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CASE REPORT

Pembrolizumab-induced interstitial lung disease following thoracic surgery in a patient with non-small cell lung cancer

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Abstract

The safety of treatment with immune-checkpoint inhibitors prior to thoracic surgery in patients with non-small cell lung cancer (NSCLC) remains unclear. Here, we describe the case of a 62-year-old woman with NSCLC with programmed death ligand 1 expression on 85% of tumor cells. The patient was initially considered to have unresectable stage IIIB disease and received pembrolizumab monotherapy. After 12 cycles of pembrolizumab, the primary tumor was reduced, but a small lung nodule in another lobe was unchanged. Based on the course of image findings, the nodule was considered to be an old inflammatory change. The clinical stage was changed to stage IB and partial resection was performed. Three days after thoracic surgery, the patient began to complain of coughing and shortness of breath. A CT of the chest revealed ground-glass opacity in the bilateral lung fields, suggesting interstitial lung disease (ILD) associated with pembrolizumab. Corticosteroid therapy was started and a chest X-ray showed a reduction in the opacity with improved oxygenation. This is the first case of immune-checkpoint inhibitor-related ILD triggered by thoracic surgery following long-term immune-checkpoint therapy.

Introduction

Immune-checkpoint inhibitors (ICIs) are widely used for the treatment of advanced non-small cell lung cancer (NSCLC) in clinical practice.[1–4] Pembrolizumab, anti-programmed death 1 (PD-1) antibody, significantly improved a progression-free survival and an overall survival compared with platinum-based chemotherapy in patients who had previously untreated advanced NSCLC with programmed death ligand 1 (PD-L1) expression on at least 50% of tumor cells and with no sensitizing epidermal growth factor receptor mutations and anaplastic lymphoma kinase translocations.[3,5] In addition, durvalumab, anti-PD-L1 antibody, significantly prolonged a progression-free survival and an overall survival compared with placebo in patients with stage III, unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy.[6] Recently, some groups have investigated the efficacy of neoadjuvant treatment with anti-PD-1/PD-L1 antibodies prior to curative lung surgery in patients with resectable NSCLC.[7] This neoadjuvant immunotherapy may be promising but the safety of treatment with ICIs prior to thoracic surgery has not been fully elucidated. Here, we report the case of a female patient with NSCLC who experienced interstitial lung disease (ILD) associated with pemblolizumab treatment after thoracic surgery.

Case report

A 62-year-old female with a history of smoking 32 packs per year was referred to our hospital because of an abnormal chest X-ray. Computed tomography (CT) scan showed a mass lesion in the right middle lobe and a subpleural small nodule in the right lower lobe (Fig 1a). She was diagnosed with clinical stage IIIA (cT4N0M0) lung squamous

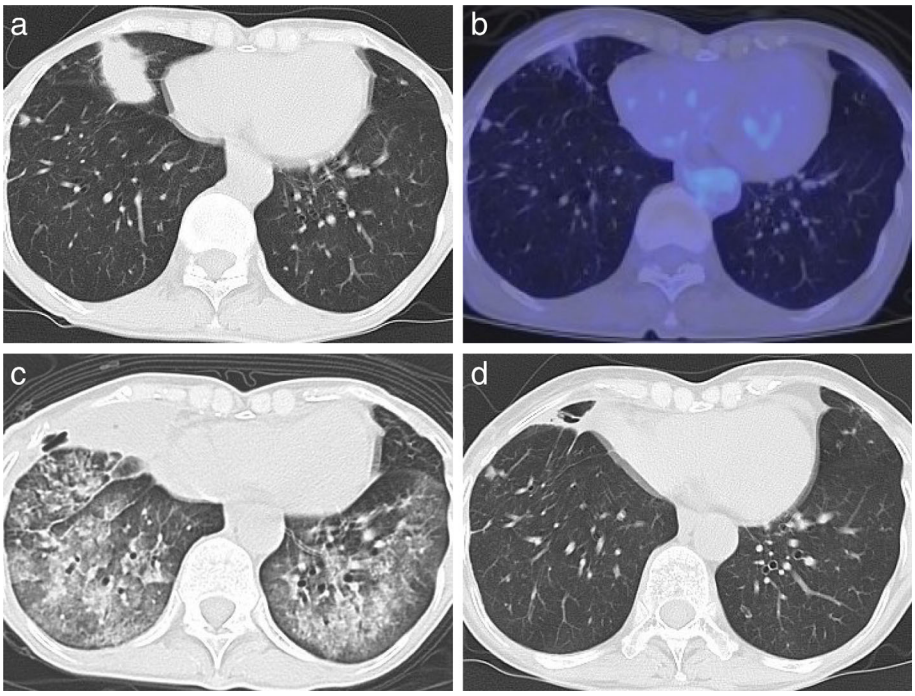

Figure 1 (**a**) Computed tomography (CT) scan of the chest showed a mass lesion in the right middle lobe and a subpleural small nodule in the right lower lobe at diagnosis. (**b**) Positron emission tomography showed a radiologic partial response and a metabolic complete response in the primary tumor after 12 cycles of pembrolizumab. (**c**) CT scan 15 days operatively demonstrated extensive bilateral ground-glass opacities and consolidation. (**d**) The interstitial lung infiltrates resolved after steroid therapy.

cell carcinoma harboring 85% tumor proportion score of PD-L1 (Fig 2a), and treated with pembrolizumab (200 mg) for three weeks. After 12 cycles of pembrolizumab, positron emission tomography/CT scan showed a radiologic partial response and a metabolic complete response in the primary tumor, although the subpleural small

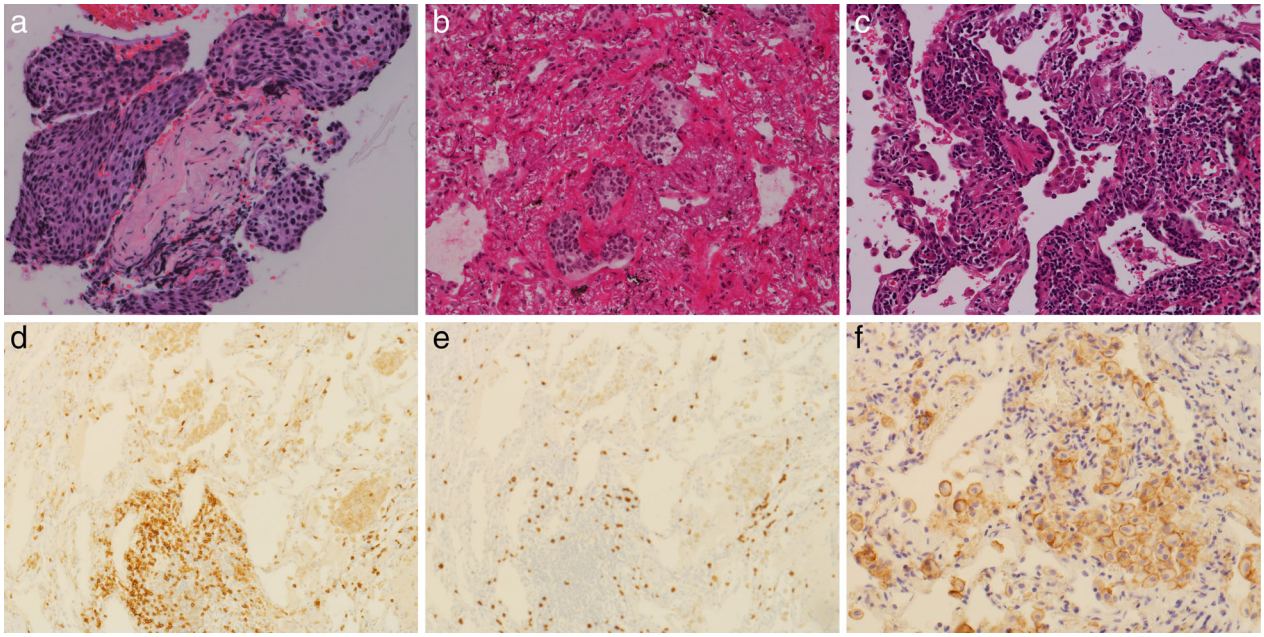

Figure 2 (**a, b**) Tumor tissue specimens (hematoxylin and eosin; original magnification ×200). (**a**) Before the administration of pembrolizumab and (**b**) after administration. (**c**) Normal tissues distant from the tumor showed the thickness of interalveolar septa with lymphocytic infiltration in the specimens from resected lung (hematoxylin and eosin; original magnification ×200). (**d–f**) Immunohistochemistry showed the specimens (**d**) contained CD4 lymphocytes, (**e**) CD8 lymphocytes and (**f**) macrophages expressing PD-L1. Brown color indicates CD4, CD8 and PD-L1.

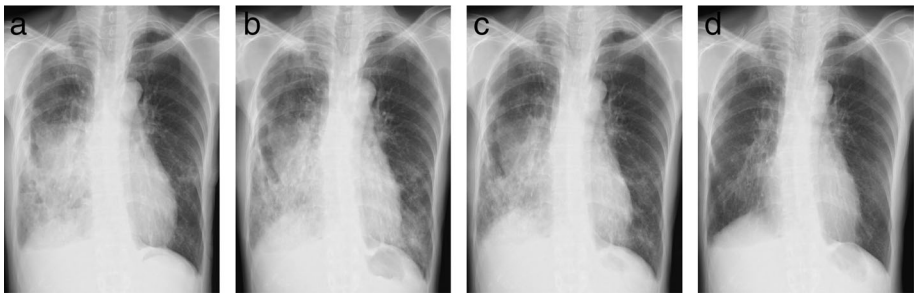

Figure 3 (**a**) Chest X-ray revealed new reticular opacities in the left lower lung field, as well as postsurgical pleural effusion and infiltrates in the right lung field eight days after right middle partial resection. (**b**) The reticular opacities in the left lower lung field worsened 15 days postoperatively. (**c**) Following steroid pulse therapy, the opacities had slightly reduced. (**d**) All findings improved after oral corticosteroid therapy over five months.

nodule had not changed in size (Fig 1b). The nodule was diagnosed as an old inflammatory change and the initial clinical stage was amended to stage IB (cT2aN0M0). A right middle partial resection was subsequently performed two months following the last administration of pembrolizumab. The pathological findings of the resection showed more than 90% regression of the primary tumor (Fig 2b). Three days after surgery, the patient began to complain of coughing and shortness of breath. On postoperative Day 8, a chest X-ray showed new reticular opacities in the left lung lower field (Fig 3a). The chest CT scan 15 days postsurgery demonstrated ground-glass opacities and consolidation with mild bronchiectasis in the bilateral lower lobes (Fig 1c). On examination, her body temperature was 37.5°C and oxygen saturation on room air was 90%. Fine crackles were audible in the bilateral lung fields. Clinical laboratory tests indicated a white blood cell count of 15 300/μL with 81.0% neutrophils and 11.0% lymphocytes, C-reactive protein level 14.26 mg/dL, serum lactate dehydrogenase (LDH) 299 IU/L, Sp-D 378 ng/mL and KL-6 266 U/mL. The resected specimens were re-examined which indicated thickness of interalveolar septa with lymphocytic infiltration without severe fibrosis in the lung tissue distant from the tumor (Fig 2c). Additionally, the specimens contained CD4 and CD8 lymphocytes influx (Fig 2d,e) and macrophages expressing PD-L1 (Fig 2f). In conjunction with the clinical course, pembrolizumab-induced ILD was strongly suspected, although pathological evaluation by bronchoscopy could not be performed because of her clinical state. Corticosteroid pulse therapy (intravenous methylprednisolone at a dose of 1000 mg for three days) was commenced which successfully alleviated her symptoms and improved the radiographic findings (Fig 3b,c). Subsequently, oral corticosteroid (prednisolone at a dose of 0.5 mg/kg) was initiated and tapered over five months. Based on the results of the imaging findings, the ILD was considered to have resolved (Figs 1d and 3d). Recurrence of the ILD and lung cancer have not been observed for over one year since the discontinuation of steroid therapy.

Discussion

To our knowledge, this is the first case report of pembrolizumab-induced ILD triggered by thoracic surgery. In this case, infiltration of T lymphocytes and abundant macrophages expressing PD-L1 were observed in normal tissues in the post-immunotherapy specimens, which is consistent with previous reports.[7,8] We assumed that the PD-1 blockade reactivated T-cell effector function resulting in focal inflammatory changes in lung parenchyma (pathological ILD) prior to the thoracic surgery.

Thoracic surgery has been known to be a risk factor for acute respiratory distress syndrome (ARDS) and acute exacerbation of ILD is a major cause of postsurgical ARDS.[9] Although the precise mechanisms of postoperative acute exacerbation of ILD have not yet been elucidated, it may be associated with a release of inflammatory cytokines and reactive oxygen species from immune cells. Previous reports demonstrated that levels of IL-6 and oxidative stress were elevated in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF) compared with those with stable IPF.[10,11] The pathogenesis of ILD in this case may not be the same as that of postoperative acute exacerbation of IPF because steroid therapy in this case was more effective than that for postoperative acute exacerbation of IPF. ICIs-related ILD is mostly low grade event and improves with drug discontinuation and immunosuppression.[12] In this case, we speculated the pembrolizumab-induced pathological ILD deteriorated into radiological ILD due to an enhancement of T-cell effector function by surgical stress.[13] Thoracic surgery following immunotherapy may have a risk of developing immunotherapy-related ILD, and careful monitoring is required for early detection of ILD after surgery.

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Disclosure

The authors declare that they have no conflicts of interest.

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