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HRCT Findings of Bleomycin-Related Lung Toxicity : A Report of 2 Cases[1]

Jeong Geun Yi, M.D., Won Ho Jang, M.D., Dae Young Yoon, M.D., Sang Hoon Bae, M.D.

Many drugs can result in a variety of pathologic reactions in the lung, especially the cytotoxic drugs. Among cytotoxic drugs bleomycin is a prototype. Bleomycin-related pulmonary toxicity is usually known as dose-dependent and can be enhanced with concurrent oxygen therapy, irradiation, or other chemotherapeutic agents. The incidence of bleomycin-induced pulmonary toxicity has been reported as varying from 2 to 46 %, and 1 % of fatal lung disease.

We describe the radiographic and HRCT findings of bleomycin-related pulmonary toxicity developed in two patients: one in ovarian teratocarcinoma, the other malignant lymphoma patient. Chest radiographs and HRCT of these patients showed ground-glass opacities, consolidation, linear and reticular opacities, and interlobular septal thickening. These abnormalities were bilateral, and symmetrical and were found predominantly in the area of mid- and lower-lung zone.

Index Words : Bleomycin
Computed tomography(CT), high-resolution
Lung, CT
Lung, fibrosis

Bleomycin is a glycopeptide antitumor antibiotic agent isolated from *Streptomyces verticillus* by Umezawa and co-workers (1). It is an important chemotherapeutic agent used in the treatment of a variety of tumors such as squamous cell carcinoma, germ cell tumor and malignant lymphoma (2, 3).

Although bleomycin is suitable against the neoplasms because of its predictable action and lack of myelosuppression (2), it has several side effects. Pulmonary toxicity is, however, the most serious side effect and limit the dosage tolerated by many patients (2-4). Incidence of pulmonary toxicity has been reported as varying between 2 and 46% (2, 3), but the majority of authors report the incidence of pulmonary fibrosis as 2 to 3% and of fatal lung damage as 1% (2). The pulmonary toxicity of bleomycin is known to be dose-dependent and can be enhanced with concurrent oxygen therapy, irradiation, or other chemotherapeutic agents (4, 5).

We report the radiographic and high-resolution computed tomographic (HRCT) manifestations of bleomycin-related pulmonary toxicity which developed in two patients.

[1]Department of Radiology, College of Medicine, Hallym University
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Address reprint requests to : Jeong Geun Yi, M.D., Department of Radiology, College of Medicine, Hallym University, Kangdong Sacred Heart Hospital, Gil-dong 445, Kangdong-gu, Seoul # 134-701, KOREA. Tel. 82-2-224-2312 Fax. 82-2-473-8101

Case Reports

Case 1

An 18-year-old woman complained of cough and dyspnea after four courses chemotherapy of ovarian teratocarcinoma. The regimen consisted of bleomycin, etoposide and cisplatin, with a total bleomycin dosage of 120 units.

A chest radiograph showed bilateral ground-glass attenuation, air-space consolidation and reticulation in the mid- and lower-lung zones (Fig. 1A). HRCT carried out four days after the chest radiograph showed ground-glass attenuation, consolidation, bronchial dilatation and interlobular septal thickening (Fig. 1B). These abnormalities were bilateral and symmetrical in

distribution.

The results of pulmonary function test (PFT) measured a total lung capacity (TLC) of 31% of that predicted, a forced vital capacity (FVC) of 37% of that predicted (severe restrictive pattern), and a diffusing capacity of 68% of that predicted (decreased diffusing capacity).

A pathologic specimen obtained after transbronchial lung biopsy (TBLB) at the anterior-basal segment of the left lower lobe showed intraalveolar fibrotic plugs and interstitial fibrosis with inflammatory cell infiltrations (Fig. 1C).

Case 2

A 54-year-old man with abdominal non-Hodgkin's lymphoma complained of dyspnea and fever. He had beeen treated with five cycles of a chemotherapeutic regimen consisting of cyclophosphamide, epirubicin, vincristine, prednisolon, bleomycin and procarbazine. The total administered dosage of bleomycin was 112 units.

A chest radiograph showed air-space consolidation and reticular opacities in the subpleural area of mid- and lower-lung zones, suggesting bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia (BOOP/COP) or chronic eosinophilic pneumonia (Fig. 2A). HRCT showed linear and reticular opacities with interlobular septal thickening and consolidation in the posterior subpleural area of both lungs (Fig. 2B).

The results of PFT measured a TLC of 38% of that predicted, a FVC of 60% predicted (moderate restrictive pattern), and a diffusing capacity of 47% predicted (decreased diffusing capacity). TBLB was done at the lateral-basal segment of the left lower lobe and the pathologic findings were compatible with BOOP/COP.

After pathologic confirmation (Fig. 2C), bleomycin was discontinued and steroid treatment was started. A follow-up chest radiograph and the results of PFT showed improvement.

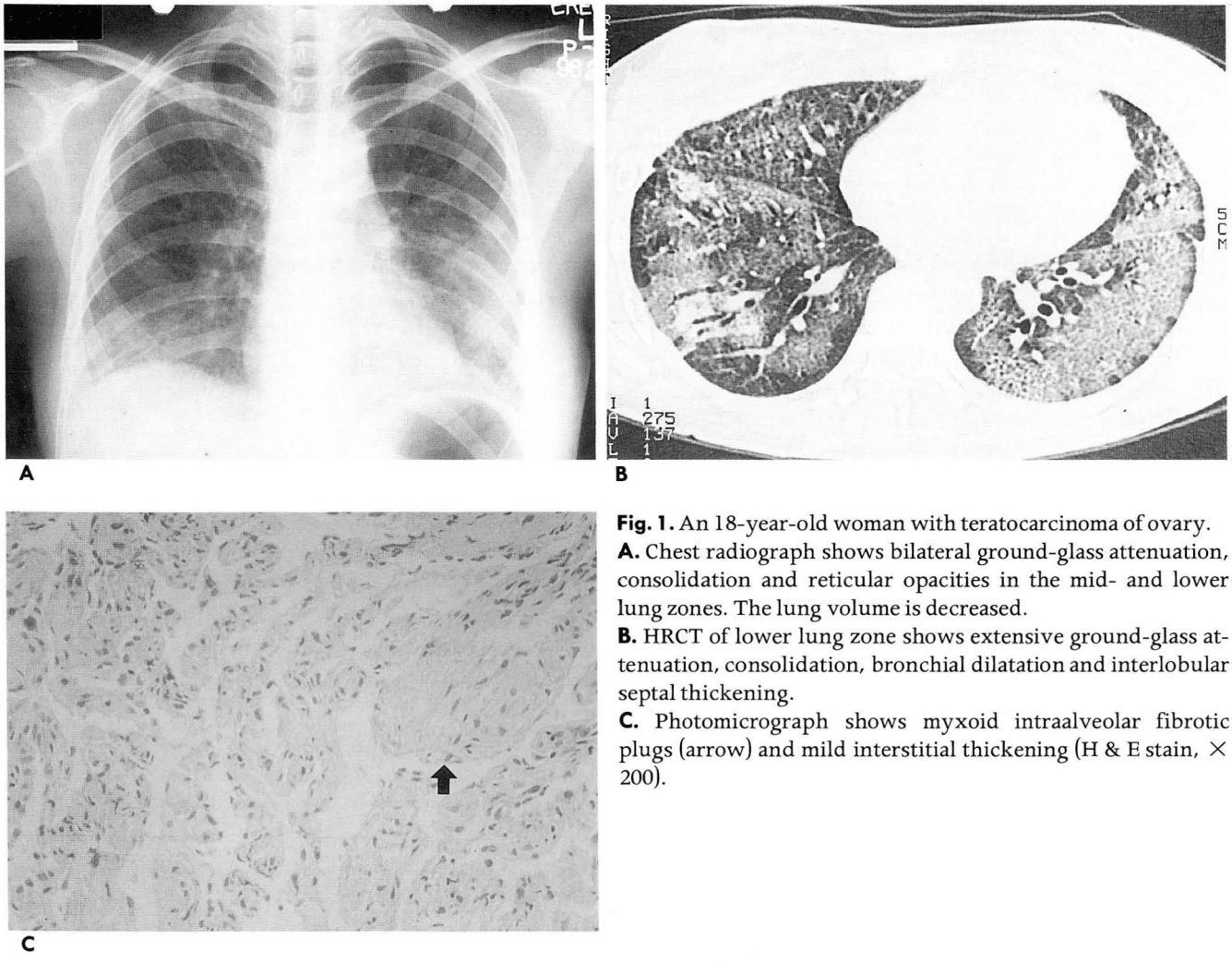


Fig. 1. An 18-year-old woman with teratocarcinoma of ovary.
A. Chest radiograph shows bilateral ground-glass attenuation, consolidation and reticular opacities in the mid- and lower lung zones. The lung volume is decreased.
B. HRCT of lower lung zone shows extensive ground-glass attenuation, consolidation, bronchial dilatation and interlobular septal thickening.
C. Photomicrograph shows myxoid intraalveolar fibrotic plugs (arrow) and mild interstitial thickening (H & E stain, × 200).

Discussion

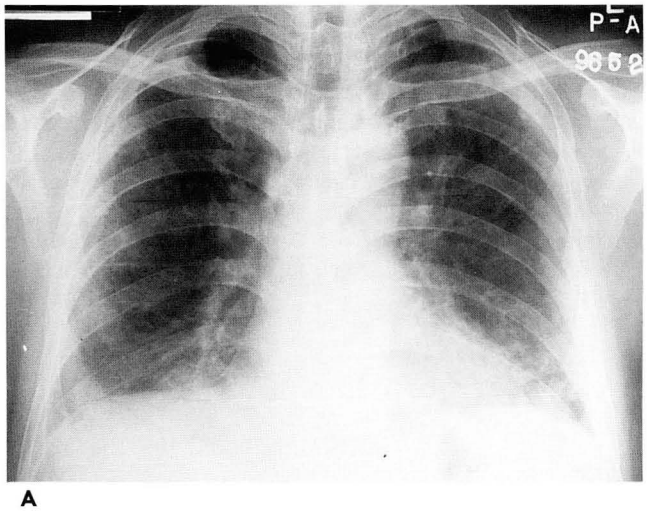
Many drugs can result in a variety of pathologic reactions in the lung, but the highest incidence of adverse effects occurs with cytotoxic agents (5-7). Among them, bleomycin is a prototype (2-4).

The initial histopathologic abnormality of bleomycin-related lung toxicity is swelling of capillary endothelial cells with the appearance of vesicles between these cells and the basement membrane. This vascular damage is followed by edema of the interstitium and necrosis of type 1 pneumocytes, monocytes and proliferation of type 2 cells. Eventually there is widespread fibrosis in the septa and in the alveoli and perivascular and peribronchial spaces. These changes are most frequently found subpleurally and around the septa (2-4). This stage is the "final common pathway" of many forms of interstitial fibrosis (9).

Because drug-induced lung diseases generally lack specific histopathologic features, a diagnosis of drug-associated lung damage can only be established after other possible causes have been excluded; the patient most at risk for drug-induced lung disease is also the patient most at risk for pulmonary infection, progression of underlying disease, congestive heart failure, pulmonary emboli, and pulmonary hemorrhage. All of these can present with similar signs, symptoms and even similar radiologic features of drug toxicity.

Bleomycin-related lung injury is usually dose-dependent to a certain degree (4, 5), and lung damage is rare at doses below 150 units (2). Lung injury can develop, however, sporadically at lower doses in combination chemotherapy regimens (8), as in our cases; the interaction of bleomycin with other agents may contribute to unexpected toxicity at such low doses (5, 8). There has also been a report that CT findings do not correlate with total dosage of bleomycin (9).

Cisplatin and etoposide are commonly used with bleomycin for the treatment of germ cell tumors, as in our first case. Although etoposide occasionally causes pulmonary venoocclusive disorder (7), these drugs are



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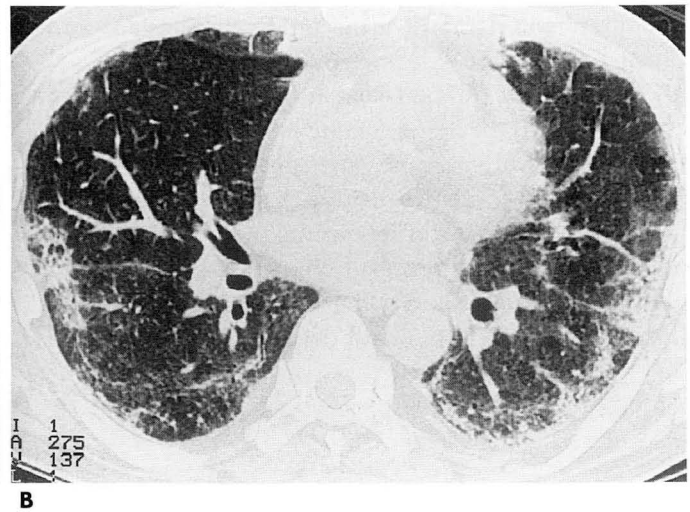

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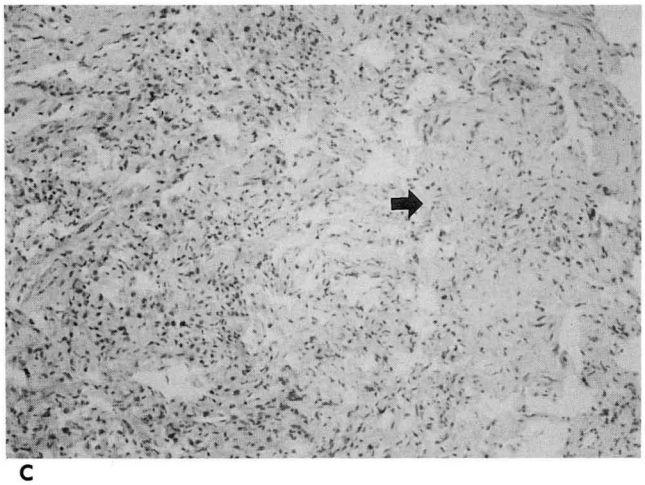

C

Fig. 2. A 54-year-old man with abdominal non-Hodgkin's lymphoma.
A. Chest radiograph shows consolidations and reticulation in the sulpleural area especially in the mid- and lower lung zones.
B. HRCT of mid-lung zone shows consolidation, septal thickening and linear and reticular opacities predominently in the sulpleural portion.
C. Photomicrograph shows intraalveolar fibrotic plug (arrow) and interstitial thickening by inflammatory cells (H & E stain, ×100).

generally not known to cause remarkable pulmonary toxicity (3, 5, 7, 9).

Cyclophosphamide can cause hypersensitivity reaction (5, 7), ARDS (7), usual interstitial pneumonitis (UIP) (5) and BOOP/COP (7). Procarbazine can induce hypersensitivity reaction (5) and vincristine can induce UIP (6). The incidences of the above reactions are very low, however (5-7). Epirubicin and prednisolon are not known to cause any pulmonary toxicity (5, 7).

The improvement of pulmonary abnormalities after discontinuation of bleomycin also supports the belief in case 2, that initial pulmonary pathology was induced mainly by bleomycin.

Bleomycin-related pulmonary toxicity is reversible if detected early in the course of treatment (2, 3, 9), but in cases of late fibrosis, improvement is seldom seen (3). The early detection of pulmonary toxicity is thus important because prompt discontinuation of the drug can result in improvement of lung function and healing of pulmonary damage.

Although plain radiographs can show the nodular and reticular opacities of bleomycin-related lung changes (8), CT is more sensitive than simple radiographs in demonstrating pulmonary lesions and can also show more extensive pulmonary changes (2, 3, 9). The extent of pulmonary damage as seen on CT also correlates with the degree of impairment as assessed by PFT of lung volumes and gas transfer measurements (3). HRCT is even more sensitive than conventional CT in the early detection of interstitial pulmonary pathology, including drug reaction. The known CT findings of bleomycin lung toxicity include linear reticulations, fibrotic bands, nodular/ill-defined opacities, and consolidations, all of which are more prominent posteriorly, at the periphery of both lungs and lung bases (3, 9).

In conclusion, we stress the radiographic and HRCT abnormalities in patients who receive chemotherapeutic agents containing bleomycin. The most important role of HRCT is in the early detection of bleomycin-related pulmonary toxicity, since pulmonary damage induced by bleomycin is reversible if detected early.

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블레오마이신과 관계된 폐독성의 고해상 전산화단층촬영 소견 : 2예 보고[1]

[1]한림대학교 의과대학 진단방사선과학교실

이정근 · 장원호 · 윤대영 · 배상훈

여러 약품이 폐조직에 부작용을 일으킬 수 있는데, 그 가운데에서 블레오마이신이 특히 유명하다. 블레오마이신에 따른 폐독성 정도는 쓴 양에 대체로 비례하지만 산소 치료나 방사선 치료를 함께 하면 또는 다른 항암제와 서로 작용하면 예상 밖으로 일찍 그리고 심하게 나타나기도 한다. 블레오마이신 폐독성은 2－46% 빈도로 나타나고 환자의 1%는 생명이 위태롭다고 알려져 있다.

블레오마이신이 포함된 항암제 레지멘(regimen)으로 치료받은 난소 기형암종과 복부 악성 림프종 환자 두 명에게 생긴 폐독성의 단순 흉부 X선 사진과 고해상 전산화단층촬영 소견을 보고하는 바이다.