Formosan Journal of Surgery (2011) 44, 136–140

available at www.sciencedirect.com

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journal homepage: www.e-fjs.com

MINI-REVIEW

Thymic carcinoma: A rare cancer requiring special attention

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Received 1 March 2011; received in revised form 20 May 2011; accepted 16 June 2011
Available online 14 September 2011

KEYWORDS
complete resection;
Masaoka staging system;
thymic carcinoma;
thymic epithelial cells

Summary Thymic carcinoma is a rare but highly aggressive, easily metastasizing cancer derived from thymic epithelial cells and has a very poor prognosis. Unlike thymoma, which is usually found because it is associated with paraneoplastic syndrome, thymic carcinoma is almost always found at an advanced stage because patients often have atypical symptoms. There is no known tumor marker for thymic carcinoma screening. Because most tumors are discovered at an advanced stage, the Masaoka staging system, which is widely used for thymoma, is of questionable value for thymic carcinoma. Complete resection of the tumor is the mainstay of treatment and leads to the best survival rate for patients. However, the complete resection rate is only approximately 50% and the recurrence rate after complete resection is high, up to 40%. The role of postoperative radiotherapy or chemotherapy is still controversial. For tumors that cannot be completely resected, the result of debulking surgery is not different from that of a biopsy. The efficacy of preoperative radiotherapy, chemotherapy, or concurrent chemoradiation therapy is still debatable because most studies on these topics were for only a small number of patients and were retrospective in nature. The overall 5-year survival rate for patients with thymic carcinoma is only 30–50%. A prospective randomized study requires multi-center collaboration and the establishment of an optimal treatment protocol to increase the survival rate of patients with thymic carcinoma, for which there is no predictive screening biomarker or a suitable staging system at present.

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1682-606X/$ - see front matter
doi:10.1016/j.fjs.2011.08.007

1. Introduction

Thymic carcinoma, a cancer derived from thymic epithelial cells, was first recognized by Shimosato et al in 1977 in their study of squamous cell carcinoma of the thymus.[1] Additional variables of thymic carcinoma were reported in a later study by Snover et al in 1982.[2] The relationship between thymoma and thymic carcinoma is still controversial. The adenoma–carcinoma model in other solid organ malignancies, a term that describes the stepwise progression from normal to dysplastic epithelium to carcinoma associated with the accumulation of multiple clonally selected genetic alterations,[3] cannot be applied to thymoma and thymic carcinoma because thymoma may recur and metastasize without any overt cytological features of malignancy. Most articles in the literature suggest that thymic carcinoma occurs *de novo* from thymic epithelial cells instead of from thymoma.[4,5] In 1999, histologic classification of thymic epithelial tumors according to the World Health Organization (WHO) relied on histological assessment of the morphology of neoplastic epithelial cells and the relative amount of a non-neoplastic lymphocytic component. The term type C thymoma was introduced to stress the thymic epithelial origin of carcinomas.[6] Neuroendocrine carcinoma consisting of carcinoid, atypical carcinoid, and small- and large-cell carcinoma was included in type C thymoma in the newly defined WHO histological classification in 2004.[7]

Thymic carcinoma (type C thymoma), unlike thymoma, exhibits distinctly more aggressive behavior and a much poorer prognosis.[5] Articles in the literature describing thymic carcinoma are relatively rare. This review addresses issues in relation to thymic carcinoma that require specific attention.

2. Incidence of thymic carcinoma

The first report on a large number of cases ($n = 60$) with thymic carcinoma was published in 1991 by Suster and Rosai.[8] In 2003, Kondo and Monden[9] reported the largest series, consisting of 227 cases collected from 115 institutions in Japan. Reports of more than 20 cases of thymic carcinoma from a single institution are rare.[10] According to the literature, the incidence of thymic carcinoma is only 0.06% of all thymic neoplasms.[10] We have retrospectively reviewed reports on several large series on thymic carcinoma[11–21] and the results are summarized in Table 1. We found that the incidence of thymic carcinoma might have geographic differences. Confirmation of such differences requires additional investigation of this relatively rare cancer. We retrospectively reviewed our experience in treating 207 patients with thymic epithelial tumors from June 1988 to November 2009. Some 37% of these patients had thymic carcinoma. We are still investigating the reason for such a high incidence of thymic carcinoma in the southwest part of Taiwan.

3. Signs and symptoms of thymic carcinoma

Thymic carcinoma occurs most frequently in adults between 30 and 60 years of age.[5,8,10] In some cases, thymic carcinoma is found incidentally on routine chest X-rays (20% in our series). Once a patient has symptoms, which are usually atypical chest symptoms due to mediastinal compression or invasion (53% in our series), the cancer is already at an advanced stage. Because of the anterior mediastinal location and high invasiveness, the superior vena cava syndrome is not rare. A paraneoplastic syndrome has also been reported for patients with thymic carcinoma, but is rare. Pure red cell aplasia or hyper- or hypoglobulinemia occurs primarily in thymoma rather than in thymic carcinoma.[10] Myasthenia gravis is commonly found in patients with thymoma, but rarely occurs in patients with thymic carcinoma unless there is a concomitant thymoma component.[9,10,20] We previously described one patient with thymic carcinoid combined with myasthenia gravis.[22] Cushing syndrome and multiple endocrine neoplasia type I have also been reported in patients with thymic carcinoid.[9,23] Pan et al reported that thymoma has a higher incidence of associated malignancy, which suggests a forgotten associated paraneoplastic syndrome.[24] It has also been suggested that the risk of a second malignancy in thymoma patients is intrinsic and unrelated to other oncogenic factors.[24] We have found that thymic carcinoma, especially neuroendocrine carcinoma, also has a higher incidence of associated malignancy.[25] Thus, long-term follow-up of patients harboring thymic carcinoma is recommended. Because most patients with thymic carcinoma are identified at an advanced stage without specific signs or symptoms, finding a biomarker for early detection of this egregious cancer is of paramount importance.

4. Histology and specific stains for differential diagnosis

According to the WHO classification, type C thymoma comprises a large number of histological types of thymic carcinoma.[5,7,8] Because most of these cancers clinically resemble cancers from other organ sites, thymic carcinoma should always be a diagnosis of exclusion.[5,7] Metastasis from other organs should be ruled out before establishing the diagnosis. Differentiation of thymic carcinoma from cancer metastasized from other organs is still difficult. It has been reported that lymphoid markers expressed in the tumor cells of thymic carcinoma, such as CD5 and CD70, are markers for differential diagnosis; however, they are valid only for differentiating thymic carcinoma from thymoma.[5,26,27] Overexpression of c-kit (CD117) in thymic carcinoma is a promising finding[28,29] because most types of thymoma and squamous cell carcinomas from other organ systems do not express this marker, and squamous cell carcinoma is the most common type of thymic carcinoma.[5,9]

5. Staging

The Masaoka staging system is the most popular and most widely accepted system for staging and predicting thymoma prognosis.[9,12,15,30] However, because most patients with thymic carcinoma are at an advanced stage (in our