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# Young woman with multiple lung nodules: a pulmonary oxymoron

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**DR HIROMU TANAKA (RESPIRATORY SPECIALIST TRAINEE)**

A 31-year-old Japanese woman was referred to our outpatient clinic after multiple nodules were incidentally discovered on a chest X-ray during her medical check-up. She had no fever, cough, dyspnoea or a history of illness, and her family had no history of neoplastic or autoimmune diseases. Her age at menarche was 14 years, her menstruation was regular with a 30-day cycle, and she had given birth to one child by normal delivery 2.5 years prior. She had never used female hormonal medications and had no history of smoking or exposure to tuberculosis.

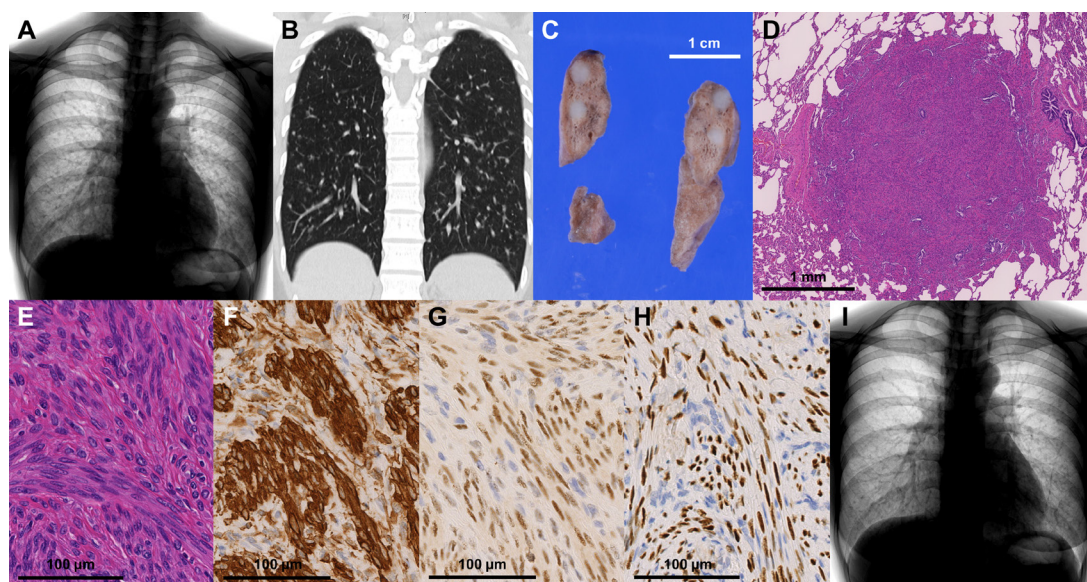
At her visit, she was afebrile (36.8°C), her blood pressure was 110/64 mm Hg, and her oxygen saturation was 97% on room air. On physical examination, both lungs were clear to auscultation, and there were no obvious abnormal findings. Blood cell counts, renal function, liver function and inflammatory markers were all normal, and there were no coagulation abnormalities. In addition, infection work-up revealed negative blood and sputum cultures. The beta-D glucan and interferon-gamma release assays were also normal.

**DR HIROKI KABATA (RESPIRATORY CONSULTANT)**

Detailed analysis of the imaging findings is essential for a diagnosis in this case. The chest X-ray showed multiple nodules scattered throughout the lungs, and no cavity formation, lymph node swelling or pleural effusion was present (figure 1A). We then performed chest CT which showed numerous, well-circumscribed, rounded nodules ranging from 1 to 7 mm in diameter, but there was no large lesion suggestive of a primary lesion in the lungs (figure 1B). The nodules were randomly distributed throughout the lungs and some of them were located on the pleura, but there was no distribution along the airways or lymphatic vessels. What do we think about the differential diagnosis for this case?

**DR HIROMU TANAKA (RESPIRATORY SPECIALIST TRAINEE)**

In general, the differential diagnosis of multiple lung nodules is classified as tumours (primary/metastatic lung tumours and lymphomas), infection (tuberculosis, nontuberculous mycobacteria, cryptococcus, pneumocystis, aspergillus and parasites),



**Figure 1** Radiographic and pathological findings of the patient. (A) chest X-ray showing multiple small nodules distributed throughout both lung fields. (B) Chest CT revealing multiple nodular lesions randomly distributed throughout the lung. (C) Lung specimen by surgical biopsy containing well-defined white lesions. (D, E) pulmonary nodular lesions consisting of spindle-shaped tumour cells with mild atypia (H&E stain). (F, G) The tumour cells express the smooth muscle marker,  $\alpha$ -SMA (F), and the female genital organ marker, WT-1 (G). (H) The tumour cells express oestrogen receptor. (I) Chest X-ray showing shrinkage and disappearance of multiple nodular shadows 6 months after the introduction of hormone therapy.

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inflammation (sarcoidosis, granulomatosis with polyangiitis and rheumatoid nodules), vascular disorders (arteriovenous malformations and pulmonary infarction) and others (amyloidomas). Importantly, the distribution of the nodules helps to narrow down the differential diagnosis. A random distribution of well-circumscribed rounded nodules, as in this case, suggests that the nodules were spread haematogeneously. Therefore, metastatic lung tumours, disseminated tuberculosis, disseminated nontuberculous mycobacteria, septic emboli and multiple pulmonary infarctions were considered as differential diagnoses in the present case. Furthermore, since she was asymptomatic and had no abnormalities on blood and culture tests, infectious diseases and multiple emboli are less likely. In addition, there were no abnormal examination or serological findings suggestive of inflammatory diseases, such as sarcoidosis, granulomatosis with polyangiitis or rheumatoid nodules. Hence, despite a low likelihood of malignancy at her young age, metastatic lung tumours were the most likely diagnosis.

#### DR HIROKI KABATA (RESPIRATORY CONSULTANT)

There were no elevated tumour markers for lung cancers, including carcinoembryonic antigen, cytokeratin 19 fragment and progastrin releasing peptide. Positron emission tomography (PET) was then performed to find a possible primary tumour lesion. However, there was no fluorodeoxyglucose uptake in the nodules, lymph nodes and other organs. We then performed a surgical biopsy for diagnosis.

#### DR KYOHEI MASAI (RESPIRATORY SURGEON)

Surgical biopsy using video-assisted thoracoscopic surgery revealed multiple nodules of approximately 5 mm scattered throughout the lung parenchyma. These nodules were white in colour and slightly firm to the touch. These findings were compatible with those of metastatic lung tumours.

#### DR KATSURA EMOTO (CONSULTING PATHOLOGIST)

The excised lungs contained multiple well-defined white lesions with a maximum diameter of 2.5 mm (figure 1C). H&E staining showed bundles of spindle-shaped cells proliferation in the nodules. The cellular atypia was mild, and few nuclear mitoses were observed in the lesion (figure 1D,E). Immunostaining was positive for  $\alpha$ -smooth muscle actin (figure 1F), desmin and the Ki67 positivity was <5 %, suggesting low-grade smooth muscle tumours. Other immunostains and in situ hybridisation were negative (thyroid transcription factor-1, myogenin, cytokeratin AE1/AE3, S-100, CD34, erythroblast transformation-specific-related gene (ERG), signal transducer and activator of transcription 6 (STAT6), c-kit, discovered on gastrointestinal stromal tumours 1 (DOG1), ALK, and Epstein-Barr virus in situ hybridisation). Histologically, no granulomas and vasculitis were observed.

#### DR HIROKI KABATA (RESPIRATORY CONSULTANT)

The pathological results revealed low-grade smooth muscle tumours, but we could not find any primary lesions using CT and PET. While we struggled to find the location of the primary lesion, we recalled a rare hormone-dependent disease in young women, namely pulmonary benign metastasizing leiomyomatosis (PBML). We then consulted the pathologist for additional immunostaining and a gynaecologist for examination of the gynaecological organs.

#### DR KATSURA EMOTO (CONSULTING PATHOLOGIST)

Additional immunostaining was positive for WT-1 (figure 1G), oestrogen receptor (ER) (figure 1H) and progesterone receptor (PgR). In addition, HMB-45 was slightly positive, while melan A was negative, which suggests the possibility of PBML.

#### DR SHIGENORI HAYASHI (CONSULTING GYNAECOLOGIST)

Patients with PBML may have a history of uterine fibroids or hysterectomy, neither of which was present in this case. Pelvic MRI revealed a 1 cm lesion in the uterus suspected of being a fibroid or adenomyosis, however, this lesion was not evident on transvaginal ultrasonography.

#### DR KATSURA EMOTO (CONSULTING PATHOLOGIST) AND DR KOICHI FUKUNAGA (PROFESSOR OF RESPIRATORY MEDICINE)

PBML is a hormone-dependent lung disease, as is perivascular epithelioid cell tumour (PEComa) including lymphangiomyomatosis (LAM), and these diseases generally affect women of child-bearing age.<sup>1</sup> The common origin of these diseases is considered to be the uterus; the tumour cells express ER and PgR, and female hormones are involved in tumour growth. LAM is pathologically characterised by abnormal smooth muscle cell proliferation with a large amount of eosinophilic cytoplasm, which forms multiple cystic lesions in the lung. Therefore, the radiographic and pathological findings of LAM were different from this case. PEComa is a mesenchymal tumour derived from perivascular epithelioid cells, typically comprising bright spheroid cells called 'clear cells,' and has been reported to metastasise to the lung. It is pathologically characterised by positive immunostaining for multiple melanocyte markers<sup>2</sup>; however, so is LAM. In the present case, regarding the markers for melanocytes, MelanA was negative, but HMB-45 was weakly positive. Therefore, the possibility of the pulmonary metastasis of PEComa could not be completely ruled out. However, the histology of this case showed a homogeneous tumour with spindle-shaped smooth muscle cells, which was different from PEComa. In addition, since HMB-45 can be positive in uterine leiomyosarcoma, HMB-45 alone is not enough to diagnose PEComa.<sup>3</sup> We thus diagnosed this case as PBML.

#### DR HIROMU TANAKA (RESPIRATORY SPECIALIST TRAINEE)

Benign metastasizing leiomyoma (BML) was first described by Steiner in 1939 as a fibroleiomyomatous hamartoma with malignant metastatic properties that is histologically benign.<sup>4</sup> BML is classified as a benign tumour because of its low mitotic features, lack of cellular atypia, slow tumour growth rate and lack of evidence of invasion, but it is thought to metastasise haematogenously from the uterus, resulting in PBML. Possible reasons for PBML metastasis include low-grade sarcomatous changes that lead to metastasis and surgical trauma that causes the tumour to spread into the veins. Indeed, PBML commonly occurs in patients with a history of hysterectomy or uterine leiomyoma. However, it is reported that there are cases without it. In a case series of 23 PBML patients from a single institution, two patients (8.7 %) had no uterine leiomyoma and three patients (13.0 %) had no history of gynaecological surgery.<sup>5</sup> Although the median age at diagnosis of PBML was reported at 46 years,<sup>5</sup> PBML may develop at a younger age without any specific cause, including female hormonal medications. It is estimated that approximately 70% of PBML cases are asymptomatic, therefore, these tumours are often discovered incidentally. In this case, PBML was discovered incidentally during annual medical check-up, and such

regular chest X-rays may have been one of the reasons for the diagnosis of PBML at a young age in our patient.

#### DR KOICHI FUKUNAGA (PROFESSOR OF RESPIRATORY MEDICINE)

What is the treatment and follow-up for this case?

#### DR HIROKI KABATA (RESPIRATORY CONSULTANT)

As PBML depends on oestrogen and progesterone for growth, hormonal control is essential for treatment. In the past, bilateral oophorectomy was reported to be effective in inhibiting tumour growth; however, medical castration with drug therapy is now an option. In the present case, gonadotropin-releasing hormone analogue (leuprorelin) was administered at 1.88 mg three times at 1 month intervals, followed by progestin (dienogest) at 1 mg daily. The multiple lung nodules showed a tendency to shrink and disappear on subsequent chest X-rays after 6-month treatment (figure 11). The patient is now expecting her second child, and the nodules are reportedly regressing spontaneously during the pregnancy. Therefore, I am planning to suspend the hormone therapy.

#### DR HIROMU TANAKA (RESPIRATORY SPECIALIST TRAINEE) AND DR HIROKI KABATA (RESPIRATORY CONSULTANT)

This was a case of multiple asymptomatic pulmonary nodules in a young woman of childbearing age. In the case of multiple pulmonary nodules, it is useful to consider the distribution of the nodules on CT findings to narrow down the differential diagnosis. Although PBML is a rare disease, respiratory specialists should keep it in mind as a differential diagnosis for pulmonary nodules in young women.

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