

Lung Fibrosis 10 Years after Cessation of Bleomycin Therapy

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Bleomycin (BLM) is a chemotherapeutic agent used for the treatment of several types of malignancy, including germ cell tumors, lymphoma, and certain types of squamous-cell carcinoma. The common adverse effect of BLM is interstitial pneumonitis, followed by pulmonary fibrosis. BLM-induced pneumonitis occurs in up to 46% of patients treated with BLM-containing chemotherapy and lung toxicity usually appears during treatment. Here we describe a patient with lung fibrosis, who presented with slow progressive breathlessness and pneumothorax more than 10 years after cessation of BLM therapy. A 15 year-old girl presented with abnormal shadows on chest X-ray. The patient had a yolk sac carcinoma in the sacral region at 1 year of age and obtained complete remission after being treated with tumor resection, radiation, and several anti-cancer drugs including BLM. There were no abnormal findings in chest X-ray until she reached 3 years of age, when she had developed respiratory distress that worsened with age. The patient had experienced an episode of pneumothorax at 13 years of age. Chest CT at the time revealed interstitial reticular opacities. Radiological findings and pathological examination of the lung tissue obtained during bullectomy with video-assisted thoracic surgery were compatible with BLM-induced pneumonitis. The present study suggests that lung fibrosis may surface more than 10 years after cessation of BLM therapy at the age of 1 year, with no chest radiographic findings 1 year after completion of chemotherapy. The use of BLM in infants requires strict supervision and observation and careful long-term follow up. ———

Bleomycin; child; pneumonitis; pneumothorax

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Bleomycin (BLM) is a chemotherapeutic agent used for the treatment of several types of malignancy, including germ cell tumors, lympho-

ma, and certain squamous-cell carcinoma. Most significant adverse effect of BLM is interstitial pneumonitis, followed by pulmonary fibrosis.

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BLM-induced pneumonitis occurs in up to 46% of patients treated with BLM-containing chemotherapy (Sleijfer 2001). The mortality of patients with BLM-induced pneumonitis is 3% (Levi et al. 1993). The clinical manifestations of BLM lung toxicity usually occur during treatment, but pneumonitis can develop up to two years after completion of BLM therapy (Uzel et al. 2005).

We here describe a 15-year-old patient with lung fibrosis, who presented slowly progressive shortness of breath and pneumothorax, over ten years after BLM therapy at 1 year old, in spite of no chest radiographic findings at one year after completion of chemotherapy.

CLINICAL FINDINGS

A 15-year-old female patient presented with dyspnea on exertion and distorted growth, and abnormal shadows on chest X-ray. She had had yolk sac carcinoma in the sacral region at an age of 1 year and had obtained complete remission after undergoing tumor resection, radiation, and anti-cancer drugs. She had been treated with five cycles of bleomycin (BLM) as a part of the PVB (cisplatin, vinblastine, and BLM) regimen and combination chemotherapy consisting of cyclophosphamide, adriamycin, etoposide, and actinomycin D for six cycles. She had received a total of 86 mg BLM. Although tachypnea had been observed during chemotherapy with BLM, there

were no abnormal findings in chest X-ray until she was 3 years old. Respiratory distress worsened with age. The patient had experienced pneumothorax in the right lung at 13 years of age. Chest CT taken at that time revealed interstitial reticular opacities. Bullectomy for pneumothorax was performed by video-assisted thoracoscopic surgery (VATS).

The patient was 144.1 cm tall and weighed 28.2 kg. Vital signs on admission were as follows: chest: respiratory rate, 56 per minute; oxygen saturation, 93% in room air, which fell to 83% after walking only 50 m. Wheeze in all lung fields was found by auscultation. Pulmonary function tests showed severe restrictive dysfunction of vital capacity (VC) of 0.52 L (21.5% of predicted), a forced expiratory volume at one second (FEV₁) of 0.51 L (100% of predicted). Arterial blood gas analysis on room air indicated hypoxia as PO₂ 69.3 mmHg, PCO₂ 45.4 mmHg, HCO₃⁻ 28.3 mmol/L, and pH 7.408. The serum level of KL-6 increased to 831 U/mL (normal: 0-500). Chest X-ray on admission showed reticular shadows in all lung fields (Fig. 1A). Chest CT films indicated linear and nodular opacities based in peripheral pleura and thickening of pleura and interlobular septa (Fig. 1B). Histological findings of lung tissue obtained during bullectomy revealed interstitial and intra-alveolar fibrosis with replacement of alveoli by fibrous tissues in

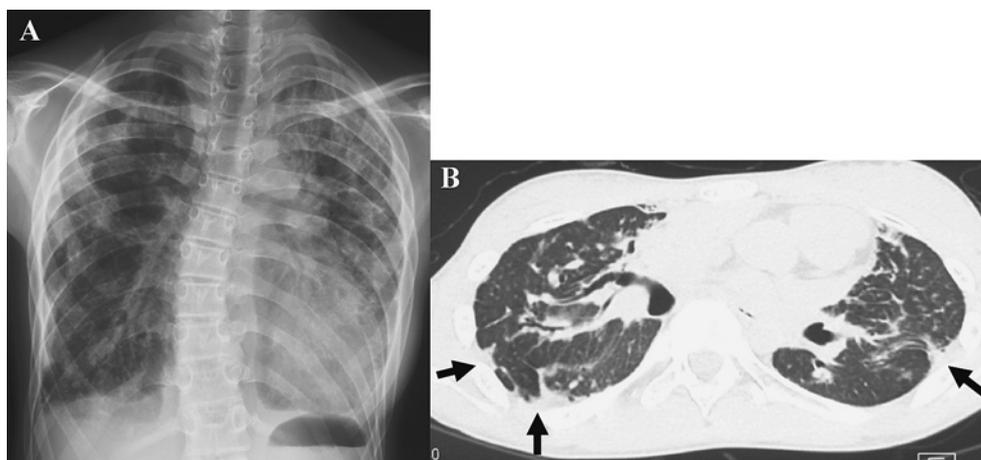


Fig. 1. Chest X-ray and CT films on admission. A: Chest X-ray film shows reticular shadows in all lung fields. B: Chest CT image indicates linear and nodular opacities based in peripheral pleura (Indicated by arrows).

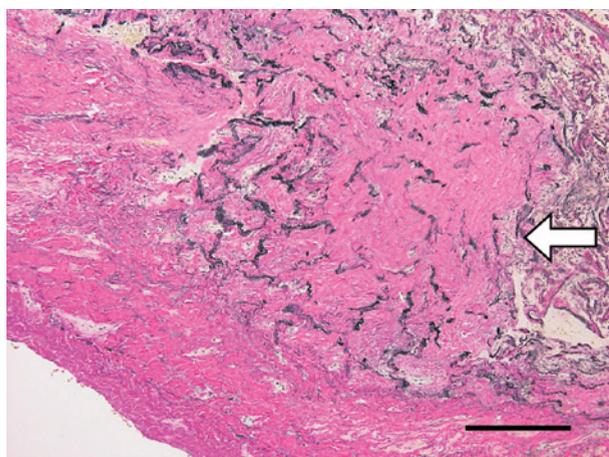


Fig. 2. Photomicrograph of lung tissue obtained during bullectomy with VATS at the age of 13 years. Interstitial and intra-alveolar fibrosis is observed with filling of alveoli by fibrous tissue in the adjacent subpleural area (Indicated by the arrow). Pleura present with fibrotic thickening. Elastica van gieson stain. bar = 0.02 mm.

the adjacent subpleura (Fig. 2). Fibrosis was also observed around the centriacinar bronchovascular bundle. In some areas, the fibrotic change appeared to be continuous from the centrilobular area to the subpleural fibrosis. Pleura showed fibrotic thickening and blebs.

CT and pathology findings were compatible with an advanced BLM-induced pneumonitis. Other differential diagnoses were cystic fibrosis and immotile cilia syndrome because of the age of onset or CT findings. However, these findings were discounted because there was no abnormality on examination of sweat chloride concentration and sinus CT, indicative of other disorders. Corticosteroids are usually used for BLM-induced pneumonitis (White et al. 1984), but in our patient, steroid therapy could not be employed because of the apparent prolonged course of the disease in the patient, advanced state of fibrosis, and risk of infection. The patient was discharged and started home oxygen therapy and respiratory rehabilitation.

DISCUSSION

BLM is an antibiotic agent with antitumor activity isolated from *Streptomyces verticillus* in

1966 (Umezawa et al. 1966). Because of the lack of the BLM-inactivating enzyme BLM hydrolase in the lungs and skin, BLM-induced toxicity occurs in these organs (Ohnuma et al. 1974).

Radiographic findings observed with BLM-induced pneumonitis are bibasilar reticular or fine nodular infiltrates. With more severe involvement, infiltrates progress to the middle and upper areas of the lungs. On CT scanning, abnormal findings due to BLM appear earlier than on chest radiographs. Damage to the lungs is seen as pleural-based linear and nodular irregularities and is the most evident at the posterior lung bases (Bellamy et al. 1985). Spontaneous pneumothorax by BLM-induced pneumonitis has also been reported (Jain et al. 2005). Histologically, BLM-induced pneumonitis shows a wide variety of interstitial pneumonia such as diffuse alveolar damage (DAD) or bronchiolitis obliterans organizing pneumonia (BOOP) on acute phase; moreover, interstitial and intra-alveolar fibrosis is present with replacement of alveoli by fibrous tissue in advanced BLM-induced pneumonitis (Katzenstein 1997). Pleural fibrosis and blebs may explain pneumothorax. Pathological and radiological findings of CT observed in our patient were commonly-noted within BLM-induced pneumonitis and fibrosis. However, these findings are not always specific to BLM induced lung disorders; we concluded that BLM potentially related to the lung fibrosis in our patient.

BLM-induced pneumonitis occurs in 3% to 5% of patients receiving a cumulative dose of < 300 mg of BLM, while 20% of patients develop BLM-induced pneumonitis when treated with > 500 mg (Collis 1980). However, even a tiny amount of BLM (14 mg) administered with adriamycin, cyclophosphamide, vincristine, methotrexate and dexamethasone was reported to cause pneumonitis (Bauer et al. 1983). There is an increased risk when the patient age is over 70 years old, receiving oxygen therapy, concomitant administration of other chemotherapeutic drugs or thoracic irradiation, renal dysfunction, and smoking history (Sleijfer 2001). In the present case, only concomitant administration of other chemotherapeutic drugs such as, adriamycin and cyclo-

phosphamide was risk factor of BLM-induced pneumonitis.

In most patients, the insidious changes of BLM-induced pneumonitis in lung start during BLM treatment, and the symptoms became obvious days to weeks after the initiation of treatment. However, few delayed onset cases were reported. White et al. (1984) reported one patient developed BLM-induced pneumonitis six month after discontinuation of the chemotherapy. In another case, patient with nonseminomatous testicular cancer developed pneumonitis two years after completion of BLM treatment (Uzel et al. 2005). In our patient, tachypnea had been observed during chemotherapy with BLM, and therefore BLM-induced pneumonitis might have been present around the same time, in spite of there being no chest radiographic findings one year after completion of chemotherapy. The patient's dyspnea worsened with age, especially after the age of 10 years, and she experienced pneumothorax at 13 years of age. It is possible that the increase in the size of the thorax with growth exacerbated dyspnea and caused pneumothorax, because of the severe restrictive disorder caused by BLM-induced pneumonitis during infancy.

Physical finding such as fine rales by auscultation is important in order to detect pulmonary disorders by BLM in early phase, since it occurs prior to the appearance of symptoms and radiographic abnormalities. Chest radiograph is reported to be inadequate to detect an early stage of BLM-induced pneumonitis (Bellamy et al. 1985), however the 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) is considered as a potent useful tool for early diagnosis (Buchler et al. 2007). Although reduction of diffusing capacity for carbon monoxide in pulmonary function test is an index for continuation of BLM during treatment, the vital capacity and the total lung capacity are more specific values for detecting early phase of BLM-induced pneumonitis (Sleijfer 2001). However, FDG-PET and pulmonary function test are not always applied to all

patients especially to children.

In conclusion, this is an extremely rare case of lung fibrosis potentially related to BLM, which presented with slow progressive breathlessness and pneumothorax that surfaced more than 10 years after cessation of BLM therapy. Strict monitoring of respiratory rate, oxygen desaturation or fine rales is important to detect the pulmonary disorders due to BLM at an early stage in infants.

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