A case of multiple pulmonary cavernous hemangioma

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Abstract
A 61-year-old male who originally visited a different hospital, underwent a health checkup in which multiple lung nodules were detected. Multiple well-defined small nodules were observed in both lungs, with lesions reaching the arteries. Metastatic lung cancer, with unknown origin, was suspected. A computed tomography-guided percutaneous lung biopsy was performed; however, a pathological diagnosis could not be established. Then the patient was referred to our hospital for surgical lung biopsy. Macroscopically, the nodule was dark-red in color and solid without a capsule. Microscopically, the nodule was composed of dilated vascular spaces lined by flattened bland cells. They were positive for CD34, but negative for TTF-1, consistent with lesions of endothelial origin. Microscopic and immunohistochemical findings supported the diagnosis of multiple pulmonary cavernous hemangiomas. After diagnosis, the lesions were left untreated and thereafter showed no signs of deterioration.

Introduction
Cavernous hemangiomas are benign vascular tumor most commonly seen in the head and neck region in childhood; however, cases involving the lungs multiple pulmonary cavernous hemangiomas (PCH) have been reported in both adults and children, but rarely. PCH should not be overlooked in cases where multiple lung nodules are detected radiologically.

Case Report
Multiple lung nodules were detected in a 61-year-old male during a regular health checkup. Though metastatic lung cancer was suspected, the referee hospital was unable to establish a diagnosis using computed tomography (CT)-guided percutaneous lung biopsy. Therefore, the patient was referred to our hospital for diagnosis by surgical lung biopsy. In a chest X-ray (Fig. 1a) and CT (Fig. 1b, c), a number of multiple well-defined nodules measuring up to 10 mm were observed, with some reaching into the pulmonary artery. Metastatic lung neoplasm, arteriovenous malformation in Osler-Weber-Rendu syndrome, intrapulmonary hematoma epithelioid hemangioendothelioma, and Kaposi’s sarcoma were all considered as differential diagnoses. High uptake of both primary malignant lesion and multiple lung nodules was not detected on positron emission tomography; a thoracoscopic surgical lung biopsy was performed on one of the metastatic tumors in right middle lobe to reveal the unknown primary. Macroscopically, the biopsied nodules removed from right middle lobe, were dark-red, well defined, and located on the surface of visceral pleura (Fig. 2a). Microscopically, the nodule was composed of dilated vascular spaces of various sizes, which were lined with flattened bland cells (Fig. 2b). Immunohistochemically, the lining cells showed positive for CD34 (Fig. 2c) and factor VIII but negative for TTF-1 (Fig. 2d), and were considered as endothelial lesions. In the end, the patient was diagnosed with PCH and as the lung nodules showed no deterioration in follow-up visits, no more therapy was required.
Discussion

Benign lung tumors represent 2–5% of primary lung neoplasm with hamartoma making up the vast majority of cases. Cavernous hemangiomas of the lung, on the other hand, are exceedingly rare. Arrigoni et al. reported only one pulmonary hemangioma case out of 130 benign lung tumors [1]. A review of the literature reports that PCHs

Figure 1. (a) Chest X-ray shows the multiple lung nodules (arrow). (b,c) Chest computed tomography (CT) revealed that the well-demarcated nodules reach to the pulmonary artery.

Figure 2. (a) Formalin-fixed specimen shows small black nodule on surface of the resected lung. (b) Microscopically, the nodules were composed of dilated vascular spaces lined by flattened bland cells (HE x100). (c) They are positive for CD34 stain (x100). (d) They are negative for TTF-1 stain (x100).
Table 1. Characteristics of reported pulmonary cavernous hemangioma cases.

| No. | Year | Author      | Age | Sex | Symptoms                      | Number  | Growth | Size (mm) | Capsule |
|-----|------|-------------|-----|-----|-------------------------------|---------|--------|-----------|---------|
| 1   | 1947 | Whitaker    | 44  | F   | Cough, sputum, dyspnea        | Multiple | Unknown | Unknown   | +       |
| 2   | 1947 | Forsee      | 20  | M   | Cough, slightly dyspnea, pale | Single   | −       | −         | −       |
| 3   | 1954 | Sano        | 43  | F   | Hemoptysis                    | Single   | +       | 80        | +       |
| 4   | 1957 | Ooba        | 51  | F   | Bloody sputum                 | Single   | −       | 40 × 35 m | +       |
| 5   | 1957 | Goodall     | 56  | M   | Cough, hemoptysis             | Single   | Unknown | Unknown   | Unknown |
| 6   | 1963 | Tsunekawa   | 58  | F   | None                          | Single   | Unknown | 50 × 50 m | +       |
| 7   | 1964 | Noda        | 24  | F   | Loss of weight, nausea        | Single   | +       | 30 × 28 × 30 | +       |
| 8   | 1976 | Ichikawa    | 56  | M   | Bloody sputum, cough          | Single   | +       | 35        | +       |
| 9   | 1976 | Katsumura   | 65  | F   | Bloody sputum                 | Single   | +       | 28 × 23 × 20 | +       |
| 10  | 1983 | Ikeda       | 67  | M   | Cough, sputum, fever          | Single   | +       | 35 × 30  | +       |
| 11  | 1985 | Mori        | 61  | F   | None                          | Multiple | ×       | Like red-bean or walnut | −       |
| 12  | 1992 | Kawamata    | 22  | M   | None                          | Single   | Unknown | 40 × 25   | Unknown |
| 13  | 1996 | Ienaga      | 45  | F   | None                          | Single   | −       | 10        | −       |
| 14  | 1988 | Sugiyama    | 58  | F   | Bloody sputum                 | Single   | +       | 100 × 80  | −       |
| 15  | 1998 | Tanaka      | 7   | M   | None                          | Single   | Unknown | 30 × 40 × 30 | Unknown |
| 16  | 1996 | Wu          | 7   | M   | Chest pain, hemoptysis, dyspnea| Multiple | +       | Unknown   | Unknown |
| 17  | 1996 | Taniguchi   | 36  | F   | None                          | Single   | Unknown | 10        | Unknown |
| 18  | 1997 | Nakamura    | 46  | M   | None                          | Single   | Unknown | 55 × 50 × 40 m | −       |
| 19  | 2000 | Kase        | 29  | F   | None                          | Single   | +       | 10        | −       |
| 20  | 2001 | Fujita [4]  | 44  | F   | None                          | Single   | Unknown | 10 × 10   | −       |
| 21  | 2003 | Sirmali     | 54  | M   | Hemoptysis                    | Single   | −       | 40 × 30   | −       |
| 22  | 2003 | Kobayashi   | 15  | F   | None                          | Single   | −       | 2, 3–25   | −       |
| 23  | 2004 | Fine [5]    | 84  | M   | None                          | Multiple | Unknown | 9         | −       |
| 24  | 2006 | Maeda       | 54  | M   | None                          | Single   | +       | 50 × 40   | +       |
| 25  | 2009 | Kunitani    | 16  | M   | None                          | Multiple | Unknown | 70 × 50   | +       |

Generally, most of PCHs are solitary lesions and there have been no radiological characteristic findings. In most of these cases, surgical biopsies have been performed in order to determine the presence of metastatic lung cancer. As of yet, there have been no radiological characteristic findings and most of the cases have shown solitary well-defined small nodule that reach into the arteries of multiple lung fields. Macroscopically, PCH lung nodules lacking capsules seem hemorrhagic and, histologically, they are composed of dilated vascular spaces lined by flattened bland cells. Immunohistochemical studies of the nodule lining cells have revealed positiveness for CD34 and factor VIII, but have been negative for EMA and CAM 5.2 as epithelial markers. Furthermore, PCH lining cells have had negative immunoreactivity to TTF-1, leading us to believe that these results including gross, microscopic, and immunohistochemical findings support the diagnosis for PCH [3]. On the other hand, in cases involving Kaposi’s sarcoma, which often grows around large blood vessels or spreads into lymphatic canals and which is characterized by a spindle cell proliferation with nuclear atypia, immunocompromised patients, such as those suffering from HIV infection, are generally affected. These features are all inconsistent with PCH. In cases regarding primary angiosarcoma of the lung, which are very rare and not so difficult to distinguish from PCH, the presence of metastatic lung neoplasms should be expected. Unlike PCH, angiosarcoma is histologically characterized by spindle cells proliferated with high-grade nuclear atypia and shows considerable numbers of mitotic cells. Epithelioid hemangioendothelioma is also very rare and unlike PCH normally shows multifocal vascular neoplasm, which is characterized by a proliferation of round to oval cells with abundant eosinophilic cytoplasm and large nuclei, embedded in a myxoid or hyaline stroma. Although epithelioid hemangioendothelioma may exhibit tumor cells with large intracytoplasmic vacuoles, these spaces, although similar to, should not be confused with the expanded vascular channels identified in pulmonary cavernous hemangioma.

Although PCH is an extremely rare disease, and in the majority of cases, patients are asymptomatic, PCH should not be overlooked in cases where multiple lung nodules are detected radiologically. Surgical lung biopsy is sometimes...
needed to diagnose when we can’t get diagnosis despite the transbronchial or CT-guided lung biopsy.

Disclosure Statements
No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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