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Benign metastasising leiomyoma: a rare but possible cause of bilateral pulmonary nodules in Chinese patients

良性轉移平滑肌瘤：華裔患者一個罕有及能引致多發性肺結節的成因

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 We report three cases of benign metastasising leiomyoma, which is a rare cause of multiple lung nodules, in three Hong Kong Chinese females. One patient presented with pleuritic chest pain, another was asymptomatic, while the last presented with haemoptysis. All three patients had previously undergone surgical resection of uterine leiomyomas. Multiple lung nodules mimicking lung metastases were demonstrated on chest radiographs, and all three diagnoses were obtained from lung biopsies. Hormonal therapy was given to two patients with variable responses. To the best of our knowledge, this is the first report of benign metastasising leiomyoma in Hong Kong Chinese population. It highlights the importance of considering this rare and benign disease in premenopausal females presenting with multiple lung nodules.

本文報告三個良性轉移平滑肌瘤的香港華人病例。病者均為女性，其中2人的臨床症狀分別為胸痛及咯血，其餘1人並無任何症狀。3名病者均曾接受子宮平滑肌瘤切除手術，其肺部X光照片皆顯示出類似肺轉移之多發性肺結節現象，而病者的肺組織切片檢查亦確定此診斷。其中兩位病者曾接受賀爾蒙療法，但其效果並不一致。本文為首個香港華人患有良性轉移平滑肌瘤之病例報告。在為閉經前的女性診斷多發性肺結節病症時，應要考慮此罕有的成因。

Key words:

Hormone replacement therapy;
 Leiomyoma;
 Lung neoplasms;
 Neoplasms metastasis;
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關鍵詞：

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Introduction

Benign metastasising leiomyoma (BML) is a rare disease with approximately 50 cases reported mainly in the western literature, although it has also been reported in Japan.^{1,2} We describe three Chinese females diagnosed with BML between 2002 and 2003. All three were in their 40s and had undergone prior surgical removals of uterine leiomyomas. The diagnoses were established by surgical biopsy and histology.

Case report

Case 1

A 49-year-old premenopausal woman presented in August 2003 with a 1-month history of pleuritic chest discomfort without fever, chill, weight loss, haemoptysis, or other respiratory symptoms. She had a history of uterine leiomyoma (12 cm in diameter) requiring



Fig 1. Computed tomographic scan of the thorax shows multiple contrast-enhancing, well-circumscribed nodules ranging from a few millimetres to 3.6 cm in size



Fig 2. The tumour nodule is composed of interlacing bundles of smooth muscle
Entrapped respiratory epithelium is present, imparting a leaf-like pattern (H&E, x100)

myomectomy and ventrosuspension in 1984. As a non-smoker working in a garment factory, she had otherwise enjoyed good past health.

Physical examination revealed no pallor, jaundice, cyanosis, or finger clubbing. Blood pressure was 114/68 mm Hg, respiratory rate was 16 breaths per minute, and body weight was 58 kg. Examination of the head, ears, eyes, and throat was unremarkable. No lymphadenopathy, breast lumps, or thyroid nodules were noted. No abnormalities, such as palpable masses, hepatosplenomegaly, or ascites, were discovered in the abdomen apart from a lower abdominal scar from the earlier gynaecological surgery. Auscultation of the lungs revealed normal breath sounds.

Laboratory studies including arterial blood gas, complete blood picture, renal and liver functions, cardiac enzymes, calcium level, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, and tumour markers including alpha-fetoprotein, carcino-embryonic antigen, and cancer antigen 125 were all within normal ranges.

Chest X-ray showed bilateral nodular opacities, and computed tomography (CT) of the thorax revealed multiple contrast-enhancing, well-circumscribed nodules ranging in size from a few millimetres to 3.6 cm (Fig 1). Bronchoscopy revealed no abnormalities, and a transbronchial biopsy under fluoroscopic screening yielded no positive diagnosis. Positron emission tomographic scan showed numerous hypometabolic nodular lesions in both lungs (maximum standardised uptake value [SUV], 1.4). A surgical biopsy of the

right lower lobe was performed under video-assisted thoracoscopy (VAT). Histology revealed multiple well-defined nodules composed of interlacing bundles of smooth muscle cells with entrapped respiratory epithelium giving rise to a focally leaf-like pattern (Fig 2). The smooth muscle cells contained regular cigar-shaped nuclei and a fair amount of eosinophilic cytoplasm. No nuclear atypia, mitosis, or necrosis were identified, and the findings were consistent with BML. Immunohistochemical studies showed positive nuclear staining for oestrogen and progesterone receptors on the smooth muscle cells.

The patient was referred to gynaecologists and monthly injections of Triptorelin, a luteinising hormone releasing hormone (LHRH) analogue (Decapeptyl CR; Ferring Pharmaceuticals, Kiel, Germany) were started. Chest X-ray taken after 3 months of treatment showed regression of lung nodules, and the patient remained well 9 months after the diagnosis.

Case 2

A 41-year-old woman was referred by her general practitioner in February 2002 due to an incidental finding of multiple lung shadows on a chest X-ray taken during a routine health check. A non-smoker with otherwise good past health, she had a history of uterine fibroids with a hysterectomy performed 9 years earlier. Despite the alarming radiological features, she was free of any respiratory or systemic symptoms. Chest auscultation was clear, with normal breath sounds. Apart from a midline hysterectomy scar over the lower abdomen, no abnormalities were revealed on physical examination.

Chest X-ray showed multiple lung nodules over both lung fields, and thoracic CT confirmed the presence of multiple lung nodules ranging from 2 mm to 11 mm in size. Blood tests, sputum, and bronchoscopy findings were all normal. A lung biopsy was obtained from the right lung under VAT, which revealed multiple reddish nodules over all lobes. Histology revealed multiple nodules composed of interlacing fascicles of smooth muscle cells with entrapped respiratory epithelium forming papillae and clefts at the periphery producing a leaf-like pattern. The smooth muscle cells had cigar-shaped nuclei and eosinophilic cytoplasm without nuclear atypia. Mitotic figures were rare (<1/50 high-power field) with no coagulative necrosis. Features were consistent with BML. Immunohistochemically, the smooth muscle cells were positive for oestrogen and progesterone receptors.

The patient was given megestrol acetate 80 mg twice daily (Megace; Bristol-Myers Squibb, Munich, Germany) and has been monitored regularly by oncologists. Her radiological picture remained static and asymptomatic 26 months after diagnosis.

Case 3

A 45-year-old woman had a similar incidental finding of bilateral lung nodules on a chest X-ray, taken in early 2003 for an episode of blood-stained sputum, with no other associated symptoms. The patient had undergone hysterectomy for uterine fibroids 9 years earlier. Physical examination was unremarkable with the exception of a hysterectomy scar over the lower abdomen. The chest X-ray showed bilateral lung nodules, which ranged in size from a few millimetres to 1 cm on subsequent thoracic CT. Positron emission tomographic scan showed mildly increased uptake in a solitary nodule in the right upper lobe (maximum SUV, 2.0), but no uptake was found elsewhere. Bronchoscopy revealed no endobronchial lesions. No diagnosis of the patient's haemoptysis was obtained from examinations of her sputum and bronchial aspirate. Because the subsequent fine needle aspiration of her lung nodules also gave no positive result, open biopsy and wedge resection of some of the nodules were subsequently performed under VAT. Histology revealed interlacing bundles of smooth muscle with rare mitotic figures (<1/20 high-power field) and no nuclear atypia or necrosis, which was consistent with BML. Although hormonal therapy was refused, the patient remained asymptomatic with a static radiological picture 1 year after diagnosis.

Discussion

Benign metastasising leiomyoma is rare. Only around 50 well-documented cases have been reported since 1939, most from western populations.³ To the best of our knowledge, these three patients are the first reported BML cases in the Chinese population. The lungs are the most commonly affected site, but other organs can also be involved.² Most reported cases have been in females near 40 years of age with histories of uterine leiomyomas or their operative removals, as in our three cases. However, three male cases have also been reported, with the primary lesions in the saphenous vein, diaphragm, and soft tissues.⁴ Most patients are asymptomatic with lung lesions being discovered from chest X-rays taken for other reasons. The relatively mild symptoms of our first and third patients might not be directly attributed to BML, but they did necessitate radiographic chest examinations. The clinical course is usually chronic and benign, but progressive disease leading to respiratory failure and even death has been described.^{5,6} In a series of BML cases involving excision of the pulmonary lesions, the median survival was 94 months.⁷

Histologically, these tumours consist of well-differentiated, benign-looking smooth muscle cells lacking anaplasia or vascular invasion. Although the diagnoses of BML were beyond doubt, it is unfortunate that the pathological specimens of the initial uterine leiomyomas of our patients, taken nearly a decade ago, were not available for histological correlation with the present pulmonary lesions. The aetiology of BML has been controversial and includes metastases from uterine leiomyoma⁸ and hormonally induced non-neoplastic hyperplasias arising from lungs.⁹ The hormonal relationship is supported by the observation that regressions occurred following oophorectomy,¹⁰ pregnancy,⁶ and menopause.¹ Also, oestrogen and progesterone receptors have been found in BML, as in our cases.¹¹ This is the rationale behind the use of hormonal therapy, including progesterone and LHRH analogues, or hysterectomy and bilateral salpingo-oophorectomy in reported cases.

Hysterectomy removes the primary source of metastasis while oophorectomy depletes oestrogen, leading to tumour regression.^{6,10} In addition, Winkler et al¹² performed staged thoracotomies with resection of multiple leiomyomas in two patients, with no recurrence in 6 years. As noted, a median survival of 94 months has been reported in a series involving surgical resection of the lesions.⁷ Hague et al⁹ reported on the use of an LHRH analogue to produce a medical

castration by causing pituitary desensitisation to endogenous LHRH, which results in reversible gonadal suppression. Consequently, oestrogen levels fall resulting in tumour regression. Winter¹³ has suggested the use of tamoxifen, which blocks the effects of oestrogen at the tissue level. Progesterone may inhibit subsequent production of oestrogen receptors and abolish the vasomotor symptoms of oestrogen depletion following oophorectomy; however, the treatment results to date have not been impressive.¹⁴ Cytotoxic therapies, such as high-dose ifosfamide, have been used with little beneficial effect.¹¹ On the other hand, anastrozole, an aromatase inhibitor, and raloxifene, a selective oestrogen receptor modulator (SERM), were described as useful in a recent case report.¹⁵

No standard management guidelines or clinically proven treatment modalities exist for this rare disease. Apart from the gynaecological procedures necessary for the removal of uterine leiomyomas and/or the source of continuing oestrogen secretion, resection of the pulmonary lesions may be an option for good surgical candidates with appropriate lesions. For patients with symptomatic or progressive disease, hormonal therapy such as LHRH analogues, progestogens, aromatase inhibitors, or SERMs may be considered. Although benign metastasising leiomyoma is a rare differential diagnosis, it may be considered in local Chinese females presenting with the radiological findings of bilateral pulmonary nodules.

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