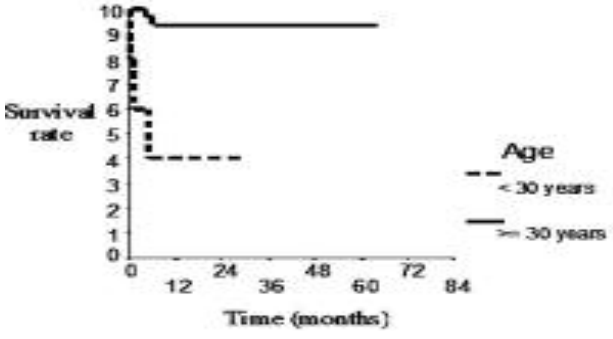


Figure 4 : survival curves according age



DISCUSSION

In our retrospective study of 40 cases of thymoma, univariate analysis suggests that Masaoka stage, extent of surgical resection, and age are prognostic factors for thymoma. In multivariate study, the age was the only prognostic factor.

The classification of thymomas is controversial because prediction of the biological behaviour of these tumors from their morphologic appearance is difficult.

Many classifications have been proposed. Bernatz et al classified thymomas into four categories based on the lymphocyte/epithelial cell ratio and the shape of the epithelial cells: predominantly spindle cell, predominantly lymphocytic, mixed and predominantly epithelial cell (1). In 1989, Marino and Muller-Hermelink classified thymic tumours in medullary, mixed, predominantly cortical, cortical thymoma, well differentiated thymic carcinoma and high-grade thymic carcinoma (2). In new classification schema was introduced by the World Health Organization in an attempt to standardize nomenclature and facilitate the diagnosis of primary thymic epithelial neoplasms. Six types were distinguished on the basis of the morphology of the epithelial cells and the lymphocyte-epithelial cell ratio: A, AB, B1, B2, B3, and C (3). In 2004, the WHO updated the classification and distinguished two major categories: five types of thymomas (types A, AB, B1, B2, B3) and thymic carcinomas. Two particular rare types of thymomas were introduced: metaplastic thymoma and micronodular thymoma with lymphoid stroma (4).

Thymomas occur in adult with a peak of incidence at 40-60 years (4). They are rare in adolescent and children (5, 6). Mean age in our series is comparable to that reported in American (7), European (8, 9, 10) and Asiatic studies (11, 12). There is equal sex incidence or a slight female predominance (7, 8, 10) that is found in our series.

Approximatively, one third of patients presented with an asymptomatic anterior mediastinal mass detected on chest X-ray (10% in our series). Of those with symptoms, they present with signs related to compression of adjacent mediastinal structures including cough, chest pain, dyspnea and/or systemic symptoms (general weakness and fever). Superior vena cava syndrome is generally related to an aggressive tumour (13% in our serie) (6).

Paraneoplastic syndromes associated with thymoma include myasthenia gravis (30-50%), pure red cell aplasia and hypogammoglobulinemia. About 15% of patients with myasthenia gravis have a thymoma (13, 22, 24). The incidence of myasthenia gravis in our series is lower than that reported in other series.

Computed tomography is helpful in staging thymoma especially for preoperative diagnosis, evaluation of tumour extension and relationship to adjacent organs but it is of limited value in differentiating histologic subtypes according to the WHO histologic classification (14, 15).

Surgery remains the mainstay of treatment of thymomas. The primary aim is to achieve a complete macroscopic surgical resection (6, 15, 16). In advanced unresectable tumors, a debulking surgery associated to an adjuvant therapy should be considered (15).

In our study, the most frequent histologic type was B2 followed by type AB. A similar distribution was reported in the majority of European (9, 17) and Asiatic (11, 13, 18) studies, whereas, American series (7) found a predominance of types AB and B3. In our series, type A was more unusual (2.5%) than in the other studies (12, 17, 19).

Myasthenia gravis is associated more frequently in the patients with types AB, B1, B2 and B3 rather than other types and is not associated in types A, metaplastic thymoma or micronodular thymoma with lymphoid stroma (9, 11, 13, 18). A similar distribution of MG was seen in our series.

Several authors agree that Masaoka stage is the most important prognostic factor. Previous studies have demonstrated that the propensity of invasion to neighbouring negatively affects prognosis (20). They demonstrated that difference in survival between stages I and II and between stages III and IV was statistically significant. However, no significant difference in survival was found between stage I and II disease and between stage III and IV (12, 18, 21, 22). We confirm this thesis because in our series we found a statistically significantly better prognosis in patients with stage I and II than those with stage III and IV.

Surgical resection represents also an important prognostic factor (4, 6). Most published series have shown a significant difference in survival between complete resection compared with incomplete resection or biopsy (9, 10, 22, 23, 24, 25). This finding was also demonstrated in our study.

Only few reports have evaluated the prognostic prevalence of WHO histologic classification and showed that it is an independent predictive factor with a better prognosis for types A, AB and B1 than types B2 and B3 (11, 18, 22, 24). In our study it was not a prognostic factor probably because of the limited number of the cases.

The value of myasthenia gravis is controversial. It was once thought to be a worse prognostic factor (26, 27). However, most studies demonstrate that it is correlated to a better prognosis in patients with thymoma (13, 24). This better prognosis is probably linked to earlier diagnosis (6). Other reports showed no difference in survival of patient with or without myasthenia gravis (9).

In our series, younger age (<30 years) is correlated to a worse prognosis in our series in uni and multivariate analysis. This fact was previously reported in only two studies of Lewis (28) and Resbeut (29). Whereas, Chalabreysse shows that young patients had a significatively better prognosis (9).

CONCLUSION

In our study, univariate analysis suggests that Masaoka stage, extent of surgical resection, and age are prognostic factors for thymoma. In multivariate study, the age was the only prognostic factor. These findings should be emphasizing by other larger Tunisian studies.

References

1. Bernatz, PE, Harrison, EG, Clagett, OT. Thymoma: a clinicopathologic study. J Thorac Cardiovasc Surg 1961; 42: 424-444.
2. Marino M, Muller-Hermelink HK. Thymoma and thymic carcinoma. Relation of thymoma epithelial cells to the cortical and medullary differentiation of thymus. Virchows Arch A Pathol Anat Histopathol. 1985;407:119-49.
3. Rosai J, Sobin, LH Histological typing of tumors of the thymus. World Health Organization international histological classification of tumors 2nd ed. 1999. New York : Springer-Verlag.
4. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Tumors of the thymus, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. IARC Press: Lyon 2004.
5. Pescarmona E, Giardini R, Brisigotti M, Callea F, Pisacane A, Baroni CD. Thymoma in childwood: A clinicopathological study of five cases. Histopathology 1992; 21: 65-8.
6. Detterbeck FC, Parsons AM. Thymic tumors. Ann Thorac Surg 2004; 77: 1860-9.
7. Quintanilla-Martinez L, Wilkins EW, Efird J, Hug E, Harris NL. Thymoma. Histologic subclassification is an independant prognostic factor. Cancer 1994; 74: 606-17.
8. Gripp S, Hilgers K, Wurm, Schmitt G. Thymoma. Prognostic factors and treatment outcomes. Cancer 1998; 83: 1495-503.
9. Chalabreysse L, Roy P, Cordier JF, Loire R, Gammondes JP, Thiovolet-Bejui. Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis. A retrospective study of 90 tumors. Am J Surg Pathol 2002; 26: 1605-11.
10. Rea F, Marulli G, Girardi R et al. Long-term survival and prognostic factors in thymic epithelial tumors. Eur J Cardiothorac Surg 2004; 26: 412-8.
11. Chen G, Marx A, Wen-Hu C et al. New World Health Organization classification predicts prognosis of thymic epithelial tumors. A clinicopathologic study of 200 thymomas from China. Cancer 2002; 95: 420-9.
12. Nakagawa K, Asamura H, Matsuno Y et al. Thymoma; A clinicopthological study based on the new World Health Organization classification. J Thorac Cardiovasc Surg 2003; 126: 1134-40.
13. Kondo K, Monden Y. Thymoma and myasthenia gravis: a clinical study of 1,089 patients from Japan. Ann Thorac Surg 2005; 79: 219-24.
14. Tomiyama N, Johkoh T, Mihara N al. Using the World Health Organization classification of thymic neoplasms to describe CT findings. AJR 2002; 179: 881-6.
15. Sumiyama Y, Yoshida Y. Thymoma. Ann Thorac Cardiovasc Surg 2004; 10: 321-3
16. Bacha E, Chapelier A, Macchiani P, Fadel E, Fadel E, Dartevelle P. Surgery for invasive primary mediastinal tumors. Ann Thorac Surg 1998; 66: 234-9.
17. Engel P, Marx A, Muller-Hermelink HK. Thymic tumors in Danemark. A retrospective study of 213 cases from 1970-1993. Pathol Res Pract 1999; 195: 565-70.
18. Okumura M, Mitsunori O, Tateyama H et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma. A clinical study of 273 patients. Cancer 2002; 94: 624-32.
19. Kuo TT, Lo SK. Thymoma: a study of the pathologic classification of 71 cases with evaluation of the Muller- Hermelink system. Hum Pathol 1993; 24: 766-71.
20. Moore K, McKenzie P, Kennedy C, Mc Caughan B et al. Thymoma: Trends over time. Ann Thorac Surg 2001; 72: 203-7.
21. Asamura H, Nakagawa K, Matsuno Y, Suzuki K, Watanabe I, Tsuchiya R. Thymoma needs a new staging. J Thorac Cardiovasc Surg 2004; 3: 163-7.
22. Kondo K, Monden Y. Therapy for epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003; 76: 878-85.
23. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. Cancer 1987; 60: 2727-43.
24. Maggi G, Casadio C, Cavallo A, Cianci R, Molinatti M, Ruffini E. Thymoma results of 241 operated cases. Ann Thorac Surg 1991; 51: 152-6.
25. Blumberg D, Port JL, Weksler B et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg 1995; 60: 908-13.
26. Wilkins KB, Sheikh E, Green R, Patel M, George S, Takano M, et al. Clinical and pathologic predictors of survival in patients with thymoma. Ann Surg 1999; 230:562-74.
27. Ruffie P, Gory-Delabaere G, Fervers B, Lehmann M, Regnard JF, Resbeut M. Standards, options and recommendations (SOR) for clinical care of malignant thymoma. Groupe de Travail SOR. Bull Cancer 1999;86:365-84.
28. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. Cancer 1987;60:2727-43.
29. Resbeut M, Mornex F, Richaud P, Bachelot T, Jung G, Mirabel X, Marchal C, Lagrange JP, Rambert P, Chaplain G, et al. Radiotherapy of thymoma. Study of the literature apropos of a retrospective and multicenter series of 149 cases. Bull Cancer Radiother. 1995;82: 9-19.