Letter to the Editor

Misdiagnosis of giant pulmonary mucinous adenocarcinoma in a posterior mediastinum mass: a case description and literature analysis

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Introduction

According to the latest classification of the World Health Organization (WHO) in 2021, primary pulmonary mucinous adenocarcinoma (PPMA) is classified as a special subtype of lung adenocarcinoma with a very low incidence and a lack of specific clinical manifestations, which makes it easy to misdiagnose (1,2). Computed tomography (CT) helps to improve the early diagnosis rate of the disease, and pathological diagnosis is the gold standard. We report a rare case of posterior mediastinal mucinous adenocarcinoma. The pathological and CT imaging findings are quite different from those of typical thymic mucinous adenocarcinoma and pulmonary mucinous adenocarcinoma. To deepen the understanding of this tumor subtype, we reported this case and reviewed the literature.

Methods

Clinical data

The patient, a 66-year-old male, had experienced occasional bloody sputum, tiredness, shortness of breath, nervousness, chest distress, and fatigue for more than 2 years and complained of an irritating dry cough with no obvious predisposing cause. With his condition worsening over the recent 3 months, the patient visited our hospital for medical advice. The laboratory tests results were as follows: cancer antigen 125 (CA125), 79.60 U/mL; CA199, 1,153.80 U/mL; high-sensitivity C-reactive protein (hs-CRP), 42.01 mg/L; white blood cell (WBC) count, 19.08×10^9/L; red blood cell (RBC) count, 3.42×10^9/L; and neutrophil (NEUT) count, 16.56×10^9/L.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Pathological examination

The surgical specimen was fixed with 10% neutral formalin

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(formaldehyde) fixative solution, routinely dehydrated, embedded in paraffin, cut into sections approximately 5 μm thick, and stained with hematoxylin and eosin (HE). Immunohistochemical (IHC) staining was performed using the EnVision 2-step method for cluster of differentiation 5 (CD5), cytokeratin (CK), CK7, CK19, CK20, CD117, CD99, villin, CDX-2, carcinoembryonic antigen (CEA), estrogen receptor (ER), P63, PS, thyroid transcription factor-1 (TTF-1), terminal deoxynucleotidyl transferase (TdT), napsin A, and Ki-67 (Fujian MXB Biotechnologies, Foochow, China). Operating procedures were carried out strictly according to the instructions on the test kit.

Imaging examination

Toshiba 320CT (Toshiba, Brisbane, CA, USA) chest 2-stage enhanced scanning was used with the following parameters: 100–125 kV, 125–200 mAs, field of view (FOV) =25 cm, matrix =512×512, layer thickness =0.5 cm, and layer spacing =0.5 cm. The contrast medium used was 300 mg of iohexol in 60 mL saline solution.

Surgical treatment

Prior to the surgery, we made a preliminary diagnosis of primary thymic mucinous adenocarcinoma based on the clinical, laboratory, and imaging results. The patient underwent left pneumonectomy, complex mediastinal tumor resection, pleural adhesion release, and esophageal rupture repair. Eventually, the postoperative pathological diagnosis was PPMA. The patient had pleural atresia in the left lung, and the pulmonary fissure on the left side was not developed. The lesion, containing a large amount of pale grey-red gelatinous tissue, with a volume of approximately 2,000 mL, extended to the middle and posterior mediastinal space and further to the right thoracic cavity, enveloping and invading the left main bronchi and resulting in a 3.0×0.8 cm^2 oval abscess. It invaded the middle section of the esophagus, under the aortic arch to the upper border of the left inferior pulmonary vein, affecting approximately 1/3 of the circumferential diameter of the esophagus. The wall of the esophagus was thin and weak, and the area of rupture was approximately 5.0×2.0 cm^2. The mediastinum and the left hilar lymph nodes were significantly enlarged.

Pathological results

Macroexamination

The specimen was a solid cystic tissue of grey-brown appearance, with a size of approximately 17.0×18.0×4.5 cm^3. Part of the membrane was missing, and the area was grey-red and gelatinous, with a range of approximately 11.0×9.0 cm^2. In addition, 4 groups of embedded lymph nodes were also tested.

Microscopic examination

Tissue specimens were obtained by surgical excision of the tumor. Cytomorphologic observations were then made using a microscope.

Immunolabelling

The tumour cells were positive for CK7, CK19, CK20, and villin and negative for CD5, CD117, CD99, CDX-2, CEA, ER, P63, PS, TTF-1, TdT, and napsin A, and the Ki-67 proliferation index was approximately 20%.

Pathological diagnosis

Based on the results of cell morphology and histology, the patient's condition was initially diagnosed as pulmonary mucinous adenocarcinoma, T3N0M0, showing nerve bundle invasion (+) and vascular invasion (–). No cancer was observed in the bronchial stump, and no metastasis was observed in the lymph nodes.

Literature review

Based on the literature published from 2003 to 2021 regarding mucinous adenocarcinoma of the thymus, we found that the male:female incidence ratio of the disease was 0.73:1, suggesting that the number of female patients was greater than that of male patients, with an age range from 15 to 82 years and a maximum tumor diameter of approximately 3.5 to 14.5 cm. Among those cases, 11 cases were diagnosed as a tumor with cystic cavities. Mucinous adenocarcinoma of the thymus was often positive for CK7, CK20, CD5, and CEA and negative for TTF-1 (3-17).

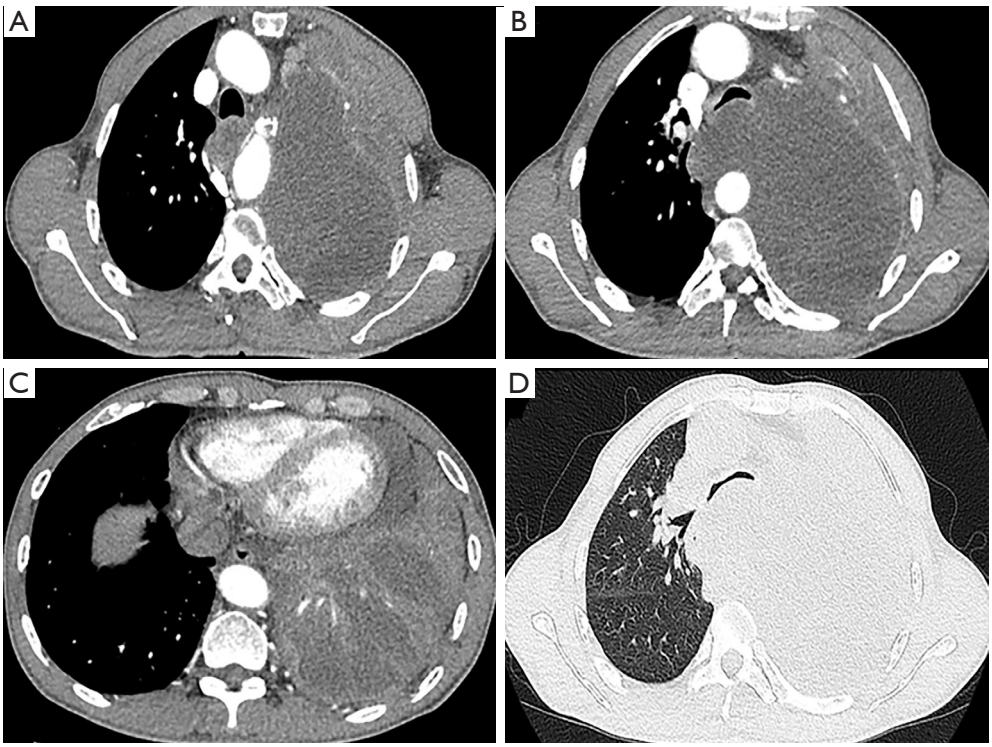

Figure 1 CT imaging findings. (A-D) Show the CT images: plain CT scan of the posterior mediastinum and the left thoracic cavity of the patient showed a large solid cystic space-occupying lesion with a size of approximately 14.8×10.7×18.5 cm^3, thin-walled with no visible mural nodules. A contrast-enhanced CT scan showed that the cyst wall was significantly enhanced, whereas the cystic part was not. The cyst wall and the intrathoracic mass were enhanced to different degrees, with the latter being mildly enhanced, and pathological examination confirmed it as the undeveloped left lung. The adjacent trachea, esophagus, left lung, and left lung arteries and veins were compressed and narrowed, and the boundaries were not clear. Additionally, atelectasis of the left lung, rightward deviation of the mediastinal structure, and multiple enlarged lymph node shadows in the left upper mediastinum and near the hilum of the left lung were observed. No exact abnormal density shadow was seen in the anterior mediastinum. Imaging and gastrointestinal endoscopy did not reveal abnormalities in other systems, such as the gastrointestinal tract and the urinary tract. CT, computed tomography.

PPMA is a rare histological subtype of lung adenocarcinoma (18), which is a low-grade malignant lung tumor and accounts for only 2–5% of lung invasive adenocarcinomas (19).

Multi-slice computed tomography (MSCT) images may present signs of lobulation, speculation, vascular convergence, pleural indentation, cavitation, and so on, and the density of the mass and the degree of enhancement vary greatly according to the proportion of the parenchymal and mucus components. Some patients with primary invasive mucinous adenocarcinoma (PIMA) show pneumonia-like changes, such as irregular shapes and large patches in MSCT images (20) (*Figure 1*).

This case report is in line with the latest classification criteria of lung mucinous adenocarcinoma of the World Health Organization (WHO) in 2021.

(I) Histology and morphology: the tumor cells are composed of columnar cells and goblet cells with a large amount of mucus in the cytoplasm. The nucleus of the tumor is located at the base, with almost no nuclear atypia or slight nuclear atypia. The alveoli around the tumor are often filled with mucus (*Figure 2*).

(II) IHC: tumor cells express CK7, CK19, CK20, and villin and often do not express TTF-1, CD5, or napsin A (*Figure 3*). The nuclear receptor HNF4α is not expressed in normal human lung tissue, but is abnormally expressed in approximately 90% of IMA cases, serving as an auxiliary diagnostic marker for IMA (21).

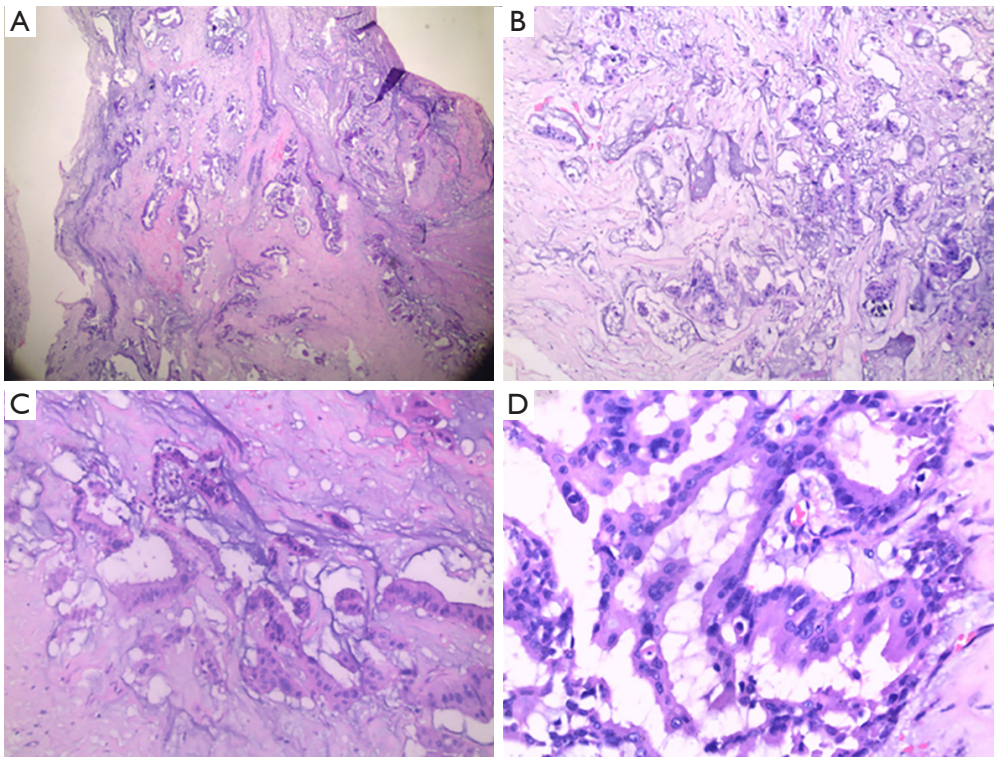

Figure 2 Histopathological images. In (A) (HE, ×40) and (C) (HE, ×200), tumorous epithelial cell nests can be seen against a large amount of mucus background, with cells in cubic, columnar, acinar, papillary, and sieve-like structures, and a cystic cavity can be seen locally. Images (B) (HE, ×100) and (D) (HE, ×400) display a multilayer, glandular duct-like structure, and no residual thymus tissue is seen at the periphery. No cancer metastasis was found in the lymph node examination (0/6). HE, hematoxylin and eosin.

(III) Imaging and IHC exclude metastatic mucinous adenocarcinoma (pancreatic mucinous adenocarcinoma expresses CK20 and MUC2; colon mucinous adenocarcinoma expresses CK20 and CDX2 but rarely expresses CK7 and TTF-1).

Discussion

In the current case, the mass was located in the posterior mediastinum, and no abnormalities in systems such as the gastrointestinal tract or the urinary tract were found by imaging or gastrointestinal endoscopy, so metastasis of mucinous adenocarcinoma in other parts of the body was ruled out. After this case was identified as mucinous adenocarcinoma based on the results of microscopic cytology and histology tests, imaging suggested that the tumor might have originated in the lung. As the lesion was relatively large, spanning from the mediastinum to the thoracic cavity, and the mucus lake occupied the main body of the lesion, the entire lesion had a cystic appearance. A pathology test of the left thoracic mass detected during a plain CT scan confirmed that it was the undeveloped left lung. During the review process, lung tissue was also found. Although IHC supports the negative indicators of TTF-1 and napsin A in pulmonary tumors, many reports state that pulmonary mucinous adenocarcinoma can be negative for these indicators (22). In conclusion, this case meets the latest classification criteria of the WHO in 2021 (1,2).

The histological characteristics of thymic mucinous adenocarcinoma are similar to those of mucoid carcinoma in other sites. Tumorous epithelial cell nests can be seen against a large amount of mucus background, with cells in cubic, columnar, acinar, papillary, and sieve-like structures, and residual thymus tissue can be seen at the periphery (8,11,12). The case reported here had the above histological features, but no thymic tissue was found. In addition, the IHC expression of CD5, CK7, CK19, CK20, and villin in this case was positive. CD5 is a marker of thymic tumors and T lymphocytes and has long been considered strong evidence for tumors of thymic origin (23). However,

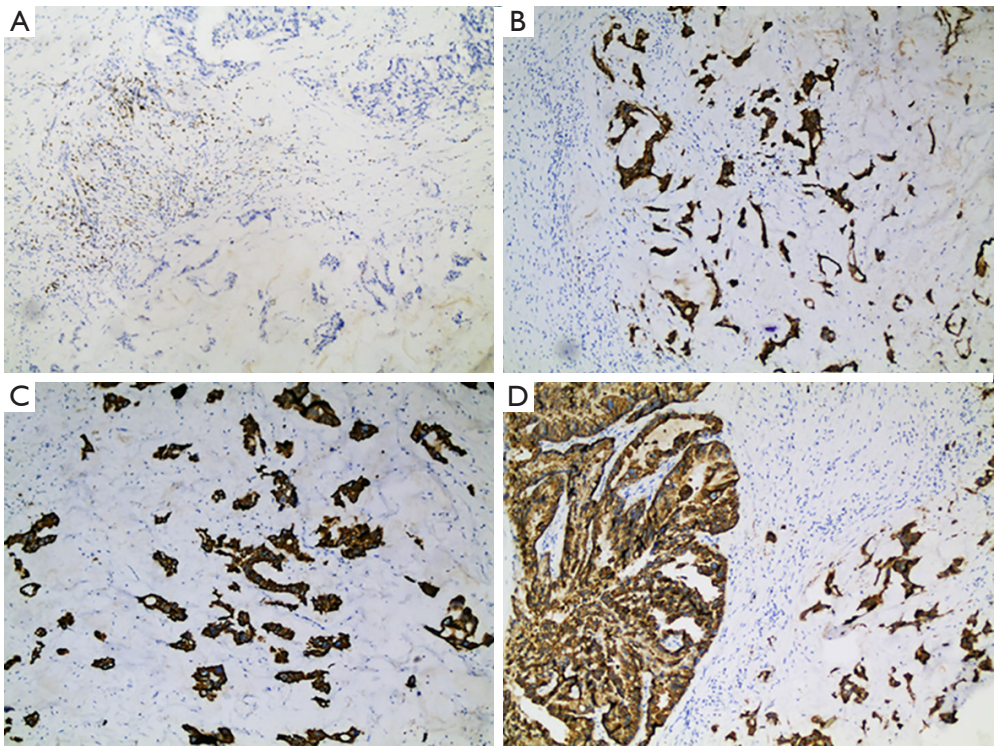

Figure 3 Immunohistochemical pathological images (×100). (A) The tumor cells are depicted as negative for CD5, whereas the CD5-positive cells represent lymphocytes. (B) The tumor cells that are positive for CK7. (C) The tumor cells that are positive for CK19. (D) The tumor cells that are positive for villin.

CD5 in this case was only positive in the cells around the tumor, and the tumor cells themselves were not positive, so the pathological diagnosis may have been misdiagnosed as originating from the thymus. The antibodies for the markers of lung-derived tumors are TTF-1 and napsin A. In this case, both indicators were negative, which may be another cause of misdiagnosis, since many lung-derived tumors can be negative for TTF-1 and napsin A. Thymic carcinomas originate in a high proportion (approximately 33%) of thymic cysts, especially multilocular cysts (7). The cases in the literature review (11/18) all contained cysts, and the data showed that cysts may be one of the most obvious imaging signs of primary mucinous adenocarcinoma of the thymus. The most striking feature of the reported cases is the large cystic cavity, which may be a major cause of misdiagnosis.

Understanding how much of the lung tissue on the slice can be used as a cue for locating the tumor source during re-examination is the main concern. If the tumor is derived from the lung, it may originate from hypoplastic lung tissue or inflammatory lung mucinous adenocarcinoma, but the mucus lake is an especially obvious sign. If the tumor is derived from the thymus, it would be classified as an ectopic posterior mediastinum thymic mucinous adenocarcinoma, which is very rare and is located in the left posterior mediastinum; in the presence of ectopic thymus and cystic foci, malignant transformation will lead to the occurrence of tumors, which is too far-fetched for this case.

At present, mucinous adenocarcinoma is treated mainly by radical surgical resection supplemented by radiotherapy and chemotherapy when necessary. This case followed the standard treatment, namely, the tumorous mass and the left lung tissue of the patient were removed, the esophagus was repaired, and radiotherapy and chemotherapy were administered when necessary. Our 6-month follow-up showed that the patient's quality of life was acceptable. However, when searching the literature, we found that patients with this tumor subtype had a poor prognosis and a shorter survival time, which may be caused by the higher degree of malignancy in this tumor subtype and the difficulty of diagnosing this subtype in the early stage, which results in delayed treatment. Bradbury *et al.* (24) reported 17

patients who received surgery/chemotherapy/radiotherapy, 4 who received radiotherapy alone, and 2 who received chemoradiotherapy, and the median survival time of the entire population was 16.1 months; another study found that the 5-year recurrence-free and overall survival rates were 70.4% and 81.5%, respectively (25). Therefore, we interpret that the clinical staging and histological grading of tumors and reasonable clinical treatment schemes are important factors affecting the prognosis of patients.

Conclusions

In this paper, we reported the process of diagnosing and treating a case of mucinous adenocarcinoma in the posterior mediastinum and summarized the imaging, histological, and IHC features of this tumor subtype. The undeveloped lung, the cystic mass in the posterior mediastinum, and the unique IHC manifestations caused some interference in our diagnosis of the tumor origin. Except for the location of the lesion in the posterior mediastinum, its IHC indicators and CT imaging performance all pointed to an origin of the lung and met the latest WHO classification criteria in 2021 for thymic adenocarcinoma. However, the presence of lung tissue in one of the sections seems to indicate more convincingly that the tumor originated in the lung. We conclude that tracing the origin of cystic adenocarcinoma in the posterior mediastinum should be a combination of imaging and pathological examinations: (I) it is necessary to exclude the possibility of metastasis of the mucinous adenocarcinoma from other sites to the posterior mediastinum through medical history and imaging. (II) The location of the lesion can help to identify the source. Mucinous adenocarcinoma located in the posterior mediastinum is more likely to come from the lung; there is also the possibility of malignant transformation of ectopic thymic cystic lesions, but the probability is very low. (III) IHC shows that lung-derived tumors often express TTF-1 and napsin A, and thymus-derived tumors often express CD5. (IV) Gene mutation detection shows that KPAS mutation in invasive pulmonary mucinous adenocarcinoma can reach 90%, and there may be NRG1 fusion gene mutations.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-141/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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