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*Case Report*

# Thymic mucoepidermoid carcinomas: a clinicopathologic case study and literature review

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**Abstract:** Mucoepidermoid carcinoma occurs frequently in the salivary glands but is rare in the thymus. In this paper we provide a literature review on this condition and discuss the clinical data of a case of thymic mucoepidermoid carcinoma (TMEC). Here, we report a case of TMEC in an elderly female patient who showed no obvious symptoms or positive signs for TMEC during her physical examination. However, a chest CT revealed a mass in the anterior mediastinum, which did not appear enhanced upon contrast-enhanced CT. After surgical excision, TMEC was confirmed by histopathologic and immunohistochemical examination. The clinical manifestation of the disease is not obvious, and physical examination is often not enough for diagnosis, hence diagnosis mainly relies on histopathology. Currently, surgery is still the only way to cure TMEC.

**Keywords:** Thymic carcinoma, mucoepidermoid carcinoma, case report, historical article

## Introduction

Thymic mucoepidermoid carcinoma (TMEC) is a rare pathologic subtype of thymic epithelial tumor, represented by a malignant neoplasm of epidermoid, mucous, and intermediate cells in the thymus. There are currently only 24 individual cases of TMEC that have been reported. Only two cases have ever been reported in China, and a comprehensive analysis of this disease, including its symptoms, physical and imaging characteristics, and treatment and prognosis, is still lacking. Here, we report a case of TMEC that was confirmed by histopathologic and immunohistochemical examination after resection of the mass. We compared the pathology and complete clinical and imaging data, diagnosis, and treatment with the available literature in order to provide insights for subsequent clinical work.

## Case presentation

The patient was a 68 year old female who presented with a mediastinal mass that was discovered after a physical examination that was performed 6 days prior to the resection. The patient visited the Department of Thoracic Surgery of the Hebei Medical University Fourth Hospital on August 10, 2017, but no chest pain, shortness of breath, or dry or wet cough were observed at the time of her visit. A physical examination of the patient showed no enlargement of the superficial lymph nodes throughout her body, no sternal tenderness, symmetrical thorax, symmetrical tactile fremitus, clear to percussion bilaterally, no dry or wet rales, an 80 beats/min heart rate, regular cardiac rhythm, no pathologic murmur, normal limbs and spinal column, and no pathological reflexes. The patient's blood, urine, and liver and kidney function test results were within the reference range according to laboratory examinations. Carcinoembryonic antigens (CEA), soluble cytokeratin fragments (CYFRA), neuron-specific enolase (NSE), serum progastrin-releasing peptides (PROGRP), and squamous cell cancer antigens (SCC) were all within the reference range. A cystic-solid mass was identified in the left anterior mediastinum by a contrast-enhanced CT scan of the chest, which was believed to be of thymic origin. The scan of the mass showed no contrast enhancement, but it did show a shadow of calcification at the tumor margin (**Figure 1**). The patient had no prior history of chest surgery or surgical contraindications

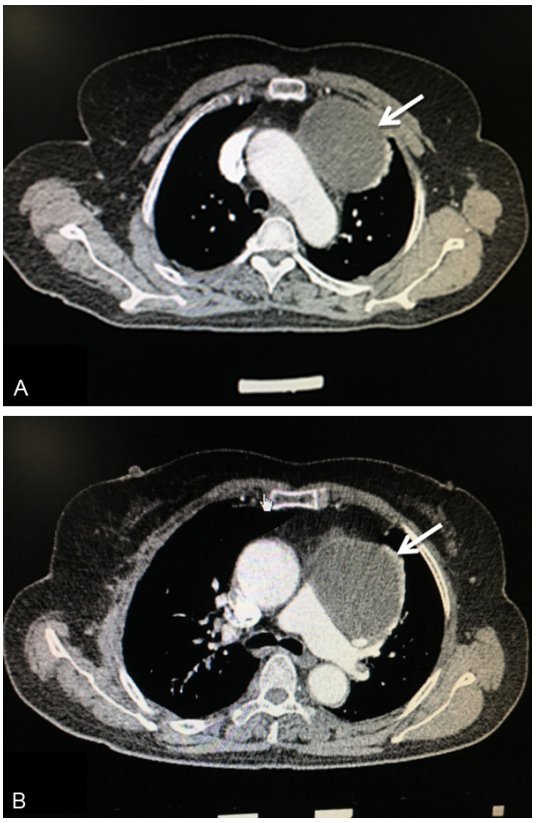


**Figure 1.** The left anterior mediastinum tumor was shown by a contrast-enhanced CT scan of the chest. A: Contrast-enhanced CT scan of the aortic arch level, with the tumor indicated by the arrow. B: Contrast-enhanced CT scan of the pulmonary artery level, the tumor indicated by the arrow.

such as diabetes, coronary heart disease, or hypertension, and was preliminarily diagnosed with a lesion of significant volume in the left anterior mediastinum. The patient underwent thoracoscopic surgery under general anesthesia on August 14, 2017. The location of the mass in the left anterior mediastinum was confirmed by intraoperative examination. The mass was cystic and tough and measured about 7 cm by 7 cm by 3 cm in size with an intact capsule. Its upper portion and left side were severely adhered to the left upper lobe, and its lower portion was severely adhered to the pericardium. The capsule was damaged during the isolation of the mass. Given that the mass could not be fully isolated by thoracoscopic surgery, the operation was changed to a thoracotomy. The mass was completely resected along with adipose tissue that was located anterior to the phrenic nerve and inferior to the innominate veins on both sides. Postoperative incision of the mass showed multiple septa inside the mass, between which a substantial amount of yellowish brown viscous liquid was visible. The postoperative pathology report indicated that the 8 cm by 6 cm by 5 cm cystic mass was TMEC. The wall of the mass was 0.2-0.5 cm thick, and a 2.5 cm by 1.5 cm mastoid region was visible along the wall. A histopathological examination showed that the tumor was comprised of epidermoid, intermediate, and mucous cells. Cystic cavity formation was visible in some parts of the mass, and the cystic gaps were lined with mucous cells accompanied by intermediate and epidermoid cells (**Figure 2**). An immunohistochemical (IHC) examination of the mass revealed that it was CK(+), Vim(-), CK5/6(+), P63(+), CK7(+), P53 (5%+), CDla (partially+), CK19(+), CEA (scattered+), and Ki67 (40%+) (**Figure 3**). The patient was discharged from the hospital 6 days after surgery, and re-examinations of the patient at 1 month and 3 months post-surgery indicated a good mental status. Postoperative blood, urine, liver and kidney function, and tumor marker re-examinations all demonstrated normal results. The chest CT report showed post-mediastinal lumpectomy changes but no local recurrence.

## Discussion

Mucoepidermoid carcinoma (MEC) is a type of malignant tumor consisting of mainly epidermoid, mucous, and intermediate cells. MEC frequently occurs in the salivary glands, lungs, and bronchus, but very rarely in the thymus. In fact, TMEC only accounts for 2% of primary thymic malignancies [1-4]. Thymic epithelial tumors are primarily comprised of thymoma and thymic carcinoma. Thymomas are histologically classified into types A, B, and C, where type C is thymic carcinoma [5]. Thymic carcinoma can be classified as low-grade and high-grade, where low-grade includes SCC, MEC, and basal cell carcinoma, and high-grade includes sarcomatoid carcinoma, lymphoid epithelioid carcinoma, and papillary carcinoma [6]. In 1982, TMEC was reported for the first time [7]. TMEC is so rare that only 24 cases have been reported until now [1]. Of the reported cases, disease onset occurred at a mean age of 47 years (8-84 years), and the male to female patient ratio was 1.3:1, suggesting that TMEC is more common among males [8-10]. The pathogenesis of TMEC remains elusive, given that there are

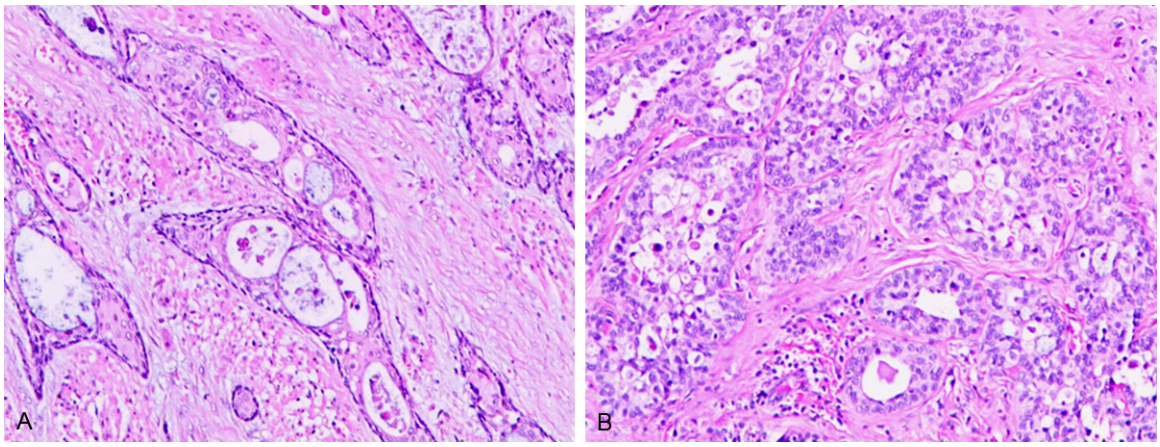


**Figure 2.** The histopathological features of TMEC are shown in the figure. A: Cystic cavity formation is visible in some parts of the mass, and the cystic gaps are lined with mucous cells accompanied by intermediate cells and epidermoid cells (H&E 100×); B: The epidermoid cells and intermediate cells of the solid area, and a small number of mucous cells are seen. The basal-like intermediate cell proliferation is dominant, the cell atypicality is large, and the mitotic image is increased. (H&E 100×).

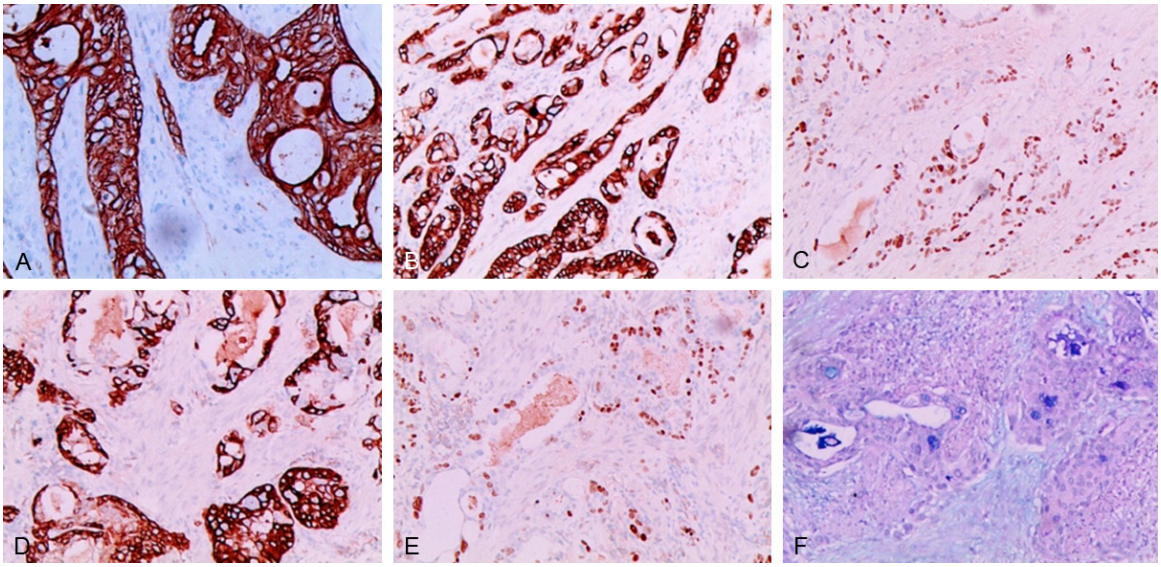


**Figure 3.** The immunohistochemical staining of the tumor is shown as CK (A) positive (Envision 100×), CK5/6 (B) positive (Envision 100×), p63 (C) positive (Envision 100×), CK7 (D) positive (Envision 100×) and Ki67 (E) positive cells over 40% (Envision 100×). Moreover, other elements include AB mucous cells (F) positive (Envision 100×).

very few reports of TMEC in the medical literature. It was previously reported that TMEC originates from thymic epithelial cells, and these benign thymic epithelial cells can transform into malignant cells when exposed to certain stimuli [11]. TMEC is a type of thymic carcinoma. The oncogene MUC1A was shown to be expressed by 94% of thymic carcinomas, and MUC1 can cause transformation of normal cells and inhibit cell apoptosis [12]. A previous study showed that a strong association between MEC and t(11;19)(q21;p13) has been observed; furthermore, CRTC1/3-MAML2 fusions have been related with the favorable clinicopathological features of mucoepidermoid carcinoma [13]. MAML2 rearrangement is a valuable molecular diagnostic tool in the evaluation of thymic malignancies, especially differentiating TMEC from squamous cell carcinoma and adenosquamous carcinoma [14]. However, a CRTC1/3-MAML2 fusion and MAML2 rearrangement-negative TMEC can occur, indicat-

ing that a different molecular pathway is involved in the generation of tumors [15].

Most TMEC patients have no apparent clinical symptoms or positive signs. A few cases exhibit chest-associated symptoms, such as posterior sternal pain and dyspnea, sometimes with or without myasthenia gravis. Neck and facial swelling, hoarseness, diaphragmatic eventration, systemic fatigue, and weight loss can all be manifestations of tumor invasion [11]. However, in most cases, this disease presents no clinical symptoms and is usually only identified after a physical examination, which may be due to the cystic and cystic-solid natures of TMEC. Here, we reported a case of TMEC that was identified by chest CT during a physical examination. The patient showed no signs of discomfort such as chest pain, chest congestion, shortness of breath, nor dry or wet cough. There was no enlargement of the superficial lymph nodes throughout the patient's body and no sternal tenderness, which is consistent with previous studies [8, 11]. In some cases, it has been reported that direct compression from the tumor can cause patients to exhibit respiratory symptoms, such as chest congestion, chest pain, shortness of breath, and dyspnea. Some patients were confirmed with pathologic fractures of all four extremities [8].

There is currently no specific diagnostic marker for TMEC, and the imaging examination is an important diagnostic tool for this disease. For most patients, preoperative enhanced CT scans of the chest indicate cystic and cystic-solid changes with no significant enhancement. One case report revealed an oval, solid nodular mass with unclear margin in the right anterior mediastinum [9]. This mass had uneven internal density and significant uneven intensification upon enhancement. The signal within the region of significant enhancement was similar to that of blood vessels. Similarly, a cystic-solid mass with an unclear margin and uneven internal density was found in the anterosuperior region of the mediastinum [10]. The chest CT scan of our patient revealed a cystic-solid mass in the left anterior mediastinum, with shadows of calcification at the margin but no intensification upon enhancement (**Figure 1**). Since TMEC is relatively rare, it can be easily mixed up with mediastinal thymoma with cystic changes, and hence will require histopathological examination for identification and diagnosis.

Given that TMEC has a low incidence rate and lacks specific clinical and imaging characteristics, we relied mainly on histopathological examination for the diagnosis of this disease. The masses identified in most TMEC cases have a mixture of cystic and solid properties, in which the cystic region is filled with a mucous-like substance while the solid region appears nodular with fibrous cords [16]. Histopathological examination of the mass reveals the presence of epidermoid, mucous, and intermediate cells, along with clear cells (**Figure 2A**). Mucus is often visible in the interstitium, along with lymphocyte infiltration, foam cells, cholesterol crystals, and fibrosis. Focal calcification or ossification may also be present. Non-neoplastic thymic tissue adjacent to the neoplasm may display cystic or mucinous metaplasia [17]. A histopathological examination of the tumor revealed that the epidermoid, intermediate, and mucous cells were distributed in patches [10]. Specifically, the epidermoid cells showed a nest-like or sheet-like arrangement, whereas the mucous cells showed a focal or scattered distribution. Some parts of the mass showed the formation of cystic cavities, and the cells had clear margins. Furthermore, atrophic thymic tissue was also visible within the surrounding tissues. In our case, the tumor was comprised of epidermoid, intermediate, and mucous cells. Cystic cavity formation was visible in some parts of the mass, and the cystic gaps were lined with mucous cells accompanied by intermediate and epidermoid cells (**Figure 2**). These observations were consistent with those in previous reports [9, 10] and in line with the pathological characteristics of TMEC. IHC may sometimes be used as an auxiliary diagnostic tool to distinguish between type B3 thymoma and thymic carcinoma because of their highly similar histomorphology. Previous studies have found that c-kit and CD5 are expressed at high levels in thymic carcinoma but low levels in type B3 thymoma. Therefore, c-kit and CD5 may be used as important IHC markers for distinguishing thymic carcinoma and type B3 thymoma [6]. The IHC examination of the 2 cases of TMEC in China indicated that the tumor was negative for CD5 and CK8/18, but positive for CD5/6, CD19, and EMA [9, 10]. The IHC examination of our patient showed that the tumor was positive for CK5/6, P63, CK7, CK19, and Ki67 (40%) (**Figure 3**), which is consistent with previously reported cases [8-10].

There is currently no global standard in the treatment regimen for TMEC due to its rarity. The current preferred treatment for TMEC is surgical resection, which is also the only way to cure the disease. Radical resection, including complete lumpectomy and removal of surrounding adipose tissues, should be performed immediately once a patient is definitively diagnosed with TMEC. Radiation therapy and chemotherapy are not effective against TMEC and are mainly used for inoperable patients. For the treatment of cancer patients who are inoperable or have recurrence or metastasis, genetic studies and targeted therapy have become increasingly important. It has been shown that EGFR promotes the proliferation and infiltration of TMEC cells. Lujan *et al*. believe that high-grade MEC is usually a result of a high EGFR gene copy number and high pERK1/2 expression [18]. In addition, another study has demonstrated that EGFR expression can be found in 45 of 60 (75%) samples of MEC. Therefore, EGFR may become a new therapeutic target and a potential prognostic marker for TMEC [19].

The degree of malignancy, extent of invasion, and extent of dissection are closely associated with the prognosis of TMEC [20]. Since TMEC patients lack specific clinical manifestations and are usually diagnosed with the disease during physical examination, peripheral tumor invasion may have already occurred in some patients at the time of diagnosis. A review of the literature demonstrated that 45-92% of newly diagnosed cancer patients were already in the advanced stages [21]. Most patients with low-grade malignancy have a good prognosis and long-term survival without the need of other postoperative treatments. However, patients with high-grade malignancy not only have a poor prognosis, but they may also show metastasis or even die within a short period. The clinical data from the follow-up of 10 TMEC patients showed that 1 patient with low-grade malignancy exhibited local recurrence, 7 patients with low-grade malignancy showed good prognosis, and 2 patients with high-grade malignancy died within a year of definitive diagnosis and treatment [8]. In this study, our patient was re-examined at 6 months post-surgery and her condition is currently stable.

In summary, TMEC is a rare primary thymic carcinoma with no obvious clinical symptoms but unique chest CT and postoperative histopathological features that are important for its clinical diagnosis. Surgery is currently the primary treatment for TMEC as radiation therapy and chemotherapy have been shown to be ineffective. As molecular biology research continues to progress, this will most likely open up new options for a specific molecularly targeted treatment of TMEC patients.

## Disclosure of conflict of interest

None.

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