Case report

A Case of Biphasic Pulmonary Blastoma

Hiroyuki Ito[*1], Yasufumi Hayashi[*1], Takamitsu Maehara[*1], Yoshinori Takanashi[*1], Yukio Nakatani[*2] and Yoshiaki Inayama[*2]

Abstract: **Background**: Biphasic pulmonary blastoma is a rare disease. On the basis of mesenchymal components, this tumor was classified into high-grade adenocarcinoma of fetal lung type (H-FLAC) and low-grade adenocarcinoma of fetal lung type (L-FLAC). **Case**: A 69-year-old woman had a cough, shortness of breath, and dyspnea in December 1994, and these symptoms gradually worsened. A local physician found an abnormal shadow on a chest radiogram in April 1995, and the patient was subsequently admitted to our hospital. A computed tomographic scan of the chest revealed a solid tumor in S^6 of the left lung. Histopathological examination of a specimen obtained by transbronchial biopsy showed evidence of malignancy, but a definitive diagnosis could not be established. The tentative diagnosis was a primary malignant tumor of the lung, and a left pneumonectomy was performed in June 1995. Pathological examination, including immunohistochemical analysis, suggested a biphasic pulmonary blastoma, which had an epithelial component of high-grade adenocarcinoma of fetal lung type. **Conclusion**: We describe a case of biphasic pulmonary blastoma associated with H-FLAC epithelial components.

〔Japanese Journal of Lung Cancer 41 (2): 131～135, 2001〕

Key words: Pulmonary blastoma, Lung neoplasm, Adenocarcimoma

Introduction

In 1952, Barnard described[1] a lung tumor resembling fetal lung and referred to it as "embryoma of the lung". Spencer subsequently named this tumor"pulmonary blastoma"[2]. Histologically, most pulmonary blastomas contain both immature embryonal-like mesenchymal and epithelial components. Some regions of pulmonary blastoma resemble embryonal lung tissue found at a gestational age of up to 3 to 4 months[3]. On the basis of mesenchymal components, Nakatani et al[4] classified this tumor into high-grade adenocarcinoma of fetal lung type (H-FLAC) and low-grade adenocarcinoma of fetal lung type (L-FLAC). H-FLAC carries a poor prognosis, has a peak incidence in the seventh decade, and arises mainly in men. We describe a case of biphasic pulmonary blastoma associated with H-FLAC epithelial components.

[*1] First Department of Surgery, Yokohama City University, School of Medicine

[*2] The Division of Anatomical Pathology, Hospital of Yokohama City University

Reprint requests : Hiroyuki Ito Division of General Thoracic Surgery, Kanagawa Cancer Center

1-1-2 Nakao, Asahi-ku, Yokohama, Japan 241-0815

TEL : 045-391-5761

FAX : 045-361-4692

Case

A 69-year-old woman had a cough and dyspnea in December 1994, and these symptoms gradually worsened. She consulted a local physician, who found an abnormal shadow near the lung hilus on a chest X-ray film. The patient was referred to our hospital in May 1995. The patient had smoked 15 cigarettes per day for 25 years. There was no family history of related disease. She had been given a diagnosis of bronchial asthma 10 years previously and received medication, which she voluntarily discontinued because of no recent attacks recently. On auscultation, no respiratory sounds were audible on the left side of the chest. Laboratory data showed no clinically relevant abnormalities, except for elevated concentrations of carcinoembryonic antigen (CEA)(10.3 ng/ml) and alpha-fetoprotein (14.0 ng/ml) in serum. On arterial blood gas analysis, the partial pressure of oxygen was 72.2 mmHg and the partial pressure of carbon dioxide was 42.1 mmHg. A chest X-ray film revealed a large circular shadow at the left lung hilus (Fig. 1). A computed tomographic (CT) scan of the chest showed a round tumor 8.0 cm in diameter in the lower lobe of the left lung (Fig. 2). No lymph node swelling was evident. The tumor was

Fig. 1. A chest X-ray film obtained on admission, revealing a large circular shadow at the left lung hilus. There was atelectasis of the left lower lobe, and the mediastinum had shifted to the left.

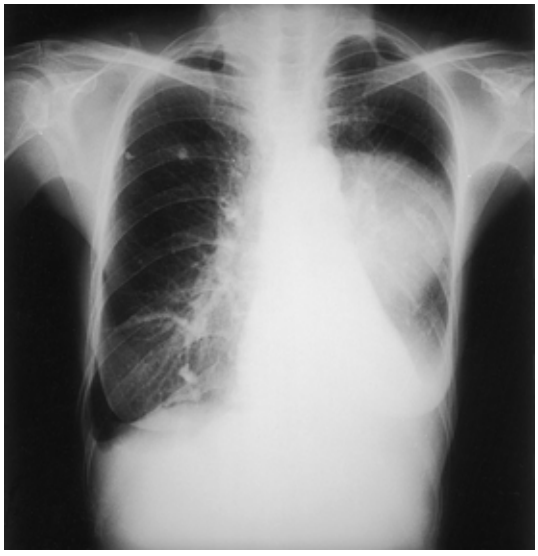
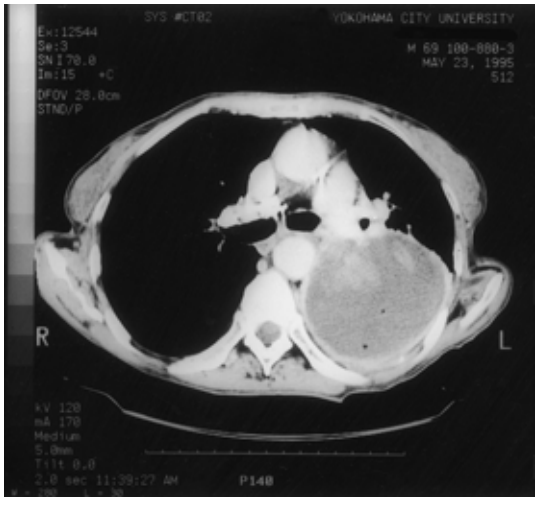
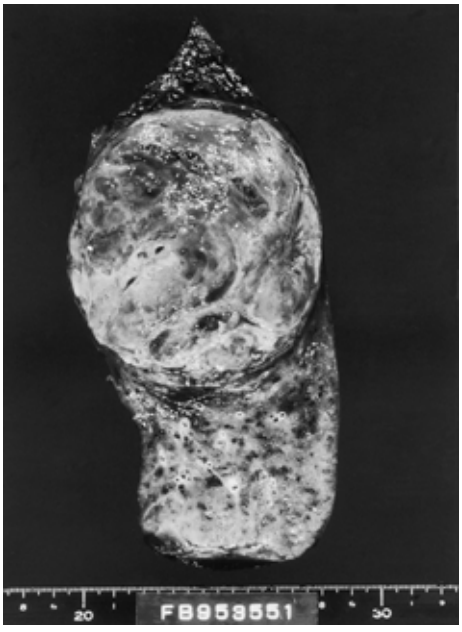


Fig. 2. A computed tomographic scan of the chest, showing a round irregularly emphasized tumor, compressing the left lung and occluding the left bronchus. With enhancement, the margin and internal tissue were irregularly emphasized ; the non-emphasized part of the lesion was apparently necrotic.



adjacent to the lung hilus and compressed the left main pulmonary trunk ; the pulmonary artery of the lower lobe could not be detected. Lung-perfusion scintigraphy performed after the injection of macroaggregated albumin particles labeled with technetium-99m showed virtually no blood flow to the left lung. Spirometry revealed that the vital capacity（VC）was 1840 ml, the% VC was 89%,

Fig. 3. Gross photograph of the well-demarcated neoplastic nodule seen in S^6 of the left lung. The cut surface of the tumor showed geographic necrosis with hemorrhage.



the forced expiratory volume in one second（$FEV_{1.0}$）was 1220 ml, and the $FEV_{1.0}$% was 74%. Bronchoscopic examination showed a white polypoid tumor projecting from B^6 of the occluded lower branch of the left lung. The tumor bled readily on contact. Transbronchial biopsy of the tumor was performed twice, but the specimens consisted primarily of necrotic tissue and an exact diagnosis was not possible. The results of cytological examination were positive for malignancy. Percutaneous needle biopsy was done, but yielded no further information. No other primary or metastatic lesions were found. On the basis of these findings, the diagnosis was a primary malignant lung tumor, and a thoracotomy was performed. There was no pleural effusion, dissemination, or lymphadenopathy. The tumor was mainly located in the lower lobe and broadly invaded S^{1+2} of the upper lobe, compressing the pulmonary artery. We therefore performed a left pneumonectomy. Postoperative respiratory function was predicted to be adequate. Operative blood loss was 420 ml and operation time was 275 minutes. The operation was successful.

Grossly, the tumor was a well-circumscribed solid mass, measuring 9.5×8.0×7.5 cm and located in left S^6（Fig. 3）. Microscopically, it was composed chiefly of irregularly branching, atypical glands, loosely distributed in large areas of sarcomatous stroma. The atypical glandular cells had relatively abundant clear cytoplasm and oval-to-round

hyperchromatic nuclei. Many nuclei had shifted to the luminal surface or showed pseudostratification (Fig. 4). Morphologically, these neoplastic glands resembled fetal type bronchial epithelia. Most of the sarcomatous cells were short and spindle-like and had oval, hyperchromatic nuclei and inconspicuous cytoplasm (Fig. 5). Some neoplastic cells had abundant eosinophilic granular cytoplasm, suggesting myomatous differentiation. Foci of chondroid differentiation were also noted within the sarcomatous lesions. In addition, neuroendocrine differentiation of the neoplastic cells was suggested by the presence of rosette formation. Mitotic figures were often observed in both carcinomatous and sarcomatous components. There was no evidence of morules or epidermoid differentiation. Immunohistochemically, glandular cells stainly positively for keratin (CAM 5.2), whereas sarcomatous cells did not. Positive reactions for NSE, synaptophysin and N-CAM were noted in some neoplastic cells. Positive staining for Ki-67 (MIB-1) was evident not only in adenocarcinoma cells but also in sarcomatous cells. Positive staining for p53 (DO7) was also noted in many neoplastic cells. No cells were positive for alpha-fetoprotein.

Fig. 4. A high-power view of the carcinomatous glands. The neoplastic cells show clear cytoplasm, and many vesicular nuclei are shifted toward the lumen, resembling fetal airway epithelium.

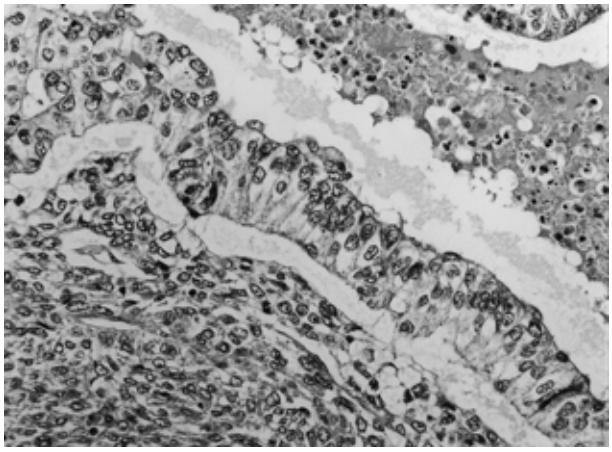
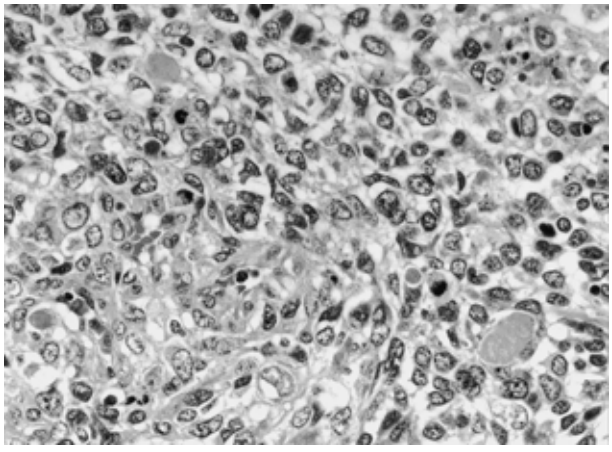


Fig. 5. A high-power photograph of the sarcomatous lesion. Most sarcomatous cells have oval nuclei and inconspicuous cytoplasm. Neoplastic cells with abundant eosinophilic cytoplasm are also evident, suggesting muscular differentiation.



These morphologic and immunohistochemical findings led to a diagnosis of biphasic pulmonary blastoma with H-FLAC-type epithelial components. Microscopically, the tumor invaded the left upper lobe, with no lymph node involvement. The postoperative course was uneventful. The patient was discharged from the intensive care unit (ICU) on the day after operation, and had only mild dyspnea on effort. However, pulmonary arrest developed during the night 14 days after operation, resuscitation was immediately carried out, the patient was returned to the ICU. She received mechanical ventilation, but did not regain consciousness or spontaneous respiration. This patient died of respiratory failure 21 days after the operation. Pulmonary arrest was attributed to a severe attack of bronchial asthma or mucoid impaction of the right main bronchus. Autopsy was not permitted.

Discussion

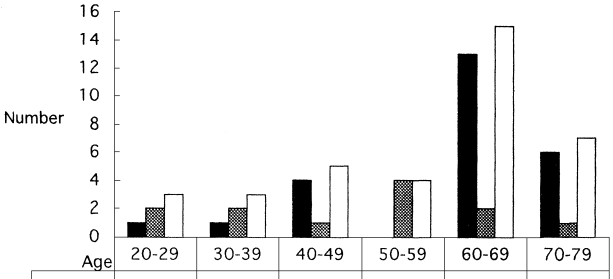
Pulmonary blastoma is a very rare type of malignant tumor, estimated to account for 0.25% to 0.50% of all lung tumors[3]. Histologically, pulmonary blastomas are characterized by immature mesenchyma or epithelium (or both) that morphologically mimics the embryonal structure of the lung. Recently, pulmonary blastomas have been classified into several subtypes. In 1988, Manivel et al.[5] described pleuropulmonary blastoma (PPB), designated a distinct entity from pulmonary blastomas arising in adults. PPB occurs in children and consists of stromal and epithelial components that represent entrapped airway epithelium or mesothelium. Manivel et al. considered nearly all tumors previously designated as pulmonary blastomas of childhood were to be PPB. In 1982, a pulmonary endermal tumor resembling fetal lung (PET) was described by Kradin et al.[6] Histologically, this tumor resembled a pulmonary blastoma with no sarcomatous components. In 1984, Kodama et al.[7] described six cases of well differentiated fetal adenocarcinoma that simulated fetal lung tubules and lacked sarcomatous components, similar to

PET. In 1991, Koss et al.[8] reviewed biphasic and monophasic types of pulmonary blastomas [well-differentiated fetal adenocarcinomas (WDFA) that histologically resemble PET]. The male : female ratio was similar for both types, but the peak incidence of biphasic type was in the fifth decade and was higher than the peak incidence of monophasic type, which occurred in the fourth decade. Only 14% of the patients with monophasic-type blastoma died of their tumors, as compared with 52% of those with biphasic-type blastoma. These studies reveal several important differences between WDFA/PET and well differentiated fetal adenocarcinoma simulating fetal lung tubules, as described by Kodama et al.[7] The latter tumor had a poor prognosis, was diagnosed at a mean age of 53.5 years, and occurred exclusively in men. Histologically, well differentiated fetal adenocarcinoma simulating fetal lung tubules did not contain morules and had more marked atypical components than did WDFA/PET. To distinguish between these two types of tumors, the terms H-FLAC and L-FLAC have recently been introduced[4]. Histologically, H-FLAC, identical to the tumor described by Kodama et al.[7], is distinguished from L-FLAC or WDFA/PET by the presence of disorganized glands, large vesicular nuclei, prominent nucleoli, pronounced anisonucleosis, no morules, transition to conventional adenocarcinoma, broad areas of necrosis, desmoplastic stroma, overexpression of p53 protein, and production of alpha-fetoprotein. Clinically, the peak incidence of H-FLAC occurs in the seventh decade, as compared with the fourth decade for L-FLAC. H-FLAC affects men more often than women, in contrast to L-FLAC. The Third Edition of the Histological Typing of Lung and Pleural Tumors issued by the World Health Organization classifies L-FLAC as a variant of adenocarcinoma, termed well-differentiated fetal adenocarcinoma.

On the other hand, H-FLAC is included in the category of clear cell adenocarcinoma[9].

In Japan, pulmonary blastoma has been described in about 70 reports. Biphasic pulmonary blastoma (BPB) is defined as a tumor with both a malignant epithelial component and a sarcomatous component. Thirty-seven of the reports discuss the histological features of BPB. These reports probably included many cases of H-FLAC and L-FLAC, but differential diagnosis of these subtypes difficult on the basis of histological findings only. We reviewed the case reports on BPB to examine the clinical features of these tumors. The male : female ratio was 2.1 : 1 (25 patients were men and 12 were women). The average age at diagnosis was 57.0 years (60.8 years for men and 48.7 years for women). Table 1 shows the age and sex distribution of the 37 patients descrbed in the literature. In men, the peak incidences were in the fifth and seventh decades. In women, the peak incidence was in the sixth decade only, but other decades had only slightly lower incidences. Men and women combined showed two peak incidences, one in the fifth and the other in the seventh decade. The incidence of BPB according to age and sex was similar to that shown in Figure 9, reported by Nakatani et al.[4] and support the characteristics of pulmonary blastoma as described by Francis and Jacobsen[3]. Among the 37 case reports we reviewed, the frequency of BPB on the right side (22 patients) was slightly higher than that on the left (15 patients). The mean dimensions of the tumor were 68.7×61.4 mm. The most commonly reported symptom was cough, reported by 17 patients (40.6%), followed by bloody sputum (9 patients, 24.3%), chest or back pain, and dyspnea. No symptoms were reported by 9 patients (24.3%), all of whom underwent chest radiography during a routine health check up. Eleven patients had high serum CEA levels and 6 had high serum alpha-fetoprotein levels. Preoperative diagnosis was difficult. Tumor was diagnosed preoperatively in only two patients (5%), who underwent transbronchial biopsy and percutaneous biopsy, respectively. Some of the other patients underwent needle biopsy or transbronchial biopsy, several times, but a correct diagnosis could not be made. In our patient, we could see the tumor directly on bronchoscopy and performed a biopsy twice, but could not confirm the diagnosis. Surgery was generally the treatment of choice, similar to other malignant lung tumors. BPB has been treated by chemotherapy and radiotherapy[10], but the outcome was unsatisfactory. Among the 37 patients with BPB, 31 received surgery, including 27 who underwent at least lobectomy. The median duration of follow-up was 8.0

Table 1. Numbers of patient according to decade



	20-29	30-39	40-49	50-59	60-69	70-79
■Male	1	1	4	0	13	6
▨Female	2	2	1	4	2	1
□Total	3	3	5	4	15	7

months（range, 1～108 months）. Eleven patients died of recurrence, and median survival was 6.5 months. All six patients who received palliative therapy died, with a median survival of 4.5 months after diagnosis. However, firm conclusions regarding prognostic factors cannnot be made because follow-up was short in many patients.

In conclusion, previous reports of BPBs probably include cases arising from L-FLAC as well as those arising from H-FLAC. Further studies are required to define the clinicopathological features of these two different types of BPB.

References

1）Barnard WG : Embryoma of lung. Thorax 7 : 299-301, 1952.
2）Spencer H : Pulmonary blastomas. J Pathol Bacteriol 82 : 161-165, 1961.
3）Francis D, Jacobsen M : Pulmonary blastoma. Curr Top Pathol 73 : 265-294, 1983.
4）Nakatani Y, Kitamura H, Inayama Y, et al : Pulmonary adenocarcinomas of the fetal lung type. Am J Surg Pathol 22 : 399-411, 1998.
5）Manivel JC, Priest JR, Watterson J, et al : Pleuroplumonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 62 : 1516-1526, 1998.
6）Kradin RL, Young RH, Dickersin GR, et al : Pulmonary blastoma with argyrophil cells and lacking sarcomatous features（pulmonary endodermal tumor resembling fetal lung）. Am J Surg Pathol 6 : 165-172, 1982.
7）Kodama T, Shimosato Y, Watanabe S, et al : Six cases of well differentiated adenocarcinoma simulating fetal lung tubules in pseudoglandular stage. Am J Surg Pathol 8 : 845-854, 1984.
8）Koss MN, Hochholzer L, O'Leary T : Pulmonary blastomas. Cancer 67 : 2368-2381, 1991.
9）Travis WD, Colby TV, Corrin B, et al : Histological Typing of Lung and Pleural tumours. World Health Organization, International Histological Classification of Tumours. Third edition, Springer, Heidelberg, pp43-44, 1999
10）Novotny JE, Huiras CM : Resection and adjuvant chemotherapy of pulmonary blastoma. Cancer 76 : 1537-1539, 1995.

（Received October 7, 2000/Accepted for publication January 10, 2001）