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A Metastatic Paraganglioma presenting as Multiple Intrapulmonary Nodules[1]

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A 24-year-old man that had previously undergone a complete resection of a cervical paraganglioma presented with multiple well-defined intrapulmonary nodules on contrast-enhanced computed tomography. All of the nodules showed homogeneously intense enhancement. The largest nodule was a hot spot on F-18 fluorodeoxyglucose positron emission tomography. It was diagnosed as a paraganglioma using wedge resection via video-assisted thoracoscopic resection. Paragangliomas are rare neuroendocrine tumors and are exceedingly rare in the lung parenchyma. A few reports have described one or two intrapulmonary lesions, including primary tumors and metastases. We report a unique case of a multiple metastatic paraganglioma in the parenchyma of both lungs.

Index words : Paraganglioma
Extra-adrenal
Neoplasm metastasis
Tomography, X-ray computed

Paragangliomas are rare neuroendocrine tumors. Most of the tumors (85 - 90%) arise in the adrenal medulla, and the tumors are denoted as pheochromocytomas. Extra-adrenal paragangliomas account for the remaining 10 - 15% of lesions and can be found in practically every site of the normal paraganglia (1 - 3). Thoracic paragangliomas constitute only 1 - 2% of all paragangliomas and the tumors are mostly found in the mediastinal compartment (2).

A metastatic paraganglioma is very rare disease that is diagnosed by local recurrence or a distant metastasis after total resection of the primary mass, as in the present case (3, 4). An intrapulmonary paraganglioma, either primary or metastatic, is extremely rare (2 - 4). This report describes a case of multiple metastatic paragangliomas arising in the parenchyma of both lungs, with a review of the imaging and pathological features.

Case Report

A 24-year-old man presented with multiple lung nodules. Although the patient had no symptoms, the patient had recently undertaken chest radiographs for exemption from military service. The laboratory findings were normal, including levels of tumor markers. Fourteen years earlier, the patient underwent a complete resection of a paraganglioma arising in the right neck. There was no family history of endocrine tumors or a particular syndrome. Chest radiographs revealed several well-defined nodules in both lungs. Contrast-enhanced computed tomography (CT) demonstrated multiple, vari-

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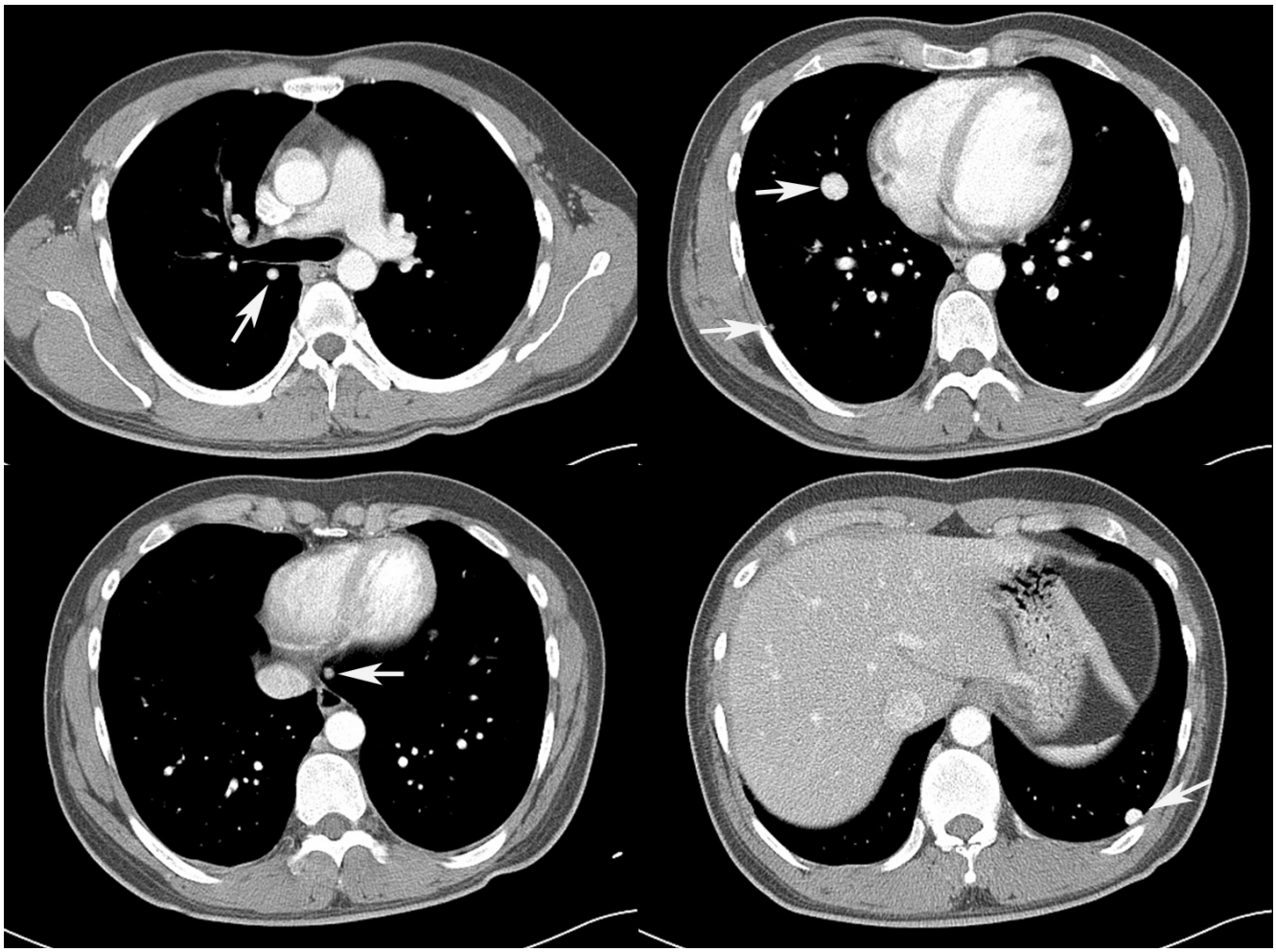
able-sized, circumscribed, intrapulmonary nodules. These homogeneously well-enhancing solid nodules had neither inner necrotic portions nor intratumoral calcifications (Fig. 1A). There was no zonal predominance. The nodule diameters ranged from 4 to 18 mm. The largest nodule in the right middle lobe (Fig. 1A) corresponded to an intense hotspot seen on F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) (Fig. 1B). There was no other hot-uptake on FDG-PET. The preoperative diagnosis was a hematogenous



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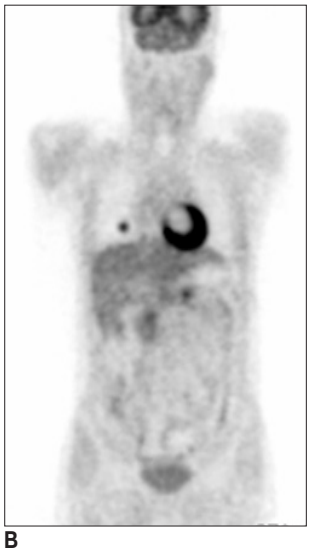

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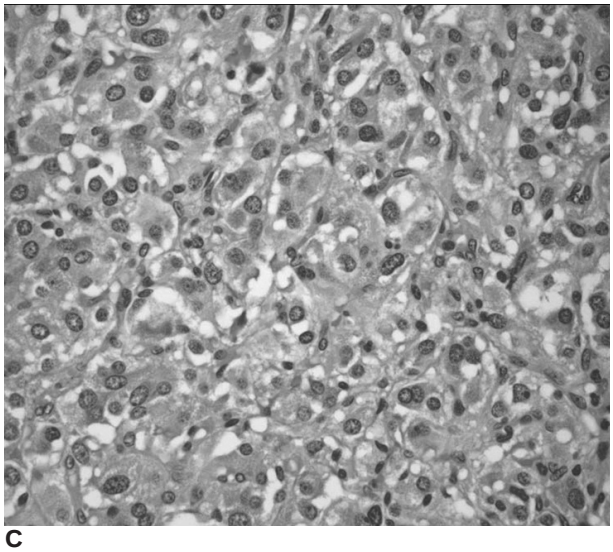

C

Fig. 1. A. Contrast-enhanced computed tomography shows multiple variable-sized, well-defined, solid nodules (arrows) with intense enhancement in both lungs. There is no zonal predominance.

B. F-18 fluorodeoxyglucose positron emission tomography demonstrates a focal hot spot in the right middle lobe, which corresponds to the largest nodule.

C. A photomicrograph reveals the characteristic Zellballen appearance of the paraganglioma (×200, H and E stain).

metastasis or benign pulmonary nodules, such as an inflammatory pseudotumor or hemangiopericytoma.

The patient subsequently underwent a wedge resection via video-assisted thoracoscopic resection (VATS), as the possibility of a hematogenous metastasis could not be excluded entirely. The cut surface of the specimen showed a well-defined ovoid, creamy yellow, solid nodule. The specimen measured about 1.3×0.7 cm. Hematoxylin-eosin staining revealed the characteristic Zellballen pattern (Fig. 1C). Immunohistochemical staining showed chromogranin and synaptophysin immunoreactivity in the tumor cells and S-100 immunoreactivity in the sustentacular cells. The final diagnosis was a paraganglioma. Four months later, the chest CT was repeated. The remaining nodules had not changed in number, size, or location.

Discussion

Paraganglionic cells are neural crest derived cells of the neuroendocrine system (3, 5). Paraganglia are paired along the prevertebral and paravertebral sympathetic chains, along the sympathetic nerve branches that innervate the pelvic organs and retroperitoneum, and along the parasympathetic cranial nerve ganglia (5). Although extremely rare, intrapulmonary paragangliomas can theoretically arise when paraganglia-like structures appear in the peri-arterial pulmonary interstitium (4).

Although most paragangliomas are solitary, multicentricity occurring either synchronously or metachronously has been documented (5). The incidence of multiplicity is approximately 10%, and is most common in the neck, involving the branchiomeric paraganglia (2, 5). A higher prevalence has been noted in hereditary disorders, such as multiple endocrine neoplasia syndromes and neuroectodermal syndromes (5).

To metastasize, the tumor spreads via the bloodstream or the lymphatics (3). The annual incidence of metastasis is 1/10,000,000 (6). There have been fewer than ten published cases between 1985 and 1996 (7). The risk factors of metastasis in terms of gender, race, and age are not clear. The time interval for metastasis is variable, and the mean time is about 6 years (3). Say et al. (8) reported distant metastasis in 3.2% of cervical paraganglioma cases. The reported metastatic sites were bone, cervical and mediastinal lymph nodes, liver, heart, and lung. Of these sites, the most common was the vertebral body (3, 4). The number of reported lung parenchymal lesions never exceeded two (2, 4, 5).

Paraganglioma, especially of an extra-adrenal origin, may not be detected on either anatomic [CT or magnetic resonance imaging (MRI)] or functional [^{131}I (or ^{123}I) metaiodobenzylguanidine (MIBG) scintigraphy or F-18 FDG PET] imaging modalities (9). On CT, most paragangliomas appear as well-enhancing nodules, as in the present case. Some nodules have extensive hemorrhage or cystic degeneration, resulting in large areas of low attenuation (1, 2). On MRI, the nodules show homogeneous or heterogeneous intermediate signal intensity on T1-weighted images and increased signal intensity on T2-weighted images, as compared with that of the liver. The advantage of the utilization of MR over CT is its ability to characterize the vascularity of the lesion, which is seen as a signal void (10).

For detecting a paraganglioma, ^{131}I MIBG scintigraphy has a sensitivity of 87% and a specificity of 90%. However, a fault in any process affecting MIBG within the tumor may result in a false-negative study. Coincidence FDG-PET can detect and localize the tumor, especially extra-adrenal paragangliomas that are not detected using conventional imaging. Paragangliomas take up FDG to variable degrees that depend on multiple factors, such as the tumor size. The non-uptake of FDG in some nodules in the present case may be due to their small size (9).

An metastatic paraganglioma is diagnosed by local recurrence or the presence of a distant metastasis after total resection of the primary mass (3, 4). The histological appearance is insufficient for discriminating between benign and malignant types (3 - 5). However, three pathological features of malignancy have been suggested in previous reports (3 - 5). The first feature is the less apparent organoid pattern associated with central necrosis of the Zellballen pattern. For a benign paraganglioma, the Zellballen patterns classically present as nests or cords of chief neuroectodermal cells surrounded by sustentacular cells, which are separated by fine, delicate blood vessels (3). The second feature is the decreased expression of neuropeptides as measured on an immunohistochemical assay, because of the reduced number of sustentacular cells. This finding is related to a worse prognosis (4). The last feature is minimal staining for S-100 protein on sustentacular cells (5). None of these findings was seen in the present case.

A distant metastatic paraganglioma can be fatal, with an 11.8% 5-year survival rate (4, 7). The primary management is complete resection. For an isolated lesion,

surgical resection results in a better prognosis. The combined use of ^{131}I MIBG radiotherapy and chemotherapy with cyclophosphamide, dacarbazine, and vincristine has been proposed (3). In the present case surgical resection is impossible because of the multiplicity. Besides, the patient refused chemotherapy.

In conclusion, to the best of our knowledge, this case is the first documentation of multiple metastatic paragangliomas arising in the parenchyma of both lungs. If enhancing intrapulmonary nodules are seen in a patient that had previously undergone complete resection of a paraganglioma, the nodules might suggest the presence of metastatic paragangliomas.

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양폐야의 다발성 결절로 보이는 전이성 부신경절종[1]

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최승아 · 최나미 · 박재성 · 백상현 · 고은석[2] · 신화균[3] · 차장규 · 홍현숙

경부에 발생한 부신경절종에 대한 완전 절제를 시행 받았던 24세 남자에서 우연히 양폐야의 다발성 결절이 발견되었다. 이 결절들은 흉부 전산화단층촬영에서 다양한 크기로, 경계가 분명하였으며 강하게 조영증강 되었다. 가장 큰 결절은 F - 18 fluorodeoxyglucose의 양전자방출단층촬영에서 높은 섭취를 보였다. 이 병변은 비디오 내시경을 이용한 생검술을 통하여 부신경절종으로 진단되었다. 부신경절종은 드문 신경내분비계 종양으로서, 폐실질에 발생하는 경우는 매우 드물다. 지금까지 보고된 폐실질의 부신경절종의 개수는 두 개 이하이며 다발성 결절에 대한 증례는 없었다. 이에 우리는 폐실질에서 발생한 전이성 다발성 부신경절종에 대해 보고하려 한다.