Case Report

KRAS mutation-positive mucinous adenocarcinoma originating in the thymus

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Abstract: Thymic carcinoma is a rare, aggressive disease with a low 5-year survival rate. The most common histological neoplastic thymic tumor subtype is squamous cell. We describe an interesting case of a 39-year-old woman who presented with mucinous adenocarcinoma that originated in the thymus and was treated via radical resection and venoplasty of the superior vena cava (SVC). Macroscopically, the resected tumor contained a solid region and multiple cysts with abundant mucin. Microscopic examination showed a papillary growth pattern of goblet cells with round nuclei. Based on the histopathological and immunohistochemical findings and other inspections, the tumor was eventually diagnosed as a mucinous adenocarcinoma of the thymus. It was classified as Masaoka-Koga stage III owing to tumor invasion into the left brachiocephalic vein and pericardium. Polymerase chain reaction identified a Kirsten rat sarcoma viral oncogene homolog (*KRAS*) G12V mutation in the tumor. There were no mutations in the epidermal growth factor (*EGFR*) gene or a fusion gene of the echinoderm microtubule-associated protein-like 4 (*EML4*) and the anaplastic lymphoma kinase (*ALK*). A year later, multiple lung metastases were detected, and the patient underwent chemotherapy. She is alive 34 months after the initial surgery. This is the first report of a *KRAS* mutation-positive mucinous adenocarcinoma originating in the thymus. The treatment, diagnosis, and pathological findings of the patient are discussed.

Keywords: Thymus neoplasms; immunohistochemistry; polymerase chain reaction

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Introduction

Thymic carcinoma is a rare, aggressive disease with a low 5-year survival rate (1-4). Previous report showed that most frequent subtypes were mucinous and papillary subtypes, among 43 cases of thymic adenocarcinoma (5). Primary thymic mucinous adenocarcinoma must be differentiated from metastasis from an extrathymic disease by immunohistochemical findings (5,6).

The detection of *KRAS* mutation in the mucinous proliferations provides further evidence of their neoplastic nature, and such *KRAS* positive mucinous adenocarcinoma of the pancreatic, colorectal, and lung have been associated with a more aggressive clinical course (7-9).

Here we describe a case with a *KRAS* mutation-positive thymic mucinous adenocarcinoma. The diagnosis and treatment of the patient as well as the association between *KRAS* mutation and prognosis are discussed.

Case presentation

A 39-year-old, previously healthy woman was referred to our hospital because of an abnormality on a chest computed tomography scan. The scan revealed a heterogeneous mass 6.5 cm in size in the anterior mediastinum (*Figure 1*). The tumor had invaded the left brachiocephalic vein

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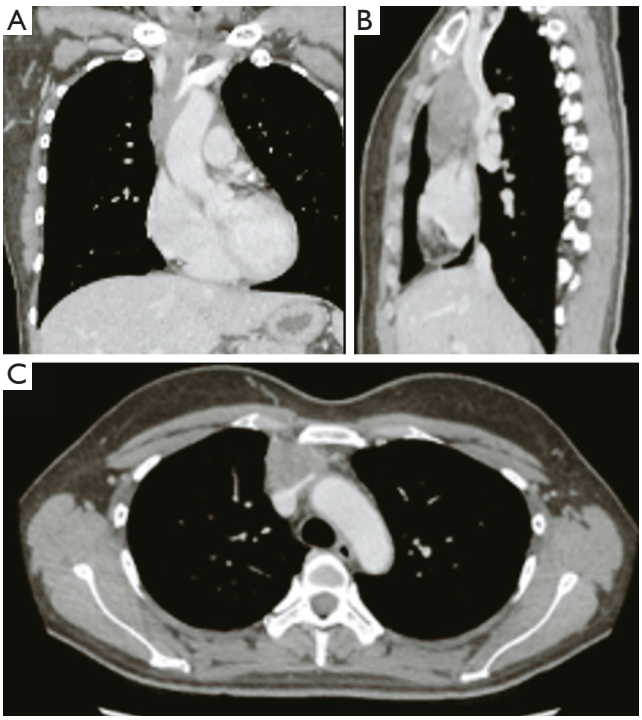

Figure 1 Contrast-enhanced computed tomography of the chest shows a solid heterogeneous structure in the anterior mediastinum. (A) Coronal section; (B) sagittal section; (C) transverse section. The tumor directly extended to the left brachiocephalic vein and pericardium.

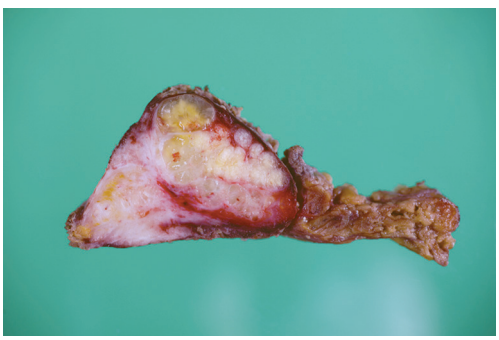

Figure 2 The tumor was mainly solid and contained multiple cysts with abundant mucin.

and pericardium. ^{18}F-fluorodeoxyglucose positron emission tomography showed uniform, mild accumulation of ^{18}F-fluorodeoxyglucose (standardized uptake value: 4.77) in the mediastinal mass. The serum level of carbohydrate antigen 19-9 (CA19-9) was 80.5 U/mL (normal: 0–37 U/mL), while the levels of other markers were within the normal range.

The patient underwent radical resection via median sternotomy following a preoperative clinical diagnosis of thymic carcinoma. During the operation, combined resection of the pericardium, right phrenic nerve, right internal artery, and left brachiocephalic vein was performed owing to tumor invasion. Partial resection and venoplasty with a pericardium patch for the superior vena cava (SVC) were also performed via a temporal bypass between the left brachiocephalic vein and right atrial appendage, using a 6-mm polytetrafluoroethylene graft. The total operation time was 699 min, and amount of blood lost was 702 mL.

Macroscopically, the resected tumor was 6.5 cm × 3.5 cm in size and contained a solid region and multiple cysts with abundant mucin (*Figure 2*). Microscopic examination showed a papillary growth pattern of goblet cells with round nuclei (*Figure 3A*). On immunohistochemistry, the resected tumor was positive for caudal type homeobox 2 protein, cytokeratin 7, and cytokeratin 20 (*Figure 3B-D*), focally positive for CD5, and negative for thyroid transcription factor RNA polymerase I and surfactant apoprotein A; these findings suggest intestinal or ovarian differentiation of the tumor. Subsequent gastrointestinal endoscopy, colonoscopy, abdominopelvic sonography, and imaging analysis did not provide any indication of another primary origin. The serum level of CA19-9 temporarily decreased after the surgery.

Based on the histopathological and immunohistochemical findings and those of other inspections, the tumor was eventually diagnosed as a mucinous adenocarcinoma of the thymus. It was classified as Masaoka-Koga stage III owing to tumor invasion into the left brachiocephalic vein and pericardium.

Polymerase chain reaction identified a G12V mutation in the *KRAS* gene in the tumor. There were no mutations in the *EGFR* gene or *EML4-ALK* fusion gene. The postoperative course was uneventful, and the patient was discharged on postoperative day 5 while undergoing anticoagulation therapy because of the SVC venoplasty. A year later, multiple lung metastases were detected, and the patient underwent chemotherapy. She is alive 34 months after the initial surgery.

Discussion

Primary thymic adenocarcinomas are exceptionally rare, and the most common subtype is squamous cell (1). Although an evidence-based standard treatment for thymic adenocarcinoma has not been established, surgical resection is typically performed in resectable cases, whereas

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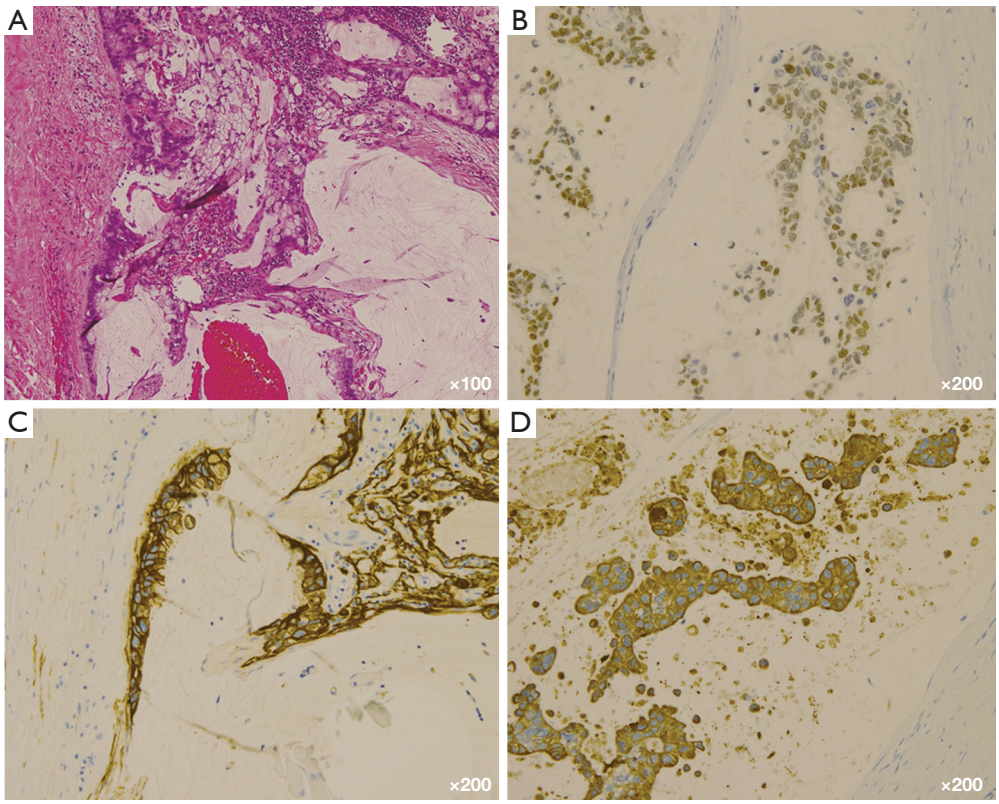

Figure 3 Microscopic findings reveal (A) a papillary growth pattern of goblet cells; (B) immunohistochemical staining of caudal type homeobox 2 protein; (C) cytokeratin 7; (D) cytokeratin 20.

chemotherapy, radiation, or both may be indicated in unresectable or metastatic cases (2,3). However, complete removal of thymic malignancy is often difficult because the tumor is frequently invades into the surrounding organ and tissue. In current case, adjuvant therapy was not conducted due to patients' preference, however multiple lung metastases were detected a year after surgery. A recent nationwide cohort study indicated that a significant overall survival benefit with postoperative radiation therapy was found among the patients with thymic malignancies who received chemotherapy (4).

Among the 43 primary thymic adenocarcinomas examined in a recent study, most were the mucinous or papillary subtype (5). Mucinous adenocarcinoma of the thymus resembles mucinous adenocarcinoma of the gastrointestinal tract, pancreas, breast, lung, and ovary. The carcinoma cells contain abundant amounts of mucin in their cytoplasm and often assume a goblet cell or signet ring cell morphology. In cases of mucinous thymic adenocarcinomas, it is necessary to exclude metastasis from other organs (6). Although various immunoprofiles for thymic adenocarcinomas have been reported, the immunohistochemical findings in the study by Moser *et al.* (5) were the same as those described here. However, no previous studies reported *KRAS* gene mutations in mucinous thymic adenocarcinomas.

KRAS mutations are particularly common in pancreatic, colorectal, and lung cancers. In addition, several studies have shown that tumors with *KRAS* mutations have a worse prognosis than do those without *KRAS* mutations (7-9). *KRAS* mutations may indicate tumor aggressiveness in thymic carcinomas as well, and further studies should be performed to examine this possibility. Determination of the clinical significance of *KRAS* mutations in mucinous adenocarcinomas originating in the thymus will further our understanding of their behavior and may aid in their detection and treatment.

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Footnote

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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