Int J Clin Exp Med 2019;12(1):1115-1121
www.ijcem.com /ISSN:1940-5901/IJCEM0079324

Case Report

Treatment and prognosis of WHO type A thymoma based on Masaoka-Koga stage

Wenxian Wang*, Zhengbo Song*, Yiping Zhang

*Department of Chemotherapy, Zhejiang Cancer Hospital, NO. 1 East Banshan Road, Gongshu District, Hangzhou 310022, Zhejiang Province, China. *Equal contributors.*

Received August 25, 2017; Accepted October 13, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: For WHO type A thymoma, recurrence or metastases are rare and a few cases have been reported previously. Treatment of recurrence or metastases A thymoma are still undefined. We explored the treatment and prognosis of patients with WHO type A thymoma from June 2006 to March 2016 in Zhejiang Cancer Hospital. Seven patients were included in this study. According to the Masaoka-Koga system, stage I in five patients, stage III and IV in 2 patients at diagnosis. Five stage I patients received surgery and were all alive without recurrence. The stage III patient received postoperative radiotherapy and chemotherapy. The stage IV patient received first line chemotherapy and efficacy evaluation was stable disease (SD). The 5-year disease-free survival and overall survival rates were 71.4% (5/7) and 100% (7/7), respectively. Our retrospective study indicated that Masaoka stage could affect the survival of patients with type A thymoma. And type A thymoma has potential in recurring or have malignant biological characteristics. However, disease progression in type A may be more slowly than other types such as type B or type C.

Keywords: Type A, thymoma, recurrence, metastasis

Introduction

Thymoma, which originates from the epithelial cells of the thymus, is the most common tumors of the anterior mediastinum and about 50% of all cases in adults [1, 2]. In 1999, the WHO introduced a uniform classification including six types: A, AB, B1, B2, B3 and C [3]. In the revised 2004 version, the designation type C was as thymic carcinoma and the concept of type A, AB, and B1-B3 was regarded for thymomas [4]. Primary thymic neoplasms are staged according to the Masaoka-Koga system, stage I comprised encapsulated tumors, stages II and III showing direct local invasion, and stage IV showing metastatic spread [5]. In general, thymomas are typically indolent-growing tumors and have relatively good prognoses. The type A and AB thymomas are as benign tumors [4]. It is reported that few patients of type A/AB thymoma experience metastasis or recurrence, however the frequency of recurrent was 28.6% and over 50% for patients with type B and type C, respectively [6]. Type A is usually low stage as most at stage I~II and has the best prognosis [7]. Then in the 2015 revised version, a new addition is the delineation of an "atypical type A thymoma variant" which differs from conventional type A thymomas and necrosis appears to be correlate with advanced stage [8].

Therefore, type A thymoma also has malignant potential, it has a tendency to infiltrate surrounding tissues as well as locally spread mainly to the pleura, the pericardium, and the lungs. The type A thymoma has a tendency for late local recurrence even after complete thymectomy. To our knowledge, there are no established treatment strategies to manage metastatic or recurrent type A thymoma. The aim of this study is to evaluate the treatment and prognosis of patients with type A thymoma based on Masaoka-Koga stage. And we review a cohort of type A thymoma which happened metastasis or recurrence in previous reports.

Materials and methods

Patients

Patients with pathological WHO type A thymoma who had undergone treatment at

Table 1. Characteristics of 7 patients in type A thymoma

Case	Gender/age	Masaoka-Koga stage	Surgery	treatment	Metastasis sites (During disease)	DFS/PFS, months	OS, months
1	F/60	I	Yes	No	No	95.1	95.1
2	F/43	III	Yes	Radiotherapy + Chemo	Lung; Supraclavicular LN	35.5	84.2
3	F/65	I	Yes	No	No	74.3	74.3
4	F/30	I	Yes	No	No	71.1	71.1
5	F/55	I	Yes	No	No	65.2	65.2
6	M/59	IV	No	Chemo	Lung	46.2-	63.6
7	M/45	I	Yes	No	No	130.9+	130.9+

Zhejiang Cancer Hospital between June 2006 and January 2012 were retrospectively identified. The histologic types were determined based on the 2004 WHO classification [4]. Patients' clinical stages were determined according to the Masaoka-Koga staging system [5]. Recurrence or metastases were confirmed using chest computed tomography (CT), as well as bone scan and/or computed tomography of the abdomen. Patients who died from another disease not related to thymic carcinoma were excluded from the current study.

Follow-up

For patients who underwent a surgical intervention, all were examined in the outpatient clinic at 3-month intervals for the first 2 years and, thereafter, at 6-month intervals. For patients at an advanced stage, the follow-ups were at 6 to 8 weeks apart. The last follow-up time point was March 27, 2017. The median follow-up of patients was 83 months, ranging from 63 to 130 months

Statistical analysis

Disease-free survival (DFS) encompassed the time from surgery to documented progression or death from any cause. Progression-free survival (PFS) was defined from the date of the treatment to the date of confirming overall disease progression. The definition of overall survival (OS) was determined from the date of treatments and the last known follow-up or date of death. The statistical analysis was performed using SPSS version 19 (SPSS Inc, Chicago, IL, USA), assuming that $P < 0.05$ is statistically significant. Kaplan-Meier method and log-rank test were applied to evaluate the DFS, PFS and OS.

Results

Patient characteristics

According to 2004 WHO classification, 7 patients of type A thymoma were included in the study. Clinical characteristics of all patients were listed in **Table 1**. According to the Masaoka-Koga system, stage I in five patients after surgery, and one was stage III, one was stage IV. In case 2, she underwent surgical resection of the tumor, which was no obvious capsule and infiltrated pleura (Stage III). In case 6, computed tomography (CT) scans revealed a 4.6*3.3 cm mass at anterior superior mediastinum and multiple nodules in both lungs (Stage IV) (**Figure 1A**, **1B**).

Histologic and molecular findings

All seven cases showed similar morphological characters, the presence of a spindle cell proliferation (**Figure 2A**). However, in case 2, after surgery, the tumors infiltrated supraclavicular lymph node. In case 6, the tumor transferred to lung and lung biopsy showed type A thymoma (**Figure 2B**). Immunohistochemistry (IHC) analysis demonstrated the patient was positive in cytokeratin (CK) 5/6, CK19, P63, cluster of differentiation (CD) 3 and Ki-67 (3%), and negative in CK7, Napsin A, CD20, CD56, CD117\c-kit and TdT. In addition, PIK3CA gene mutation was detected by next generation sequencing (NGS) in tumor tissue (3DBiopharm, Shanghai China) when disease progression for case 6.

Treatment and prognosis

Five stage I patients after surgery did not receive any treatment and all were alive without recurrence.

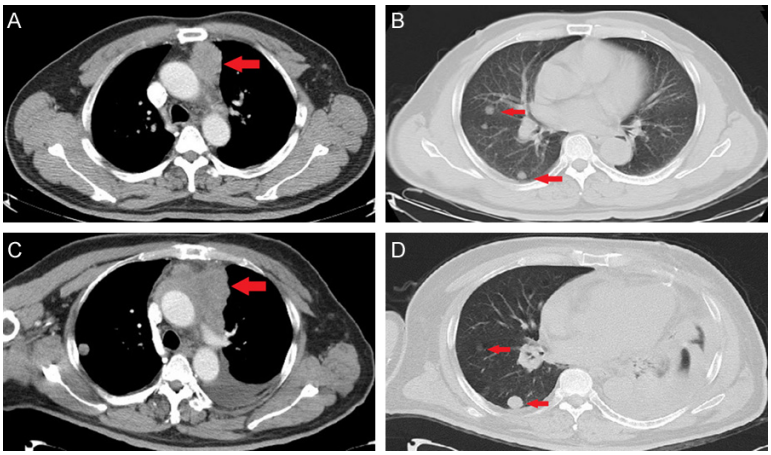

Figure 1. Computed tomography (CT) scans in case 6. A. CT scans showed a 4.6*3.3 cm mass (arrrow) at anterior superior mediastinum at diagnosis. B. Multiple nodules (arrrow) in both lungs at diagnosis. C. CT scans showed disease progression of pleural effusion in left lung and tumors mass (arrrow) increased of anterior superior mediastinum after first line chemotherapy treatment. D. Multiple nodules in both lungs (arrrow) after first line chemotherapy treatment.

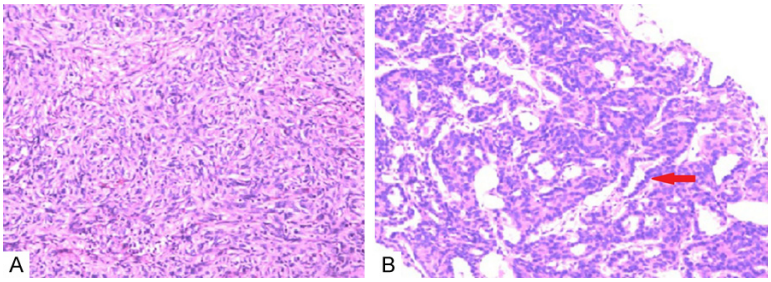

Figure 2. Pathology of Hematoxylin and eosin (HE) in type A thymoma. A. The microphotograph showed a hypocellular area with vague myxoid changes in case 2 (HE, ×100). B. Needle biopsy of lung tumor showed spindle cell thymoma (arrrow) in case 6 (HE, ×400).

For stage III patient (case 2), she received postoperative radiotherapy and chemotherapy with six cycles of DP regimen (docetaxel 75 mg/m^2 d1; Nedaplatin 25 mg/m^2 d1-3). Disease progression was in March 2013 and the disease free survival (DFS) was 35.5 months. The patient showed the presence of metastases in left supraclavicular tissue and left lung oblique fissure. Needle biopsy indicated the pathological pattern was type A thymoma. Then she received chemotherapy in April 2013 with four cycles of vinorelbine single treatment and supraclavicular tumor radiotherapy. The patient was alive with no evidence of progression disease to date.

For stage IV patient (case 6), he received first line chemotherapy (gemcitabine 1250 mg/m^2 d1, 8; cisplatin 25 mg/m^2 d1-3) in February 2012 with four cycles and efficacy evaluation was stable disease (SD). Unfortunately, he felt chest distress in November 2015 and CT scans showed pleural effusion in left lung, tumors mass increased of anterior superior mediastinum and multiple nodules in both lungs (**Figure 1C**, **1D**). The lung tumor biopsy showed the pathological type was A thymoma (**Figure 2B**). Then he received second line chemotherapy (paclitaxel 175 mg/m^2 d1; carboplatin AUC = 5 d1, every 3 weeks) in November 2015 with four cycles. The efficacy was SD. The progression free survival (PFS) of first-line was 45.7 months and he was alive without progression disease after second-line treatment.

The 5-year disease-free survival and overall survival rates were 71.4% (5/7) and 100% (7/7), respectively.

Discussion

The majority of thymomas have been classified as benign tumors appearing thymic epithelial cells mixed with variable proportions of lymphocytes. Type A thymoma composes mainly of spindle/oval epithelial tumor cells and lacking in nuclear atypia or lymphocytes [9]. Type A is usually low stage and has the best prognosis [4, 10]. However, it also has malignant biological ehavior. Morphological features are not considered as an independent prognostic factor. Some prior studies have demonstrated malignant behavior in type A thymoma and we summarized these reports in **Table 2**. Vladislav et al [15] showed that the presence of tumoral necrosis in type A thymomas was associated with recurrence or metastases. Moreover, in 2015 WHO version, atypical type A thymoma was a new addition variant from conventional type A thymoma and necrosis appears to be correlated with poor out-

Table 2. Reports of type A thymoma patients with recurrence or metastases from 2008 to 2016

Study ID	Published year	Number of cases	Masaoka stage at diagnosis	Disease free survival (DFS)	Recurrence/metastasis location	Treatment at recurrence	Survival
Gamboa et al [12]	2008	1	I	14 months	Brain and liver	WBRT and SRS for brain lesions	31 months
Huang et al [13]	2009	1	IV	NA	Lung	NA	NA
Jain et al [14]	2010	9	5 in stage II 1 in stage IV (Pleura)	NA	Pleura/Lung/Liver/Bone/Brain/Peritoneum	NA	A mean duration of 61.8 months (6 months to 20 years)
Kinoshita et al [15]	2012	1	I	7 years	Lung	Metastasectomy for lung nodule	More than 7 years
Vladislav et al [16]	2013	11	1 in stage I 3 in stage II 2 in stage III 5 in stage IV	7 to 107 months (six patients)	Pleura/Lung/Liver/Neck/Bones	NA	18 months to 103 months
Hirono et al [17]	2014	1	IV	-	Lung	Surgery	More than four years
Laperuta [18]	2014	1	I	2 years	Skeletal muscle	Surgery and adjuvant treatment	Alive (more than 2 years)
Sandri et al [19]	2014	2	NA	More than 10 years	NA	NA	More than 10 years
Green et al [20]	2015	1	IV	NA	NA	NA	NA
Kim et al [21]	2016	1	II	6 years	Liver	Chemotherapy (cyclophosphamide + doxorubicin + cisplatin) and surgical excision	NA
Nose et al [22]	2016	1	I	36 months	Pleural	Surgery	NA

Abbreviations: WBRT, whole brain radiation therapy; SRS, gamma-knife stereotactic radiosurgery; NA, not applicable.

comes. Therefore, the tumor stage was also important and could be as a significant prognosis factor [22, 23]. Although the most of type A thymoma is encapsulated or microinvasive regarded as Masaoka stage I, this type still can progress beyond stage I and eventually metastasize. Roden et al [24] reported 2 out of 18 patients with type A in stage I and 2 out of 8 with stage II occurred recurrence. Five patients were stage III at diagnosis and the median follow-up was 4.5 years. Jain et al [13] indicated that the frequency of stage III and IV was 19% and 1.6% in type A and AB. Green et al [19] reported type A and AB thymomas were 4.1% of stage III and 1.7% of stage IV.at the time of resection. In our report, two out of seven type A patients had malignant behavior. One was stage III and one was IV at diagnosis. Hence, a combination of stage and histological subtype should be considered as predicting the clinical behavior of thymomas and survival.

Surgery is the main treatment in thymic tumors and they are completely removed. Roden et al [24] illustrated that overall survival of recurrence or metastasis type A thymoma was longer than other types. The 5-year survival of completely resected patients was 90%, 90%, 60% and 25% for stages I, II, III and IV [25]. The time to relapse for stage I was 10 years, and 3 years for patient of stage II-IV. Type A has an excellent OS rate of more than 90-95% at 10 years. The average disease-free time was inconsistent in different reports [26]. In our study, the DFS in case 2 was 35.5 months which similar to the previous reported. Therefore, although type A thymoma occur recurrence or metastasis, the survival would be better than other types.

On the other hand, adjuvant radiotherapy plays an important role in the treatment of invasive and incompletely excised thymomas [28, 29]. A Korean single-institutional analysis showed that postoperative radiation therapy (PORT) improved disease-free survival (DFS) in stage II to III thymomas [29]. Lim et al [30] reviewed that the potential survival benefit of PORT in stage III to IV thymomas with macroscopically complete resection. And chemotherapy is considered as a useful treatment strategy in metastatic thymomas [29]. Nowadays, treatments for recurrence or metastatic thymomas have no standards. In our case 6, the patient received first line chemotherapy and the PFS was 45.7 months. Then, in case 2, after recurrence, the patient received single chemotherapy and after 41 months he was without disease progression. Kim et al [20] reported patient received chemotherapy combination with surgery for liver metastases. We thought that type A compared to other subtypes (type B or C) might have indolent growth pattern and its prognosis was better than other types. For advanced disease, patients should receive surgery again, chemotherapy only or other methods. And for advanced disease, although during stable condition, it needs to go regular review because of type A thymoma may behave in an aggressive manner. It is also valuable for clinicians to be aware of an appropriate treatment plan in recurrence or metastasis thymomas.

In recent years, targeted therapy is research focus and the researches on recurrent thymoma have started. Epidermal Growth Factor Receptor (EGFR) has a high expression in the cells of thymoma, but mutations are rare, so EGFR tyrosine kinase inhibitors may not be effective. A case report shows that a patient with EGFR mutation fails to respond to gefitinib [31]. However, some EGFR strong expression positive patients achieved partial response after cetuximab treatment [32, 33]. In our case, it was the first reported PIK3CA gene mutation had been detected by next generation sequence (NGS). Because of stable disease after second line chemotherapy, he did not receive relevant target inhibitors. However, it was meaningful that NGS might apply to detect drive gene and guide clinical individual treatment in the future. It needed more prospective clinical studies.

The major limitations of our study are its retrospective analysis and small number of patients. However, with no cases in prospective clinical studies and treatment is lack, our retrospective study can also be considered to be meaningful.

In conclusion, type A thymoma may develop recurrent disease several years from initial diagnosis or metastasis at the time of diagnosis. Although the prognosis of type A is better, oncologist should realize that type A has malignant behavior. It is needed to optimize treatment strategies for thymoma patients based on tumor stage, WHO classification and gene detection.

Disclosure of conflict of interest

None.

Address correspondence to: Yiping Zhang, Department of Chemotherapy, Zhejiang Cancer Hospital, NO. 1 East Banshan Road, Gongshu District, Hangzhou 310022, Zhejiang Province, China. Tel: +86 15158190034; E-mail: yi_ping_zhang@163.com

References

[1] Venuta F, Anile M, Diso D, Vitolo D, Rendina E, De Giacomo T, Francioni F, Coloni G. Thymoma and thymic carcinoma. Eur J Cardiothorac Surg 2010; 37: 13-25.

[2] Spaggiari L, Casiraghi M, Guarize J. Multidisciplinary treatment of malignant thymoma. Curr Opin Oncol 2012; 24: 117-122.

[3] Rosai J, Sobin L. Histological typing of tumours of the thymus. Springer Berlin Heidelberg 1999; 9-22.

[4] Travis WD. Pathology and genetics of the lung, pleura, thymus and heart. IARC Press 2004; 87: 532-534.

[5] Detterbeck FC, Nicholson AG, Kondo K, Van SP, Moran C. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011; 6: S1710-1716.

[6] Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003; 76: 878-884.

[7] Ruffini E, Filosso PL, Oliaro A. The role of surgery in recurrent thymic tumors. Thorac Surg Clin 2009; 19: 121-131.

[8] Marx A, Chan J, Coindre J, Detterbeck F, Girard N, Harris N, Jaffe E, Kurrer M, Marom E, Moreira A, Mukai K, Orazi A, Strobel P. The 2015 world health organization classification of tumors of the thymus: continuity and changes. J Thorac Oncol 2015; 10: 1383-1395.

[9] Scorsetti M, Leo F, Trama A, Angelillo R, Serpico D, Macerelli M, Scorsetti M, Zucali P, Gatta G, Garassino M. Thymoma and thymic carcinomas. Crit Rev Oncol Hematol 2016; 99: 332-350.

[10] Pan C, Chen W, Chiang H. Spindle cell and mixed spindle/lymphocytic thymomas: an integrated clinicopathologic and immunohistochemical study of 81 cases. Am J Surg Pathol 2001; 25: 111-120.

[11] Gamboa E, Sawhney V, Lanoy R, Haller N, Powell A, Hazra S. Widespread metastases after resection of noninvasive thymoma. J Clin Oncol 2008; 26: 1752-1755.

[12] Huang J, Rizk N, Travis W, Riely G, Park B, Bains M, Dycoco J, Flores R, Downey R, Rusch V. Comparison of patterns of relapse in thymic carcinoma and thymoma. J Thorac Cardiovasc Surg 2009; 138: 26-31.

[13] Jain R, Mehta R, Henley J, Kesler K, Loehrer P, Badve S. WHO types A and AB thymomas: not always benign. Mod Pathol 2010; 23: 1641-1649.

[14] Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. Pulmonary metastasis from encapsulated cervical ectopic type a thymoma. Ann Thorac Surg 2012; 94: e141-142.

[15] Vladislav I, Gökmen-Polar Y, Kesler K, Loehrer P, Badve S. The role of histology in predicting recurrence of type A thymomas: a clinicopathologic correlation of 23 cases. Mod Pathol 2013; 26: 1059-1064.

[16] Hirono M, Nonaka M, Himuro N, Tomita Y, Kataoka D, Kadokura M. Two cases of thymoma with pulmonary metastasis: a case report. World J Surg Oncol 2014; 12: 114.

[17] Laperuta P, Napolitano F, Garzi A, Amato B, Vatrella A, Di Crescenzo V. Extrathoracic recurrence of type A thymoma. Int J Surg 2014; 12: S16-18.

[18] Sandri A, Cusumano G, Lococo F, Alifano M, Granone P, Margaritora S, Cesario A, Oliaro A, Filosso P, Regnard J, Ruffini E. Long-term results after treatment for recurrent thymoma: a multicenter analysis. J Thorac Oncol 2014; 9: 1796-1804.

[19] Green A, Marx A, Ströbel P, Mason M, Lim E, Jordan S, Ladas G, Dusmet M, Rice A, Nicholson A. Type A and AB thymomas: histological features associated with increased stage. Histopathology 2015; 66: 884-891.

[20] Kim H, Park Y, Ki M, Lee S, Beom S, Han D, Park Y, Park J. Spontaneous rupture of hepatic metastasis from a thymoma: a case report. World J Gastroenterol 2016; 22: 9860-9864.

[21] Nose N, Higuchi K, Chosa E, Ayabe T, Tomita M, Nakamura K. Port-site implantation of type A Masaoka stage I thymoma after video-assisted thoracic surgery: a case report. J Surg Case Rep 2016; 25: 164.

[22] Chen G, Marx A, Chen W, Yong J, Puppe B, Stroebel P, Mueller-Hermelink H. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002; 95; 420-429.

[23] Okumura M, Ohta M, Tateyama H, Nakagawa K, Matsumura A, Maeda H, Tada H, Eimoto T, Matsuda H, Masaoka A. The world health organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002; 94; 624-632.

[24] Roden A, Yi E, Jenkins S, Donovan J, Cassivi S, Garces Y, Marks R, Aubry M. Diagnostic significance of cell kinetic parameters in world

health organization type A and B3 thymomas and thymic carcinomas. Hum Pathol 2015; 46: 17-25.
[25] Regnard JF, Magdeleinat P, Dromer C, Dulmet E, de Montpreville V, Levi JF, Levasseur P. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996; 112: 376-384.
[26] Awad W, Symmans P, Dussek J. Recurrence of stage I thymoma 32 years after total excision. Ann Thorac Surg 1998; 66: 2106-2108.
[27] Chang J, Kim H, Wu H, Kim J, Kim Y. Postoperative radiotherapy for completely resected stage II or III thymoma. J Thorac Oncol 2011; 6: 1282-1286.
[28] Spaggiari L, Casiraghi M, Guarize J. Multidisciplinary treatment of malignant thymoma. Curr Opin Oncol 2012; 24: 117-122.
[29] Kondo K. Optimal therapy for thymoma. J Med Invest 2008; 55: 17-28.
[30] Lim Y, Kim E, Kim H, Wu H, Yan J, Liu Q, Patel S. Survival impact of adjuvant radiation therapy in Masaoka Stage II to IV thymomas: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys 2016; 94: 1129-1136.
[31] Nakagiri T, Funaki S, Kadota Y, Takeuchi Y, Shiono H, Akashi A, Okumura M. Does gefitinib have effects on EGFR mutation-positive thymoma-case report of thymoma recurrence. Ann Thorac Cardiovasc Surg 2014; 20: 674-676.
[32] Palmieri G, Marino M, Salvatore M, Budillon A, Meo G, Caraglia M, Montella L. Cetuximab is an active treatment of metastatic and chemorefractory thymoma. Front Biosci 2007; 12: 757-761.
[33] Farina G, Garassino M, Gambacorta M, La Verde N, Gherardi G, Scanni A. Response of thymoma to cetuximab. Lancet Oncol 2007; 8: 449-450.