CASE REPORT

Progressive Pleural Effusion as an Immune-Related Adverse Event in NSCLC: A Case Report

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have improved the clinical outcome of NSCLC. However, immune-related adverse events (irAEs) such as pneumonitis, thyroiditis, and colitis have been reported with the increasing use of ICIs. The diagnosis of irAEs relies on exclusion. With proper management, most patients may still benefit from ICI treatment. Pleural effusion is a rare presentation of an irAE. Here, we report a patient who experienced progressive bilateral pleural effusions during the first-line treatment of cisplatin, pemetrexed, and pembrolizumab. Serial study and surgical pleural biopsy found the possible cause of irAE. His pleural effusion subsided after discontinuing therapy. IrAE may present as pleural effusion and physicians should be alert to unknown causes of pleural effusion in patients under ICI treatment.

Keywords: Non–small cell lung cancer; Immunotherapy; Immune-related adverse event; Pleural effusion; Case report

Introduction

The clinical presentation of immune-related adverse events (irAEs) is varied and heterogeneous. Pleural effusion as irAE has been reported in limited publications. We present a detailed evaluation with pathologic findings of probable immunotherapy-related pleural effusions. The effusion resolves after withholding immunotherapy.

Case Presentation

A 57-year-old man presented with progressive dyspnea and bilateral pleural effusions. He was diagnosed with right upper lung adenocarcinoma of stage T1N3M1c (American Joint Committee on Cancer, eighth edition) 9 months before this presentation. He had no driver mutations in *EGFR, ALK, ROS1*, and *NTRK* among others. Immunohistochemistry (IHC) analysis of the tumor revealed a programmed death-ligand 1 (PDL-1) tumor proportion score of less than 1% (PDL-1 22C3 IHC assay). He received four cycles of cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), pembrolizumab (200 mg) and then eight cycles of maintenance therapy with pemetrexed plus pembrolizumab. Follow-up chest computed tomography revealed persistent regression of the primary tumor. However, he had progressive bilateral pleural effusions since the eighth cycle of the maintenance regimen (Fig. 1) and required serial thoracentesis. Analysis of the bilateral pleural effusions revealed elevated lactate dehydrogenase (222 U/liter), total protein (4100 mg/dL), and a predominant

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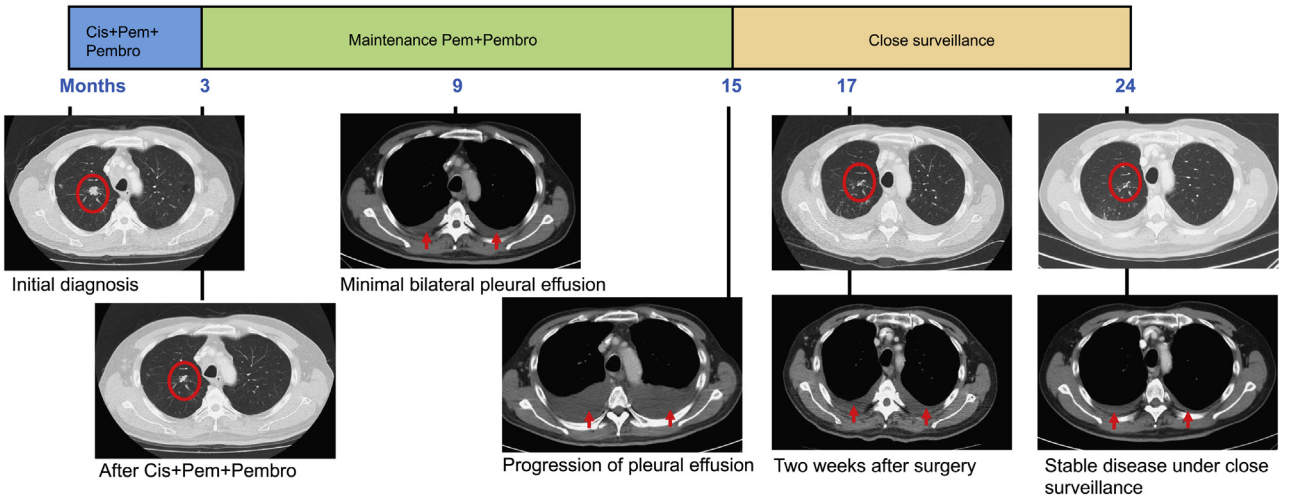

Figure 1. The clinical course of the patient. The primary tumor (circle) and pleural effusion (arrow) are illustrated. Cis+Pem+Pembro, cisplatin plus pemetrexed and pembrolizumab; Pem+Pembro, pemetrexed plus pembrolizumab.

lymphocyte cell count (lymphocytes: 90%; neutrophils: 10%). A serial cytologic evaluation revealed negative findings, and infections of bacterial and fungal etiologies were excluded from the culture. Serum autoimmune markers including antinuclear antibody, double-stranded DNA, rheumatoid factor, and immunoglobulin G4 were within normal range. He underwent ultrasound-guided needle pleural biopsy on the left side, which revealed signs of chronic inflammation. Because of the unknown cause of bilateral pleural effusions, the patient underwent a surgical pleural biopsy on the right side, which revealed fibrotic thickening and chronic

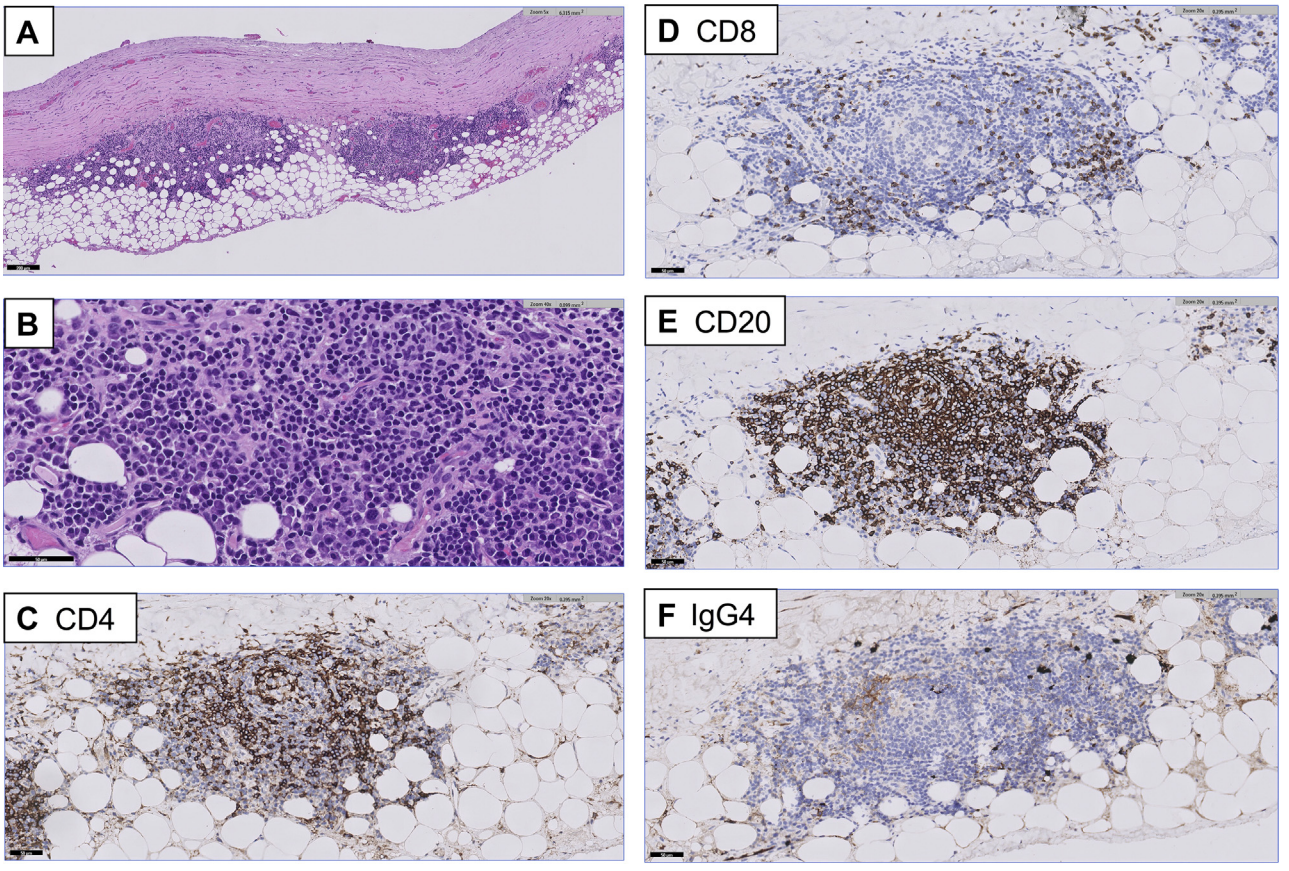

Figure 2. Pathologic findings of the pleura. (*A*-*B*) Fibrotic thickening and infiltration of chronic inflammatory cells with many lymphoid aggregates. (*C*-*E*) CD4, CD8, and CD20 immunohistochemical stains illustrated mixed B-cell and T-cell infiltration. (*F*) Scantly positive for IgG4 staining. IgG, immunoglobulin G.

inflammatory cell infiltration with many lymphoid aggregates (Fig. 2*A* and *B*). IHC staining revealed mixed B- and T-cell populations in the lymphoid aggregates (Fig. 2*C–E*). Only scant immunoglobulin G4–positive plasma cells were observed (Fig. 2*F*). These findings were consistent with chronic pleuritis. Because his tumor remained under regression, an irAE was suspected. We withheld his anticancer treatment pemetrexed and pembrolizumab while following close surveillance. His bilateral pleural effusions improved gradually, and the cancerous lesion remained stable for 10 months (Fig. 1).

Discussion

The combination of ICIs and chemotherapy has been proven as a first-line treatment for patients with NSCLC without driver mutations; however, different presentations of irAEs, including pneumonitis and dermatitis, have been reported.[1] Pericardial effusion and life-threatening cardiac tamponade are rare but have been reported in several cases.[2,3] In this case, we present pleural effusion and pleuritis as probable irAEs after long-term pembrolizumab treatment. The diagnosis of irAEs is difficult and mostly depends on exclusion. We performed several serology and microbiology tests and serial cytology evaluations to determine possible etiology. Pemetrexed has been reported to be associated with fluid retention in a few cases.[4] All these cases were accompanied by peripheral or facial edema, which did not occur in our case. The pemetrexed-related adverse effect was considered unlikely in our case owing to the clinical presentation. The pathologic evaluation of the pleural biopsy revealed many characteristic lymphoid aggregates, which were nonspecific but indicative of an irAE. By discontinuing therapy and under close surveillance, his tumor remained stable, and effusion decreased gradually. Steroids were not administered given that the pleural effusion did not reaccumulate after discontinuing therapy. Therefore, irAE with pleuritis and pleural effusion induced by pembrolizumab was a favorable diagnosis. Pleural effusion as an irAE has been reported but rarely in ICI treatment.[2,5] Yanagihara et al.[6] reported the case of a patient with tumor-infiltrating lymphocyte-mediated pleuritis after nivolumab treatment in renal cell carcinoma. They used flow cytometry to evaluate the patient's pleural effusion and discussed the possible mechanism.[6] We further reported a thorough pathologic evaluation and confirmation by the clinical course. Physicians can be made aware of the unknown causes of pleural effusion in patients under ICIs and provide appropriate management.

Conclusion

In conclusion, irAE is among the possible causes of pleural effusion in patients under ICIs treatment.

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