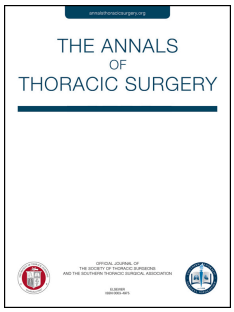

Coincidence of Thyroid Transcription Factor-1 Positive Thymoma and Pulmonary Adenocarcinoma

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Coincidence of Thyroid Transcription Factor-1 Positive Thymoma and Pulmonary Adenocarcinoma

Running Head: TTF-1 positive thymoma and lung cancer

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Abstract

Thyroid transcription factor-1 (TTF-1) has been widely used as a marker of primary lung cancer. However, there have been few reports on TTF-1 expression in thymomas. We here report the case of an asymptomatic 63-year-old man who presented with a right upper lung nodule and cystic mid-mediastinal tumor. The right upper lobe of the lung and the mediastinal tumor were resected. Histological examination of the operative specimen revealed TTF-1-positive type B2 thymoma and invasive pulmonary adenocarcinoma. Although rare, thymoma should be included in the different diagnosis of TTF-1-positive tumors.

Thyroid transcription factor-1 (TTF-1), a tissue specific transcription factor, is normally expressed in the healthy thyroid, lung and brain[1]. It is considered a reliable marker for distinguishing between primary lung cancer and other tumors[1]. However, TTF1 has reportedly been detected in other tumors besides lung and thyroid, including colorectal, ovarian, and breast cancer[2]. There have been a few reports of TTF-1-positive thymomas but, to the best of our knowledge, none of TTF-1-positive thymoma and TTF-1-positive primary lung cancer in the same patient. We herein report a patient with TTF-1-positive invasive pulmonary adenocarcinoma and TTF-1-positive type B2 thymoma, which posed difficulties in diagnosis.

A 63-year-old asymptomatic man was referred to our hospital after discovery of abnormal findings on a routine chest radiograph. He had a history of hypertension, nonalcoholic fatty liver disease, and a 20-pack-year smoking habit. Contrasted-enhanced computed tomography (CT) showed a 10 mm nodule in the upper lobe of the right lung (Fig 1A) and a 30 mm cystic tumor in the mid-mediastinum (Fig 1B). Positron emission tomography (PET)-CT revealed slight uptake of ^{18}F-fluorodeoxyglucose (maximum standardized uptake volume, 1.93 to 2.84) in the lung tumor (Fig 1C). In contrast, there was intense uptake of ^{18}F-fluorodeoxyglucose (maximum standardized uptake volume, 17.9 to 22.9) in the mediastinal tumor (Fig 1D). He had no symptoms suggestive of myasthenia gravis and serum anti-acetylcholine receptor antibody concentration was within the normal range. The only high tumor marker was carcinoembryonic antigen (8.4 ng/mL).

Wedge resection of the lung tumor together with resection of the mediastinal tumor was performed by video-associated thoracoscopic surgery from the right side. The mediastinal tumor was successfully separated from the azygous vein, trachea, and superior vena cava. Intraoperative rapid diagnostic examination suggested that the lung tumor was adenocarcinoma, whereas the mediastinal tumor was comprised poorly differentiated tumor cells in a papillary-like pattern and no definitive diagnosis could be reached. Thus, right upper lobectomy with

systematic mediastinal lymph node dissection was subsequently performed. Final histological examination revealed that the lung tumor was a moderately differentiated, papillary predominant, invasive adenocarcinoma with some acinar components (Fig 2A). The pathological stage was pT1aN1M0, pl0, G2, v0, ly0. The mediastinal tumor showed cystic and solid areas and consisted of epithelial immature tumor cells with pleomorphic nuclei and lymphocytes covered by a thick fibrous septum. Inflammatory cells, including hemosiderin-containing macrophages, were detected near the lumen of the cystic area, indicating there had been bleeding into it (Fig 3A). The tumor cells grew in solid and partially glandular patterns (Fig 3B). On immunohistochemical staining, the mediastinal tumor cells were positive for TTF-1 (Fig 3C) and AE1/AE3, and negative for p40, CD5, CD20, CK5/6, CK7, Napsin A, c-kit, and EBER. The lymphocytes infiltrating the mediastinal tumor were positive for CD3 and CD99 (Fig 3D). No immunohistochemical evidence of neuroendocrine differentiation was identified with synaptophysin, chromogranin A and CD56. The lung tumor cells were positive for TTF-1, CK7, and Napsin A (Fig 2B through 2D). The lung and mediastinal tumors were both positive for TTF-1; however, their histological characteristics and immunohistochemical findings differed except for the TTF-1 positivity. The eventual diagnosis for the mediastinal tumor was type B2 thymoma, Masaoka stage I. After the surgery, we suggested additional thymectomy, but he refused. The patient underwent postoperative adjuvant chemotherapy for lung cancer and was doing well 10 months postoperatively, with no evidence of recurrence.

Comment

Patients with thymomas have an increased risk of developing other malignancies, the overall risk of a second cancer reportedly being approximately three times higher in patients with thymomas than in control patients[3]. In particular, they are at significantly increased risk of second malignancies of lung and bronchus[3]. Thymomas consist of a mixture of neoplastic epithelial cells and non-neoplastic T lymphocytes[4]. In the World Health Organization

classification, there are five main subtypes, types A, AB, B1, B2 and B3, distinguishing features being the shapes of the epithelial cells and proportion of lymphocytes[4]. Thymomas may exhibit tubular and pseudo-papillary patterns[4] that can be mistaken for metastatic adenocarcinoma. In our case, the mediastinal tumor was considered to be a primary thymic tumor because it contained CD99-positive immature T lymphocytes. Histological examination with hematoxylin–eosin stain revealed solid sheets of immature epithelial tumor cells with some papillary-like patterns. Thus, additional immunohistochemical staining was necessary to distinguish between a thymic metastasis from the pulmonary adenocarcinoma and a primary thymic tumor.

TTF-1, a specific marker for pulmonary adenocarcinoma and thyroid cancer, is less frequently positive in other malignancies[2]. Yan and colleague reported one case of type AB TTF-1 positive thymoma[5]. Of 30 spindle cell thymomas reported by Weissferdt and colleagues, only one was TTF-1 positive[6]; spindle cell thymomas (WHO classification type A and AB) are rarely TTF-1 positive. Scorer and colleagues reported TTF-1 positivity on immunohistochemical analysis in 19 of 59 thymomas and thymic carcinomas[7]. In particular, TTF-1 was positive in six of 22 type B1 and four of 10 type B2 tumors, thus, more frequently being present in type B1 and B2 than in type A and AB tumors[7]. However, Pan and colleagues found no cases of TTF-1 positivity in 35 thymomas[8]. Thus, the rate of TTF-1 positivity in thymomas differs markedly between different reports. These discrepancies may be in part attributable to the antibody clone used: Scorer and colleagues[7] reported that using SPT24 as a clone of TTF-1 antibody resulted in a higher rate of TTF-1 positive thymomas than rates reported by others. In support of this possibility, TTF-1 is also highly specific for pulmonary adenocarcinoma; however, its sensitivity and specificity have been shown to differ between antibody clones[2]. In a comparative study of TTF-1 antibody clones 8G7G3/1, SPT24 and SP141 were more sensitive than 8G7G3/1[2].

Our patient's thymic tumor was TTF-1 positive, which does not rule out metastatic adenocarcinoma from the lung. However, PET–CT showed a large difference in ^{18}F -

fluorodeoxyglucose uptake between the lung and mediastinal tumors. There was evidence of previous hemorrhage into the mediastinal tumor, suggesting that it had grown rapidly, which was considered to explain the intense ^{18}F-fluorodeoxyglucose accumulation. Additionally, on immunohistochemical staining the pulmonary adenocarcinoma was positive for CK7 and Napsin A, whereas the mediastinal tumor was negative for both of these markers, effectively ruling out the diagnosis of thymic metastasis from the pulmonary adenocarcinoma. The final diagnosis of the mediastinal tumor was type B2 thymoma. Consistent with this, its histopathological morphology differed from that of the lung tumor and lymph node metastasis. TTF-1 is a useful diagnostic marker for pulmonary adenocarcinoma, but may also be positive in thymomas. It is therefore important to ensure an accurate diagnosis by taking into consideration all clinical and imaging findings and pathological features, including immunohistochemical markers.

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Figure Legends

Fig. 1. (A, B) Contrasted-enhanced computed tomography (CT) showed a 10 mm nodule in the upper lobe of the right lung (arrow) and a 30 mm cystic tumor in the mid mediastinum (arrow). (C, D) The lung tumor shows slight ^{18}F-fluorodeoxyglucose uptake (maximum standardized uptake volume, 1.93 to 2.84) (arrow), whereas the mediastinal tumor has intense ^{18}F-fluorodeoxyglucose accumulation (maximum standardized uptake volume, 17.9 to 22.9) (arrow).

Fig. 2. (A) Photomicrograph of hematoxylin and eosin-stained section showing that the lung tumor is papillary predominant, invasive pulmonary adenocarcinoma (×40). (B–D) Photomicrographs of immunohistochemical stained-sections showing the lung tumor was positive for TTF-1 (B), CK7 (C) and Napsin A (D) (×40).

Fig. 3. (A, B) Photomicrograph of hematoxylin and eosin-stained section showing that siderophages were observed near the lumen of the cystic area (A) and the mediastinal tumor consisted of neoplastic cells with highly pleomorphic nuclei and lymphocytes (B) (×100). (C) The mediastinal tumor cells were TTF-1-positive (×200). (D) The lymphocytes infiltrating the mediastinal tumor were CD99-positive (×200).