

**Figure 1**

(A) Chest X-ray and (B) computed tomography images taken in June 2008 showing nodular lesions distributed in the entire lungs. (C) Positron emission tomography (PET) image similarly obtained in June 2008 showing slight accumulation of nodular lesion in the uterus (arrow).

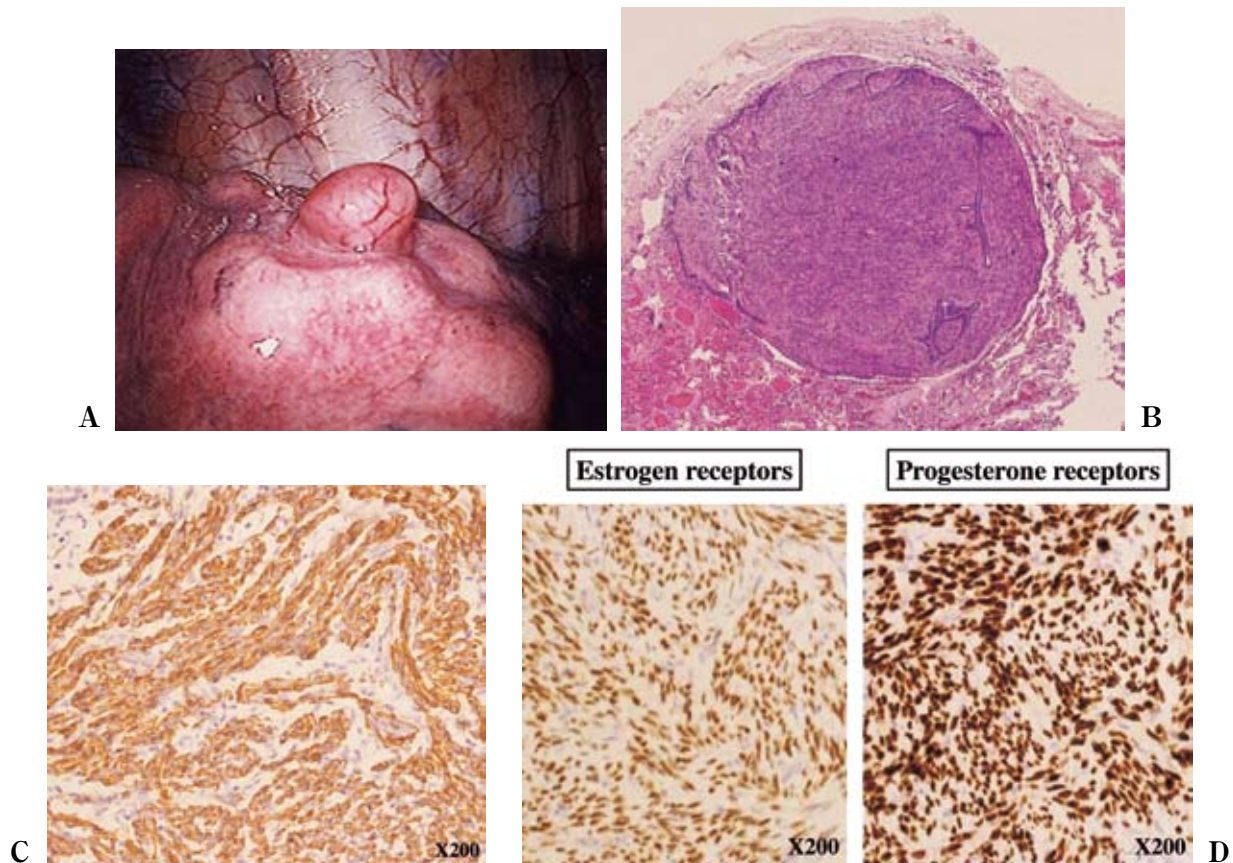
However current reports describe BML as a very rare disease with little information regarding its pathology. Here, we report a case of pulmonary BML occurring after uterine myomectomy.

### CASE REPORT

A 42-year-old woman presented with a 2-week history of dry cough on exertion upon visiting our hospital in June, 2008. Chest radiography and computed tomography (CT) revealed bilateral multiple nodular lesions (Fig. 1A and B). The patient had a history of uterine myoma and previously underwent myomectomy in 2003.

Physical examination revealed no abnormalities and her oxygen saturation while breathing room air was 96%. Laboratory test results were as follows: white blood cells 6900/ $\mu$ l; neutrophils 60.0%; eosinophils

5.0%; lymphocytes 30.0%; serum C-reactive protein 0.1 mg/dl (normal, < 0.3 mg/dl); creatinine 0.69 mg/dl (0.46–0.82 mg/dl); lactate dehydrogenase 145 IU/l (200–400 IU/l); carcinoembryonic antigen < 1.0 ng/ml (< 5.0 ng/ml); carbohydrate antigen (CA) 19-9 8 U/ml (< 37 U/ml); CA125 14 U/ml (< 37 U/ml); squamous cell carcinoma related antigen 1.6 ng/ml (< 1.5 ng/ml); sialyl stage-specific embryonic antigen-1 35 U/ml (< 38 U/ml); soluble interleukin-2 receptor 316 U/ml (220–530 U/ml); immunoglobulin (Ig) G 1204 mg/dl (870–1700 mg/dl); IgA 101 mg/dl (107–363 mg/dl); IgM 139 mg/dl (46–260 mg/dl); cytoplasmic-anti-neutrophil cytoplasmic antibody < 10 EU; perinuclear-anti-neutrophil cytoplasmic antibody < 10 EU; anti-nuclear antibody 20x; anti-Sjögren's syndrome (SS) A (anti-SSA/Ro) negative (< 20 index);  $\beta$ -D glucan 3.2 pg/ml (< 10 pg/ml); Crypto-



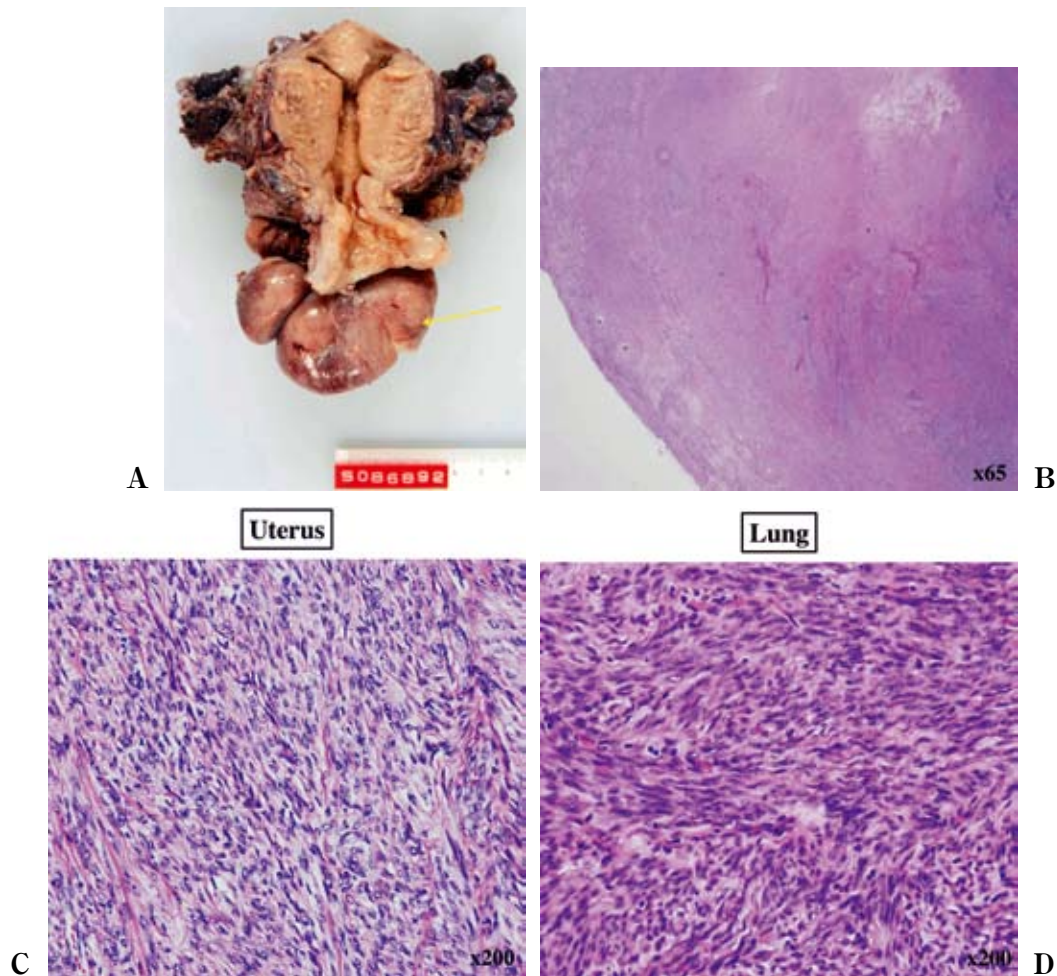
**Figure 2**

(A) Video associated thoracoscopy of the lung surface performed in July 2008 showing multiple elevated smooth lesions. (B) Hematoxylin and eosin (H&E) staining (original magnification,  $\times 65$ ) showing scattered nodular lesions of up to 3 mm diameter composed of bundles of spindle cells and columnar epithelial cells incorporated into the nodule resembling hamartoma. Few mitotic figures can be seen and the proliferating cells fall short of anaplasia which might lead to a diagnosis of a spindle cell sarcoma. (C) Immunostaining for  $\alpha$  smooth muscle actin in spindle cells (original magnification,  $\times 200$ ). (D) Histologic examination of progesterone and estrogen receptors in spindle cells found in lung nodular lesions.

coccus neoformans antigen negative. Urinary examinations were normal.

Positron emission tomography (PET) performed in June, 2008 showed the absence of nodular lesion accumulation in the entire lung but slight accumulation in the uterus (Fig. 1C). Although bronchoscopy with accompanying bronchoalveolar lavage and transbronchial lung biopsy was performed, a definitive diagnosis could not be made. Subsequently, video associated thoracoscopy was carried out the following month, which demonstrated multiple elevated smooth lesions on the lung surface (Fig. 2A). Histological examination of hematoxylin and eosin (H&E)-stained biopsy specimens obtained by video associated thoracoscopic surgery (VATS) from the right S4 region demonstrated scat-

tered nodular lesions of up to 3 mm diameter composed of bundles of spindle cells and columnar epithelial cells incorporated into the nodule resembling hamartoma (Fig. 2B). Mitotic figures were scarce, but the proliferating cells fell short of anaplasia which could indicate a diagnosis of spindle cell sarcoma. Immunostaining revealed the expression of  $\alpha$  smooth muscle actin ( $\alpha$ SMA) (Fig. 2C). Furthermore, spindle cells were positive for estrogen and progesterone receptors (Fig. 2D). From these histopathologic features, a definitive diagnosis of pulmonary BML of uterine origin was made. As for BML treatment, gonadotropin-releasing hormone was initially administered, and 1 month later in August, 2008, the patient underwent both complete hysterectomy and bilateral salpingo-oo-



**Figure 3**

(A) Complete hysterectomy and bilateral salpingo-oophorectomy were performed in August 2008 as treatment for BML. Grossly, two uterine myomas (arrow) were found, as well as myomas with <1 cm diameter in the uterine fundus [B (original magnification,  $\times 65$ ) and C ( $\times 200$ )] and lung tissue [D ( $\times 200$ )]. Histopathologic findings in lung tissue were consistent with those in typical uterine leiomyoma.

phorectomy. Bilateral ovarian findings revealed neither cystic lesions nor any abnormalities. Grossly, two myomas were observed in the uterine body, as well as <1 cm myomas in the uterine fundus (Fig. 3A). Histopathologic findings in lung tissue (Fig. 3D) were consistent with those in typical uterine leiomyoma (Fig. 3B, 3C). On follow-up examination in November, 2008, her serum progesterone and estradiol levels were 0.19 ng/ml (<0.44 ng/ml) and 10 pg/ml (<21 pg/ml), respectively, a clinical state resembling postmenopause. Six months after surgery, chest CT showed that both the size and number of lung multiple nodular lesions did not increase compared with those before surgery.

## DISCUSSION

The pathogenesis of pulmonary leiomyoma is considered to result from metastasis of benign uterine leiomyoma via unknown mechanisms, as well as low-grade uterine leiomyosarcoma, primary multiple leiomyoma or hamartoma. Caballes reported that BML develops in patients who previously underwent surgery for uterine leiomyoma<sup>4</sup> and suggested that leiomyoma cells metastasize into the lungs after surgery through the hematogenous route and thereafter undergo tumor progression<sup>4</sup>. On the other hand, patients have also shown good recovery from BML following metastectomy<sup>5</sup>. In particular, most BML patients are

women aged 36–64 years (average 44 years), and they are given an additional life expectancy of approximately 0 to 24 years following hysterectomy or myomectomy<sup>6–9</sup>. Bilateral, unilateral, and single lung lesion patterns have been demonstrated in 70 %, 17 %, and 13 % of BML cases<sup>10</sup>. In histopathologic examinations, the diagnosis of myoma must be differentially specified as either leiomyoma or leiomyosarcoma. A recent trend in the classification of uterine smooth muscle neoplasms into clinically benign or malignant groups has been to move from exclusive reliance on using mitotic index to other approaches<sup>11</sup>. The presence or absence of coagulative tumor cell necrosis and cytologic atypia has been regarded as important in the classification of smooth muscle neoplasms<sup>11</sup>.

For BML treatment, several studies have reported the efficacy of surgery for lung lesions, as well as bilateral salpingo-oophorectomy and/or hormonal therapy using gonadorelin acetate and progesterone<sup>5</sup>. However, specific and highly effective treatments have not yet been established. In some BML cases, convalescence has been observed without treatment<sup>3,6</sup>. In the present case, histopathologic examination of the lung showed low cytologic atypia, absence of coagulative tumor cell necrosis,  $\alpha$ SMA expression, and positivity for progesterone and estrogen receptors in spindle cells. Moreover, the histopathologic features of the lung nodular lesions were similar to those of the uterine leiomyoma obtained by complete hysterectomy, leading to a definitive diagnosis of pulmonary BML originating from uterine leiomyoma. The clinical features of this case, such as reproductive age and postmyomectomy, were also consistent with previous reports of BML<sup>6</sup>. Complete hysterectomy and bilateral salpingo-oophorectomy following hormonal therapy were used as treatment in the present case, and this therapy induced a subsequent decrease in the serum level of progesterone and estrogen to the standard level corresponding to postmenopause. Although the level of efficacy of this treatment was not fully clarified, it has at least suppressed the progression of lung multiple nodular lesions. It is imperative that lesion progression must subsequently be followed by radiography and CT.

When lung multiple nodular lesions are encountered in women, a detailed clinical history regarding previ-

ous uterine surgeries must be taken. And BML is suspected when PET showed the absence of nodular lesion accumulation in the entire lung but accumulation in the uterus<sup>12</sup>. To arrive at a definitive diagnosis of BML, histopathologic examination following VATS instead of bronchoscopy is recommended.

## REFERENCES

- 1) Steiner PE : Metastasizing fibroleiomyoma of the uterus. *Am J Pathol* **15** : 89–109, 1939.
- 2) Jautzke G, Müller-Ruchholtz E, Thalmann U : Immunohistological detection of estrogen and progesterone receptors in multiple and well differentiated leiomyomatous lung tumors in women with uterine leiomyomas (so-called benign metastasizing leiomyomas). A report on 5 cases. *Pathol Res Pract* **192** : 215–223, 1996.
- 3) Mikami I, Yamamoto M, Nishimura H, et al : Multiple lung tumors found 17 years after hysterectomy--a case of benign metastasizing leiomyoma. *Jpn J Thorac Cardiovasc Surg* **46** : 634–638, 1998.
- 4) Caballes RL : The mechanism of metastasis in the so-called "benign giant cell tumor of bone". *Hum Pathol* **12** : 762–767, 1981.
- 5) Maheux R, Samson Y, Farid NR, et al : Utilization of luteinizing hormone-releasing hormone agonist in pulmonary leiomyomatosis. *Fertil Steril* **48** : 315–317, 1987.
- 6) Ishibashi H, Ohta S, Hirose M, et al : Pulmonary benign metastasizing leiomyoma from uterine myoma : report of a case. *Kyobu Geka* **59** : 951–954, 2006.
- 7) Bachman D, Wolff M : Pulmonary metastases from benign-appearing smooth muscle tumors of the uterus. *AJR Am J Roentgenol* **127** : 441–446, 1976.
- 8) Schneider T, Kugler C, Kayser K, et al : Benign, pulmonary metastatic leiomyoma of the uterus. *Chirurg* **72** : 308–311, 2001.
- 9) Wentling GK, Sevin BU, Geiger XJ, et al : Benign metastasizing leiomyoma responsive to megestrol : case report and review of the literature. *Int J Gynecol Cancer* **15** : 1213–1217, 2005.
- 10) Ohtsuka T, Nomori H, Watanabe K, et al : Benign metastasizing leiomyoma of the lung. Report of a case. *Nihon Kokyuki Gakkai Zashi* **43** : 89–102, 2005.
- 11) Bell SW, Kempson RL, Hendrickson MR : Problematic uterine smooth muscle neoplasms. A clinicopathologic

study of 213 cases. Am J Surg Pathol **18** : 535-558, 1994.

12) di Scioscio V, Feraco P, Miglio L, et al : Benign metas-

tasizing leiomyoma of the lung : PET findings. J Thorac Imaging **24** : 41-44, 2009.