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Original contribution

Thymic epithelial neoplasms with rhabdomyomatous component: a clinicopathological and immunohistochemical study of 7 cases☆

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Summary Seven primary thymic epithelial neoplasms, 3 thymomas and 4 thymic carcinomas, with rhabdomyomatous component are herein described. The patients are 2 women and 5 men between the ages of 42 and 62 years (average, 52 years). Clinically, the patients presented with nonspecific symptoms of cough, chest pain, and dyspnea. None of the patients had history of myasthenia gravis or of previous malignancy. Diagnostic imaging revealed the presence of an anterior mediastinal mass in all the patients. Surgical resection was accomplished in all the cases. The 3 thymoma cases were encapsulated tumors: histologically, 2 were lymphocyte rich (World Health Organization type B1), and 1 was an atypical thymoma (World Health Organization type B3). All the thymic carcinomas were ill-defined tumor masses with infiltrative borders and histologically were high-grade carcinomas. In each tumor, in different proportion, there were easily identifiable areas with rhabdomyomatous component characterized by larger cells with eosinophilic cytoplasm and eccentrically placed nuclei. Immunohistochemical stains in all cases showed clearly demarcated presence of the epithelial component (keratin positive/desmin and myoglobin negative) and the rhabdomyomatous component (desmin and myoglobin positive/keratin negative). The 3 patients with thymoma are alive and without recurrence 3 and 5 years after surgical resection, whereas 3 patients with carcinoma died between 2 and 3 years after surgical resection. One patient with thymic carcinoma was lost to follow-up. The current cases highlight the ubiquitous distribution of myoid cells in different types of thymic epithelial neoplasms.

1. Introduction

The existence of myoid cells in the normal thymus is well recorded in the literature and possibly dates back to the 18th century. However, Hammar is credited for introducing the term myoid cells in 1905, and subsequently, others were able to document the presence of these myoid cells [1-3]. Histologically, myoid cells seem to be located in the medulla of the thymus and seem to be more easily identified in the thymuses of reptiles and birds than in the human thymus [4]. Their existence in the human thymus is not well understood, and different arguments have been put forward to account for their presence including neural crest origin, derived from myoepithelial cells, or somatic transformation from germ cells [5,6]. In some pathological conditions, these myoid cells seem

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to be increased in thymuses of patients with myasthenia gravis or thymic hyperplasia [7,8]. Also, striated muscle cells seem to be more common in fetal and perinatal thymuses somewhere between 32 and 38 weeks of gestation. The presence of these myoid cells in the thymus has been of interest mainly because of the association of the thymus with conditions such as myasthenia gravis, myocarditis, and myositis [9]. On the other hand, some authors consider that myoid cells may be involved in thymic development by producing cytokines and chemokines [10].

The occurrence of these myoid cells in association with thymic epithelial neoplasms, namely, thymoma or thymic carcinoma, remains an unusual phenomenon. Nevertheless, the cases herein described show that the myoid component in these tumors may be encountered not only in patients without history of myasthenia gravis but also in a wide spectrum of histopathological growth patterns, and it does not seems to be restricted to some histologic types.

2. Materials and methods

The 7 cases herein presented were encountered in a review of more than 400 cases of thymic epithelial neoplasms, namely, thymomas and thymic carcinomas from the surgical pathology files at MD Anderson Cancer Center, Houston, TX, and from the personal files of one of the authors (C. A. M.) over a period ranging from 2001 to 2016 following approved institutional review board guidelines. In all the cases, the material available corresponded to thymectomy specimens. All available clinical information including pathological stage, histopathological features, and follow-up information was evaluated.

For histopathological evaluation, the number of hematoxylin-eosin sections varied from 5 to 8 (average, 6.5 sections per case). Immunohistochemical stains were performed in all the cases including the following: keratin cocktail (1:200, clone AE1/AE3; Dako, Santa Clara, CA), myoglobin (1:800; Dako), and desmin (1:15; Dako). Appropriate controls were run concurrently.

3. Results

3.1. Clinical features

The patients are 5 men and 2 women between the ages of 42 and 62 years (average, 52 years) who presented with nonspecific symptoms including chest pain, cough, and dyspnea. None of the patients had a history of myasthenia gravis or any other history of malignancy. Diagnostic imaging revealed the presence of an anterior mediastinal mass. Initial biopsy in 3 cases was interpreted as thymoma, whereas in 4 cases, the initial interpretation was that of thymic epithelial neoplasm. All the patients underwent surgical resection of the anterior mediastinal mass.

3.2. Macroscopic features

Three tumors were described as well-circumscribed tumor masses measuring in size from 4 to 5 cm in greatest diameter. The tumors showed a firm, slight lobulated cut surface, tan in color without hemorrhage or necrosis. On the contrary, 4 tumors were described as ill-defined tumor masses with infiltrative borders. These tumors measured from 4.5 to 6 cm in greatest diameter. They were firm and light tan in color, and in 1 case, focal areas of hemorrhage were present. None of the tumors seemed to infiltrate adjacent structures.

3.3. Microscopic features

In 3 tumors, the epithelial neoplasm corresponded to thymoma. Two of these thymomas were lymphocyte-rich (World Health Organization [WHO] type B1) characterized by the presence of a proliferation of lymphocytes admixed with epithelial cells in a slight lobular growth pattern. Higher magnification, in some areas, showed the presence of clusters of larger cells with abundant eosinophilic cytoplasm and displaced nuclei toward the periphery (Fig. 1). In the third case, the tumor showed predominantly an epithelial cell proliferation arranged in sheets or ribbons of cells admixed with clusters of similar myoid cells (Fig. 2A and B). The 3 tumors were completely encapsulated. Contrary to these cases, the other 4 cases were characterized by the presence of loss of the lobular growth pattern and showed the presence of islands of epithelial cells composed of medium-size cells with moderate amounts of cytoplasm and round nuclei and prominent nucleoli embedded in extensive areas of fibrocollagen. Cellular atypia and mitotic

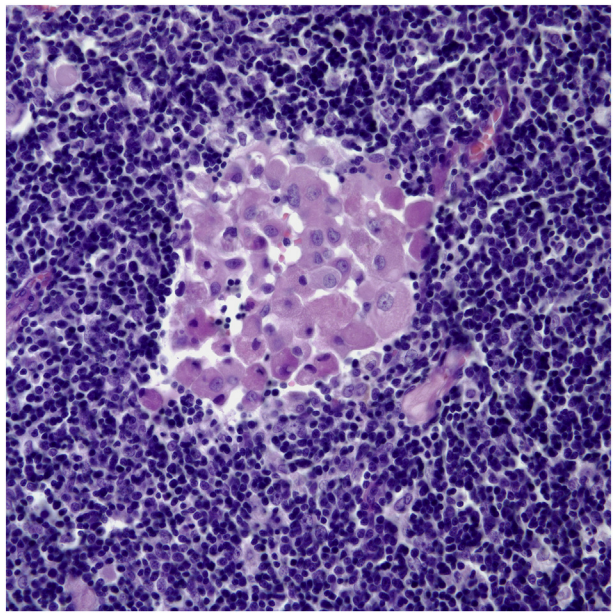

Fig. 1 Thymoma with prominent lymphocytic component (WHO type B1) with clusters of myoid cells (hematoxylin and eosin, original magnification ×40).

activity was present in these 4 tumors. In addition, within the clusters of malignant cells, there was the presence of larger cells with eosinophilic cytoplasm corresponding to myoid cells (Fig. 3A and B). The 4 tumors were not encapsulated and showed tumor extension into adjacent adipose tissue.

The thymomas were staged as Masaoka stage I/Moran stage 0. Regarding thymic carcinomas using the Masaoka system, they would be stage I, whereas using the Moran system, those tumors will be T1 N0.

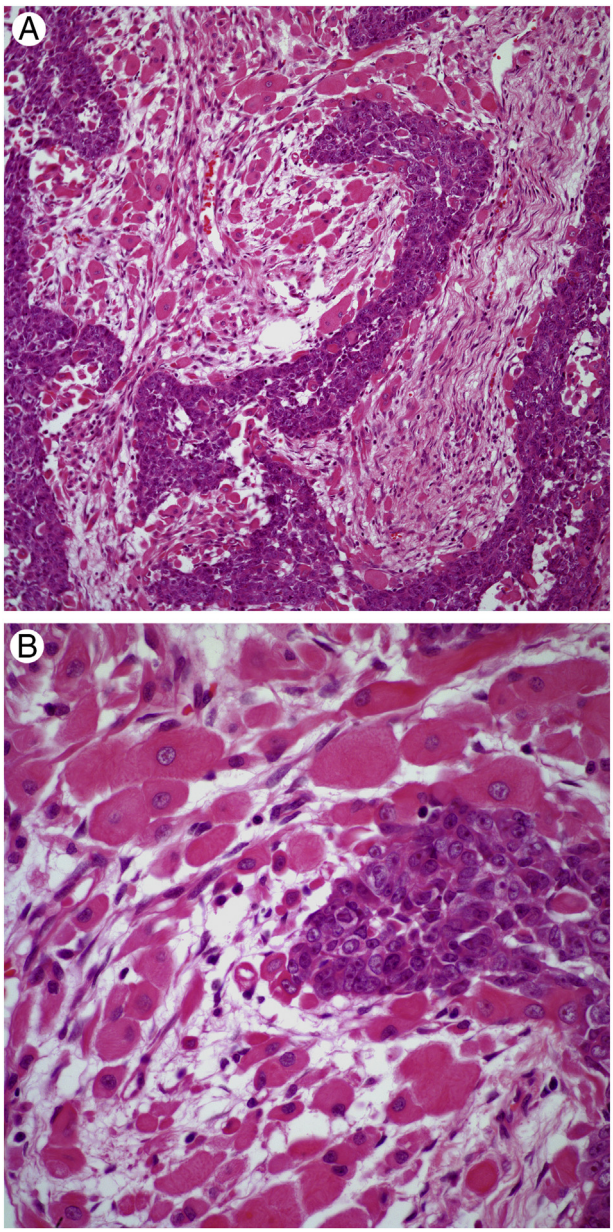

Fig. 2 A, Low-power magnification of a thymoma (WHO type B3) preserving some fibrous bands and admixed with numerous muscle cells (hematoxylin and eosin, original magnification ×20). B, Higher magnification showing clearly 2 different populations—epithelial and myoid (hematoxylin and eosin, ×60).

3.4. Immunohistochemical features

The areas of epithelial component showed strong positive reaction for keratin cocktail (Fig. 4A), whereas the large myoid cells showed positive staining for desmin and myoglobin (Fig. 4B) and negative for keratin.

3.5. Clinical follow-up

The 3 patients with thymoma remain alive and without recurrence 3 and 5 years after surgical resection. On the other

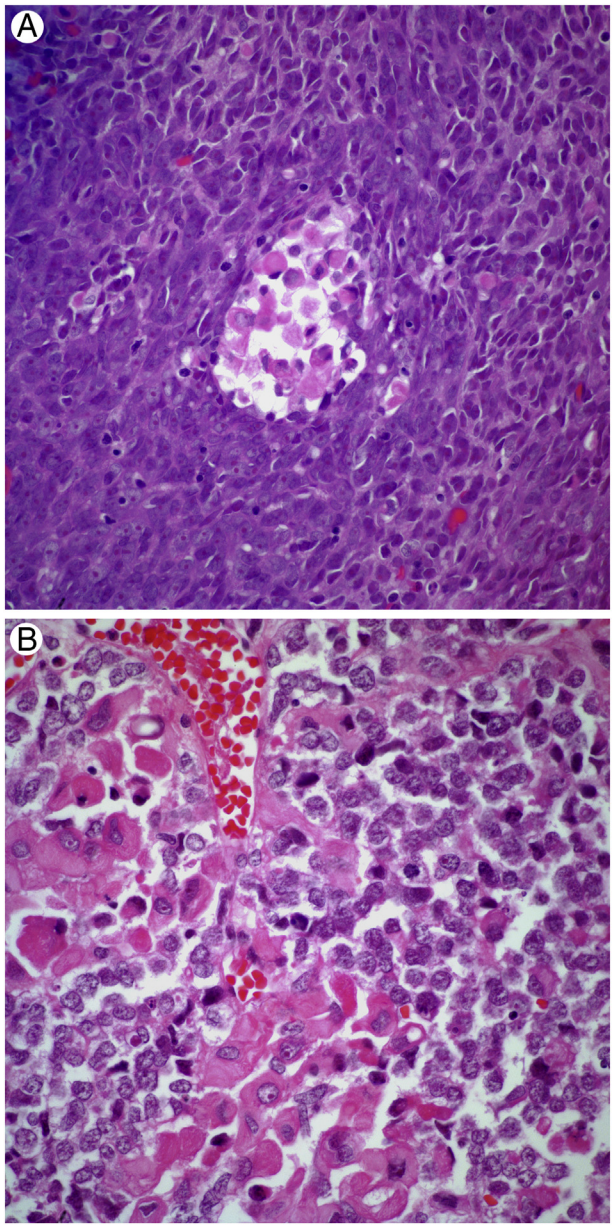

Fig. 3 A, Thymic carcinoma showing sheets of epithelial cells with a cluster of myoid cells (hematoxylin and eosin, original magnification ×40). B, Higher magnification of different areas where the myoid cells are more conspicuous (hematoxylin and eosin, ×60).

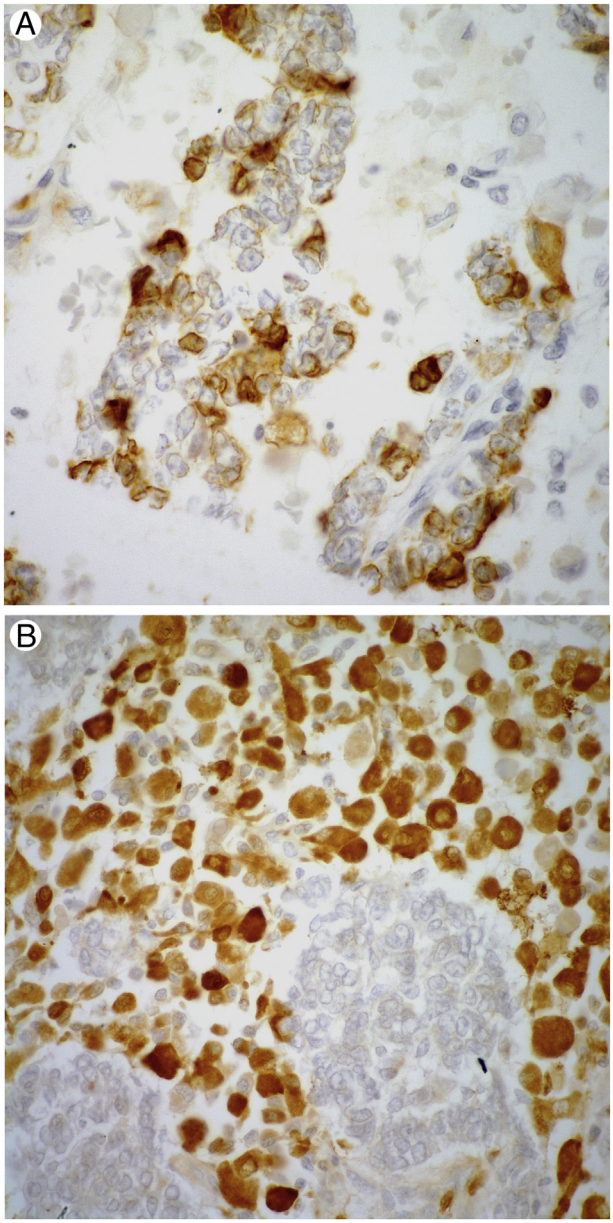

Fig. 4 A, Immunohistochemical stain for keratin is positive in the epithelial component (original magnification ×60). B, Immunohistochemical stain for myoglobin is positive in the myoid cells (×60).

hand, 3 of the patients with thymic carcinoma died within 2 and 3 years after surgical resection. One patient was lost to follow-up.

4. Discussion

The occurrence of myoid cells in different thymic tumors is a known fact that has been recorded in the literature. Myoid cells have been observed in thymolipomas, thymomas, and thymic carcinomas [11-18]. In addition, tumors of skeletal muscle and smooth muscle have also been described in the thymic region [19-21]. Another association that has been described in some thymic tumors is the occurrence of lipomatous tumors with muscle differentiation [22]. In addition, a group of tumors coded under the designation of carcinosarcomas of the mediastinum with skeletal muscle differentiation has also been described [23,24]. Therefore, the wealth of evidence regarding the presence of muscle differentiation, muscle component, or muscle tumors in the mediastinal pathology is well recognized.

However, it is important to highlight one important aspect—that the description of skeletal differentiation is often in reference to malignant skeletal muscle component. On the contrary, the presence of benign myoid component is much more unusual and uncommon in the background of thymic epithelial neoplasm, namely, thymoma and thymic carcinoma. In addition, it is important to highlight that the occurrence of muscle differentiation in most tumors with myoid component has been in tumors lacking significant lymphocytic component.

In some reported cases, although the tumors may have had an epithelial and myoid component, it is likely that the tumors in question may have had a different origin. For instance, Eimoto et al [17] reported 2 cases, which the authors coded as "thymic sarcomatoid carcinomas with skeletal differentiation." However, in closer attention to the description of at least one of the cases, the author stated that a focus of osteosarcoma was identified, which raises the possibility of a germ cell tumor with somatic transformation. In addition, judging by the illustrations presented, it is possible that these 2 tumors may in reality be sarcomas rather than thymic epithelial neoplasms with rhabdomyomatous component. Also, in the cases described by Okudela and Suarez Vilela [23,24] as thymic carcinosarcomas, the tumors showed true malignant mesenchymal component. Therefore, in these cases, it is somewhat expected that a mesenchymal component, in the form of either rhabdomyoma or rhabdomyosarcoma, be present.

In the cases of thymoma or thymic carcinoma, the issue is somewhat different as one would not expect the presence of myoid component. However, it is of interest to note that in the thymoma cases described, the tumors have been the type of thymoma that have scant presence of lymphocytes, which also is the same occurrence with thymic carcinoma. In some of the earlier cases of thymomas reported, although no specific designation was provided besides thymoma, it is possible that in at least one of those cases, in today's nomenclature, such tumor may have belonged to the atypical thymoma (WHO type B3) [13], whereas in others, the specific designation has been of spindle cell thymoma [15]. Regarding thymic carcinoma and rhabdomyomatous component, the case described by de Queiroga et al [16] is interesting because of the anatomic location of the tumor in the posterior mediastinum, which is highly unusual for a primary thymic epithelial neoplasm.

It is important to highlight that the description of myoid cells seems to be more common in normal thymuses of children or adolescents, and although thymic epithelial neoplasms are not common in children, those tumors that have been described in this group so far have lacked the presence of myoid cells. In the series of 10 cases of thymic epithelial neoplasms

reported by Ramon y Cajal and Suster [25], which includes thymomas and thymic carcinomas, none of the cases were reported as having muscle differentiation. Also, in the series of cases reported by Pescarmona et al [26], which included 5 cases of thymoma, none of the reported cases had muscle differentiation. This phenomenon has been described only in adult patients so far.

One other important observation is that in 2 of our cases, the tumors were lymphocyte rich, which is in contrast to most of the cases of thymoma that have been described containing myoid cells. Because this type of thymomas is also more common in myasthenia gravis patients, one would expect that such occurrence be more common in those thymomas resected from patients with this medical disorder. However, the 2 cases herein described are in non-myasthenic patients, which raises another important question—that myoid component can be seen in different types of histologic variants of thymoma. Nevertheless, we observed that the presence of rhabdomyomatous component is more prominent in tumors with less lymphocytic component.

Although the diagnosis of these tumors is rather straightforward in resected specimens, the diagnosis may not be so easily done in mediastinoscopic biopsies in which other tumoral conditions may be considered. Germ cell tumors are to be considered in male patients, as such tumors are more common in this group of patients, whereas true sarcomas or carcinosarcomas should be considered in all patients. One important differential diagnosis is with thymic carcinoma with rhabdoid features. Tropani et al [27] described such tumor as a single-case report in a 67-year-old man. The tumor was described as containing approximately 30% of the rhabdoid component. It is important to note that in this case the authors did not perform any muscle markers such as desmin or myoglobin to definitely exclude the possibility of muscle differentiation. However, judging by the illustrations provided and the description of positive staining of the rhabdoid cells for keratin, one can conclude that this tumor is not a rhabdomyomatous thymic carcinoma, therefore representing a true differential diagnosis for thymic carcinomas with rhabdomyomatous component.

One the other hand, one can argue that the rhabdomyomatous component is malignant, which would render this interpretation more of sarcoma if that were correct. However, the follow-up information in the thymoma cases coupled with the histology presented in some of those tumors would argue against the possibility of mixed epithelial/mesenchymal neoplasm. Regarding thymic carcinoma, the concept of "carcinosarcoma" becomes an important issue; however, the exclusive presence of myoid cells in the absence of more conventional features of rhabdomyosarcoma would be against such possibility.

In short, we have described 7 thymic epithelial neoplasms with rhabdomyomatous differentiation, 3 thymomas and 4 thymic carcinomas. The presence of myoid cells in these cases does not alter the prognosis in these tumors, as it is based on pathological stage of the tumor at the time of diagnosis. However, the presence of myoid cells in any given thymic tumor is rather unusual and may pose some problems in the interpretation of the tumor in small mediastinoscopic biopsies. The use of immunohistochemical stains may be of aid in these cases. However, it is important to properly identify this rhabdomyomatous component and not to misinterpret such occurrence of rhabdomyosarcomatous change.

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