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Mucinous adenocarcinoma of the thymus: A distinct variant of thymic carcinoma

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ABSTRACT

Background: Primary thymic mucinous adenocarcinoma is a recently described subtype of thymic carcinoma, which behaves aggressively.
Methods: The authors analyzed the clinical and pathological findings of three cases of thymic mucinous adenocarcinoma, and reviewed five cases previously reported in the English literature.
Results: The patients were two males and one female between the ages of 38 and 55 years. Macroscopically, the tumors were mostly solid and white to yellowish–white. Areas with a gelatinous appearance were present. Histologically, all of the tumors were adenocarcinomas with abundant mucin production, which resembled the mucinous adenocarcinomas of other organs. Malignant tumor cells in nests, tubules and cribriform structures floated in pools of extracellular mucin. In one case, associated thymic cysts were found at the periphery of the tumor. The cyst wall was partially lined by malignant mucinous epithelium, which showed transition from benign thymic epithelium. Immunohistochemically, all of the tumors showed positive immunoreactivity for cytokeratin (CK) 20 and carcinoembryonic antigen (CEA). CD5 was diffusely positive in one case, and focally positive in the other two cases. The prognoses of these cases were extremely poor, and two of the patients died within 24 months.
Conclusion: Growing evidence suggests that mucinous adenocarcinoma is a distinct morphological variant of primary thymic carcinoma. We believe that clinicians and surgical pathologists should include thymic mucinous adenocarcinoma in the differential diagnosis of mediastinal adenocarcinoma.

1. Introduction

Primary thymic carcinomas are uncommon neoplasms that occupy the anterior mediastinum and frequently infiltrate adjacent organs, such as the lungs, pericardium and great vessels, even at the initial presentation [1–7]. The variability in the histology of thymic carcinomas has raised many diagnostic and therapeutic challenges for both clinicians and pathologists. Continuous efforts to identify distinct morphological entities among malignant tumors are indispensable, even in the era of molecular medicine. Since Shimosato et al. [1] established squamous cell carcinoma of the thymus as an entity in 1979, several other histological subtypes have been recognized, including basaloid, mucoepidermoid, lymphoepithelioma-like, sarcomatoid, clear cell and neuroendocrine carcinomas, as well as papillary adenocarcinoma [2–11]. Here, we present mucinous (colloid) adenocarcinoma of the thymus as a distinct entity of thymic carcinoma. The first case of thymic mucinous adenocarcinoma was recently reported by Choi et al. [12] in 2003, and five cases have been documented in the literature [12–15]. In this report, we define the clinical and pathologic features of this distinct morphological variant of thymic carcinoma, reporting three additional cases from our institutions, so that this entity will become better recognized among clinicians and surgical pathologists.

2. Patients and methods

Cases of thymic mucinous adenocarcinoma diagnosed between January 2000 and April 2008 were retrieved from the surgical pathology files of Mitsui Memorial Hospital and the University of

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Table 1
Antibodies used in this study

Antibody	Clone	Dilution	Vendor
Pan-cytokeratin	AE1/AE3	1:100	Dako
Epithelial membrane antigen (EMA)	E29	1:100	Dako
Cytokeratin 7	OV-TL 12/30	1:100	Dako
Cytokeratin 20	Ks 20.8	1:25	Novocastra
CD5	4C7	1:50	Novocastra
Carcinoembryonic antigen (CEA)	II-7	1:50	Dako
Thyroid transcription factor 1 (TTF-1)	SPT24	1:100	Novocastra
Surfactant apoprotein A (Sp-A)	PE-10	1:100	Dako
Synaptophysin	Polyclonal	1:100	Dako
Chromogranin A	Polyclonal	1:200	Dako
Calretinin	5A5	1:100	Novocastra
MUC2	Ccp58	1:200	Novocastra
MUC5AC	CLH2	1:100	Novocastra
MUC6	CLH5	1:100	Novocastra
CDX2	CDX2-88	1:50	BioGenex

Tokyo Hospital. During this period, 119 primary thymic tumors were resected at the institutions. The cases included 94 thymomas, 11 thymic carcinomas, 10 germ cell tumors, 3 malignant lymphomas, and 1 case of adenocarcinoma arising from an immature teratoma. The resected thymic carcinomas consist of several histological subtypes: five squamous cell carcinomas, three mucinous adenocarcinomas, two well-differentiated neuroendocrine carcinomas, and one poorly differentiated neuroendocrine carcinoma. Formalin-fixed paraffin-embedded tissues were used for histopathological, histochemical and immunohistochemical studies. Immunohistochemistry was performed on deparaffinized sections using the primary antibodies listed in Table 1. Heat-induced antigen retrieval in sodium citrate buffer (pH 8.5) was performed for all of these antibodies, except for chromogranin A. The immunohistochemical reactions were performed in a Ventana BenchMark XT autostainer. Antigen–antibody reactions were visualized using the labeled streptavidin–biotin method. Appropriate controls were included. Immunopositivity was assessed as follows: +++, >50% of the tumor cells were positive; ++, 25–50% of the tumor cells were positive; +, 5–25% of the tumor cells were positive; –, <5% cells were positive. All of the patients have been followed at one of the institutions. The clinical, operative, and radiological findings were reviewed retrospectively using the departmental reports and radiological images.

3. Results

3.1. Clinical findings

The clinical details of our cases along with those of reported cases are summarized in Table 2. In our series, all of the patients presented with a tumor in the anterior mediastinum. Two of the patients were men and one was a woman. The age of the patients ranged from 38 to 55 years (mean 48.3 years). Extended thymectomy with combined resection of the pericardium and adjacent great vessels was performed in all three cases. In case 3, the patient underwent concurrent upper lobectomy of the left lung for a metastatic lesion.

3.1.1. Case 1

A 52-year-old woman presented with bulging of the left parasternal region. Magnetic resonance imaging (MRI) and computed tomography (CT) of the chest revealed an anterior mediastinal mass, 7.5 cm in diameter (Fig. 1A). Small cystic lesions, 20 mm in maximum diameter, were observed at the periphery of the tumor (Fig. 1B). The serum carcinoembryonic antigen (CEA) level was within the normal range (3.8 ng/ml). A thorough physical examination, whole-body positron emission tomography (PET), and CT of the abdomen and head were performed to exclude a metastatic neoplasm to the mediastinum. These examinations revealed no evidence of a primary neoplasm elsewhere. The patient underwent extended thymectomy with combined resection of the sternum, left ribs, pericardium and left brachiocephalic vein. Since carcinoma was identified in the surgical margins on microscopic examination, chemotherapy (cisplatin + etoposide) and radiotherapy were added postoperatively. However, metastases developed in the right lung and cervical lymph nodes at 7 months. Additional chemotherapy (carboplatin + paclitaxel) proved ineffective. The patient is currently alive with disease at 11 months.

3.1.2. Case 2

A 38-year-old man presented with chest pain and was found to have an anterior mediastinal mass, 5 cm in diameter. A needle biopsy of the mediastinal mass led to a diagnosis of thymic carcinoma with mucin production. The serum CEA and carbohydrate antigen (CA) 19-9 levels were elevated at 23 ng/ml and 610 U/ml respectively. Extensive clinical examinations, thoracoabdominal CT, gastrointestinal endoscopy, abdominal ultrasound and

Table 2
Clinical features of the reported thymic mucinous adenocarcinomas

Report	Sex/age	Signs and symptoms	Tumor size (cm)	Associated thymic cyst	Treatment	Clinical course/follow-up
Current series (case 1)	F/52	Parasternal bulging	9.5 × 6.0 × 5.5	(+)	S (R1), XRT, CT	MTS: lung, cervical lymph node; AWD at 11 months
Current series (case 2)	M/38	Chest pain	8.0 × 7.0 × 3.5	(–)	S (R2), XRT, CT	MTS: bone, DOD at 12 months
Current series (case 3)	M/55	Chest tightness	13.0 × 7.0 × 4.5	(–)	S (R0), XRT, CT	MTS: bone, liver, lungs, adrenal gland; Diss: pleura, meninges; DOD at 24 months
Choi et al. [12]	M/15	Cough	8.0 × 5.0 × 4.0	(+)	S (R0), XRT	MTS: bone; DOD at 26 months
Takahashi et al. [13]	M/59	N/A	Exceeding 10 cm	(–)	XRT	DOD at 11 months
Kapur et al. [14]	M/38	N/A	10.5 × 8.0 × 2.5	(+)	S (R0), XRT, CT	MTS: lung (resected); NED at 12 months
Ra et al. case 1 [15]	F/61	Hoarseness, dysphagia, shoulder pain, fatigue	5.2 × 3.9	(–)	S (R0), XRT	MTS: retroperitoneal lymph nodes (at 5 months)
Ra et al. case 2 [15]	F/82	Shortness of breath, chest tightness, back stiffness, weight loss	14.5 × 7.0	(+)	S (R0)	Passed away from complications of surgery

M, male; N/A, no information available; S, resection; R0, complete resection; R1, microscopic residual disease; R2, macroscopic residual disease; XRT, radiotherapy, CT, chemotherapy; Diss, dissemination; MTS, metastases; DOD, died of disease; AWD, alive with disease; NED, no evidence of disease.