Primary Mucinous Adenocarcinoma of the Thymus

A Case Report and Review of the Literature

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Primary thymic mucinous adenocarcinoma is extremely rare; to our knowledge, only 2 cases have been reported to date. We describe a third case of primary mucinous adenocarcinoma of the thymus in a 41-year-old man who presented with an anterior mediastinal mass with subsequent metastasis to the lung. The initial diagnosis was of metastatic mucinous adenocarcinoma, but extensive clinical workup of the patient failed to reveal a primary tumor elsewhere in the body. The specific identification of mucinous adenocarcinoma as a primary thymic neoplasm can be difficult or impossible. Morphologic and immunophenotypic similarities to mucinous adenocarcinomas of the gastrointestinal tract can pose diagnostic challenges for surgical pathologists, especially in small biopsy specimens.

(Arch Pathol Lab Med. 2006;130:201–204)

PATHOLOGIC FINDINGS

The anterior mediastinal mass was a pink-tan tumor measuring 10.5 × 8.0 × 2.5 cm and weighing 70 g. The cut surface revealed multiple, variable sized, multiloculated cysts separated by solid, hyalinized, and somewhat gelatinous areas containing mucin. The cysts had smooth walls and contained blood-tinged mucoid material. Friable papillary tissue projected into the lumina of some of the cysts.

On microscopic examination, most of the cysts were lined by attenuated cuboidal to pseudostratified columnar epithelium. The lining cells showed moderate amounts of eosinophilic cytoplasm and bland basal nuclei. In some cysts, the lining epithelium was denuded and inflamed. There was prominent lymphoid infiltration and myofibroblastic proliferation in the cyst walls. Remnants of normal thymic tissue in the form of small epithelial islands and lymphoid tissue were seen around these cysts (Figure 1). The solid areas consisted predominantly of nests and islands of malignant cells separated by dense hyalinized stroma (Figure 2) and were frequently seen floating in large pools of extracellular mucin (Figure 3). These cells were cuboidal to columnar and had clear cytoplasm containing abundant mucin. The neoplastic cells exhibited moderate nuclear pleomorphism with prominent eosinophilic nucleoli and occasional mitoses. In one of the cysts, the carcinomatous epithelium showed focal continuity with the benign epithelium. The specimen was sampled extensively, and no teratomatous component was identified. There was no evidence of a thymoma. Four mediastinal lymph nodes were negative for metastasis. Histologic sections of the lung nodules revealed a moderately differ-
Figure 1. A cyst lined by partially denuded cuboidal epithelium. The cyst wall shows residual thymic tissue, edema, and myofibroblastic proliferation (hematoxylin-eosin, original magnification ×100).

Figure 2. The primary thymic tumor shows malignant cells with intracytoplasmic mucin. Here, the cells are arranged in small nests with focal tubular differentiation (hematoxylin-eosin, original magnification ×200).

Figure 3. Another focus of the primary thymic tumor shows malignant cells floating in large pools of extracellular mucin (hematoxylin-eosin, original magnification ×200).

Figure 4. The neoplastic cells are focally positive for cytokeratin 7 (immunoperoxidase, original magnification ×400).

Figure 5. The neoplastic cells are strongly and diffusely positive for cytokeratin 20 (immunoperoxidase, original magnification ×200).

Figure 6. The neoplastic cells are focally reactive for CD5. The adjacent thymic T lymphocytes show strong reactivity for CD5 (immunoperoxidase, original magnification ×400).
entiated adenocarcinoma with prominent glandular differentiation and minimal extracellular mucin. There were focal microcalcifications and lymphovascular invasion. Immunohistochemical stains using antibodies to cytokeratin (CK) 7, CK20, CD5, carcinoembryonic antigen, epithelial membrane antigen, CDX2, villin, MUC1, MUC2, MUC5AC, prostate-specific antigen, thyroglobulin, thyroid transcription factor (TTF)-1, and BRST-2 (all from DakoCytomation, Carpinteria, Calif) were performed according to standard protocols with appropriate negative and positive controls. Both the thymic and lung tumors revealed focal, moderate cytoplasmic reactivity for CK7 (Figure 4) and diffuse, strong cytoplasmic and membranous positivity for CK20 (Figure 5). In contrast to the adenocarcinoma, the cells lining the benign thymic cysts were strongly positive for CK7 and negative for CK20. Focal positive staining for CD5 was localized to the cell membrane in 30% of the tumor cells (Figure 6). The lymphoid tissue in the cysts and adjacent thymic tissue was positive for CD5. The lung tumors also reacted diffusely positively for carcinoembryonic antigen, epithelial membrane antigen, villin, and CDX2; focally positive for MUC1 and MUC2; and negative for MUC5AC, BRST-2, prostate-specific antigen, thyroglobulin, and TTF-1. The final diagnosis was primary mucinous adenocarcinoma of the thymus with metastases to the lung.

**COMMENT**

Thymic carcinomas exhibit a wide range of morphologic features, which are sometimes indistinguishable from carcinomas arising in other organs. Of the different morphologic types, pure adenocarcinoma of the thymus is very rare, and to our knowledge, only 10 cases have been reported to date. Although the first case of primary thymic adenocarcinoma was reported in 1989, it was only in 1997 that adenocarcinoma was proposed as a valid histologic subtype of primary thymic carcinomas. In 1998, Matsuno et al described 4 cases of papillary adenocarcinoma of the thymus, 3 of which were associated with spindle cell thymoma. Choi et al described an unusual variant of thymic adenocarcinoma characterized by an abundance of extracellular mucin, similar to the colorectal mucinous adenocarcinoma. These authors emphasized the rarity of this variant of thymic adenocarcinoma and the importance of differentiating this tumor from metastatic carcinomas and germ cell tumors. Recently, Takahashi et al described a second case of mucinous adenocarcinoma of the thymus. To the best of our knowledge, the current case is only the third report of this variant of primary thymic adenocarcinoma.

Primary mucinous adenocarcinoma of the thymus is essentially a diagnosis of exclusion. By routine morphology alone, the tumor is indistinguishable from mucinous adenocarcinoma of the gastrointestinal tract, pancreaticobiliary tract, lung, and breast. Therefore, before considering the diagnosis of primary mucinous adenocarcinoma, a metastasis from the sites listed should be excluded. In addition, adenocarcinoma arising in a mediastinal teratoma or a thymic carcinoma with prominent mucinous stroma should be considered in the differential diagnoses.

In the current case, several features favor a primary mucinous adenocarcinoma of the thymus. The absence of detectable nonthymic primary tumor after an extensive clinical workup supports a thymic primary. Although a metastasis from an occult primary is theoretically possible, it is very unlikely that a metastasis will manifest as a large tumor in the thymus with no evidence of tumor elsewhere in the body. The absence of teratoma or thymoma, after thorough sampling of the tumor, supports a de novo thymic adenocarcinoma.

Choi et al emphasized the association of this tumor with thymic cysts and the transition from the benign to malignant epithelium as a feature favoring a thymic origin of this tumor. Thymic cysts can be acquired or congenital in origin. Acquired cysts are multiloculated and are the result of cystic dilatation of medullary ducts commonly associated with inflammation/fibrosis and neoplasms, such as thymomas, germ cell tumors, and lymphomas. The lining epithelium can be cuboidal, columnar, or squamous, with islands of thymic tissue present in the cyst wall. The cysts in our case fulfill all the criteria for acquired multicellular thymic cysts. It has been postulated that the thymic epithelium has the potential to undergo glandular differentiation, as evidenced by the presence of ciliated and mucinous-type cells in the epithelium of the cyst and Hassall corpuscles. A rare instance of malignant transformation of thymic cyst has been described. Although transition from the benign to malignant epithelium was noted focally in our case, it is not possible to rule out intraepithelial spread of the tumor along the lining epithelium of the cysts.

CD5 is a leukocyte marker expressed on differentiating thymocytes. It has been found to be useful in differentiating thymic from nonthymic carcinomas. The majority of thymic carcinomas demonstrate diffuse membrane staining. In the present case, the staining pattern for CD5 was membranous and focal, with weak to moderate intensity. A similar staining pattern was noted in the 2 previously described cases. In a study by Tateyama et al, some of the nonthymic adenocarcinomas, such as adenocarcinoma of the lung, stomach, and colon, showed weak to moderate staining for CD5. This raises the issue that CD5 may not be very useful in discriminating primary thymic from metastatic mucinous adenocarcinoma. Moreover, the focal nature of the staining pattern may result in a false-negative diagnosis.

The tumor showed diffuse and strong reactivity for CK20 in 90% of the tumor cells and only focal positivity for CK7 in 20% of the tumor cells. The epithelium of the benign cyst demonstrated strong cytoplasmic and membrane staining for CK7 and was negative for CK20. Choi et al noted only focal positive staining for CK20 and CK7 in their case. The normal thymic epithelium, including the cyst, was moderately positive for CK7 and negative for CK20. In contrast, the thymic mucinous adenocarcinoma reported by Takahashi et al was strongly positive for CK7 and negative for CK20; there was no associated thymic cyst. The CK7-positive/CK20-positive immunophenotype of this tumor is similar to that of pancreaticobiliary and gastrointestinal tract adenocarcinomas, highlighting both the diagnostic dilemma when dealing with small biopsy specimens and the importance of clinical and radiologic findings before considering the diagnosis of primary thymic mucinous adenocarcinoma.

The morphology of the lung metastasis, unlike the primary tumor, was characterized by prominent glandular differentiation with scant mucin production. Although the staining pattern for CK7, CK20, and CD5 was similar to that of the primary tumor, the positive staining for villin and CDX2 was an interesting finding. In fact, based on...
this immunohistochemical profile, a gastrointestinal primary was strongly suspected and resulted in gastrointestinal endoscopic examinations and biopsies being performed, all of which turned out to be negative.

While it is difficult to determine the prognosis on the basis of a small number of cases, it appears that thymic mucinous adenocarcinoma may behave more aggressively than the nonmucinous adenocarcinomas. The 2 patients with thymic mucinous adenocarcinoma described previously died 26 and 11 months after diagnosis. Our patient is alive with no evidence of disease 44 months after the initial diagnosis.

In conclusion, primary thymic mucinous adenocarcinomas are extremely rare tumors that require comprehensive clinical, radiologic, and morphologic workup. The absence of any characteristic histologic and immunophenotypic features and the focal staining pattern for CD5 can be a diagnostic challenge to surgical pathologists, especially when dealing with small biopsy specimens.

References