Thymomas With Extensive Clear Cell Component

A Clinicopathologic and Immunohistochemical Study of Nine Cases

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ABSTRACT

Objectives: Nine cases of thymomas with an extensive clear cell component are presented.

Methods: The patients were six men and three women aged between 45 and 62 years (mean, 52 years). Presenting symptoms included shortness of breath, chest pain, and cough. Diagnostic imaging revealed anterior mediastinal masses in all patients, and all underwent thymectomy.

Results: Grossly, the tumors varied from 3 to 9 cm in the greatest dimension. Four cases were invasive and five encapsulated. Histologically, the tumors were characterized by an epithelial cell component with extensive clear cell change, admixed with lymphocytes in varying proportions. Immunohistochemically, the tumors demonstrated the typical immunophenotype of thymomas characterized by positive staining of the epithelial cells for pancytokeratin and cytokeratin 5/6, absent expression of CD5 and c-kit, and reactivity of the lymphocytes for terminal deoxynucleotidyl transferase. Clinical follow-up available for six patients showed that all were alive and well 12 to 24 months after surgical resection.

Conclusions: The cases herein presented highlight an unusual feature in thymoma that has more commonly been ascribed to thymic carcinoma. They also emphasize the importance of correct diagnosis to determine the appropriate treatment strategy and to accurately predict prognosis.

Thymomas and thymic carcinomas are unusual epithelial neoplasms that may show a vast spectrum of growth patterns and cellular components. Numerous histopathologic descriptions deal in great measure with the different patterns and histologic changes that these tumors may show.1-5 Traditionally, it has been stated that the presence of a clear cell component in these tumors correlates with thymic carcinoma, and such notion has been well documented in the literature.6-9 The presence of an extensive clear cell component, however, is an unusual feature that has not been ascribed to thymomas and one that may pose considerable diagnostic challenge mainly when dealing with limited material for evaluation such as a mediastinoscope biopsy specimen. It is logical to assume that if confronted with such a case, a pathologist is more likely to favor a carcinoma over thymoma, since clear cell change has traditionally been associated with thymic carcinoma.

The cases herein presented highlight not only the presence of such a phenomenon in thymoma but also underscore a more important issue: the limitations that a pathologist may face when dealing with small mediastinoscopic biopsy specimens in cases in which the histology departs from the conventional patterns. As illustrated by these cases, final interpretation of thymomas and thymic carcinomas is best performed only after complete surgical resection and appropriate sampling of the tumor has been accomplished. Failure to follow such parameters may lead to incomplete evaluation and possible misinterpretation of the findings.
Materials and Methods

The nine cases depicted in this series were identified during a review of more than 350 cases of thymomas from the files of the Department of Pathology at MD Anderson Cancer Center in Houston, Texas. All cases were derived from thymectomy specimens, and in all the cases, H&E-stained sections were available for review, ranging from 8 to 14 tumor sections. Each case was specifically staged using the MD Anderson Thymoma Staging Protocol. Unstained sections were available in all cases and were used for immunohistochemical evaluation. Immunohistochemical studies with concurrent adequate controls were performed using antibodies against pancytokeratin (CK) (1:100; Dako, Carpinteria, CA), CK5/6 (1:100; Dako), CD5 (1:20; Thermo Fisher Scientific, Fremont, CA), c-kit (1:400; Dako), and terminal deoxynucleotidyl transferase (TdT) (1:50; Dako). Clinical information and follow-up were obtained from review of the medical charts. The study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board.

Results

Clinical Findings

The most important clinicopathologic features are depicted in Table 1. The patients were six men and three women between the ages of 45 and 62 years (mean, 52 years). Clinically, eight patients had nonspecific symptomatology, which included chest pain, dyspnea, shortness of breath, and cough. A single patient had myasthenia gravis, which prompted radiologic investigations. Diagnostic imaging revealed the presence of an anterior mediastinal mass in all patients, and resection of the tumors was performed by median sternotomy.

Gross Findings

The resected tumors varied from 3 to 9 cm in the greatest dimension. Eight of these tumors were described as well-defined tumor masses with a homogeneous light tan-colored cut surface and firm consistency with no areas of necrosis or hemorrhage. In one case, the tumor was described as ill-defined with an infiltrative pattern into adjacent structures.

Histologic Findings

At low power, the tumors were characterized by sheets of epithelial cells with abundant clear cytoplasm admixed in areas with a variable proportion of small lymphocytes and oval nuclei with inconspicuous nucleoli, and ample clear cytoplasm. Although all cases contained some areas demonstrating the more typical features of thymoma, most tumors showed clear cell changes, representing approximately 70% to 80% of the tumor volume. Mitotic activity was absent in the epithelial component, and areas of hemorrhage and necrosis were not present either by gross inspection or microscopically. In five cases, the tumor was completely encapsulated while in three lesions, the capsule was breached and the tumor became minimally invasive into perithymic adipose tissue. Only in one of the cases, the tumor extended beyond the perithymic fat and was noted to infiltrate the pleura and lung parenchyma.

Immunohistochemical Findings

Immunohistochemical studies using CK and CK5/6 clearly outlined the epithelial clear cell component in all cases while CD5 and c-kit were negative and terminal deoxynucleotidyl transferase (TdT) decorated the nonneoplastic lymphocytic component.

Staging

Using the Moran staging system for thymomas, five cases were completely encapsulated tumors (stage 0), three cases were invasive into perithymic adipose tissue (stage I), and one case was invasive into the pleura and lung parenchyma (stage IIA).

Table 1

Clinicopathologic Features of Nine Patients With Thymoma With Extensive Clear Cell Component

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age, y</th>
<th>Symptoms</th>
<th>Stage</th>
<th>Size, cm</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/45</td>
<td>MG associated</td>
<td>I</td>
<td>4.5</td>
<td>A&amp;W at 14 mo</td>
</tr>
<tr>
<td>2</td>
<td>M/52</td>
<td>Dyspnea, cough</td>
<td>0</td>
<td>3.2</td>
<td>A&amp;W at 24 mo</td>
</tr>
<tr>
<td>3</td>
<td>M/56</td>
<td>Chest pain, dyspnea</td>
<td>IIA</td>
<td>9.0</td>
<td>A&amp;W at 18 mo</td>
</tr>
<tr>
<td>4</td>
<td>F/47</td>
<td>Chest pain, dyspnea</td>
<td>0</td>
<td>3.5</td>
<td>A&amp;W at 24 mo</td>
</tr>
<tr>
<td>5</td>
<td>M/49</td>
<td>Chest pain, SOB</td>
<td>0</td>
<td>3.0</td>
<td>A&amp;W at 12 mo</td>
</tr>
<tr>
<td>6</td>
<td>M/53</td>
<td>Dyspnea</td>
<td>I</td>
<td>3.8</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>M/57</td>
<td>Chest pain</td>
<td>0</td>
<td>3.5</td>
<td>A&amp;W at 24 mo</td>
</tr>
<tr>
<td>8</td>
<td>M/62</td>
<td>SOB</td>
<td>0</td>
<td>3.5</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>F/54</td>
<td>Chest pain</td>
<td>I</td>
<td>4.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

A&W, alive and well; MG, myasthenia gravis; NA, not available; SOB, shortness of breath.

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Follow-up

Clinical follow-up available for six patients showed that all were alive and well 12 to 24 months after their surgical resection. For three patients, clinical follow-up was not available.

Discussion

The existence of a clear cell component in thymic epithelial neoplasms has always been attributed to thymic carcinoma but not thymoma. The latest edition of the World Health Organization’s Pathology & Genetics: Tumours of the Lung, Pleura, Thymus and Heart contains a specific entry entitled “clear cell carcinoma” for a type of thymic carcinoma composed predominantly or exclusively of tumor cells with optically clear cytoplasm. On the other hand, in the same publication, there is no mention of such component among the different histopathologic growth patterns assigned to thymomas. Therefore, one could be misled to conclude that when such changes occur in a thymic epithelial neoplasm, the diagnosis would have to be thymic carcinoma. Historically, most reports on thymic carcinoma have elaborated on the fact that some of those tumors were composed of clear cells. In the description by Snover et al,6 of five distinct variants of thymic carcinoma, clear cell...
carcinoma is documented as one of those. Similar findings have also been documented in other series of thymic carcinoma, for instance, those by Truong et al,7 Kuo et al,8 and Suster and Rosai.9 In those series, there are well-documented cases of thymic carcinomas composed of clear cells. On the other hand, despite numerous reports on thymomas demonstrating different histopathologic growth patterns, the association with clear cell changes has not been addressed or properly emphasized.

Our experience with the current group of thymomas indicates that such change is unusual and likely affects only a minority of cases. After a review of approximately 350 thymomas, an extensive clear cell component was identified in less than 3% of these tumors. We believe that these changes should not be interpreted as an “atypical” histologic feature but likely represent yet another distinct growth pattern in thymomas. As reflected by the cases of our series, staging at the time of diagnosis remains the most important parameter to evaluate prognosis in these tumors just as it does for other types of thymoma. The use of immunohistochemical studies in this context is rather limited as there is not a single immunohistochemical stain that can unequivocally separate a clear cell thymoma from clear cell thymic carcinoma. Although CD5 and c-kit are considered immunomarkers more commonly associated with thymic carcinoma than thymoma, these markers are not specific for these tumors, and especially the clear cell variant of thymic carcinoma can show variable expression for CD512,13 and is often negative for c-kit.14,15 Even though all of our cases were negative for these two markers, such results should be carefully interpreted in combination with the morphologic appearance and never based on the results of immunohistochemical staining alone. As such, final diagnosis of such tumors is best deferred until complete evaluation of the tumor after surgical resection becomes available. It has to be stressed that in such cases, emphasis should not be placed on the classification of the thymoma but rather that close attention be paid to the correct interpretation of the changes present and to the pathologic staging of the tumor at the time of surgery.

The differential diagnosis of these unusual tumors can be fairly extensive if one considers the many tumors that can show clear cell features. With regard to primary thymic tumors, the biggest challenge arises when one is confronted with a small mediastinoscopic biopsy specimen. In such cases, it may be more advisable to state that the tumor shows clear cell features rather than making an unequivocal diagnosis of thymic carcinoma based solely on the presence of clear cells. Another primary thymic tumor that enters the differential diagnosis is mucoepidermoid carcinoma, which may also show extensive clear cell features.16 In addition, as is true for any mediastinal lesion, metastatic disease to the mediastinum may need to be excluded. In this setting, close attention to the clinical history along with detailed histologic examination and the use of immunohistochemical studies aimed at the suspected primary site should lead to the correct diagnosis.

In short, we are documenting the presence of an extensive clear cell component in thymomas, alerting to the fact that such a phenomenon should not be interpreted as a feature exclusive to thymic carcinomas. In addition, it is important to be aware that limitations to the interpretation of mediastinoscopic biopsy specimens may preclude an unequivocal diagnosis of either thymoma or thymic carcinoma. Hence, final interpretation can sometimes only be
achieved after surgical resection and generous sampling of
the tumor have taken place. The cases herein discussed rep-
resent an unusual histologic variant of thymoma that must
be recognized and properly analyzed when dealing with
these tumors. Awareness of this feature should help avoid
potential diagnostic errors.

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