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Severe acute respiratory distress syndrome due to ipilimumab

To the Editor:

Ipilimumab is a T-cell-potentiating human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen (CTLA)-4, which promotes antitumour immunity by unrestrained T-cell activation [1]. It is the first agent shown to improve survival in patients with metastatic melanoma [2]. However, various ipilimumab-associated immune-related adverse events including enterocolitis, dermatitis, hepatitis, hypophysitis, meningo-radiculo-neuritis, and renal failure have been reported [3]. The few reported cases of pulmonary side-effects consist of ipilimumab-induced sarcoid-like granulomatosis [4–7]. To our knowledge, this is the first report of an ipilimumab-induced lung injury presenting as severe acute respiratory distress syndrome (ARDS).

A 64-year-old former smoker with metastatic melanoma (stage IIIC) was referred with hypoxaemic respiratory failure and oedema of both feet and hands, following administration of the second dose of ipilimumab (246 mg) 4 days earlier. After the first dose (237 mg), given 6 weeks earlier in combination with radiotherapy for inguinal lymph node metastases and topical immunotherapy with diphenylcyclopropenone 0.1% for cutaneous metastases, the patient presented with generalised exanthema in the absence of respiratory symptoms, which was responsive to oral and topical steroids. His past medical history was uneventful for pulmonary diseases, and he took no drugs other than ipilimumab and prednisone (30 mg·day^{-1}) for exanthema. He was tachycardic (120 beats·min^{-1}) and normotensive. His respiratory rate was 34 per min and a peripheral cyanosis was present. The jugular veins were not distended, but marked oedema of both the feet and hands were present. Cardiac auscultation was unrevealing, but bilateral crackles

were audible over both lungs. The results of laboratory studies were only remarkable for elevated C-reactive protein (84 $mg \cdot L^{-1}$), whereas procalcitonin was 0.23 $\mu g \cdot L^{-1}$, and pro-brain natriuretic peptide was 508 $ng \cdot L^{-1}$. The leukocyte count was $4.4 \times 10^9 \cdot L^{-1}$, with 0.7% eosinophils. A chest computed tomography revealed obvious signs of diffuse parenchymal lung disease (fig. 1). Bronchoalveolar lavage was avoided due to severely impaired oxygenation (arterial oxygen saturation measured by pulse oximetry 80%, arterial oxygen tension (P_{aO_2}) 45 mmHg and arterial carbon dioxide tension 33 mmHg while breathing 100% inspiratory oxygen fraction (F_{IO_2}) over a Venturi mask, P_{aO_2}/F_{IO_2} 45 mmHg). Echocardiography was normal. The patient was treated empirically with piperacillin/tazobactam (4.5 g three times daily), trimethoprim/sulfamethoxazole (320 mg/1.6 g every 6 h) and methylprednisolone (500 $mg \cdot day^{-1}$). Sputum samples, blood cultures and urinary legionella antigen testing were all negative. Since there were no clinical or serological findings suggesting an autoimmune disease and the patient fulfilled the Berlin definition for ARDS, ipilimumab-induced lung injury presenting as ARDS was presumed. The treatment was continued with methylprednisolone (125 $mg \cdot day^{-1}$), once daily, for the following 3 days and prednisone (80 $mg \cdot day^{-1}$, corresponding to 1 $mg \cdot kg^{-1} \cdot day^{-1}$) thereafter. He received trimethoprim/sulfamethoxazole *Pneumocystis jirovecii* prophylaxis. The patient subsequently recovered with slowly improving oxygenation. After 2 months, oxygen supplementation therapy could be stopped and the prednisone dose could be tapered to 10 $mg \cdot day^{-1}$. Pulmonary function tests had also improved to near normal values (forced vital capacity 71%, forced expiratory volume in 1 s 78%, total lung capacity 66%, diffusing capacity of the lung for carbon monoxide 52% predicted). Although partial metabolic and morphological response to ipilimumab has been stated 40 days after the second ipilimumab dose, it was no longer administered after the second dose, and progressive metastatic melanoma was found within 4 months.

Ipilimumab acts by an enhanced T-cell activation and proliferation with subsequent lymphocyte-mediated death of tumour cells, which is determined by inhibiting CTLA-4 [1]. Several ipilimumab-associated immune-related adverse events have been described. Thus, guidelines for the management of such events are provided [3]. Most of the side-effects are considered of a mild or moderate degree, with dermatitis (up to 43%) and enterocolitis (30%) being the most frequent entities. Aside from ipilimumab-induced sarcoid-like granulomatosis of the lung [4–7], reports on pulmonary toxicity are not available. In a randomised, double-blind, phase three study enrolling 511 patients with stage III or IV melanoma treated with ipilimumab 12.7% reported dyspnoea and 0.6% experienced severe dyspnoea [2]. However, no detailed information on the subject's characteristics or outcomes is available.

Our patient recovered partially from the severe ARDS, which was most likely caused by ipilimumab after other aetiologies, *i.e.* other potentially pneumotoxic drugs, relevant comorbid conditions (*e.g.* left heart failure) or infection, had been excluded. However, since ipilimumab therapy was terminated and the patient received both high dose corticosteroids and antibiotics, drug-induced lung disease cannot be ascertained. Infection, including *P. jirovecii*, cannot be excluded definitely, but seemed unlikely, as the sputum smear was negative. Whether the high doses of corticosteroids were responsible for the functional improvement remains speculative. Besides the former smoker status (3 years since cessation, cumulative 30 pack-years), our patient had no pulmonary comorbidities, which would eventually enhance the risk of pulmonary side-effects. But, it is possible that the simultaneous irradiation therapy contributed to provoke the severe pulmonary toxicity (abscopal effect) [8]. Our observation strongly suggests that ipilimumab may cause

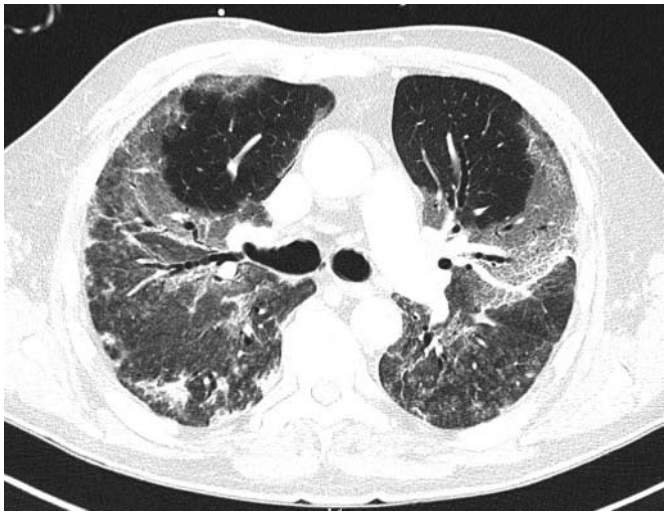

FIGURE 1 Chest computed tomography with several signs of diffuse parenchymal lung injury including extensive ground-glass opacities and micronodular changes.

non-infectious lung injury similar to other immunomodulatory agents (*i.e.* rituximab, golimumab, and tocilizumab). We expect that such events will be observed more frequently, since this agent will continue to be used for the treatment of metastatic melanoma, and in small and nonsmall cell lung cancer in the near future [9, 10].

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The first report of an ipilimumab-induced lung injury presenting as severe acute respiratory distress syndrome http://ow.ly/mxgC6

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