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CASE REPORT

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Tenascin C in radiation-induced lung damage: Pathological expression and serum level elevation

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Abstract

Radiation-induced lung damage (RILD) is a critical problem in lung cancer radiotherapy, and it is difficult to predict its severity. Although no biomarkers for RILD have been established, tenascin C (TNC) is an extracellular matrix glycoprotein involved in the remodeling of damaged tissues and has been implicated in inflammation and fibrosis. We report the unique case of a 36-year-old man with adenocarcinoma of the lung, Union for International Cancer Control stage IIIB, who was treated with radiotherapy before lung surgery. The surgical specimen showed histopathological expression of TNC in the region where radiation pneumonitis was observed radiographically. Serum TNC levels were elevated after radiotherapy. In this case, TNC is suggested to be implicated in RILD and may be a potential candidate as a biomarker for the onset and severity of the condition.

KEYWORDS

radiation fibrosis, radiation induced lung damage, radiation pneumonitis, tenascin C

INTRODUCTION

Radiation therapy plays an important role in lung cancer treatment, but radiation-induced lung damage (RILD) has remained a critical challenge. RILD can be characterized by an early phase of radiation pneumonitis (RP) and a late phase of radiation fibrosis (RF).[1–4] Most cases of RP and RF are relatively mild, but occasionally the disease becomes severe and may lead to dyspnea, lung fibrosis, and impaired quality of life. If the onset of RP can be predicted, effective countermeasures can be taken as early as possible. However, no biomarker has been established to predict the onset or severity of RP. Tenascin C (TNC) is a large extracellular matrix glycoprotein and is transiently expressed at specific sites during inflammation, wound healing, and cancer invasion.[5,6] There have been reported diverse functions of TNC, particularly in the regulation of inflammation and fibrosis[7]; TNC is also known to be one of the markers of inflammation and fibrosis.[5,8–10] We report a case of a patient with lung cancer treated with chemoradiotherapy before surgery, in which the resected specimen showed pathological findings of RILD and TNC expression, and elevated serum TNC levels were observed after radiotherapy.

CASE REPORT

A 36-year-old man was referred to our hospital because of an abnormal chest roentgenogram. He had no significant clinical symptoms. Computed tomography (CT) showed a 4.1 cm mass with mediastinal invasion in the right middle lobe (S5) and two enlarged lymph nodes (middle lobar and subcarinal). Adenocarcinoma was diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration of the subcarinal lymph node. Imaging studies, including positron emission tomography, indicated cStage IIIB

(cT4N2M0) according to the 8th edition of the Union for International Cancer Control classification (Figure 1).

The patient underwent preoperative chemoradiotherapy (CRT). CRT consisted of paclitaxel (70 mg/m^2) on days 1, 8, and 15 with carboplatin (area under the curve = 5) on day 1, and concurrent radiation therapy of 40 Gy in 20 fractions. Three-dimensional conformal radiotherapy was performed using 10-MV photon energy. The gross tumor volume (GTV) was contoured as the primary tumor and metastatic lymph nodes, and the clinical target volume (CTV) added a 5-mm margin to the GTV. The planning target volume was defined as CTV with a 5 mm margin. The verification of patient positioning was performed via imaging by portal vision or cone beam CT every session. The percentage of lung volume receiving ≥ 20 Gy or more (V20) of ipsilateral lung and both lungs were 39.2% and 21.7%; the mean lung dose and V5 of both lungs were 10.4 Gy and 35.3%, respectively. After radiotherapy was completed, the presence of a gastrointestinal stromal tumor (GIST) was identified. The GIST took about 3 months to treat, warranting the postponement of lung surgery. A right middle lobectomy with hilar and mediastinal lymph node dissection was performed 13 weeks after completion of CRT. Chest CT taken 2 days before surgery showed ground-glass opacities that were observed in the 90% isodose line of the dose distribution curve (Figure 2). The patient had no clinical presentation of cough or dyspnea and was

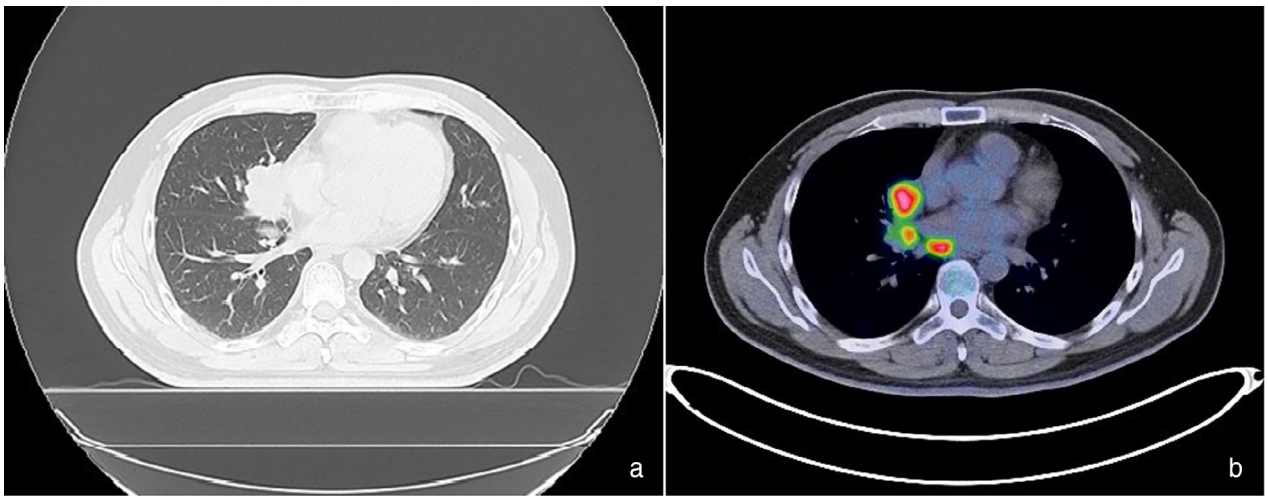

FIGURE 1 (a) Computed tomography showing a 4.1 cm mass in the right middle lobe. (b) Positron emission tomography showing lung tumor and lymph node swelling.

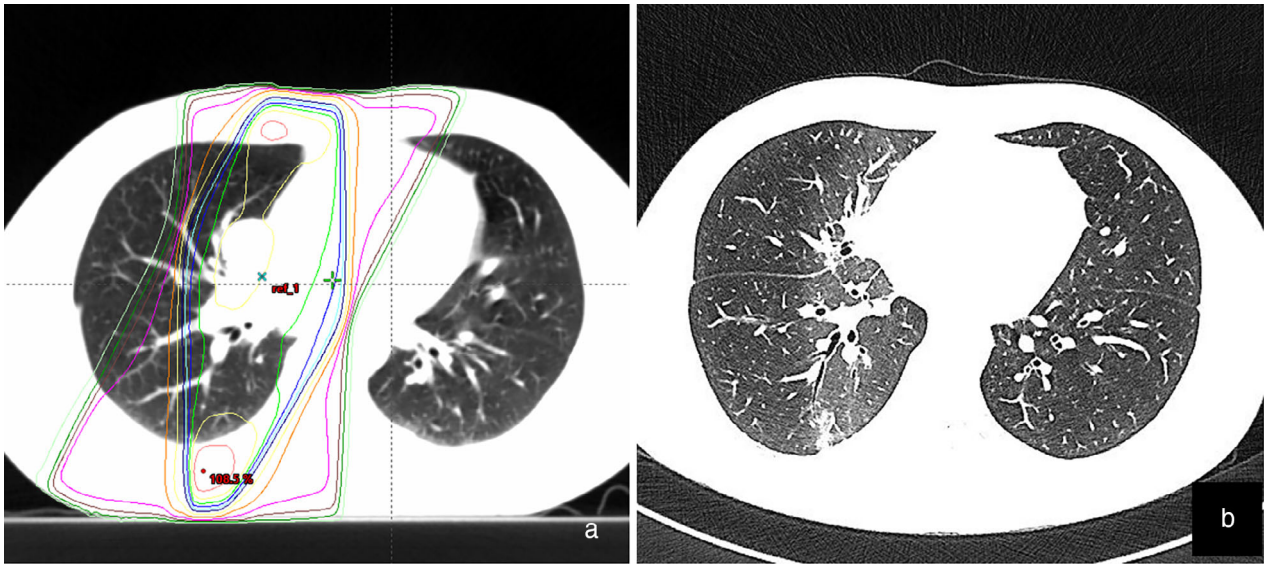

FIGURE 2 (a) Dose distribution curve. (blue line: 90% isodose). (b) Ground-glass opacities in the 90% isodose line.

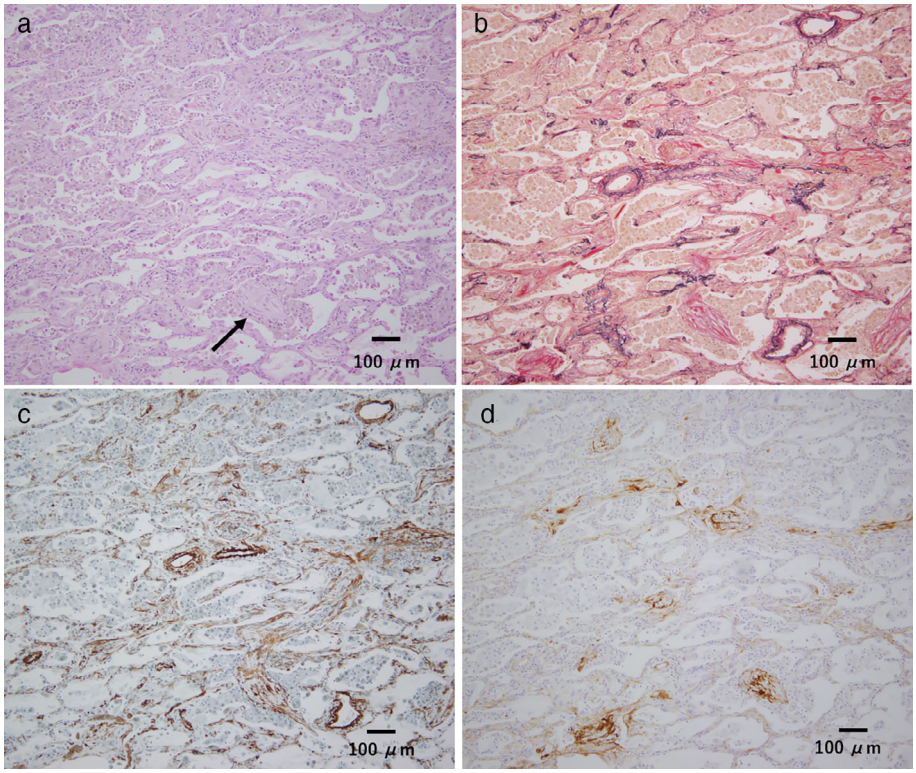

FIGURE 3 (a) Pathological specimen showing thickening of alveolar walls and macrophages. Masson body (arrow) was identified in the alveoli. (b) Immunohistological staining with Elastica Sirius red showing fibrosis in the pulmonary interstitium. (c) Myofibroblasts are shown with α smooth muscle actin (αSMA) immunostaining. (d) TNC expression was found in the interstitium.

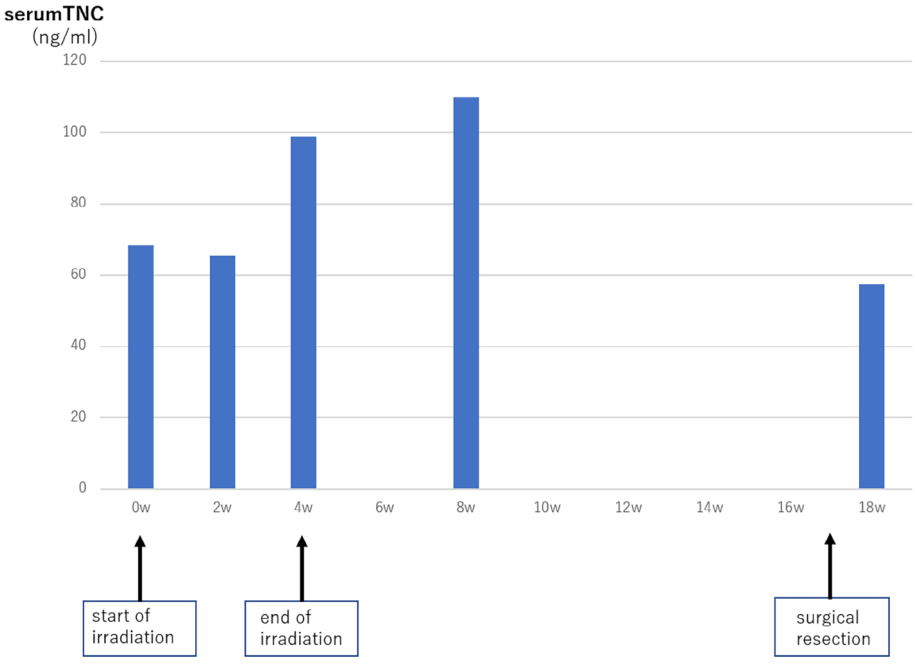

FIGURE 4 Serum tenascin C (TNC) changes over time before and after radiotherapy.

diagnosed with grade 1 RP by Common Terminology Criteria for Adverse Events version 5.0.

Postoperative pathological specimens showed thickening of alveolar walls. Inflammatory cells, such as macrophages, were observed at the site of radiation injury (Figure 3(a)). In the alveoli, fibro-inflammatory bud (Masson body) was found. Elastica Sirius red staining showed fibrosis in the interstitium (Figure 3(b)), and immunostaining showed multiple α smooth muscle actin (αSMA) positive cells in the fibrotic lesion (Figure 3(c)). The expression of TNC was also found in the interstitium (Figure 3(d)). Serum TNC was measured before the start of radiation therapy, at 2 weeks after the start of radiation therapy, at 4 weeks (at the end of radiation therapy), at 8 weeks (4 weeks after the end of radiation therapy), and at 18 weeks (7 days after surgery); TNC levels were elevated at 4 and 8 weeks after the start of irradiation (Figure 4).

DISCUSSION

This case study is a rare report examining the relationship between RILD and TNC, both in terms of histopathology and serum data. RP usually occurs about 4 to 12 weeks after completion of radiation therapy, followed by RF. In this case, chest CT was taken 12 weeks after irradiation, and a grade 1 RP was diagnosed, corresponding to the transition period from RP to RF. In most preoperative radiotherapy cases, surgery is performed within a month after irradiation. This makes it rare to obtain pathological specimens of radiation lung injury within the transition phase of RP to RF because it took 3 months to treat GIST. Pathological specimens showed infiltration of inflammatory cells and collagen fibers, suggesting a transitional phase from RP to RF. In the same specimen, intense TNC expression was observed in the fibrotic interstitium. TNC expression has been reported in lung tissues of patients with RP and RF in usual interstitial pneumonia.[11] This suggests a role of TNC in the progression of fibrotic pulmonary disorders. We have shown that TNC is also expressed in RILD.

Furthermore, we have found elevated serum levels of TNC after irradiation. High serum TNC has also been reported in various diseases including heart disease, cerebrovascular disease, and collagen disease, in which elevated serum TNC levels are used as a diagnostic marker for disease activity.[12–15] In the present case, elevated serum TNC levels at 4 and 8 weeks after the start of irradiation may suggest the progression of RP and RF. The decrease in serum TNC after surgery may be because of the resection of the tumor and part of the RILD. Therefore, measurement of serum TNC may predict the severity of RILD.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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