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Primary Intrapulmonary Thymoma Presenting as a Solitary Pulmonary Nodule

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Primary intrapulmonary thymoma (PIT) is a very rare lesion of uncertain pathogenesis. PIT should be considered when the histopathological appearance of a lung tumor shows features that are uncommon but similar to those of a thymoma. In this case report, we discuss the case of a 59-year-old female with a solitary pulmonary nodule that was confirmed to be PIT on the basis of pathological tests. Treatment with complete resection showed good results.

Key words: 1. Thymoma
2. Solitary pulmonary nodule
3. Diagnosis
4. Histology

Case report

Primary intrapulmonary thymoma (PIT) was first reported by McBurney in 1951. PIT displays the characteristic histological features of a thymoma, with the additional characteristic of being surrounded by lung or visceral pleura without evidence of a thymic lesion in the anterosuperior mediastinum [1]. Due to its rarity, variety, unclear natural course, and nonspecific features on diagnostic imaging, a formal diagnosis can be made only based on a pathological examination. Therefore, surgical resection should be considered for an exact diagnosis, unlike is the case for mediastinal thymomas. Herein, we report the case of a patient who was initially suspected to have lung cancer on the basis of a bronchoscopic biopsy but was later diagnosed with PIT after surgery followed by a pathological examination. Written informed consent was obtained from the patient for the publication of this case report and all accompanying images.

A 59-year-old asymptomatic female with a history of partial thyroidectomy for papillary thyroid cancer visited for the evaluation of pulmonary nodules observed in a low-dose chest computed tomography (CT) scan. There was a 1.1-cm nodule in the right upper lobe (RUL) and a 5-mm small ground glass nodule in the left upper lobe. The 1.1-cm RUL nodule was suspected to be primary lung cancer, and a contrast CT scan was performed. In the contrast CT scan, the RUL nodule was observed as a 1.5-cm finger-shaped lesion with a smooth margin in the subsegmental bronchus of the posterior segment. It had an expansile appearance and showed mild homogeneous enhancement (Fig. 1A). In positron emission tomography (PET) with 18-F fluorodeoxyglucose (FDG), the maximum standardized uptake value (SUV_{max}) of the RUL endobronchial nodule was 4.1 (Fig. 1B).

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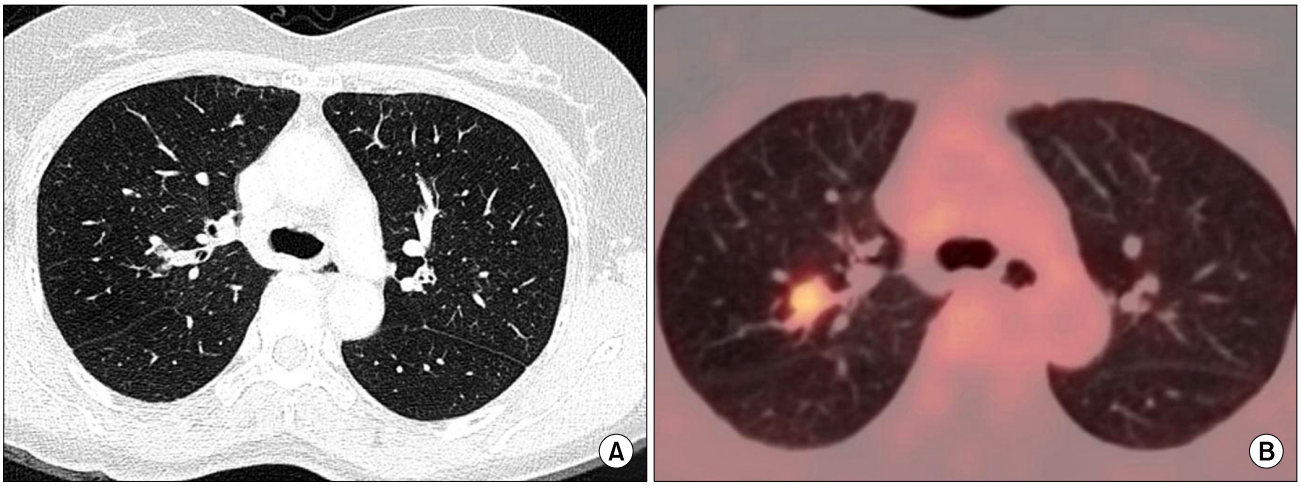

Fig. 1. (A) A chest CT scan showed a nodule obstructing the posterior bronchus in the RUL. (B) A positron emission tomography-CT scan, the standardized uptake value of the RUL nodule was 4.1, and it was presumed to be an endobronchial malignancy. CT, computed tomography; RUL, right upper lobe.

Lung cancer was strongly suspected from the findings of the radiological studies, and fiber-optic bronchoscopy was performed to confirm the tissue diagnosis.

The bronchoscopy revealed a smooth surface mass obstructing a subsegmental bronchus of the posterior segment (Fig. 2A). No malignant cells were observed in bronchial washing cytology. However, spindle cell proliferation with moderate cellularity, mild nuclear pleomorphism, and mitosis over 10 per high-power field were identified in the biopsy specimen. The clinical diagnosis was cT1aN0M0 primary lung cancer of the salivary gland type or a spindle cell tumor showing epithelial differentiation; subsequently, thoracoscopic RUL lobectomy and mediastinal lymph node dissection were performed.

In the macroscopic examination, the white-to-gray tumor measuring 1.4 cm×1.0 cm×0.8 cm showed no evidence of hemorrhage or necrosis. It was well circumscribed and confined to the lung parenchyma. A microscopic evaluation showed a relatively fascicular spindle cell pattern with round-to-oval nuclei (Fig. 2B). Immunohistochemical studies revealed diffuse immunoreactivity for pan cytokeratin, cytokeratin 5/6, p40, and p63 (Fig. 2C). It was also focally positive for CD117 and CD5 (Fig. 2D), but negative for vimentin, S-100 protein, thyroid transcription factor-1, napsin A, and smooth muscle actin. According to the World Health Organization (WHO) classification, these histopathological findings are consistent with type A thymoma. Further, all mediastinal lymph nodes were free of tumor cells.

Discussion

PIT is a rare disease, and thus far, only 37 cases of this condition have been reported. According to the epidemiological data reported by Myers et al. [1] in 2007, almost all patients were diagnosed incidentally without any symptoms. Autoimmune paraneoplastic syndromes, such as myasthenia gravis or Good syndrome, can be accompanied and are associated with a poor prognosis. The patients ranged in age from 14 to 79 years. Masses were located in the right lung in approximately 65% and in the left lung in approximately 35% of the patients. The size of the masses ranged from 9 to 129 mm in diameter. On the basis of the WHO classification, there were 7 cases of type A, 8 of type AB, 6 of type B1, 5 of type B2, and 7 of type B3 thymoma.

The pathogenesis of PIT is still unclear. It has been suggested that PIT involves thymomas with an ectopic location [2], tumors arising from an uncommitted germinative cell [3], and migration of a mediastinal thymoma into the lung. Since the theory of ectopic location is considered to have the most support, PIT has been classified as a tumor of an ectopic origin in the recently revised WHO histological classification of lung tumors [4].

The radiological findings of PIT are non-specific. In CT, most PITs present as well-circumscribed hetero-

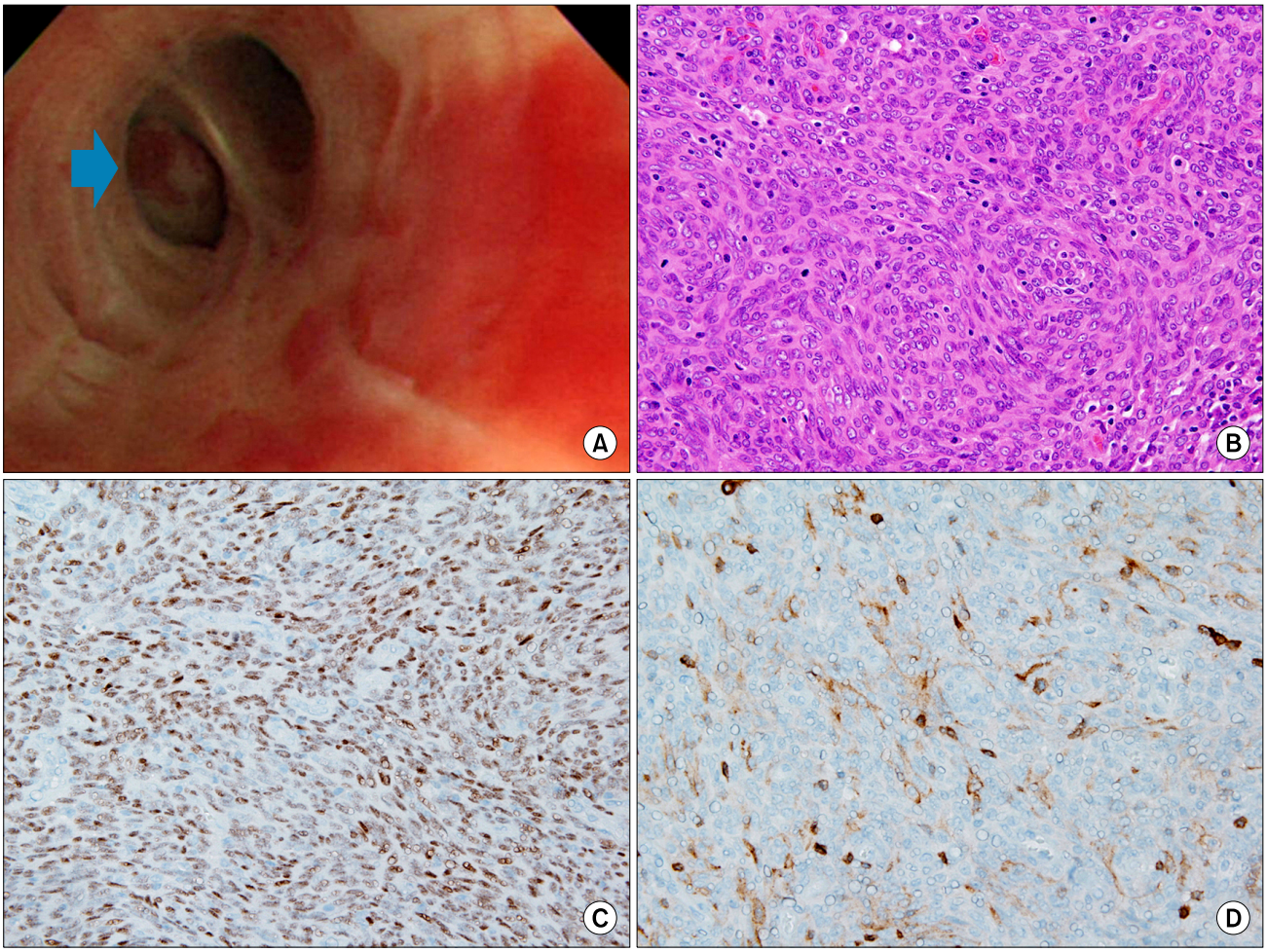

Fig. 2. (A) A smooth surface nodule obstructing the posterior bronchus in the right upper lobe was observed during bronchoscopy. (B) A hematoxylin and eosin ×300 stain showed a fascicular spindle cell pattern with round-to-oval nuclei. (C) Immunohistochemical stain for p63 shows diffuse expression (×400). (D) Immunohistochemical stain for CD5 shows weak expression (×400).

geneous masses that are not diagnostic. In the present case, the nodule was a cylindrical lesion with a smooth margin and showed a homogeneous enhancement pattern on the CT. The homogeneous enhancement pattern in this case may have been related to the small size of the lesion. A thymoma can show an increased FDG uptake in PET, as in the case of lung cancer, and the amount of the FDG uptake has been reported to have a correlation with the WHO subtype [5]. However, PET is non-specific with respect to the differential diagnosis of PIT because it is not possible to make a histological diagnosis by using SUV_{max}. The FDG uptake in the present case was not high, and the nodule was presumed to be a low-grade malignancy. However, it was not possible to suspect PIT until a pathological diagnosis was performed using a surgical specimen.

PIT has the same characteristic histological features as a mediastinal thymoma. Most PITs are diagnosed postoperatively on the basis of the histopathological features of the surgically obtained specimens.

A cytologic diagnosis based on a biopsy with a small amount of the thymoma tissue is extremely challenging. This is in part attributed to the fact that epithelial cells are difficult to recognize in lymphoid-rich aspirate smears and there is an inherent sampling error in a tumor that frequently displays heterogeneous histopathology [6]. Moreover, invasion into an adjacent tissue is difficult to identify in biopsy samples. Therefore, most cases, including ours, are typically clinically diagnosed as primary lung cancer and staged accordingly before surgery.

In the fourth edition of the WHO classification, the diagnostic criteria of thymomas have been revised to include histological features using hematoxylin and eosin-stained specimens, which are justified as obligatory criteria [7]. Optional criteria and immunohistochemical features for the diagnosis are also introduced in order to reduce previous ambiguities, improve the unsatisfactory reproducibility of the WHO classification, and help to classify thymomas with ambiguous histology. Immunohistochemical markers such as cytokeratin 19/20, p20, p63, p40, and TdT are routinely used for this purpose.

After a pathological examination of the surgical specimen, we confirmed it to be type A thymoma because of its well-circumscribed and spindle-shaped epithelial cell-rich appearance with relatively low mitotic activity and minimal atypia in comparison with its histological findings. Further, in the immunohistochemical study of our case, the surgical specimen was positive for AE1/3, indicating the epithelial keratin origin of the tumor. We assumed it to be the epithelium of the salivary gland or a lung-origin malignancy because of the positive result of the cytokeratin (AE1/3) staining of the biopsy specimen, which is also strongly associated with spindle-shaped epithelial-cell neoplasms, such as type A thymoma. Moreover, the positive result for p40 staining, which is a p53 marker that is positive in 97% of thymomas, supported this result. Additionally, p63, another maker of the spindle-shaped epithelial cells of thymoma, was positive in our case. The antigen CD20 reveals the existence of focal micronodular areas with a lymphoid stroma and is helpful in the diagnosis of type A thymoma. However, 50% of type A thymomas show a negative result for CD20, and our result was also negative [8]. CD117, a marker for epithelial cells in thymic carcinoma, was focally positive. The fourth edition of the WHO classification states that tumors should be diagnosed on the basis of hematoxylin and eosin staining; thus, we concluded that our case was type A thymoma, although some immunohistochemical studies did not follow the usual pattern of type A thymoma.

PIT should be staged according to the lung cancer staging system because PIT is classified as a malignant tumor of the lung according to the WHO histological classification. The Masaoka staging system, which is based on the extent of invasion into mediastinal structures [9], is not appropriate for the staging of PIT, because PIT exists inside of a lung, and not in the mediastinum, and has an identical anatomical condition to that of lung cancer. Further, nodal involvement was described in several cases, which shared an anatomy similar to that of primary lung cancer.

Surgical resection, lobectomy, and systematic lymph node dissection should be the treatment of choice in the case of PIT. A significantly better survival rate was reported in patients who underwent surgical treatment than in those who were conservatively treated in a systematic review by Veynovich et al. [10]. They suggested that adjuvant radiation therapy be considered in cases of incomplete resection or expansion of the tumor tissue beyond a circumscribed capsule. However, the effect of radiotherapy on the overall survival rate is unclear.

In particular, the need for lymph node dissection has not been adequately discussed because of the rarity of PIT. As previously mentioned, Terashima et al. [11] reported a case of PIT with lymphatic spread; the sites of nodal metastases were similar to those of primary lung cancer. They argued that systematic mediastinal lymph node dissection according to the lymph node map for primary lung cancer be considered for better staging and most likely, better prognosis.

In our case, video-assisted thoracic surgery lobectomy and mediastinal lymph node dissection were performed, and no adjuvant therapy was conducted subsequently, because the mass was confirmed to be type A thymoma without invasion.

In conclusion, PIT is a very rare lesion with uncertain pathogenesis. PIT should be included in the differential diagnosis when the pathology of a lung tumor shows uncommon features. An immunohistochemical examination should be performed for an exact diagnosis. Complete resection should be achieved surgically. Since the natural history of the disease has not yet been fully elucidated, regular long-term follow-ups should be performed in accordance with primary lung cancer.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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