MULTIDISCIPLINARY TREATED THYMOMAS WITH FATAL OUTCOME. A RETROSPECTIVE STUDY

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MULTIDISCIPLINARY TREATED THYMOMAS WITH FATAL OUTCOME. A RETROSPECTIVE STUDY (Abstract): The aim of the study was to assess factors concurring to fatal outcome of patients operated for thymoma with or without myasthenia gravis. Material and methods: A retrospective observational study was carried out on a series of 10 patients treated for thymoma in the IIIrd Surgical Unit of “St. Spiridon” University Hospital. Results: Mean survival time was 4.45 years and mortality rate was 38.4%. In 8 patients III and IV Osserman stage myasthenia gravis was associated. 2 patients without myasthenia gravis were diagnosed with a locally advanced stage of thymic carcinoma. According to WHO pathological classification of thymoma, 2 cases were included in type C, those without myasthenia gravis associated and the rest in type B1 (2 cases) and B2 (6 cases). According to Masaoka classification all cases presented invasive thymoma: 6 cases type II, 3 cases type III and one case with type IV. Apart of one case in stage IV, all cases benefitted of complete surgical resection. No perioperative and early postoperative mortality was recorded. On long term follow-up the cause of death was related to aggravation of myasthenia gravis in 6 cases, to cardiac failure in 2 cases (acute myocardial infarction and constrictive pericarditis) and in 2 cases to metastatic disease (thymoma related death - 20%). Conclusions: Aggravation of myasthenia gravis was the first cause of death in this series in spite of complete resection and intensive immunosuppressive treatment. Completeness of surgical resection is the most important prognostic factor. The histopathological type of thymoma with fatal outcome was type B and C after WHO classification. Key words: THYMOMA, MYASTHENIA GRAVIS, FATAL OUTCOME

Thymoma patients are a real challenge for the therapeutic team as the outcome can be unpredictable and the response to treatment sometimes refractory. Although most of the authors consider the association of thymoma with myasthenia gravis a good prognostic factor, because it speeds the disclosure of the thymoma in a resectable stage, we noticed that following an initial improvement, myasthenia gravis might become more aggressive and refractory to immunosuppressive treatment. Another important favorable prognostic factor is the completeness of surgical resection but the influence of pathological type of thymoma remains unclear. The aim of the study was
to assess factors concurring to fatal outcome of patients operated for thymoma with or without myasthenia gravis.

**MATERIAL AND METHODS**

A retrospective observational study was carried out on a series of 10 patients treated for thymoma in the IIIrd Surgical Unit of “St. Spiridon” University Hospital. From 1990 to 2010, 81 cases of thymic lesions were treated by a multidisciplinary team including neurologist, radiologist, immunopathologist, oncologist, surgeon and anesthesiologist. Thymoma patients represented 26 cases (32%) and among these patients we selected those who died postoperatively over a period of 16 years.

Demographical data, clinical staging data, tumor extension after Masaoka classification, thymoma type after WHO classification, completeness of surgery, adjuvant treatment and patient follow-up data were obtained from the patients records and from detailed patient or family interviews (tab.I). The end point was mortality of the patients till August 2013.

**TABLE I**

**Clinical and pathological characteristics of the patients.**

<table>
<thead>
<tr>
<th>No. / NAME</th>
<th>SEX</th>
<th>AGE</th>
<th>OSSERMAN</th>
<th>WHO</th>
<th>MASAOKA</th>
<th>OP</th>
<th>MTS</th>
<th>POT</th>
<th>ST</th>
<th>DEATH CAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LT</td>
<td>F</td>
<td>33</td>
<td>III</td>
<td>B2</td>
<td>III</td>
<td>CR-R at 10 Y-CR</td>
<td>R/C</td>
<td>16 y</td>
<td>IMA</td>
<td></td>
</tr>
<tr>
<td>2. ME</td>
<td>F</td>
<td>45</td>
<td>III</td>
<td>B2</td>
<td>III</td>
<td>CR</td>
<td>R/C</td>
<td>6 y</td>
<td>ARF</td>
<td></td>
</tr>
<tr>
<td>3. PP</td>
<td>F</td>
<td>45</td>
<td>III</td>
<td>B2</td>
<td>II</td>
<td>CR</td>
<td>R/C</td>
<td>3 m</td>
<td>ARF</td>
<td></td>
</tr>
<tr>
<td>4. AM</td>
<td>M</td>
<td>40</td>
<td>III</td>
<td>B2</td>
<td>II</td>
<td>CR</td>
<td>R/C</td>
<td>6 y</td>
<td>AHF</td>
<td></td>
</tr>
<tr>
<td>5. CT</td>
<td>F</td>
<td>60</td>
<td>IV</td>
<td>B2</td>
<td>II</td>
<td>CR</td>
<td>R/C</td>
<td>9 y</td>
<td>ARF</td>
<td></td>
</tr>
<tr>
<td>6. AM</td>
<td>F</td>
<td>46</td>
<td>III</td>
<td>B2</td>
<td>II</td>
<td>CR</td>
<td>C</td>
<td>1 y</td>
<td>ARF</td>
<td></td>
</tr>
<tr>
<td>7. AF</td>
<td>M</td>
<td>27</td>
<td>-</td>
<td>C</td>
<td>IV</td>
<td>BX lung</td>
<td>R/C</td>
<td>2 y</td>
<td>MTS</td>
<td></td>
</tr>
<tr>
<td>8. GM</td>
<td>F</td>
<td>31</td>
<td>-</td>
<td>C</td>
<td>III</td>
<td>CR bone</td>
<td>C/ST</td>
<td>2 y</td>
<td>MTS</td>
<td></td>
</tr>
<tr>
<td>9. PA</td>
<td>M</td>
<td>41</td>
<td>IIIB</td>
<td>B1</td>
<td>II</td>
<td>CR</td>
<td>C</td>
<td>3 m</td>
<td>ARF</td>
<td></td>
</tr>
<tr>
<td>10. IV</td>
<td>M</td>
<td>54</td>
<td>IIIB</td>
<td>B1</td>
<td>II</td>
<td>CR</td>
<td>-</td>
<td>2 y</td>
<td>ARF</td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS**

Survival time ranged between 3 months and 16 years. Mean survival time was 4.45 years and mortality rate was 38.4%.

Sex ratio F/M was 3/2 and mean age at the time of operation was 42.2 years. In 8 patients III and IV Osserman stage myasthenia gravis was associated. 2 patients without myasthenia gravis were diagnosed with a locally advanced stage of thymic carcinoma; in one case resection was feasible while in the youngest one only a biopsy could be performed.

According to WHO pathological classification of thymoma, 2 cases were included in type C, those without myasthenia gravis associated and the rest in type B1 (2 cases) and B2 (6 cases).

According to Masaoka classification which assesses the grade of tumor invasion, all cases presented invasive thymoma which is considered malignant, even in the
Multidisciplinary treated thymomas with fatal outcome. A retrospective study

absence of cells atypia; 6 cases type II, 3 cases type III and one case with type IV. Apart of one case in stage IV, all cases benefitted of complete surgical resection.

One case presented at 10 years with tumor recurrence that required re-resection with survival time of 6 years, the cause of death being not related to operation or recurrence.

The majority of patients (9 cases) received postoperative adjuvant therapy such as radiotherapy, chemotherapy or both. Radiotherapy was indicated mainly for Masaoka stage III and IV patients.

No perioperative and early postoperative mortality was recorded. At the time of hospital discharge an obvious improvement of symptoms was observed for the patients with thymoma associated with myasthenia gravis.

On long term follow-up the cause of death was related to aggravation of myasthenia gravis (60%) in 6 cases, to cardiac failure in 2 cases (acute myocardial infarction and constrictive pericarditis) and in 2 cases to metastatic disease (thymoma related death - 20%).

DISCUSSION

Thymomas are rare thymic epithelial tumors but represent the most frequent tumor of the mediastinum after the age of 40 without gender preference, unlike lymphoid thymic hyperplasia frequently encountered in young female patients (1, 3).

The presence of myasthenia gravis must be regarded as a favorable factor from the diagnostic point of view because the myasthenia symptoms alert patients to seek medical advice and thymoma in such cases can be discovered in a resectable surgical stage. But in our series the association of severe clinical form of myasthenia gravis seems to be related with fatal outcome. Even after a period of improvement postoperatively, myasthenia gravis has reappeared in aggravated and treatment refractory forms being responsible for acute respiratory failure and death. Aggravation of MG postoperatively might be explained by tumor recurrence or exacerbation of extrathymic autoimmune.

On the contrary, other studies reported that the presence of myasthenia gravis did not show statistical correlation with survival on a multivariate analysis (1, 2, 4, 9). The reported long-term outcome of thymoma patients is related to tumor stage, WHO histotype, completeness of surgical removal and type of treatment (1, 5, 6).

Morgenthaler et all. found that the prognosis is best predicted by stage of the tumor determined intraoperatively and is poorer in patients with incomplete resection. Irradiation and chemotherapy have important roles in the management of thymomas, particularly in advanced stages (3, 7, 8, 9).

The pathological type encountered in our series after WHO classification was mostly B2 and C, which are recognized as aggressive tumors.

Complete surgical resection is a good prognostic factor and when extended thymectomy is feasible the recurrence of tumor is rare. In one case, recurrence was diagnosed and reoperated at 10 years resulting in a good outcome. The patient survived 6 years after reoperation, the cause of death (acute myocardial infarction) being unrelated to thymoma.

Tumor recurrence is rare in complete resected cases. If over a period of 2 years the disease is well controlled then the chance of prolonged survival is increased. The critical period seems to be 2 years postoperatively in which the patient should be closely follow
up, such as every 3 months.

**CONCLUSIONS**

The association with myasthenia gravis facilitates the diagnosis of thymomas in an early, resectable stage, but our results suggest that despite an initial improvement, myasthenia gravis might become more aggressive and refractory to immunosuppressive treatment. Another important favorable prognostic factor is the completeness of surgical resection although the influence of pathological type of thymoma remains unclear. In our series, the histopathological type of thymoma with fatal outcome was type B and C according to WHO classification. Aggravation of myasthenia gravis was the first cause of death in spite of complete resection and intensive immunosuppressive treatment.

**REFERENCES**