J Korean Med Sci 2000; 15: 712-7
ISSN 1011-8934

Extensive Acute Lung Injury Following Limited Thoracic Irradiation: Radiologic Findings in Three patients

The aim of our study was to describe the radiologic findings of extensive acute lung injury associated with limited thoracic irradiation. Limited thoracic irradiation occasionally results in acute lung injury. In this condition, chest radiograph shows diffuse ground-glass appearance in both lungs and thin-section CT scans show diffuse bilateral ground-glass attenuation with traction bronchiectasis, interlobular septal thickening and intralobular smooth linear opacities.

Key Words: *Lung, CT; Lung Diseases; Lung, Radiography; Lung, Radiations, Injurious Effects*

Jung Hwa Hwang*, Kyung Soo Lee*, Koun-Sik Song§, Hojoong Kim†, O Jung Kwon†, Tae-Hwan Lim§, Yong Chan Ahn†, In-Wook Choo*

Department of Radiology*, Division of Respiratory and Critical Care Medicine, Departments of Medicine† and Radiation Oncology‡, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Department of Diagnostic Radiology§, Asan Medical Center, University of Ulsan, Seoul, Korea

Received: 15 February 2000
Accepted: 3 April 2000

Address for correspondence
Kyung Soo Lee, M.D.
Department of Radiology, Samsung Medical Center, 50, Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea
Tel: +82.2-3410-2511, Fax: +82.2-3410-2559
E-mail: kslee@smc.samsung.co.kr

INTRODUCTION

Radiation therapy for the palliation or cure of intrathoracic neoplasm produces some degree of damage to normal tissue within the path of the radiation beam. Radiation pneumonitis sometimes extends beyond the irradiated area of a lung and can also affect the opposite lung (1-10). In such uncommon cases, the condition cannot be explained solely on the basis of simple direct injury of the lungs by radiation. Furthermore, some reports suggest the pathogenesis of radiation injury beyond the radiation portal (4, 9, 10).

Recently, we observed acute radiation injury beyond the radiation portal in three patients with lung cancer who presented with acute respiratory failure after radiation therapy. The aim of this report was to describe the radiologic findings of extensive acute lung injury associated with limited irradiation to the lung.

MATERIALS AND METHODS

During the past four years and six months, we saw three patients who presented with extensive acute lung injury (11) after limited thoracic irradiation for lung cancer. During the same period, 375 patients with lung cancer received the radiation therapy. They were three men whose ages ranged from 58 to 64 years (median, 61 years). All patients were ex-smokers, but quit smoking after the diagnosis of lung cancer. Two patients had irradiation after lobectomy for lung cancer. In the remaining patient, irradiation was given for advanced stage of lung cancer (T2N2M0). Two patients received radiation therapy postoperatively as adjuvant therapy and one patient received radiation as a curative therapy (Table 1). The radiation portal included ipsilateral mediastinal and supraclavicular lymph node chains. Two patients had adenocarcinoma and one patient had squamous cell carcinoma. One patient received postoperative adjuvant chemotherapy (two cycles of mitomycin, vincristine and cisplatin). The patients received a total of 5040-6000 cGy in 18-33 fractions over three to seven weeks (Table 1). Irradiation was performed through both anteroposterior and posteroanterior portal of radiation. Boost with reduction of radiation field was continued with right or left and anterior or posterior oblique portals. The technique

Table 1. Patient information of acute lung injury after limited thoracic irradiation

Case/Age (yr) /Sex	Neoplasm	Location	Surgery	Radiation	Chemotherapy	Date of Sx onset after radiation therapy	Diagnostic procedure	Treatment
				Total/Daily dose/Fr				
1/61/M	Adenocarcinoma	LUL	LULobectomy	5040 cGy/180/28	Yes; 2 cycles of MVP, immediately after surgery	4 days	Lung Bx in RML and RLL	Steroid pulse
2/64/M	Adenocarcinoma	RUL	No	6000 cGy/180-200/33	No	14 days	TBLBx in LLL	Steroid pulse
3/58/M	Squamous cell carcinoma	RUL	RULobectomy	5400 cGy/300/18	No	13 days	TBLBx in lingular segment	Steroid pulse

LUL: left upper lobe, RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LLL: left lower lobe, Fr: fractions, MVP: mitomycin, Vincristin, Cisplatin, Sx: symptom, Bx: biopsy, TBLBx: transbronchial lung biopsy

was used because of the small possibility of significant irradiation of the contralateral lung to the initial tumor sites.

The patients complained of dyspnea (n=3) and dry cough (n=3). The signs at the time of admission included mild inspiratory crackle (n=3), fever (n=3) and tachycardia (n=1). Chest radiograph showed diffuse bilateral infiltrates and arterial blood gas showed hypoxemia (PaO_2/FiO_2 <300) (n=3). None showed features of cardiac failure such as edema, ascites, or cardiomegaly. Ordinary or special cultures for organisms such as *Legionella*, *Pneumocystis*, fungi, *Mycobacterium* and virus were negative in sputum, bronchoalveolar lavage fluid or biopsy specimens. The symptoms and signs developed four to 14 days after the completion of radiotherapy. Antimicrobial agents were not administered in any patients before the diagnosis of radiation-induced lung injury.

Bronchoalveolar lavage fluid in one patient obtained in the lung contralateral to initial tumor site showed mild increase of lymphocytes (total cell count; 18×10^6/mL, alveolar macrophages; 68.5%, lymphocytes; 25.0%, granulocytes; 1.7%, eosinophils; 4.8%, T4/T8 ratio; 1.08).

Open lung biopsy was performed in one patient and transbronchial lung biopsy was performed in the remaining two patients in the contralateral lung to the initial tumor site (Table 1). Immediately after the diagnosis of radiation-induced acute lung injury, steroid therapy was given to all three patients.

The initial radiographic (obtained within 6-10 days after onset of symptoms, median; 7 days) and CT findings (obtained within 7-11 days after onset of symptoms, median; 8 days) (both helical and thin-section CT) were analyzed retrospectively by two chest radiologists. Patterns of parenchymal abnormalities were classified according to the previously published descriptive terms on radiographs (12) and CT scans (13). Decisions on the findings were reached by a consensus.

RESULTS

Open lung biopsy (obtained from two lobes of the right lung) showed the findings of mixed exudative and proliferative phase of diffuse alveolar damage. The findings included intraalveolar exudation in one lobe and interstitial fibroblastic accumulation with hyperplasia of type II pneumocytes in the other lobe (Fig. 1). Transbronchial lung biopsy in two patients showed mild degrees of interstitial fibroblastic and mononuclear cell infiltration.

The chest radiograph showed diffuse ground-glass appearance in both lungs in all three patients (Fig. 1, 2). Two patients demonstrated sparing of parenchymal opacity, one in the apex and the other in the costophrenic sulcus, contralateral to the side of the tumor. Ground-glass appearance was denser in a central or paramediastinal distribution, ipsilateral to the tumor in two patients and both ipsilateral and contralateral to tumor in one. Pleural effusion was seen in two patients. In one patient in whom radiation therapy was given as a curative therapy, findings of primary tumor and mediastinal lymph node enlargement were still visible (Fig. 2). The radiographic abnormalities especially the ground-glass appearance contralateral to the initial tumor disappeared completely seven, eight and 11 days after initial radiographs, respectively, with steroid therapy.

Thin-section CT scans showed diffuse bilateral areas of ground-glass attenuation in both lungs. Denser areas of ground-glass attenuation were seen in the mediastinal side of the lung at initial tumor sites (n=2) or bilateral mediastinal sides of both lungs (n=1) irrespective of tumor site. Some areas of consolidation were seen in one

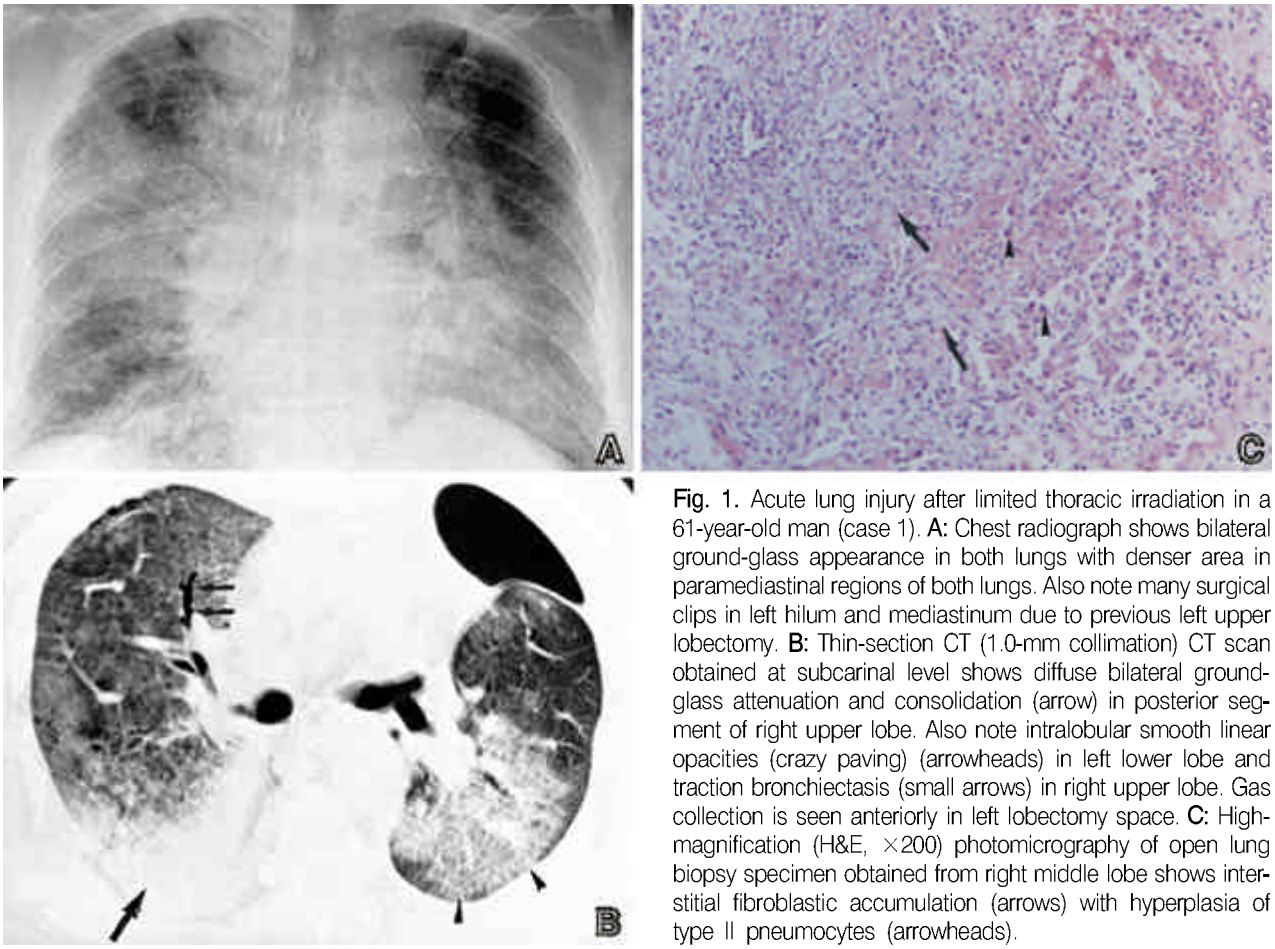

Fig. 1. Acute lung injury after limited thoracic irradiation in a 61-year-old man (case 1). **A:** Chest radiograph shows bilateral ground-glass appearance in both lungs with denser area in paramediastinal regions of both lungs. Also note many surgical clips in left hilum and mediastinum due to previous left upper lobectomy. **B:** Thin-section CT (1.0-mm collimation) CT scan obtained at subcarinal level shows diffuse bilateral ground-glass attenuation and consolidation (arrow) in posterior segment of right upper lobe. Also note intralobular smooth linear opacities (crazy paving) (arrowheads) in left lower lobe and traction bronchiectasis (small arrows) in right upper lobe. Gas collection is seen anteriorly in left lobectomy space. **C:** High-magnification (H&E, ×200) photomicrography of open lung biopsy specimen obtained from right middle lobe shows interstitial fibroblastic accumulation (arrows) with hyperplasia of type II pneumocytes (arrowheads).

patient. Scattered areas of interlobular septal thickening and intralobular smooth linear opacities were seen in all three patients (Fig. 1, 2). Traction bronchiectasis was seen in two patients (Fig. 1, 2). Small pleural effusions were present, unilateral in two patients and bilateral in one.

DISCUSSION

Among the complications that develop in the lungs following radiotherapy, radiation pneumonitis is the most serious one. This complication results in a clinical problem because it tends to be severe and fatal if it develops rapidly or extensively.

The incidence and degree of radiation damage are related to the radiation factors, including volume of irradiated lung, total dose delivered, time of dose delivery, fractionation used, and characteristics of the irradiation (1, 2). For unilateral irradiation with fractionated dose schemes, radiographic changes are almost always seen in patients who received doses greater than 4000 cGy. The volume of lung irradiated may be the most important factor (1, 2).

Several factors have been considered to intensify the damaging effects of radiation. The most important are concomitant chemotherapy (14), previous radiation therapy (2), and steroid withdrawal (15). The importance of other factors, such as habitus, age, and preexisting pulmonary disease, is debatable (16, 17).

Radiation-induced lung damage is generally considered to result from dose-related cell depletion (18). The primary cell affected is either the type II pneumocyte or vascular endothelial cell (2). Ionizing radiation results in the production of free radicals that damage cell membranes and chromosomal DNA, leading to cellular dysfunction and mitotic cell death (1, 2, 18). Subsequently, as in other examples of diffuse alveolar damage, a limited and conventional response of lung injury occurs, manifested by acute exudative phase, subacute organizing or proliferative phase, and chronic fibrotic phase (18). The first two phases correspond to the clinical and radiologic stage of radiation pneumonitis and the third phase corresponds to the stage of radiation fibrosis. These three phases appear at about 0-2 months, 2-9 months, and more than 9 months after treatment, respectively (2, 8).

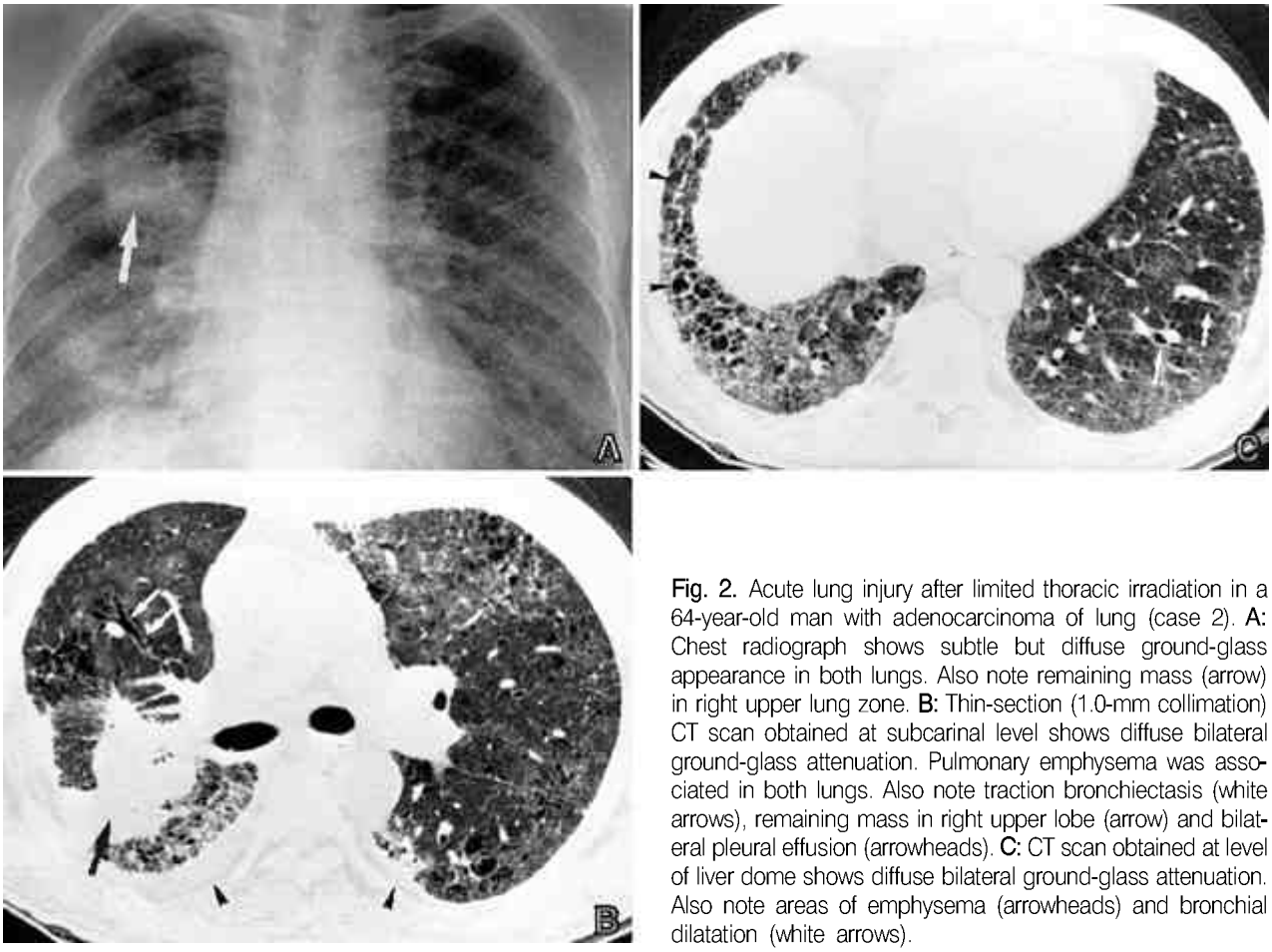

Fig. 2. Acute lung injury after limited thoracic irradiation in a 64-year-old man with adenocarcinoma of lung (case 2). **A:** Chest radiograph shows subtle but diffuse ground-glass appearance in both lungs. Also note remaining mass (arrow) in right upper lung zone. **B:** Thin-section (1.0-mm collimation) CT scan obtained at subcarinal level shows diffuse bilateral ground-glass attenuation. Pulmonary emphysema was associated in both lungs. Also note traction bronchiectasis (white arrows), remaining mass in right upper lobe (arrow) and bilateral pleural effusion (arrowheads). **C:** CT scan obtained at level of liver dome shows diffuse bilateral ground-glass attenuation. Also note areas of emphysema (arrowheads) and bronchial dilatation (white arrows).

Radiographic findings of radiation pneumonitis usually appear about 8 weeks after treatment (2) and CT findings are apparent within 4 weeks in more than half of the patients after treatment (8). In our cases, average latent period of clinical symptom onset after completion of radiation therapy was about 10 days (4, 13, 14 days, respectively) with subsequent rapid deterioration thereafter.

Reported radiographic findings of radiation-induced acute lung injury are ground-glass appearance or fine reticulation in the contralateral lung as well as ipsilateral irradiated lung (3, 5-7). Ikezoe et al. (8) saw extensive radiation pneumonitis beyond the radiation field at conventional CT in four of 17 patients with thoracic irradiation. In their cases, the pattern of abnormalities outside the portal was homogeneous or patchy consolidation. The consolidation in their study at conventional CT may correspond to the areas of ground-glass attenuation in our study at thin-section CT. However, in their study with conventional CT, they did not describe associated findings such as traction bronchiectasis, interlobular septal thickening and intralobular smooth linear opacities.

Ikezoe et al. (8) detected relatively high incidence (four of 17 (24%) patients) of extensive radiation pneumonitis beyond the radiation field at conventional CT. The incidence is much higher, compared with those of our study and other report (6). They performed a prospective study to determine how soon radiation-induced lung injury is detectable and to compare the CT findings with those on chest radiographs. Therefore, it might be possible that they could detect more frequent and early radiation changes on CT than in our study or other previous retrospective studies. In addition, other factors such as individual hypersensitivity and placement of radiation portal might play a role.

As in our cases in which radiation pneumonitis has spread to the nonirradiated or opposite lung, the pathogenesis of lung injury cannot be understood only on the basis of simple direct injury by radiation. Several explanations of this unusual phenomenon have been suggested: 1) blockage of lymphatic channels, hindering egress of alveolar macrophages (7); 2) errors in dosimetry or placement of ports (6), scattered radiation (10), or a sensitizing effect of concomitant infection (6, 10); and 3) individual hyperreactivity (3, 6, 10). The last hypothesis has been regarded to be the most plausible. Some persons

may have an inherent genetic susceptibility to the effects of irradiation (9, 10). Alternatively, an immunologically mediated reaction may occur. It has recently been reported that radiation results in increase of regional lymphocyte counts in lungs, which was proven by examination of lavage fluid, and that this phenomenon is not confined to the irradiated lung but is also visible in the opposite lung (4, 9, 10). Ga67 scanning also showed bilateral uptake of the radionuclide (2). Hypersensitive immune reaction mediated by lymphocytes was suggested (4, 9, 10, 19). Roswit et al. (3) explained the pathogenesis as delayed hypersensitivity immune reaction that can occur as a response to an antigen resulting from intensive irradiation. This antigen may elicit a sensitization of lymphocytes especially the thymic-derived T cells. The latent period for the reaction, histologic pattern, involvement of the nonirradiated lung, and response to corticosteroids seem to support this hypothesis. Nakayama and colleagues (4) recently suggested that irradiation can induce accumulation of activated T cells (human leukocyte-associated antigen and intercellular adhesion molecule-1-positive T cells) in the lung and this may be closely linked to radiation-induced lung injury.

When an atypical radiographic appearance is observed following thoracic radiotherapy, the possibilities of radiation-induced acute lung injury as in our cases, radiation-associated bronchiolitis obliterans organizing pneumonia (20), recurrent or metastatic neoplasm (1, 2), infection (1, 2), and drug-induced toxic effects (1-4) should be considered. The presence of these potential complications may be suggested by deviation from the expected temporal sequence for radiation effects. The unusual sequence includes late appearance or enlargement of a pleural effusion and development of new consolidation, mass, or cavitation after a period when radiologic findings have been stable (2). Definitive tissue diagnosis through bronchoscopy, percutaneous needle aspiration biopsy, open lung biopsy, or thoracentesis may be required.

In summary, limited thoracic irradiation occasionally results in extensive acute lung injury immediately after completion of the therapy. In this condition, chest radiograph shows diffuse ground-glass appearance also in the contralateral lung to the initial tumor site and thin-section CT scans show diffuse bilateral areas of ground-glass attenuation with traction bronchiectasis, interlobular septal thickening and intralobular smooth linear opacities.

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