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CASE REPORT

Exacerbation of gemcitabine-related pneumonia during radiotherapy for extrapulmonary lesion

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Abstract Late-onset gemcitabine pulmonary toxicity is rare and association between pulmonary toxicity and radiotherapy to the extrapulmonary sites is controversial. Here, we report a case of acute exacerbated fatal interstitial pneumonia during radiotherapy to the extrapulmonary site. A 73-year-old woman with pelvic lymph node metastases from urothelial carcinoma underwent palliative radiotherapy after failure of gemcitabine-containing and gemcitabine-non-containing chemotherapy. Gemcitabine-containing chemotherapy had finished 13 months prior to the radiotherapy due to grade 3 pulmonary toxicity. During the course of radiotherapy to the pelvic lesion, she was complicated with fatal acute interstitial pneumonia even though the lung tissue was not irradiated. To the best of our knowledge, this is the first reported case of fatal gemcitabine-related pulmonary toxicity during radiotherapy for extrapulmonary lesion. Although the association between late-onset pulmonary toxicity and radiotherapy is controversial, caution should be paid to a patient with a history of gemcitabine-related pulmonary toxicity who will undergo radiotherapy even though the lung volume is not irradiated.

Keywords Adverse events · Ionizing radiation · Pulmonary complications · Adverse events · Immunogenic

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Introduction

Concurrent radiotherapy to the chest with gemcitabine is associated with excessive pulmonary toxicity [1], but late-onset (>1 year) gemcitabine-associated lung toxicity is very rare [2]. A clear association between pulmonary toxicity and radiotherapy to the extrapulmonary sites has yet to be clarified. Here, we report a case of ureteral cancer complicated by fatal pneumonia during radiotherapy to the pelvis more than 1 year after gemcitabine-containing chemotherapy.

Case report

A 73-year-old woman with pelvic lymph node metastases from urothelial carcinoma of the left ureter was referred to our institution for palliative radiotherapy. The patient was initially diagnosed with Stage III urothelial carcinoma of the left ureter and underwent a surgical resection. Six months after surgery, pelvic lymph node metastases were found and chemotherapy with gemcitabine and cisplatin was initiated (gemcitabine 1,000 mg/m^2 days 1, 8 and 15; cisplatin 70 mg/m^2 day 2). Unfortunately, she developed grade 3 pulmonary toxicity consistent with gemcitabine-induced interstitial pneumonia after the first session. To avoid further exacerbation of pulmonary toxicity, gemcitabine was changed to multiple alternative agents consisting of methotrexate 30 mg/m^2 on days 1, 15, and 22; vinblastine 3 mg/m^2 on days 2, 15, and 22; doxorubicin 30 mg/m^2 on day 2; and cisplatin 70 mg/m^2 as a 1- to 8-h infusion on day 2. Cycles were repeated every 28–35 days. She received this multidrug chemotherapy regimen for 1 year without pulmonary toxicity, but the pelvic lymph node metastases continued to grow in size (Fig. 1a,b),

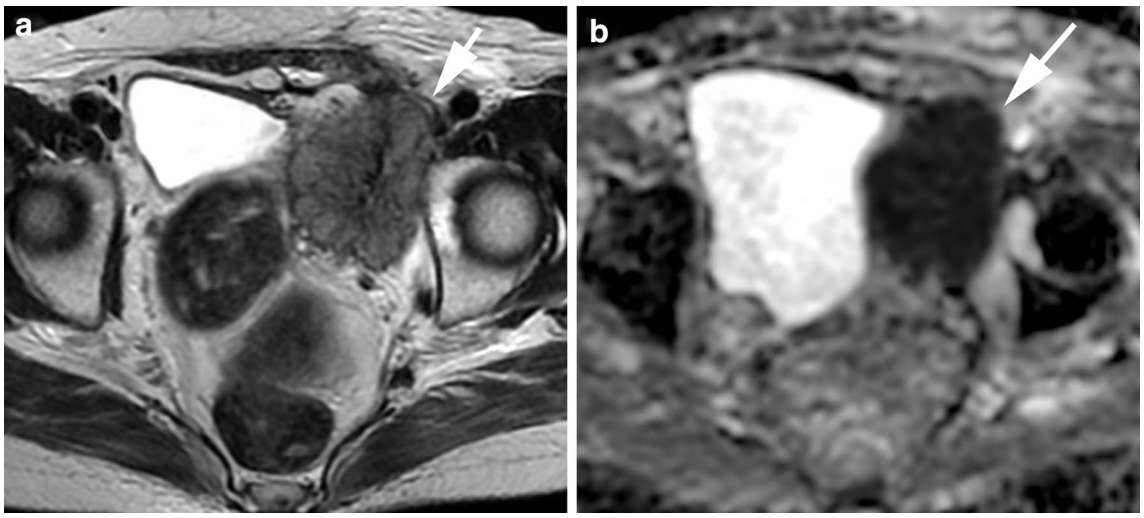

Fig. 1 **a** Axial T2-weighted fast spin-echo magnetic resonance image shows left external iliac nodal metastasis (*arrow*). **b** Apparent diffusion coefficient (ADC) map shows restricted diffusion of the lesion (*arrow*)

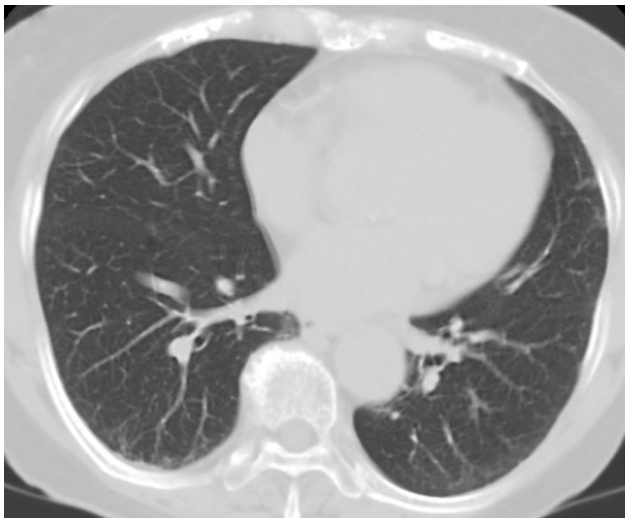

Fig. 2 Computed tomography scan of the chest 1 week before radiotherapy is normal

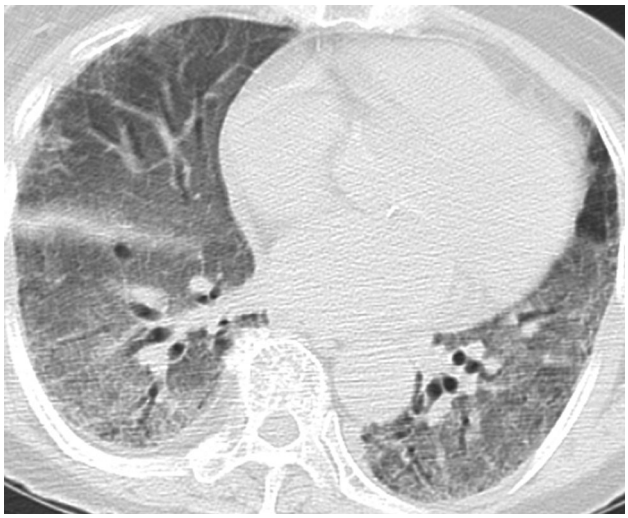

Fig. 3 Computed tomography scan performed at the *lower* level of the lung shows increased diffuse parenchymal attenuation with overlapping reticular pattern

which sometimes caused severe pain. To alleviate her cancer pain, palliative radiation therapy to the painful metastasis of the left external iliac lymph node was initiated 1 month after the last session of multidrug chemotherapy including the same doses of methotrexate, vinblastine, doxorubicin and cisplatin. She was planned to receive 30 Gy in 10 fractions to the left external iliac lymph nodes with parallel-opposed beams. CT scan of the chest was considered normal 1 week before the start of radiotherapy to the pelvic area (Fig. 2). After 6 Gy was delivered in 2 fractions, repeated CT scan was performed because of the increased dyspnea, tachypnea, and persistent cough. CT scan of the chest showed pulmonary ground-glass opacities, predominantly in the lower lobes associated with areas of smooth interlobular septal thickening (Fig. 3). Based on the CT imaging findings, clinical signs and symptoms, a diagnosis of acute exacerbation of interstitial pneumonia associated with radiotherapy was made. Soon after the CT scan, she suffered a cardiac arrest and died of acute respiratory failure despite resuscitation efforts on the very day.

Discussion

This case demonstrated the risk of acute exacerbation of interstitial pneumonia in a patient having received gemcitabine-containing chemotherapy during or after radiotherapy even though the lung volume was not irradiated.

Fatal pulmonary toxicities resulting from concurrent chemoradiotherapy for lung cancer with gemcitabine have been reported [1]. However, it is still controversial whether radiotherapy for extrapulmonary lesions would be a risk factor of gemcitabine-induced pulmonary toxicity. As far as we know, this is the first report describing that fatal pneumonia occurred during radiotherapy for extrapulmonary lesions in a patient having a history of gemcitabine-induced pulmonary toxicity.

Gemcitabine is a pyrimidine analog that is incorporated into replicating DNA, which inhibits thymidylate synthetase and ribonucleotide reductase leading to inhibition of DNA synthesis and apoptosis [1, 2]. Risk factors for gemcitabine-related pulmonary toxicity include multimodality therapy with concurrent or prior irradiation to the chest, co-administered chemotherapeutic agents, lung carcinoma, older age, female gender and lower baseline diffusing capacity of lung for carbon monoxide [3, 4]. In this patient, gemcitabine-containing chemotherapy had ended more than 1 year prior to the pulmonary adverse event. Previous study has demonstrated that the median time to the diagnosis of gemcitabine-related pulmonary toxicity is 48 days (range 1–529) after initiation of chemotherapy [5]. Late-onset (>1 year) gemcitabine lung toxicity is very rare [2, 5]. It is still unclear whether pulmonary toxicities are potentiated by radiotherapy for extrapulmonary lesions.

One possible mechanism of late-onset gemcitabine lung toxicity is the effect of gemcitabine on the immunity of patients [6–8]. It has been suggested that gemcitabine expand the immune response to subdominant epitopes and increase cross presentation of antigen to CD8+ cells and increase proliferation and functionality of them [6–8]. Radiotherapy induces the death of cancer cells, resulting in the release of tumor-associated antigens and presumably in their cross presentation by dendritic cells, upregulates MHC Class I molecules, and improves T cell infiltrate [9]. Another possible mechanism of pulmonary toxicity is the release of cytokines in the body, which could result in damage to areas throughout the body. This process could lead to capillary leak syndrome or pulmonary edema [10]. We speculate that radiotherapy in combination with chemotherapy may have enhanced both humoral and cellular immunity, resulting in acute exacerbation of interstitial pneumonia which is originally induced by gemcitabine.

In conclusion, the findings of a single case cannot be generalized to others without additional scientific verification. Nevertheless, particular caution should be paid to a patient with a history of gemcitabine-induced pulmonary toxicity who will undergo radiotherapy even though the lung volume is not irradiated.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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