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Original contribution

Thymic epithelial neoplasms with sebaceous differentiation: a clinicopathological and immunohistochemical study of 8 cases☆

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Summary Eight cases of primary thymic epithelial neoplasms corresponding to 7 thymomas and 1 thymic carcinoma with sebaceous differentiation are presented. The patients are 5 men and 3 women between the ages of 45 and 63 years (average, 54 years) who presented with nonspecific symptoms related to their mediastinal mass. All patients underwent complete surgical resection of the mediastinal mass. Grossly, all the tumors were described as round to oval measuring from 3.5 to 6.0 cm in greatest diameter. In 4 cases, the tumors were described as with infiltrative borders. Histologically, 1 tumor corresponded to thymic carcinoma characterized by irregular islands of tumors cells showing cellular atypia and mitotic activity. Six of the 7 thymomas showed mixed histologies corresponding to spindle cell, lymphocyte predominant, and mixed lymphocyte/epithelial types (World Health Organization types A, B1, and B2). One thymoma was mixed lymphocyte/epithelial (World Health Organization type B2). The areas of sebaceous differentiation characterized by clusters or strands of epithelial cells with ample clear cytoplasm were present within the lymphocytic component, whereas in the thymic carcinoma, the areas of sebaceous differentiation were identified within the epithelial component of the tumor. Follow-up information was obtained in 5 patients, showing that the patient with thymic carcinoma died 20 months after initial diagnosis, whereas the patients with thymoma whether encapsulated or minimally invasive remained alive without recurrence 12 to 24 months after initial diagnosis. The current cases represent an unusual feature that occasionally may be seen in thymomas and thymic carcinomas.

1. Introduction

Thymic epithelial neoplasms, namely, thymomas and thymic carcinomas, are tumors that display a wide spectrum of histologic features. Some of those histologic features are of the unusual type such as the presence of muscle [1,2], plasma cells [3], and papillary and pseudopapillary changes [4], or other unusual growth patterns that at times can represent a challenge in interpretation. Also interesting is that some of these unusual features may be seen in the normal thymus but rarely recapitulate in the tumor itself [5,6]. For instance, myoid cells are a component of the normal structure of the thymus. However, in thymomas and thymic carcinomas, such component has been described only rarely as an integral part of these

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tumors. Similarly, plasma cells, although more common in thymic carcinomas, are not a major component in thymomas. Other components of the normal thymus such as Langerhans cells, mast cells, and interdigitating reticulum cells only rarely have been described in primary thymic tumors [7,8]. One additional normal component of the thymus is the presence of sebaceous glands. However, the occurrence of this type of differentiation in the normal thymus is also rarely seen. Needless to say, sebaceous differentiation in thymoma and thymic carcinoma is a feature that has not been properly addressed in the literature.

The cases herein presented highlight that such occurrence, though rare, may also be encountered in thymomas and thymic carcinomas. We consider that such change does not impact prognosis, yet the identification of sebaceous differentiation may be useful in the overall characterization of these tumors.

2. Materials and methods

Eight cases of primary thymic epithelial neoplasm with sebaceous differentiation represent the basis of this report. The cases were identified after a review of approximately 550 cases of thymoma and thymic carcinoma. Therefore, representing approximately 1% of thymic epithelial neoplasms (thymoma and thymic carcinoma) with this particular differentiation in this cohort. All the cases represent surgical resections. Hematoxylin-eosin–stained sections ranging from 8 to 12 were available for review. Histochemical stain for mucicarmine was performed in all the cases. Immunohistochemical stains were also performed in all the cases using keratin 5/6 (1:50; Dako, Carpinteria, CA), keratin CAM 5.2 (1:50; BD Biosciences, San Jose, CA), and adipophilin (predilute; Fitzgerald, Acton, MA) with adequate controls. Clinical information was obtained from the respective clinical charts. This study was conducted following the guidelines of an institutional review board.

3. Results

3.1. Clinical features

The most salient clinical features are presented in Table 1. The patients are 5 men and 3 women between the ages of 45 and 63 years (average, 54 years). Clinically, the patients presented with nonspecific symptoms including shortness of breath, cough, and chest pain. None of the patients had a history of myasthenia gravis or any other autoimmune disease. Imaging disclosed the presence of an anterior mediastinal mass in all the patients. Surgical resection of the anterior mediastinal mass was performed in all the patients.

3.2. Pathological features

Macroscopically, the tumors were described as round to oval measuring from 3.5 to 6.0 cm in greatest diameter. The tumors were described as light tan without areas of necrosis or hemorrhage. In 4 cases, the tumors were described as with infiltrative borders, whereas in 4 cases, the description was of well-demarcated tumor mass.

Histologically, 1 case corresponded to a thymic carcinoma and was characterized by epithelial islands of tumor cells arranged in a haphazard pattern and embedded in a fibrocollagenous stroma. These epithelial islands were composed of medium-sized cells with eosinophilic cytoplasm, round nuclei, and prominent nucleoli. Nuclear atypia and mitotic activity was also identified. In some of these epithelial islands, there was the presence of a distinct component characterized by medium-sized cells with mildly vacuolated cytoplasm without nuclear atypia or mitotic activity. The features of this component are in keeping with sebaceous differentiation (Fig. 1). The remaining 7 cases corresponded to thymomas. Six cases of these thymomas showed mixed histologies: 2 cases showed spindle cell thymoma (World Health Organization [WHO]

Table 1 Clinical features of 8 cases of thymic epithelial neoplasms with sebaceous differentiation

Case no.	Sex/Age (y)	Symptoms	Diagnosis/Size	Encapsulate/Invasive	Follow-up
1	F/63	Shortness of breath	Carcinoma, 5.5 cm	Invasive into perithymic adipose tissue	Dead/20 mo
2	M/48	Chest pain	Thymoma, 6.0 cm (WHO B2)	Minimally invasive	Alive 14 mo
3	M/52	Cough, chest pain	Thymoma, 4.0 cm (WHO A/B1)	Encapsulated	Alive 16 mo
4	F/47	Chest pain	Thymoma, 3.5 cm (WHO B1/B2)	Encapsulated	N/A
5	M/59	Cough, chest pain	Thymoma, 5.0 cm (WHO B2/B3)	Minimally invasive	Alive 12 mo
6	M/45	Chest pain	Thymoma, 4.5 cm (WHO A/B2)	Encapsulated	N/A
7	F/57	Shortness of breath	Thymoma, 5.0 cm (WHO B1/B2)	Encapsulated	Alive 24 mo
8	M/49	Chest pain	Thymoma, 4.5 cm (WHO A/B1)	Minimally invasive	N/A

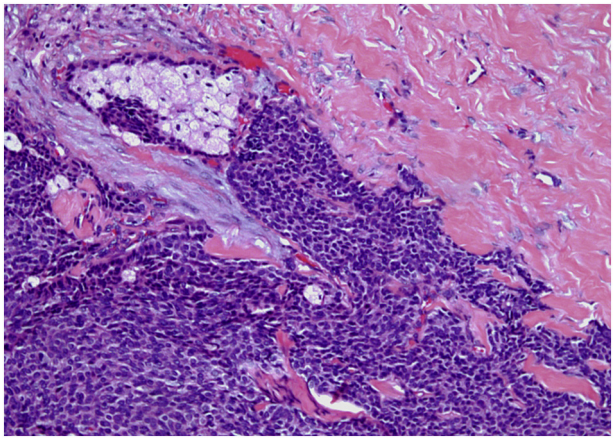

Fig. 1 A, Low-power view of a thymic carcinoma with an area of sebaceous differentiation (hematoxylin-eosin, original magnification ×20).

type A) in association with areas of lymphocyte rich thymomas (WHO type B1), and 1 showed spindle cell thymoma (WHO type A) and mixed cellularity thymoma (WHO type B2). Two cases showed a combined lymphocyte-rich thymoma and mixed epithelial/lymphocyte thymoma (WHO type B1/B2); 1 additional case showed a combination of atypical thymoma (WHO type B3) with mixed cellularity thymoma (WHO B2), whereas in 1 case, the histology was that of a mixed cellularity thymoma–epithelial/lymphocyte (WHO type B2). Of these 7 thymomas, 4 were encapsulated tumors, whereas 3 thymomas were minimally invasive (tumor breaching the capsule into perithymic adipose tissue).

In addition, in different areas, there was the presence of a cellular proliferation characterized by oval to polygonal cells with distinct cellular membrane, mildly vacuolated cytoplasm,

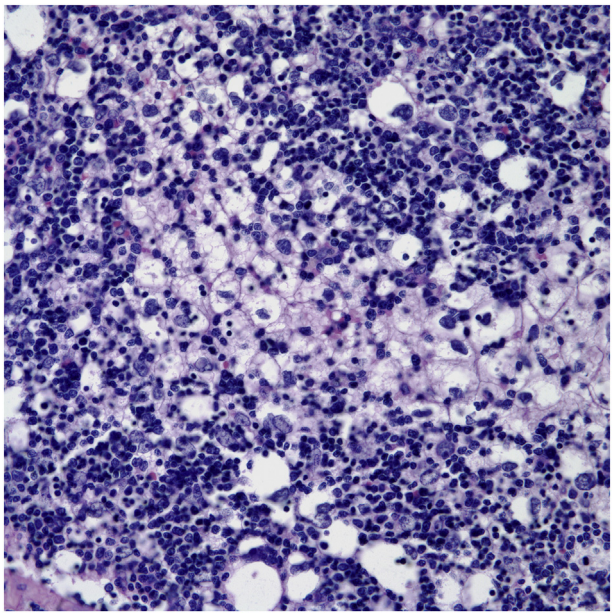

Fig. 2 Thymoma with sebaceous differentiation; note the presence of medium-sized cells with mildly vacuolated cytoplasm admixed with lymphocytes (hematoxylin-eosin, original magnification ×40).

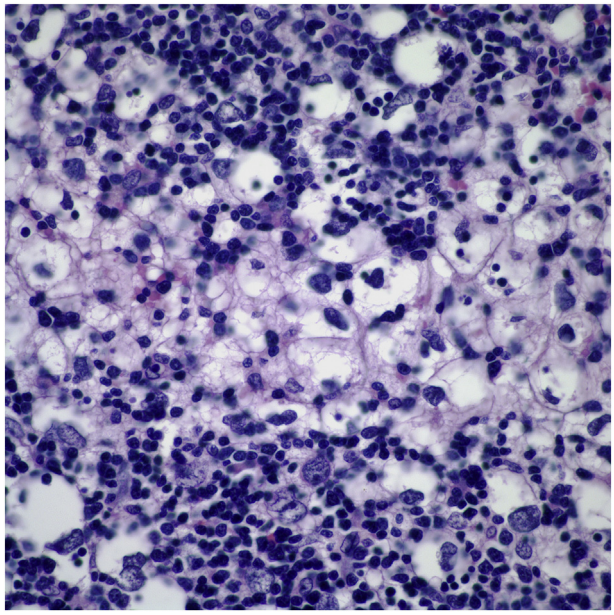

Fig. 3 Higher magnification of sebaceous differentiation in a thymoma showing absence of atypia and mitotic activity (hematoxylin-eosin, original magnification ×60).

and small nuclei. This cellular proliferation was embedded in a lymphocytic component (Figs. 2 and 3).

Histochemical stain for mucicarmine was negative in all cases, whereas immunohistochemical stains showed that the conventional stains for keratin CAM 5.2 and keratin 5/6 clearly decorated the epithelial component of all the tumors (thymomas and thymic carcinoma). In addition, adipophilin showed positive membranous vesicular staining pattern in the areas of sebaceous differentiation (Fig. 4).

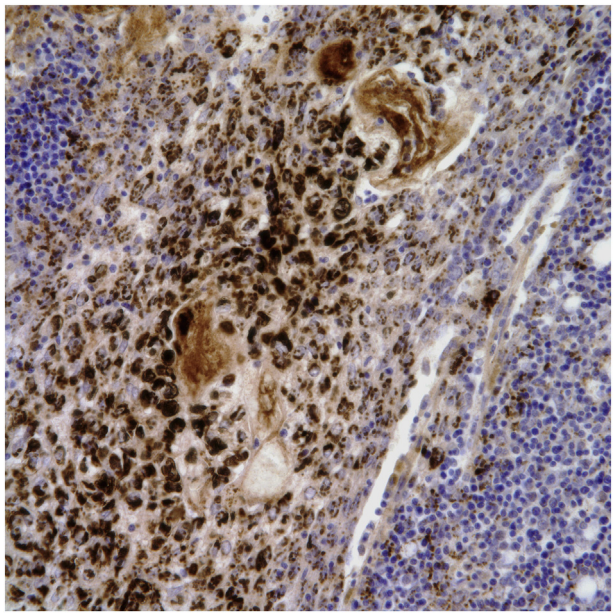

Fig. 4 Immunohistochemical stain for adipophilin showing positive staining in the areas of sebaceous differentiation (original magnification ×30).

Clinical follow-up was obtained in 5 cases, showing that 1 patient with thymic carcinoma died 20 months after initial diagnosis, whereas 4 patients with thymoma remain alive with no recurrence.

4. Discussion

Thymomas and thymic carcinomas represent some of the most common tumors in the anterior mediastinum. The overall heterogeneity of these tumors is well known, just as is the different nomenclatures and staging proposals presented over the years. In addition, the mediastinum is well known for the occurrence of tumoral conditions that are more often identified in other anatomical areas such as the salivary glands. For instance, the occurrence of primary salivary gland–type tumors of the thymus represents a small subset of unusual tumors that may give rise to some challenges in the final interpretation. Among the most common of these tumors are mucoepidermoid carcinomas but also other unusual tumoral conditions such as pleomorphic adenomas, epithelial-myoepithelial carcinoma, and thymic hyperplasia with lymphoepithelial sialadenitis–like features [9]. The descriptions of such tumors attest to the diversity of tumor pathology that can originate from the thymus. On the other hand, sebaceous differentiation has been mentioned only rarely in the literature.

Wolf et al [10] reported the occurrence of sebaceous glands within 3 thymuses, 2 of which originated from patients with myasthenia gravis. The authors clearly pointed out that the occurrence of sebaceous glands not associated with hair follicles might occur in anatomical areas such as the head and neck and the anogenital areas. Also, these glands have been described in the larynx and esophagus. The authors also stated that the origin of these sebaceous glands might be related to the reported ectodermal contribution to the developing thymus. It is important to highlight that in 2 cases, although the final diagnosis was that of thymoma, the sebaceous component was observed in the normal thymus adjacent to the thymoma and not in the thymoma itself. In addition, it is also important to highlight that, more recently, sebaceous lymphadenomas of the thymus have been described in 2 patients who presented with an anterior mediastinal tumor [11]. Such occurrence reinforces the concept of ectodermal differentiation in some thymic tumors. In addition, it reinforces the concept that many of the salivary gland tumors may recapitulate in the thymus.

The cases herein presented expand the knowledge that ectodermally derived tissues may also be part of the spectrum of differentiation of thymomas, just as they are part of the normal thymus. The cases described in this report are not any different clinically or macroscopically from other thymomas or thymic carcinomas. To some extent, the histology of these tumors can be reasonably placed into any of the current nomenclatures. However, the important aspect of these tumors is that in different areas, the tumor showed sebaceous differentiation, which has not been previously observed or at least documented in thymomas or thymic carcinomas. It is important to highlight that the sebaceous differentiation reported in normal thymus seems to be similar to the one reported in the current cases. In addition, it is important to state that the areas of residual thymic tissue in our cases did not show sebaceous differentiation. Such feature was observed in the tumor itself. However, theoretically, remnants of thymic tissue associated with the epithelial neoplasm could show sebaceous differentiation. Interestingly, in thymomas, this sebaceous differentiation seems to be present in areas in which the tumor shows lymphocytic component. However, in the case of thymic carcinoma, no lymphocytic component was associated with the sebaceous differentiation. Based on those observations, it would seem that sebaceous differentiation is a feature of the thymic epithelium that may be expressed with or without lymphocytic component. Although the occurrence of sebaceous differentiation is an unusual phenomenon in thymic tumors, the overall features present in these cases are not enough to warrant renaming these tumors as sebaceous thymomas. We also do not consider that the sebaceous differentiation is a feature that alters the prognosis in these tumors. Even in the case of thymic carcinoma in this study, it is highly unlikely that such feature had any role in the final outcome. However, such occurrence raises the possibility of unusual tumors such as sebaceous carcinomas or sebaceous thymomas.

In short, we have described 7 thymomas and 1 thymic carcinoma with areas of sebaceous differentiation, which expands the spectrum of tumor differentiation in these tumors. We do not consider that the diagnosis in any of these tumors is more difficult because of such differentiation, and it would be unlikely that such differentiation could be captured in a small mediastinoscopic biopsy. However, if such occurrence takes place, it is important to recognize that sebaceous differentiation may occur in these tumors.

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