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【 CASE REPORT 】

Severe Post-COVID-19 Organizing Pneumonia during Cancer Immunochemotherapy

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Abstract:
A 44-year-old man developed coronavirus disease 2019 (COVID-19) pneumonia during immunochemotherapy consisting of carboplatin, paclitaxel, and pembrolizumab for non-small cell lung cancer. Low-grade fever, followed by mild hypoxemia, and febrile neutropenia, were observed, and granulocyte colony-stimulating factor (G-CSF) was administered until the recovery of neutropenia, when he developed a high fever, severe hypoxemia, and hypotension accompanied by consolidation in the bilateral lungs. His conditions promptly improved after treatment including hydrocortisone and the primary and metastatic tumors remained regressed for 10 months without further treatment. Post-COVID-19 organizing pneumonia during cancer immunochemotherapy can be aggravated by immune-checkpoint inhibitors and G-CSF.

Key words: febrile neutropenia, granulocyte colony-stimulating factor, immune-checkpoint inhibitor, severe acute respiratory syndrome coronavirus 2, tumor regression

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Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide (1). The thoracic cancers international COVID-19 collaboration (THERAVOLT) registry demonstrated a high mortality rate (33%) in patients with thoracic malignancies, mostly non-small cell lung cancer (NSCLC), who developed COVID-19 (2). Impaired antiviral immunity and vascular endothelial damage, and a hypercoagulable state, especially during systemic chemotherapy, makes lung cancer patients more vulnerable to COVID-19 (3). In addition, immune checkpoint inhibitors (ICIs) and other drugs for immunotherapy and granulocyte colony-stimulating factor (G-CSF) for the treatment of chemotherapy-related febrile neutropenia may increase the risk of developing severe COVID-19 due to excessive activation of the immune system, further exacerbating the "cytokine storm" evoked by SARS-CoV-2 infection (4).

We herein present a case of severe post-COVID-19 organizing pneumonia during immunochemotherapy for lung cancer. The patient, who had presented with mild symptoms of COVID-19 pneumonia and chemotherapy-related febrile neutropenia, was treated with antibiotics and G-CSF. He then developed delayed-onset respiratory and circulatory failure with systemic inflammation after recovery from neutropenia, possibly due to severe post-COVID-19 organizing pneumonia.

Case Report

A 44-year-old man with NSCLC developed fever during hospitalization for immunochemotherapy. One year before admission, a right lung tumor was discovered when he visited a clinic due to persistent cough. Because the patient declined to undergo bronchoscopy for a histological examina-

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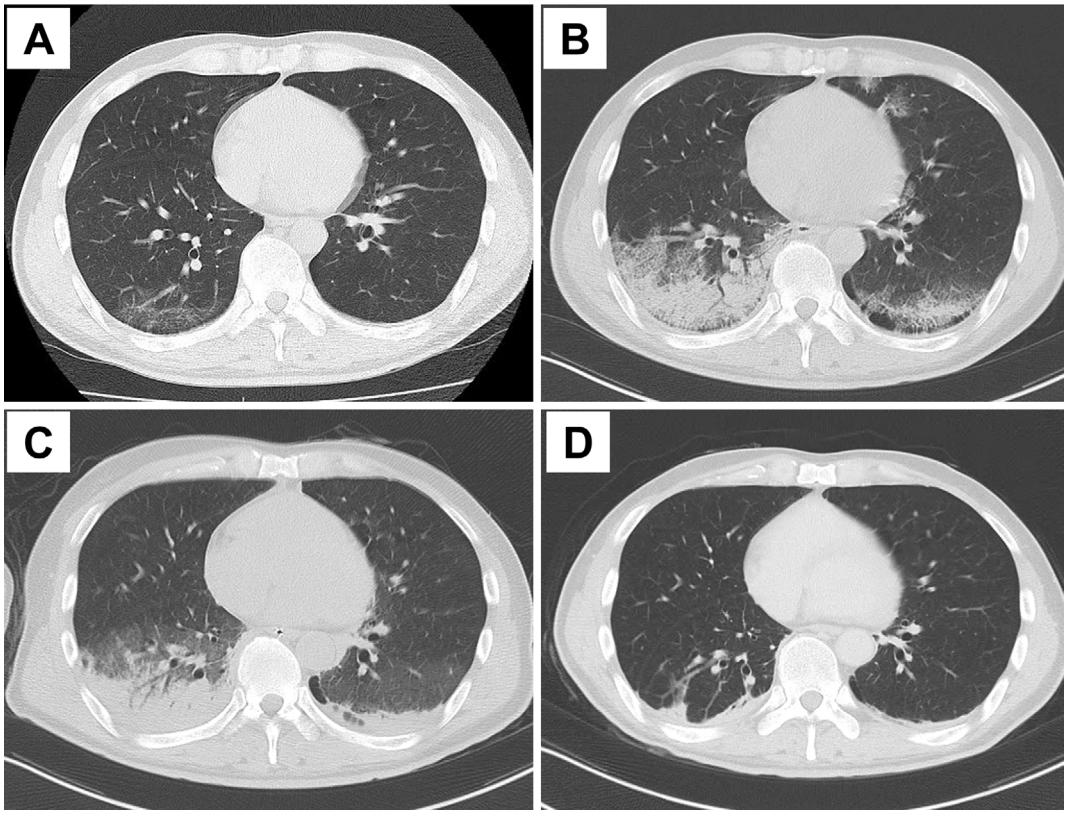

Figure 1. Thoracic computed tomography images after hospitalization. Ground-glass opacities were observed in the lower lobe of the right lung on day 4 (A), which changed into consolidation in the bilateral lungs on day 9 (B). On day 19, when the patient experienced respiratory and circulatory failure, the consolidation in the posterior basal regions increased in density (C). Consolidation in the bilateral lungs mostly disappeared on day 34 (D).

tion or chemotherapy, radiation therapy alone was performed based on the clinical diagnosis of lung cancer (cT4N2M0, stage IIIB), with 60 Gy delivered to the primary tumor and adjacent mediastinal lymph nodes and 50 Gy delivered to the right hilum.

Eight months later, regrowth of the primary tumor in the right lung occurred, accompanied by intrapulmonary metastasis. Transbronchial biopsy with bronchoscopy confirmed the diagnosis of NSCLC without mutations in the epidermal growth factor receptor or anaplastic lymphoma kinase genes. Although the tumor proportion score of programmed cell death-ligand 1 staining was >50%, immunotherapy was not selected to avoid recall pneumonitis. Three courses of chemotherapy consisting of carboplatin (area under the curve, 5) and paclitaxel (200 mg/m^3) every three weeks was administered, with modest adverse effects, but it had little effect on the primary or metastatic lesions. Therefore, at one month before admission, pembrolizumab (200 mg/body) - an ICI - was added to the fourth course of chemotherapy.

On admission, his body temperature was 36.8°C, without any new lesions on chest radiography, and he underwent the fifth course of immunochemotherapy as scheduled. The next day, his body temperature rose to 38°C, and thoracic computed tomography (CT) revealed ground-glass opacities in the right lung (Fig. 1A). Polymerase chain reaction was positive for SARS-CoV-2 ribonucleic acid (RNA). There was no hypoxemia or clinical symptoms other than low-grade fever until day 9, when he developed high fever and mild hypoxemia (percutaneous oxygen saturation, 93%), neutropenia (91/mm^3), thrombocytopenia (49,000/mm^3), with the worsening of the opacities in the bilateral lungs (Fig. 1B). Although his low-grade fever persisted, his condition stabilized and his serum level of C-reactive protein (CRP) decreased from 20.1 to 3.0 mg/dL after treatment with supplemental oxygen (2 L/min), inhaled ciclesonide and favipiravir as antiviral agents, and granulocyte colony-stimulating factor (G-CSF) and cefepime for febrile neutropenia.

On day 19, his condition suddenly deteriorated, with high fever (40°C), tachypnea (30/min), tachycardia (144/min), hypotension (systolic blood pressure of 80-90 mmHg), and severe hypoxemia. Laboratory investigations revealed neutrophilia (18,000/mm^3), increased serum levels of CRP (10.2 mg/dL), D-dimer (85.8 ng/mL), and liver and renal dysfunction (Fig. 2), although blood culture results were negative. Thoracic CT demonstrated consolidation in the right upper lobe and bilateral lower lobes of the lungs (Fig. 1C). He was placed on intermittent mandatory ventilation. Meropenem, hydrocortisone (200 mg/day for 4 days), noradrenaline, and unfractionated heparin followed by edoxaban tosi-

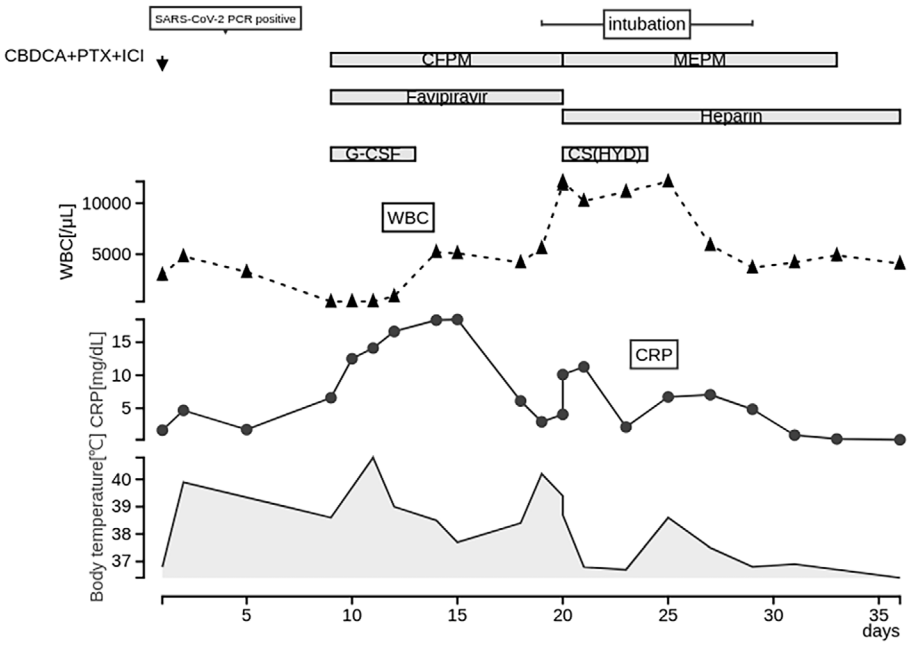

Figure 2. **Clinical course after hospitalization. The top panel shows the peripheral white blood cell (WBC) count (dotted line), the middle panel shows the serum C-reactive protein (CRP) level (solid line), and the bottom panel shows changes in body temperature. CBDCA: carboplatin, CFPM: cefepime, ICI: immune checkpoint inhibitor, G-CSF: granulocyte colony-stimulating factor, CS (HYD): corticosteroid (hydrocortisone), MEPM: meropenem, PTX: paclitaxel**

late hydrate were administered. The treatment responses were prompt; fever and consolidation in the lungs disappeared within 24 hours and the ratio of arterial oxygen partial pressure to fractional inspired oxygen improved from 82 to 346 within 4 days, and the administration of noradrenaline was stopped. The patient was successfully weaned off the ventilator on day 29 (Fig. 2). Contrast-enhanced CT on day 34 revealed no evidence of deep vein thrombosis. The patient was discharged on day 52.

Although immunochemotherapy for lung cancer was discontinued, the primary and metastatic tumors remain regressed, with the total tumor diameter decreasing from 23.5 cm on admission to 8.8 and 8.4 cm at 6 and 10 months, respectively. His serum cytokeratin 19 fragment 21-1 level also decreased from 33.8 ng/mL to 1.0 ng/mL.

Discussion

We report a case of COVID-19 pneumonia in a patient under immunochemotherapy for lung cancer and G-CSF treatment for febrile neutropenia, who developed progressive pulmonary consolidation followed by late-onset respiratory and circulatory failure with systemic inflammation. The patient recovered with unusually prompt responses to a moderate dose of corticosteroids.

COVID-19 is often associated with delayed deterioration of the respiratory condition at approximately 10 days after the onset of pneumonia (1). In some cases, this progressively develops into respiratory failure due to diffuse alveolar damage. The present case did not fit this temporal course of COVID-19, as the patient's respiratory condition was stable until day 19, when it abruptly worsened accompanied by high fever and circulatory failure. We considered the possibility of pulmonary thromboembolism because of the thrombophilic condition due to COVID-19 and underlying malignancy, and markedly elevated serum D-dimer levels (5). However, high fever could not be explained with the diagnosis of pulmonary thromboembolism, and we could not find any evidence of deep vein thrombosis after his recovery. Other possible causes that we considered were infectious diseases such as sepsis and COVID-19-associated pulmonary aspergillosis, radiation pneumonitis, or pseudoprogression of primary tumors. However, an unexpectedly prompt response to treatment with hydrocortisone and the favorable prognosis implicates the role of systemic inflammation due to hyperactivated immune systems rather than infectious diseases. Recall pneumonitis after ICI treatment or pseudoprogression of the primary tumors was unlikely because the opacity did not appear at the primary site of the tumor, which had been targeted with radiation therapy.

There have been increasing reports on cases of post-COVID-19 organizing pneumonia that progresses or reappears after the clearance of SARS-CoV-2 and which responds well to corticosteroid treatment (6-10). Although bronchoalveolar lavage or lung biopsy could not be performed due to the severe condition of the patient, the progressive pulmonary consolidation on CT and good response to corticosteroids in the present case are compatible with the pathology. However, systemic manifestations, such as high fever and acute-onset respiratory and circulatory failure are

rare in the previous reports on post-COVID-19 organizing pneumonia. Thus, we speculated that ICI and/or G-CSF administered for cancer treatment may have modified the course and manifestation of post-COVID-19 organizing pneumonia in the present case.

ICIs activate T cells and may suppress viral infection (11, 12); however, the incidence of early death is high in patients who developed COVID-19 immediately after ICI treatment (13). It has been demonstrated that approximately 80% of SARS-CoV-2-positive patients treated with ICIs require hospitalization for pneumonia (14). With regard to G-CSF treatment, its impact on COVID-19 remains controversial. A randomized clinical trial demonstrated that, in patients with COVID-19 and lymphopenia, recombinant G-CSF treatment reduced the number of patients who developed critical illness or died (15). On the other hand, a report documented three patients with underlying malignant diseases and COVID-19, who exhibited an acute worsening of hypoxemia and hypotension within 72 hours after the administration of G-CSF (16). Another patient with nasopharyngeal cancer and COVID-19 developed progressive respiratory failure 5 days after the administration of G-CSF (17). Two retrospective, observational studies of cancer patients with neutropenia and COVID-19 demonstrated that the administration of G-CSF was positively associated with hospitalization, respiratory failure, and death (18, 19). These studies demonstrated that a longer duration of treatment and higher response to G-CSF was associated with poor outcomes (18, 19). G-CSF mobilizes not only neutrophils, but also various subsets of lymphocytes (20), which may lead to the deterioration of post-COVID-19 organizing pneumonia.

Interestingly, the patient has maintained a good partial response, despite the discontinuation of lung cancer treatment since his recovery from COVID-19. Spontaneous tumor regression has been reported to occur in 1 per 14,000 cancer cases, and has been linked to tuberculosis, influenza virus infection, and other infectious diseases (21, 22). Although the SARS-CoV-2 infection was aggravated by ICI treatment, the infection may have enhanced the effects of ICI on tumor regression.

Conclusion

Patients undergoing immunochemotherapy for carcinoma are at high risk for severe COVID-19 due to multiple factors, including hypercoagulability and chemotherapy-induced immunosuppression. Physicians should also be aware that ICI and/or G-CSF can cause overactivation of the immune system and may worsen COVID-19 and post-COVID-19 organizing pneumonia.

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

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