

Birt-Hogg-Dube syndrome accompanied by pulmonary arteriovenous malformation

Noriyuki Matsutani¹, Hitoshi Dejima¹, Yusuke Takahashi¹, Hirofumi Uehara¹, Hisae Inuma¹, Fumihiko Tanaka², Masafumi Kawamura¹

¹Department of Surgery, ²Department of Pathology, Teikyo University School of Medicine, Tokyo, Japan

Correspondence to: Noriyuki Matsutani, MD. Department of Surgery, Teikyo University School of Medicine, 2-11-1 Kaga Itabashi-ku, Tokyo 173-8605, Japan. Email: matsutani1970@yahoo.co.jp.

Abstract: A 25-year-old male with Birt-Hogg-Dube (BHD) syndrome who developed hemothorax caused by ruptured of pulmonary arteriovenous malformation was reported. The patient was admitted to the hospital due to chest pain. A chest X-ray showed pleural fluid in his left lung, and a chest CT showed the presence of a tumor with enhanced contrast in the lower left lobe of approximately 5 cm in a diameter. Pleural fluid was collected by tap and indicated the presence of blood; therefore, hemothorax was suspected. Thoracoscopic surgery was performed to remove the mass for hemostasis. Pathological findings indicated that the resected tumor-like lesion was an intrapulmonary hematoma, and aggregated vascular vessels of various diameters forming incomplete media elastic lamina was observed around the hematoma; therefore, it was diagnosed as pulmonary arteriovenous malformation. Family history of the patient indicated the presence of pneumothorax and malignant diseases, and the patient presented with papules and multiple pulmonary cysts. The genetic test revealed a deletion of exon 11 of the *BHD* gene; therefore, the patient was diagnosed with BHD syndrome. This report is the first to describe BHD syndrome accompanied by pulmonary arteriovenous malformation.

Keywords: Birt-Hogg-Dube syndrome; pulmonary arteriovenous malformation; hemothorax

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A 25-year-old male visited a nearby clinic due to sudden chest pain. A chest X-ray revealed the presence of fluid in his left lung and was subsequently sent to our hospital. He did not have any significant medical history and has been living a healthy life. However, his family history indicated that his mother, mother's cousin, and maternal grandfather each suffered from pneumothorax, and his maternal grandfather suffered from colon cancer. Physical findings confirmed the presence of numerous small papules on his nose and neck regions; however, no other symptoms were found.

Blood work showed increased inflammation values (WBC: 12,700/uL and CRP: 2.37 mg/dL), although a tumor marker showed only a slightly increased value (CEA: 5.0 ng/mL). No anemia was detected.

A chest X-ray revealed fluid in his left lung and a tumor

shadow that overlapped with his heart shadow were also observed. A chest CT identified focal emphysematous changes in both lungs and a tumor with enhanced contrast, which was approximately 5 cm in diameter, in the posterior basal segment of left lung with pleural fluid (*Figure 1A,B*).

Bloody pleural fluid was identified by pleural fluid tap; therefore, we considered the possibility of hemothorax caused by a hemorrhage from a tumor-like lesion. Surgery was recommended for hemostasis to treat the hemothorax.

Surgery

Thoracoscopic findings were a large amount of dark red pleural fluid and multiple nonspecific cysts in the lung. The presence of a black tumor-like lesion that was adhered to the

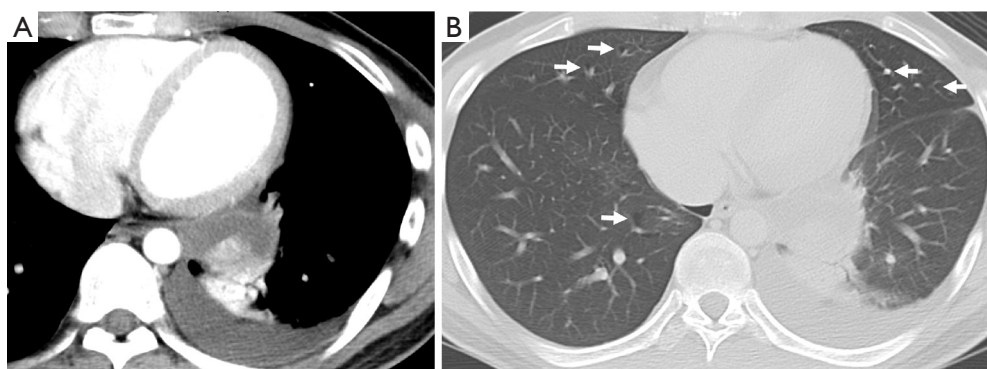


Figure 1 Chest CT findings on admission. (A) Enhanced chest CT shows a tumorous lesion, 5 cm in size with enhancement at the margins; (B) lung window of chest CT reveals many pulmonary cysts (arrow).

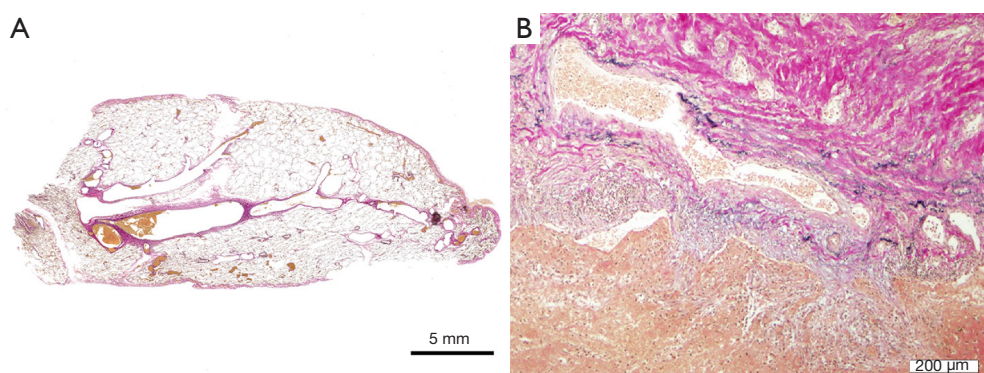


Figure 2 Histopathological examination of the surgical specimen (H&E staining) shows aggregated vascular vessels of various diameters. (A) These vascular vessels contain immature fibrous wall of tunica media; (B) the indicators show the size of 5 mm and 200 μm in *Figure 2A,B*, respectively.

diaphragm was found in the posterior basal segment of left lung and was resected. Rapid operative diagnosis indicated that the black tumor-like lesion was an intrapulmonary hematoma, no malignancy.

Pathology

The tumor-like lesion was caused by a significant hemorrhage that occurred in the pulmonary parenchyma, which was diagnosed as intrapulmonary hematoma. Aggregated vascular vessels of various diameters were found in the area surrounding the intrapulmonary hemorrhage. These vascular vessels contained an immature fibrous wall of tunica media was subsequently diagnosed as pulmonary arteriovenous malformation (*Figure 2A,B*). Pulmonary cysts characteristic of Birt-Hogg-Dube (BHD) syndrome were not found in the resected sample.

Genetic test

Family history of the patient indicated the presence of pneumothorax and malignant diseases; moreover, small papules were observed on patient's skin. Chest CT showed multiple pulmonary cysts, indicating the possibility of BHD syndrome. To confirm, we obtained informed consent from the patient to perform a genetic test. The genetic test revealed a deletion of exon 11 of the *BHD* gene; thus, he was diagnosed with BHD syndrome.

Discussion

BHD syndrome is an autosomal dominant inherited disorder by a mutation in the *FLCN* gene on 17p11.2. (1). It has three key characteristics, which are cutaneous fibrofolliculomas, renal cell tumors, and lung cysts (1,2). It is known that the

lung diseases associated with BHD syndrome are multiple pulmonary cysts and spontaneous pneumothorax. According to chest CT, pulmonary cysts and pneumothorax are found in 90% and 24% of patients with BHD syndrome, respectively. Pathological characteristics of lung diseases include basilar cysts comprised of intraparenchymal collections of air that are surrounded by either normal parenchyma or a thin fibrous wall and blebs consisting of collections of air within the pleura (3). Although these pathological findings are not specific to BHD syndrome, their predominantly basilar location contrasts with the apical distribution of other more well-recognized causes of spontaneous pneumothorax, such as emphysematous bullae and idiopathic blebs. The causes of pulmonary cysts are not well understood.

Pulmonary arteriovenous malformation is associated with congenital abnormal fistula of the pulmonary blood vessels (4,5). It is a relatively rare disease and is often diagnosed when hemoptysis is detected. The rate of intrapulmonary hemorrhage caused by pulmonary arteriovenous malformation is between 1% to 7% (4,5); therefore, there is the possibility of a massive hemorrhage, which is a fatal complication that requires treatment in the early stages in order to prevent. Catheter embolization and surgical resection are methods for treating pulmonary arteriovenous malformation (5). In this study, it was difficult to diagnose pulmonary arteriovenous malformation before the surgery; therefore, pulmonary arteriovenous malformation was treated by resecting the affected area.

The present case study is one example of BHD syndrome, which was discovered due to an intrapulmonary hemorrhage caused by pulmonary arteriovenous malformation. Association of pulmonary arteriovenous malformation with BHD syndrome has not been previously reported; therefore, the relationship is unknown. Kapoor *et al.* hypothesize that mutated FLCN may affect hypoxia-inducible factor 1- α (HIF-1 α) activation and implicate in vascular malformation on intracranial vascular pathology (6). Clarification of the relationship between pulmonary arteriovenous malformation and BHD syndrome is anticipated through

the accumulation of more BHD syndrome cases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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