

[ CASE REPORT ]

## Late-onset Pleural and Pericardial Effusion as Immune-related Adverse Events after 94 Cycles of Nivolumab

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### Abstract:

A 67-year-old man with primary lung adenocarcinoma was hospitalized due to massive bilateral pleural effusion and pericardial effusion after 94 cycles of nivolumab therapy. We were unable to identify the cause of these effusions using blood tests, cytology tests, or bacterial culture of pleural effusion and thoracoscopy. Finally, we administered corticosteroids, which immediately improved the fluid accumulation. This case may support the introduction of corticosteroids for late-onset pleural and pericardial effusion during immune checkpoint inhibitor (ICI) treatment. However, the safety of rechallenge of ICIs after the improvement of fluid accumulation is controversial.

**Key words:** lung adenocarcinoma, immune-related adverse events, pleural effusion, pericardial effusion, nivolumab

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### Introduction

Pericardial effusion has been reported as an immune-related adverse event (irAE) in patients receiving immune checkpoint inhibitors (ICIs) (1-15). However, only two cases of pleural effusion in patients on ICIs have been documented, and they were related to pseudoprogression (1). Therefore, pleural effusion has not been previously reported as an irAE.

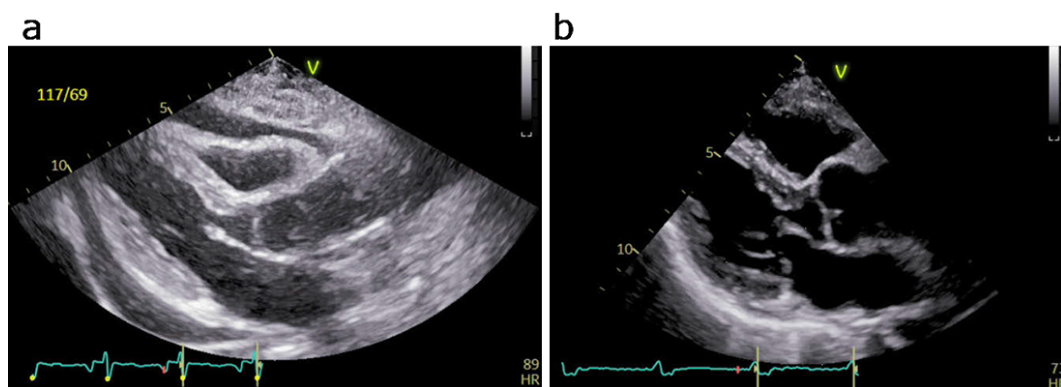
We herein report a patient with late-onset pleural and pericardial effusion on nivolumab who was successfully treated with corticosteroids.

### Case Report

A 67-year-old man with primary adenocarcinoma of the lower lobe of the left lung (cT1bN2M0, cStage IIIA) received treatment with concurrent cisplatin, pemetrexed, and radiation therapy (66 Gy/30 fractions) from February 2014

onward. In May 2016, after two cycles of pemetrexed maintenance therapy and four cycles of docetaxel, brain metastasis was detected on head magnetic resonance imaging. From June 2016, he was treated with 94 cycles of nivolumab as the third-line treatment. He had no irAEs other than early-onset thyroiditis.

In May 2020, he was hospitalized due to massive bilateral pleural effusion and pericardial effusion. He had dyspnea on exertion and non-pitting edema of the lower extremities. On hospitalization day 1, left-sided thoracentesis yielded transudative pleural fluid with adenosine deaminase and hyaluronic acid levels in the normal range along with an elevated lymphocyte count. Bacterial and mycobacterial cultures were negative. The cytology test result was class II. Blood tests showed no hypoalbuminemia or renal dysfunction and were negative for anti-nuclear antibody, anti-cyclic citrullinated peptide antibody, anti-Sjögren's-syndrome-related antigen A autoantibody, anti-aminoacyl-transfer ribonucleic acid synthetase antibody, serine proteinase 3-anti-neutrophil cytoplasmic antibody, and myeloperoxidase-anti-



**Figure 1.** Echocardiograph showing pericardial effusion (a), which almost disappeared after the introduction of corticosteroid (b).

neutrophil cytoplasmic antibody. Echocardiography detected pericardial effusion but did not detect severe cardiac dysfunction (Fig. 1a). Contrast-enhanced computed tomography (CT) showed no pericardial or pleural nodules.

We initially treated the patient with diuretics. However, this resulted in volume depletion, with poor response to the amount of pleural and pericardial effusion (Fig. 2a). On day 10 of hospitalization, we performed left-sided thoracoscopy with chest tube insertion and found no pericardial nodules and no abnormalities in the parietal or pulmonary pleura (Fig. 3). Bacterial and mycobacterial cultures were also negative. The cytology test result was class II. The patient presented with re-expansion pulmonary edema due to the removal of left-side pleural effusion that day. We were unable to exclude the possibility of nivolumab-induced pneumonitis with respiratory failure at that time and started methylprednisolone (mPSL) at 500 mg/day for 3 days, followed by mPSL at 80 mg/day for 3 days and oral prednisolone therapy (Fig. 2). One week after thoracoscopy, the pleural fluid became exudative with reduced lymphocytes.

The fluid retention showed an immediate response. On day 9 of steroid therapy, echocardiography revealed a significant reduction in the pericardial effusion (Fig. 1b). CT on day 10 showed improvement of the right-sided pleural effusion as well as that of the left side, which was drained by the chest tube (Fig. 2b). We removed the chest tube when it was finally draining 100 mL/day.

On day 32 of hospitalization, CT showed a small amount of pericardial effusion and almost no pleural effusion. We discharged the patient on day 33. We have continued to treat the patient with tapered corticosteroid therapy and have not re-initiated nivolumab treatment. His pericardial and pleural effusion have remained well-controlled (Fig. 2c, d) within a stable disease course of lung cancer.

## Discussion

A previous report described two lung cancer cases with pleural effusion during nivolumab treatment (1). Both patients were initially diagnosed with malignant pleural effu-

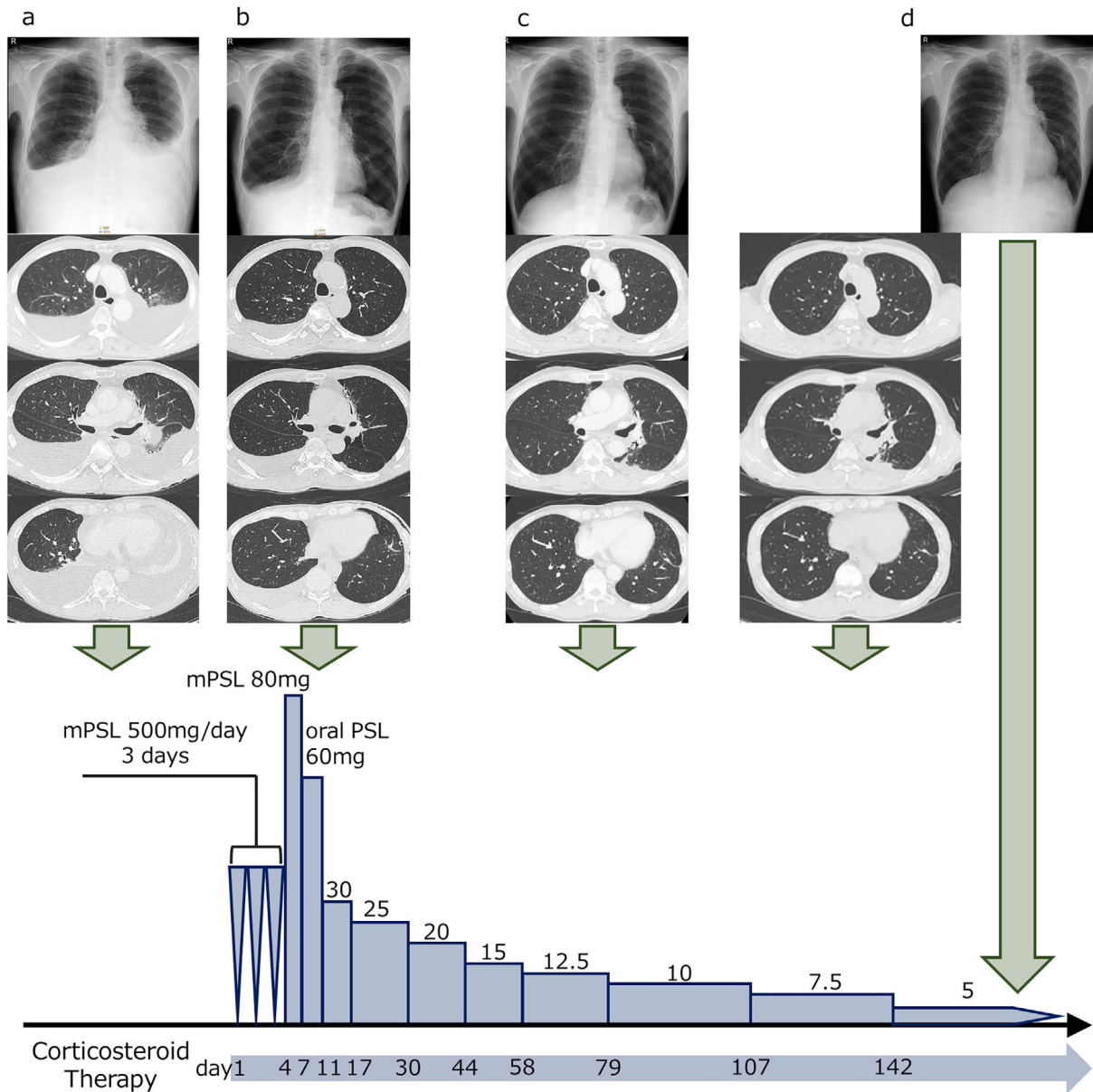
sion that increased within a few weeks of nivolumab treatment initiation. They finally considered the effusion to be pseudoprogression because of the clinical response and lack of evidence of progression. However, we have found no case reports of pleural effusion as an irAE.

In the present case study, the patient was not initially diagnosed with pleural dissemination or malignant pleural effusion. However, after evidence of massive bilateral pleural effusion, we conducted a cytology test twice but found no evidence of malignancy. Similarly, we did not detect malignant nodules on radiological imaging or thoracoscopy. We also ruled out hypoalbuminemia, cardiac dysfunction, and collagen diseases, which may cause pleural effusion. These findings and the good response to corticotherapy indicated that the effusion was an irAE. Temporary pulmonary congestion may have caused the first analysis to show transudative pleural fluid. The second analysis supported our diagnosis and the effectiveness of corticosteroids.

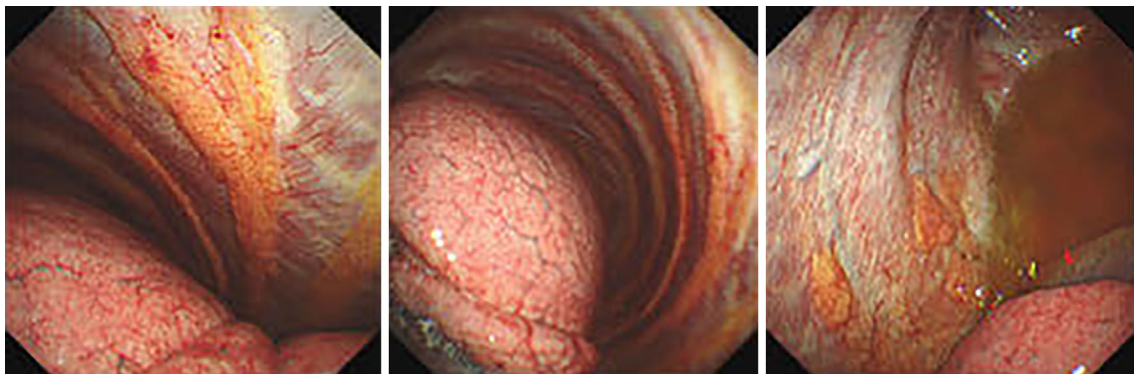
Twenty-one cases of pericardial effusion while on ICIs have been reported (1-15). Five cases were related to pseudoprogression (1-3). The other 16 cases were considered irAEs (4-15). The latest onset of effusions as described in previous reports was after 35 cycles of ICI (4). Two patients with pericardial effusion as irAEs died of cardiac tamponade (4, 15). The other 14 patients were treated with corticosteroids (5 patients), pericardiocentesis/surgical pericardial window (4 patients), or both (5 patients) (4-15).

Although we were unable to perform cardiocentesis because of the massive pleural effusion, the pericardial effusion responded to corticosteroid therapy and was also considered an irAE. Therefore, to our knowledge, this is the first case of ICI-induced serositis with a significant response to corticosteroids and has the latest onset of pericardial effusion among all cases reported.

The safety of ICI rechallenge after pericardial effusion is controversial. Shaheen et al. reported a patient who was rechallenged with the same ICI during low-dose administration of a corticosteroid with no recurrence after improvement of pericardial effusion (6). Altan et al. also reported an ICI-rechallenged patient after recovery with a pericardial



**Figure 2.** Time course of corticosteroid therapy, chest radiography, and CT. Massive bilateral pleural effusion (a: before introduction of corticosteroid) was reduced with a significant response (b: 9 days later, c: 2 months later). We tapered corticosteroid treatment and found no recurrence of pleural effusion (d: 6 months later). CT: computed tomography



**Figure 3.** Left-sided thoracoscopy showed no abnormal findings.

window who had no adverse events during rechallenge therapy; however, the patient experienced progressive disease soon after rechallenging (15). In other reports, the administration of ICIs that caused pericardial effusion was stopped. In our case, we stopped nivolumab administration and tapered corticosteroids, as the pulmonary cancer did not progress. The patient has not experienced recurrent adverse events of fluid accumulation since his discharge.

### Conclusions

We treated a case of ICI-induced serositis with corticosteroids. Our findings may support the introduction of corticosteroids for late-onset pleural and pericardial effusion during ICI treatment.

The authors state that they have no Conflict of Interest (COI).

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