Case Report

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

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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
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.

### Table 1. Characteristics of 7 patients in type A thymoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/age</th>
<th>Masaoka-Koga stage</th>
<th>Surgery</th>
<th>treatment</th>
<th>Metastasis sites (During disease)</th>
<th>DFS/PFS, months</th>
<th>OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/60</td>
<td>I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>95.1</td>
<td>95.1</td>
</tr>
<tr>
<td>2</td>
<td>F/43</td>
<td>III</td>
<td>Yes</td>
<td>Radiotherapy + Chemo</td>
<td>Lung; Supraclavicular LN</td>
<td>35.5</td>
<td>84.2</td>
</tr>
<tr>
<td>3</td>
<td>F/65</td>
<td>I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>74.3</td>
<td>74.3</td>
</tr>
<tr>
<td>4</td>
<td>F/30</td>
<td>I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>71.1</td>
<td>71.1</td>
</tr>
<tr>
<td>5</td>
<td>F/55</td>
<td>I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>65.2</td>
<td>65.2</td>
</tr>
<tr>
<td>6</td>
<td>M/59</td>
<td>IV</td>
<td>No</td>
<td>Chemo</td>
<td>Lung</td>
<td>46.2</td>
<td>63.6</td>
</tr>
<tr>
<td>7</td>
<td>M/45</td>
<td>I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>130.9+</td>
<td>130.9+</td>
</tr>
</tbody>
</table>
Treatment and prognosis of type A thymoma

For stage III patient (case 2), she received postoperative radiotherapy and chemotherapy with six cycles of DP regimen (docetaxel 75 mg/m² d1; Nedaplatin 25 mg/m² 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/m² d1, 8; cisplatin 25 mg/m² 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/m² 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 behavior. 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-

Figure 1. Computed tomography (CT) scans in case 6. A. CT scans showed a 4.6*3.3 cm mass (arrow) at anterior superior mediastinum at diagnosis. B. Multiple nodules (arrow) in both lungs at diagnosis. C. CT scans showed disease progression of pleural effusion in left lung and tumors mass (arrow) increased of anterior superior mediastinum after first line chemotherapy treatment. D. Multiple nodules in both lungs (arrow) 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 (arrow) in case 6 (HE, ×400).
## Table 2. Reports of type A thymoma patients with recurrence or metastases from 2008 to 2016

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

Abbreviations: WBRT, whole brain radiation therapy; SRS, gamma-knife stereotactic radiosurgery; NA, not applicable.
Treatment and prognosis of type A thymoma

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.

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