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Case Report

Thymoma with Pseudosarcomatous Stroma

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Thymoma with psuedosarcomatous stroma is a recently described, rare variant of thymomas that are characterized by having a biphasic histologic pattern which consists of both an epithelial and a spindle cell stromal component. So far only 11 cases having similar histologic findings have been reported worldwide. At this time we report a case of this rare variant of thymoma which occurred in a 53-year-old Korean man. This previously healthy patient presented with coughing and an anterior mediastinal mass was then detected radiographically. Mediastinal exploration revealed a $9 \times 8 \times 8$ cm-sized well-encapsulated, ovoid, cystic mass. Histological examination showed a biphasic neoplasm composed of anastomosing nests of epithelial cells and somewhat cellular stromal spindle cells that had advanced degenerative changes. Immunohistochemical staining using the antibodies for cytokeratins, EMA, e-cadherin, and p75NGFR showed a strong expression of these markers in the epithelial component but no expression in the spindle stromal cells. The epithelial tumor cells showed no reactivity to CD5 and L26 and a high proportion of the infiltrated lymphocytes were the cortical type that expressed CD99 and terminal deoxynucleotidyl transferase. Ultrastructural examinations revealed tonofilaments in the spindle cells. Follow up has been done for 5 years after the surgical excision and the patient has been free of disease during that period. Similar to previous reports, this patient had a benign clinical course that was unassociated with myasthenia gravis which appears to be a characteristic of this histologic variant of thymoma. However, our case also showed advanced degenerative features and we could demonstrate ultrastructural evidence of epithelial differentiation in the stromal spindle cells that were not mentioned in the previously reported cases. Based on the results of our studies, we suggest this entity is a distinct type of organotypic thymoma that shows cortical differentiation and abundant cellular stroma.

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INTRODUCTION

Thymomas are tumors of thymic epithelial cells that have bland cytologic features. Although there has been much controversy about the histologic classification of thymomas, thymomas are histologically characterized by showing proliferation of polygonal cortical- or spindled medullary-type epithelial cells and a variable admixture of lymphocytes but they usually show a relatively narrow spectrum of histologic findings. Except for fibrous septa, which is most prominent in the B3 type according to new WHO classification,[1] thymomas usually do not show prominent stromal tissue. Recently a few histologic variants of thymomas have been described, and two reports[1,2] described 11 cases of newly defined biphasic thymic epithelial tumors which were composed of distinct epithelial cell nests admixed with prominent spindle cell stromal components. However, these authors used a different diagnostic nomenclature for this tumor because they had a different interpretation of the nature of the stromal component. We presently report the clinicopathologic, immunohistochemical, and ultrastructural features of this rare variant of thymomas that show a biphasic histologic pattern and compare our case with the previously reported cases.

CASE REPORT

A 53-year-old man presented with a large mediastinal mass in the left side in his chest

roentgenogram. His past medical history was unremarkable except for a recently developed cough and his physical examination and laboratory studies showed no abnormal findings. A mediastinal exploration revealed a well-demarcated, ovoid, soft mass that had not invaded the adjacent normal tissue and so a mass excision was done. Grossly, the specimen was a well-encapsulated, soft, ovoid mass, weighing 470 gm and measuring 9 × 8 × 8 cm. On sections, the mass was composed of a cyst which was filled with a grayish-brown friable tissue. A solid tissue that had a fine granular calcification was noted in the center (Fig. 1). Histologic examination showed that a large proportion of the tumor was affected by advanced degenerative changes. The solid area was characterized by well-demarcated anastomosing nests and cords of cohesive epithelial tumor cells in the dense spindle cell stroma and had scattered calcifications (Fig. 2). Residual normal thymus tissue could be observed along the periphery of the mass and a capsular invasion by the tumor cells was not present. The epithelial tumor cells were polygonal in shape, showed occasional spindling and had vesicular nuclei with fairly abundant eosinophilic cytoplasm (Fig. 3). Some of the epithelial tumor cells contained intranuclear cytoplasmic inclusions (Fig. 3, inset). No mitotic activity was observed. Although some of epithelial cells were plump with vesicular nuclei, no overt cytologically atypical findings were noted. Lymphocytes showed a patchy distribution mainly in the stroma with occasional intraepithelial distribution (Fig. 4). Some aggregates as well as singly scattered foamy histiocytes were also noted in the stromal component. The abundant stromal component appeared cellular due to the proliferation of bland-looking spindle cells that formed short fascicles (Fig. 5). Immunohistochemically, the epithelial tumor cells were strongly positive to cytokeratins (monoclonal cytokeratin AE1/AE3 and polyclonal pan-cytokeratin, DAKO, Carpinteria, CA, USA) (Fig. 6), epithelial membrane antigen (DAKO), low affinity nerve growth factor receptor, p75NGFR (Neo Markers, Fremont, CA, USA), and e-cadherin (Zymed Laboratories Inc., South San Francisco, CA, USA).

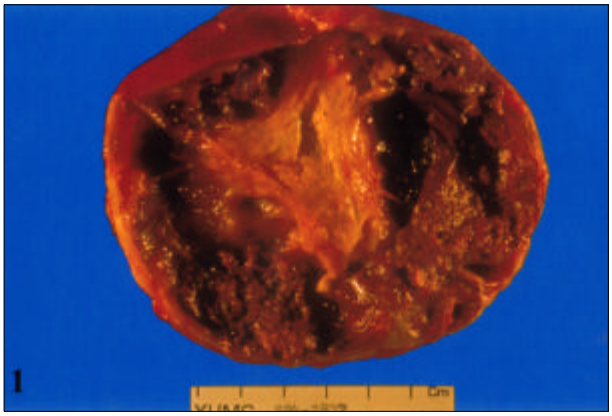

Fig. 1. Thymectomy specimen showing a well-encapsulated cystic mass having a central fibrotic portion.

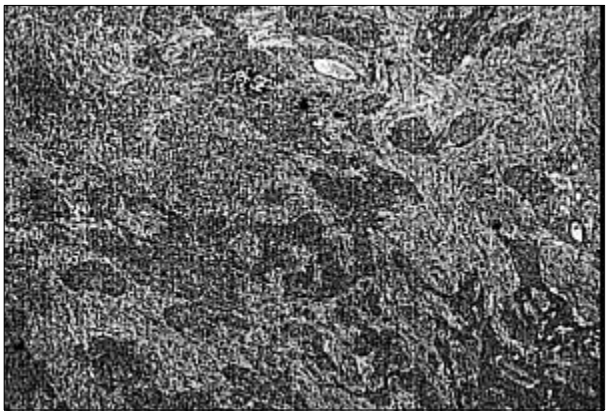

Fig. 2. Low magnification showing anastomosing nests and cords of cohesive tumor cells alternating with spindle stromal proliferation with multifocal calcifications (hematoxylin and eosin stain; original magnification, ×40).

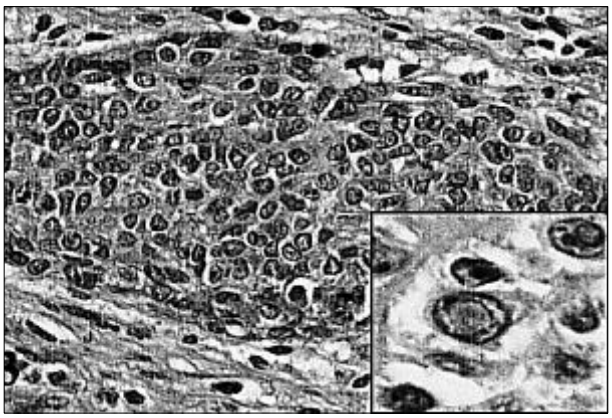

Fig. 3. High magnification of an epithelial component showing polygonal cells with occasional spindling that have vesicular nuclei and fairly abundant eosinophilic cytoplasm (hematoxylin and eosin stain; original magnification, ×400). Inset: Some of the epithelial tumor cells showed intranuclear cytoplasmic inclusions (hematoxylin and eosin stain; original magnification, ×1,000).

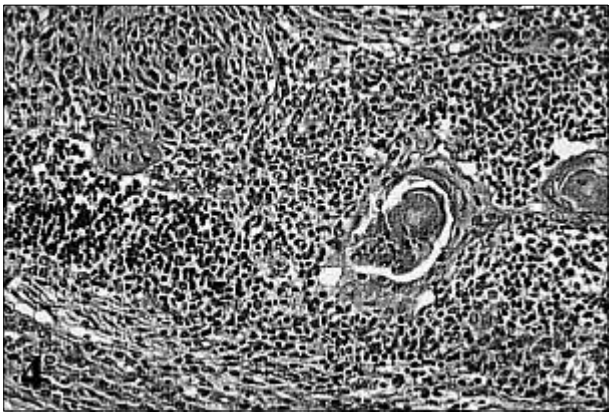

Fig. 4. Medium magnification showing stromal aggregates of lymphocytes (hematoxylin and eosin stain; original magnification, ×200).

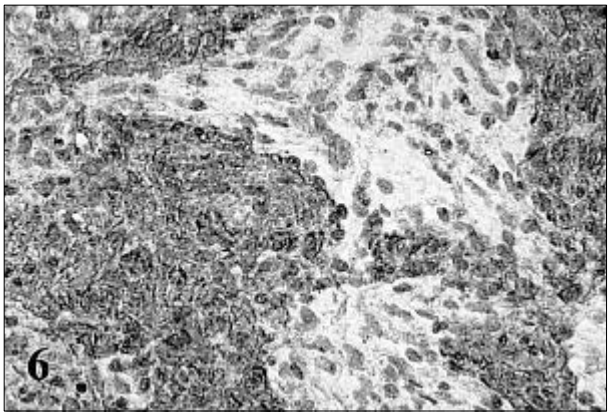

Fig. 6. Immunohistochemical staining for cytokerain AE1/AE3 showing a strong positivity in an epithelial component and a negative reaction in a stromal component (DAB with hematoxylin counterstain; original magnification, ×200).

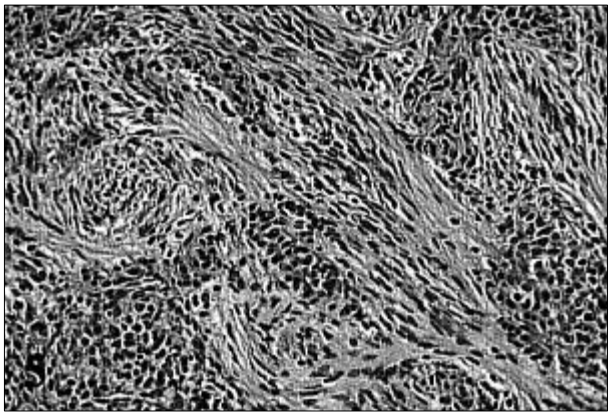

Fig. 5. Medium magnification showing a fascicular arrangement of bland-looking spindle stromal cells (hematoxylin and eosin stain; original magnification, × 200).

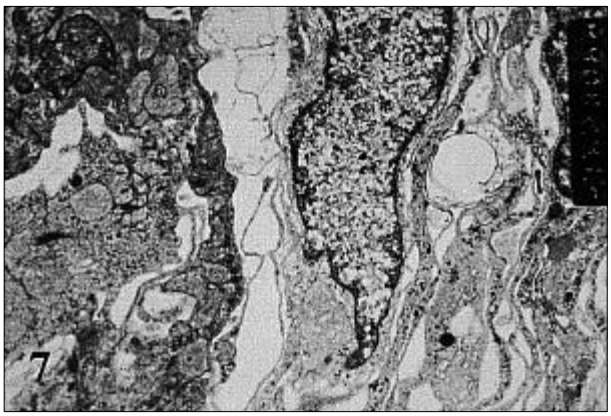

Fig. 7. Ultrastructural findings of the tumor showing well-formed desmosomes with focal basal lamina in the epithelial tumor cells. Little tonofilaments and some dilated endoplasmic reticulums are observed in the stromal spindle cells (Uranyl acetate, lead citrate, original magnification, ×890,000).

The stromal spindle cells were positive only to vimentin (DAKO) and did not express the epithelial markers previously listed. Expression of CD5 (Novocastra Laboratories Ltd., Newcastle upon Tyne, UK), and L26 (DAKO) in the epithelial cell component was not present. Some of the lymphocytes were positive to CD99 (DAKO) and terminal deoxynucleotidyl transferase (Novocastra laboratories Ltd.). Electron microscopic examination of the tumor showed well-formed desmosomes having a focal basal lamina in the epithelial tumor cells. The cytoplasm contained numerous bundles of tonofilaments and small amount of glycogen particles. Little tonofilaments and some dilated endoplasmic reticulums were observed in the stromal spindle cells but desmosomes were not present (Fig. 7).

DISCUSSION

We described a rare variant of thymomas that show a characteristic biphasic histologic pattern composed of nests and cords of polygonal epithelial cells admixed with abundant cellular spindle cell stroma. This case was identified during the process of reviewing over 100 cases of thymomas that were diagnosed in our hospital. Only 11 cases

with similar histologic features have been reported worldwide so far.[2,3] The new histogenetic classification of thymomas by Muller- Hermelink and his colleagues[4] stimulated pathologists' interest in thymomas and many papers have since been published. In contrast to thymic carcinomas which show a fairly wide histologic spectrum,[5,6] the histologic spectrum of thymomas seems to be relatively narrow and most cases can be accurately subtyped into the 5 categories of the histogenetic classification system. However, this histogenetic classification has not been universally adopted. Recently a WHO classification of thymic epithelial tumors[1] has been proposed to resolve debates about the histologic classification among pathologists. The WHO classification basically adopted the histogenetic classification of Muller-Hermelink and his colleagues but used a different nomenclature. However, our case appears to be unique and could not be classified adequately by any histologic classification system reported so far.

Thymomas usually shows a lobulated growth pattern and the stroma is indistinct except for broad fibrous bands that are characteristically observed in type B3 according to WHO classification1 and "well-differentiated thymic carcinoma" by the histogenetic classification.[4] Our case is unusual in that there is a marked stromal proliferation that is intermingled with epithelial cell nests. Recently, two groups[2,3] described a very rare variant of thymomas which were characterized by a biphasic proliferation of an epithelial and a stromal cell component as in our case. Shimosato and Mukai[6] also briefly listed this variant in their book. However, different diagnostic nomenclatures have been applied to this tumor. The paper by Suster and colleagues[2] used the nomenclature of "thymoma with pseudosarcomatous stroma" to describe this tumor while Shimosato and Mukai[6] used the designation of "epithelial cell predominant biphasic thymoma". Two years later, Yoneda and his colleagues[3] adopted the nomenclature of "low-grade metaplastic carcinomas of the thymus" and insist that their new 5 cases were different from the previously reported 6 cases of Suster et al.[2] Although the authors used different terminology, all the 11 reported cases were characteristically not associated with myasthenia gravis and the 6 cases with long-term follow up reported by Suster and colleagues[2] demonstrated a benign clinical course that was similar to our case. The discrepancy in nomenclature mainly stems from the author's different viewpoints as to the nature of the stromal component. Yoneda and colleagues[3] interpreted the stromal component to be a neoplastic component based upon the biphenotypic expression of epithelial and mesenchymal markers in the stromal cells and the gradual transition that was observed between the epithelial and stromal components, although they did not provide definite evidence by using more sophisticated molecular tests. Moreover, these authors adopted a more aggressive nomenclature, "carcinoma", for the epithelial component.[3] We performed immunohistochemical staining using classic epithelial cell markers (cyokeratins and EMA) as well as e-cadherin and $p75^{NGFR}$, which were reported to be expressed in thymomas,[7,8] but expression of these markers by the stromal spindle cells was not noted. However, ultrastructural examinations revealed a small amount of tonofilaments in the stromal spindle cells. The cytologic atypia of the epithelial cell component in our case was no more than that observed in cases of B3 type thymoma and the stromal cells of all the reported cases consistently have banal cytologic features although they are somewhat cellular. So we think that all of the 11 cases reported by the two groups using a different nomenclature and our case are in fact the same tumor but which show minor phenotypic variations. Compared with B3 type thymomas, this variant forms distinctively smaller anastomosimg epithelial cell nests. However, the cytologic features of the epithelial cells are similar and the strong expression of e-cadherin and lack of expression of L26 can be considered to be proof that supports an origin from the cortical epithelium.[7-9] Moreover, the large proportion of cortical type lymphocytes among the infiltrated lymphocytes can also be interpreted as a finding that favors the cortical nature of the epithelium. Consequently this type of thymoma might be considered to be a variant of type B3 thymoma. However the lack of association with myasthenia gravis and the benign clinical course indicates that this type of thymoma is a biologically distinct

entity different from B3 type thymoma. We think both "thymoma with pseudosarcomatous stroma" and "low-grade metaplastic carcinoma" are not appropriate nomenclatures for this type of thymic tumors because overt cytologic atypia is not observed in either the epithelial component or the stromal component. Moreover the clinical course seems to be that of a benign tumor so we think it's inappropriate to use the terminology of malignancy.

Once this variant of thymomas is recognized, the microscopic diagnosis is straightforward. Carcinosarcoma or sarcomatoid carcinoma can be easily excluded histologically by findings of overt pleomorphism.[5] If only areas that are composed of stromal cells are sampled, its morphology can mimic a type A thymoma. However, type A thymomas show no distinct epithelial cell nests and are diffusely immunoreactive for cytokeratin.

In conclusion, this report documents of an example of "thymoma with pseudosarcomatous stroma". Based on our immunohistochemical and ultrastructural examination results and clinical findings, we suggest that this entity is a rare distinct variant of organotypic thymoma that shows cortical differentiation and abundant cellular stroma.

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