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Original contribution

Primary thymic adenocarcinomas: a clinicopathological and immunohistochemical study of 16 cases with emphasis on the morphological spectrum of differentiation ☆

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Summary Sixteen cases of primary thymic adenocarcinoma are presented. The patients are 9 men and 7 women between the ages of 22 and 68 years (average, 45 years) who presented with non-specific symptoms including cough, chest pain, and dyspnea. Diagnostic imaging revealed the presence of an anterior mediastinal mass, which was surgically removed in all of the patients. Histologically, none of the tumors was encapsulated and showed different growth patterns including mucinous, non-mucinous, and papillary features. The majority of cases showed mixed growth pattern, and the tumor was limited to the mediastinum with only a few cases extending to lymph nodes or pericardium. In two cases, the adenocarcinoma was associated with a thymoma. Immunohistochemical stains were performed, and their positive staining varied depending on the histology of the tumors, showing positive staining in some cases for keratin 7, keratin 20, CEA, CD5, CD117, and CDX-2. PAX8 and TTF-1 were negative in all the tumors. Follow-up information was obtained in 10 patients over a period of 1 to 12 years, indicating that three patients had died within a period of 14 months, one with brain metastasis, while seven patients have remained alive without recurrence. The cases herein described span the spectrum of thymic epithelial tumors and highlight the importance of recognizing this particular type of carcinoma, as it may follow a different outcome and require different treatment options.

1. Introduction

Thymic carcinomas in general terms are unusual neoplasms that occur in the anterior mediastinum. Contrary to thymomas, which also occur more often in the anterior mediastinum, thymic carcinomas are rare, and only a few large series of cases have been presented in the literature [1-5].

Regarding thymic carcinomas, it is well known that the great majority of these tumors are represented by squamous cell carcinomas in different grades of differentiation. Some are keratinizing well differentiated, while others fall into the non-keratinizing poorly differentiated category. A small percentage of the remaining thymic carcinomas will fall into the unusual variants including anaplastic, rhabdoid, and hepatoid, among others [6-8]. However, even in a somewhat smaller percentage, there is another group of tumors that, although

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well recognized in the literature, may pose significant problems in determining primary site in the thymus, and that is thymic adenocarcinoma.

Herein, 16 primary adenocarcinomas are presented, in which it is highlighted not only the occurrence of these tumors in the thymus and the challenge that their diagnosis may pose but also the spectrum of histopathological growth pattern that may be seen in these tumors. Awareness of the occurrence of thymic adenocarcinomas in all its expression is important in order to properly ascribe site of origin, as these tumors in the thymus may follow a different clinical outcome and possibly may even be treated differently. This study highlights the potential challenges with the diagnosis as well as the importance of arriving at the diagnosis of thymic adenocarcinoma instead of a metastatic disease to the mediastinum, which may lead to a different clinical course and treatment.

2. Materials and methods

The 16 cases were identified in the surgical pathology files of the Department of Pathology at MD Anderson Cancer Center, Houston, TX, and the personal files of one of the authors (C.A.M.) over a period of time ranging from 2000 to 2016 following approved institutional review board (IRB) guidelines. In all of the cases, the material available corresponded to thymectomy specimens. The criteria for inclusion in this report were that none of the patients had any present or past history of adenocarcinoma anywhere, either within or outside of the thoracic cavity. In addition, cases with only biopsy material were not deemed appropriate for inclusion. All available clinical information including pathological staging, histopathological features, and follow-up, was carefully evaluated.

For histopathological evaluation, the number of hematoxylin-eosin sections varied from 8 to 15 (average: 11.5 sections per cases). In some cases, histochemical stains for mucicarmine were available. Paraffin blocks were available in 9 cases, and unstained sections were obtained to perform immunohistochemical studies. Immunohistochemical stains included CD5 (1:20, clone 4C7, Labvision, Norwell, MA), CEA (1:200, clone AB-2, Labvision), CDX-2 (1:50, clone CDX2-88, Biogenex, Fremont, CA), PAX8 (1:100, clone BC12, Biocare, Concord, CA), keratin cocktail (1;200, clone AE1/AE3, Dako, Sta Clara, CA) keratin 7 (1:100, clone OV-TL 12/30, Dako), keratin 20 (1:400, clone Ks 20.8, Dako), CD117 (1:100, polyclonal, Dako), TTF-1 (1:200, clone 8g7g3/1, Dako).

3. Results

3.1. Clinical features

The patients are 9 men and 7 women between the ages of 22 and 68 years (average: 45 years). None of the patients had prior history of malignancy, myasthenia gravis, or any collagen vascular disease. The chief complaints in these patients were chest pain, cough, and/or general malaise. Diagnostic imaging revealed the presence of an anterior mediastinal mass, and surgical resection was performed in all of the patients. The most salient features of the 16 patients are presented in Table 1.

3.2. Pathological features

Grossly, the tumors were described as soft, ill-defined tumor masses surrounded by adipose tissue and measuring from 5 to 14 cm in greatest dimension. In two cases, the tumors were described with extensive areas of gelatinous mucoid change, while in one case such change was described as focal. In two tumors, extensive areas of necrosis were noted, while in one other case, cystic changes were documented.

Histologically, none of the tumors was encapsulated, and the tumor penetrated adipose tissue and remnants of thymic tissue. In 13 cases the tumors were limited to the mediastinum, and the surgical resection borders were free of tumor. In two additional cases where the surgical borders of resection were negative for tumor, mediastinal lymph nodes showed metastatic carcinoma. In one case, the tumor invaded the pericardium. Vascular permeation of the tumor was not appreciated in any of the cases.

Essentially three main different patterns of growth were encountered in all the cases in variable proportions, and in all of the cases a minor component was also associated. These histopathological growth patterns are also depicted in Table 1.

3.2.1. Main growth patterns

3.2.1.1. Mucin-rich adenocarcinoma with features of the so-called "colloid carcinoma". The low-power view of this tumor shows extensive areas of mucin with only small clusters of malignant cells or malignant glands floating in the pools of mucin (Fig. 1A). In focal areas, the tumor may also show small cystic areas lined by mucinous type of epithelium with single malignant cells or malignant glands floating in the mucinous pools (Fig. 1B). At higher magnification, distorted small malignant glands can be seen embedded in the mucinous pools showing nuclear atypia and/or single clusters of malignant cells with marked nuclear atypia and single-cell necrosis (Fig. 1C and D). In one case, a focal area of the tumor showed areas of signet ring cell carcinoma. Of the 16 cases evaluated, three of them were composed predominantly of mucin-rich type of histology.

3.2.1.2. Non-mucinous adenocarcinoma. At low-power view, the tumor shows a proliferation of small glandular component arranged in small- or medium-size cords and embedded in a fibrocollagenous stroma (Fig. 2A). At higher magnification, the glands are formed by medium-size cells with moderate amounts of cytoplasm, round to oval nuclei, prominent nucleoli, nuclear atypia and mitotic activity (Fig. 2B). In other areas the tumor shows glandular proliferation composed of glands of different sizes with intraglandular necrosis with an intestinal-like pattern of growth (Fig. 2C),