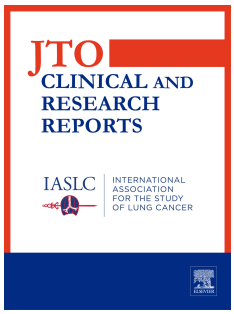

Capillary leak syndrome with pulmonary edema preceded by organizing pneumonia caused by combination therapy with nivolumab and ipilimumab: A Case Report

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Capillary leak syndrome with pulmonary edema preceded by organizing pneumonia caused by combination therapy with nivolumab and ipilimumab: A Case Report

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Keywords
immune checkpoint inhibitor, drug-induced lung injury, organizing pneumonia, capillary leak syndrome, pulmonary edema

Abstract
Treatment with drugs can cause lung disorders. Immune checkpoint inhibitors are often associated with organizing pneumonia. Capillary leak syndrome is a clinical form of drug-induced lung injury, a rare condition characterized by hemoconcentration, hypoalbuminemia, and hypovolemic shock. There have been no reports of multiple lung injury with immune checkpoint inhibitors, and although capillary leak syndrome alone has been reported in the past, there have been no reports of pulmonary edema as a complication. We report a 68-year-old woman who died of respiratory and circulatory failure due to pulmonary edema caused by capillary leak syndrome, preceded by organizing pneumonia induced by combination therapy with nivolumab and ipilimumab for postoperative recurrence of lung adenocarcinoma. Residual inflammation and immune abnormalities from prior immune-related pulmonary adverse events may have increased pulmonary capillary permeability, leading to marked pulmonary edema.

Introduction

When drug-induced lung injury occurs, it is useful to first identify the imaging pattern to predict prognosis, as treatment response varies with clinical forms. It is common for one drug to cause one pulmonary adverse event, and it is rare for a single therapeutic intervention to cause multiple imaging patterns over time. Furthermore, although a pattern of pulmonary edema due to capillary leak syndrome (CLS) is known as a clinical form of drug-induced lung injury,[1] there are no reports of that caused by immune checkpoint inhibitors (ICIs).

Case presentation

We present a 68-year-old woman with no significant medical history. A chest radiograph at physical examination showed a nodule shadow in the right lower lung field. Bronchoscopy revealed mucinous adenocarcinoma. After right lower lobectomy and lymph node dissection, the patient was diagnosed as pT4N0M0 stage IIIA with no driver gene mutation and no expression of programmed death-ligand 1. After three courses of cisplatin and vinorelbine as postoperative adjuvant chemotherapy, she was referred to our department for chemotherapy for postoperative recurrence due to multiple lung metastases on chest computed tomography (CT). Nivolumab

(anti-programmed death 1 [PD-1]) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) combination therapy was started. On the 43rd day of treatment, chest CT showed infiltrative shadows with contraction tendency in both lung lobes, and bronchoalveolar lavage showed increased total cell count with eosinophil predominance (Table 1). She was diagnosed as having an immune-related lung adverse event with organizing pneumonia pattern. As the patient was asymptomatic and the shadows were mild, administration of the drug was ceased. However, on day 48, the consolidations were enlarged (Figure 1A), so prednisolone 60 mg was started, and the dose was then reduced to 60 mg (day 49-55), 40 mg (day 56-62), 30 mg (day 63-69), 20 mg (day 70-77), and 15 mg (day 78-84), as the lung damage was improving. On day 85, prednisolone was tapered to 10 mg; however, dyspnea on exertion appeared on the same day. On day 87, the patient visited our outpatient clinic and required hospitalization with ventilator management because of acute respiratory failure. Chest CT showed extensive consolidation and ground-glass opacity in both lung lobes (Figure 1B), and bronchoscopy revealed bronchial lumen filled with yellow fluid (Figure 1C). Cytology and microbiological results were negative, and she had an increased total cell count with predominance of neutrophils (Table 1). Echocardiography showed no abnormalities in cardiac function, but the patient presented with hypovolemic shock, and despite massive infusion of fluids, no improvement in circulatory status was achieved. We administered antibiotics, cyclophosphamide, and steroid treatment with 1000 mg methylprednisolone per day, but the patient died of worsening respiratory failure due to rapidly decreased permeability of both lung fields (Figure 1D-F). Later, in retrospect, she was considered to have drug-induced CLS because hemoconcentration and hypoalbuminemia were observed on blood tests (Table 2).

Discussion

To the best of our knowledge, this is the first case report of non-cardiogenic pulmonary edema and hypovolemic shock due to CLS, preceded by organizing pneumonia caused by combination therapy with nivolumab and ipilimumab. This case report is very valuable for two reasons: the immune-related adverse events (irAEs) presented multiple imaging patterns in one individual, and the CLS caused by ICIs resulted in pulmonary edema, which has not been reported previously.

In lung cancer immunotherapy, PD-1 inhibitors, such as nivolumab, and CTLA-4 inhibitors, such as ipilimumab, play an important role in tumor control by activating T-CD8 cells and disabling regulatory T cells. However, they can cause the development

of excessive autoimmunity in various organs. Although a variety of imaging findings have been reported for drug-induced lung injury due to ICIs, the most common pattern is consolidation and ground-glass opacity suggestive of organizing pneumonia.[2] CLS is known as a pulmonary edema pattern, but it is an uncommon finding.[1] Several cases of CLS caused by ICIs for lung cancer have been reported;[3] however, none resulted in non-cardiogenic pulmonary edema. There is no knowledge of whether the combination therapy with nivolumab and ipilimumab increases the risk of capillary leak syndrome more than nivolumab alone, but a higher incidence of pulmonary irAEs induced by the combination therapy has been reported.[4] Although the exact pathogenesis of CLS is still unclear, it is thought to be caused by increased vascular permeability due to dysfunction of the vascular endothelium, resulting in leakage of plasma and proteins into the interstitium.[5] In the present case, the patient first developed lung damage in the pattern of organizing pneumonia as an irAE. The second bronchoalveolar lavage showed a change from eosinophil predominance to neutrophil predominance, suggesting a different pathogenesis from the initial irAE, and the clinical course led to the diagnosis of CLS. Although there has been no established evidence in steroid reduction methods for drug-induced lung injury, the rate of reduction may have been relatively fast in this case (from 60 mg to 10 mg in 5 weeks). In addition, it has been reported that T-CD8 cells surrounded the damaged endothelial cells of Systemic CLS.[6] Thus, it is possible that the residual inflammation caused by the relatively rapid tapering of prednisolone for drug-induced organizing pneumonia, combined with immune abnormalities involving T-CD8 cells, increased vascular permeability in the lungs, leading to CLS.

Conclusion

Drug-induced capillary leak syndrome should be considered as a differential disease when unexplained pulmonary edema occurs during treatment with ICIs, even more so in cases of prior irAE pulmonary injury.

Acknowledgement

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Conflict of interest disclosure

None of the authors have any conflicts of interest.

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Figure legends

Figure 1

(A) Chest CT on day 43 showed infiltrative shadows with contraction tendency in both lung lobes.
(B) Chest CT on day 87 showed extensive consolidation and ground-glass opacity in both lung lobes.
(C) The bronchial lumen at the junction of the right upper lobe branch and the middle bronchial trunk was filled with yellow fluid.
(D) Chest X-ray on day 87 (time of admission) revealed consolidation in both lung fields.
(E) Chest X-ray on day 87 (8 hours after admission) revealed rapid deterioration of consolidation in both lung fields.
(F) Chest X-ray on day 87 (16 hours after admission) revealed complete loss of permeability in both lung fields.

Table 1

Findings of bronchoalveolar lavage fluid.

Table 2

Blood pressure and blood test results before and after hospitalization.

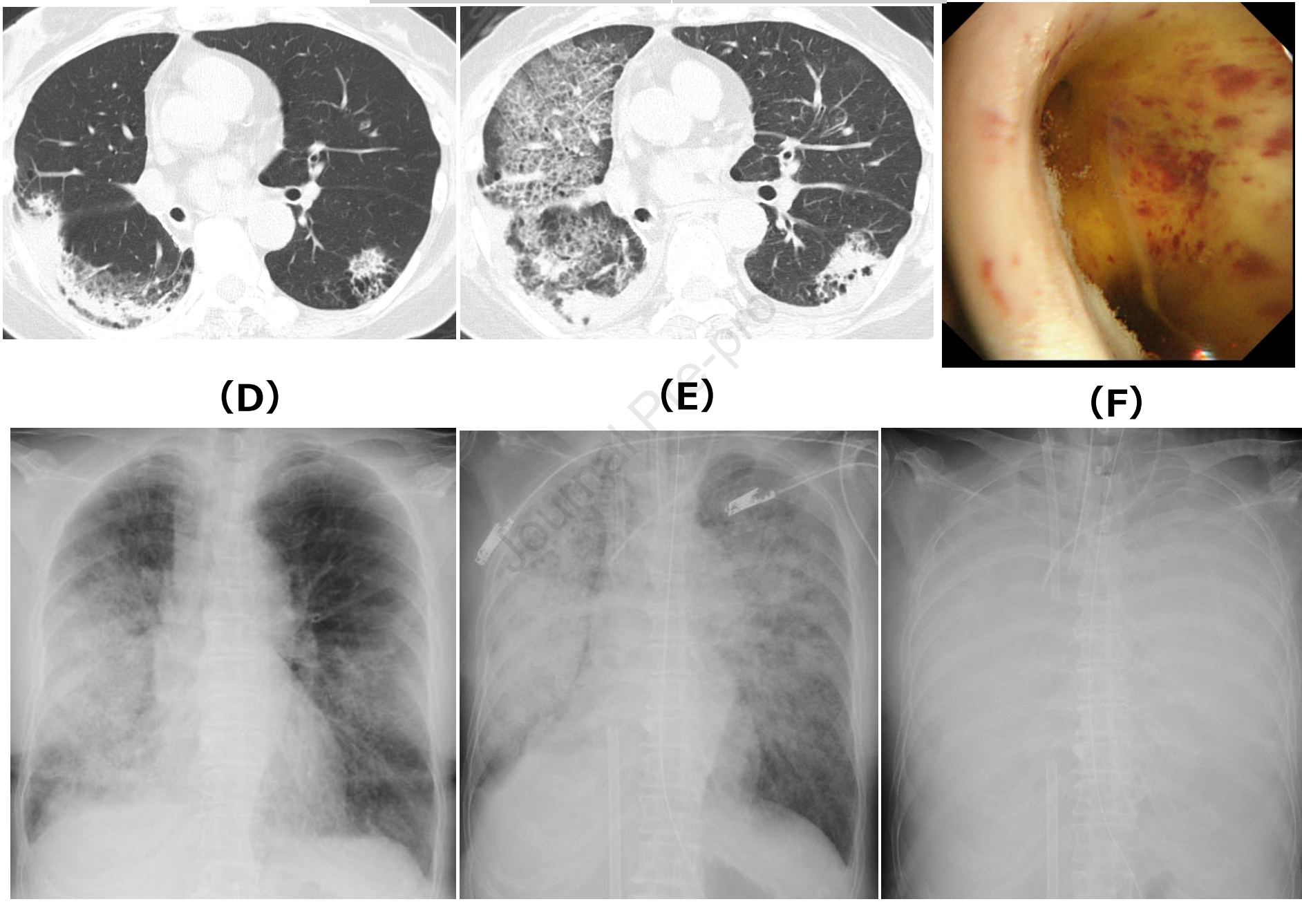
Table 1

	Initial Examination	Second Examination
Bronchus	rt.B^{5}b	rt.B^{3}b
Recover rate	30.0%	47.3%
Total cell count	3.06×10^5/ml	3.30×10^5/ml
Macrophages	79%	26%
Neutrophils	2%	65%
Lymphocytes	11%	6%
Eosinophils	8%	3%
Basophils	0%	0%
CD4/CD8 ratio	0.60	0.21
Culture	Negative	Negative
Cytology	Class I	Class I

Table 2

	Prior to Admission	At the time of admission	The day after admision
Blood Pressure (mmHg)	112/61	82/68	114/86
RBC (×10^5/μl)	3.87	555	399
Hb (g/dl)	10.8	15.6	11.1
Ht (%)	33.7	47.8	33.9
ALB (g/dl)	3.5	3.4	2.2
BUN (mg/dl)	19.7	20.1	22.2
Cre (mg/dl)	0.74	0.87	1.05

Figure 1



CRediT Statement

Hiroaki Tachi: Writing—original draft.

Atsuhito Shibagaki, Shu Teshima, Midori Hanazawa, Shihori Matsukura: Data curation, Visualization.

Kei Shimizu: Conceptualization.

Yusuke Yamamoto: Supervision, Writing—review and editing.