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CASE REPORT

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A case of cytokine release syndrome accompanied with COVID-19 infection during treatment with immune checkpoint inhibitors for non-small cell lung cancer

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Abstract

Cytokine release syndrome (CRS) is a systemic inflammatory disease caused by a variety of factors, including infections and certain drugs. A 70-year-old man who was diagnosed with a postoperative recurrence of lung adenocarcinoma received nivolumab, ipilimumab, pemetrexed and carboplatin every 3 weeks for two cycles followed by nivolumab and ipilimumab, which resulted in a partial response. Four days after the dose of nivolumab, the patient returned with diarrhea and fever. The patient was diagnosed with COVID-19 infection accompanied by severe colitis. Although intensive care was performed, the patient suddenly went into cardiopulmonary arrest. Examination revealed an abnormally high interleukin-6 level, suggesting CRS. This is the first report of a patient with CRS accompanied with COVID-19 infection during treatment with ICIs. Cytokine release syndrome (CRS) is a systemic inflammatory disease caused by a variety of factors, including infections and certain drugs. Here, we report a case of non-small cell lung cancer with CRS caused by COVID-19 infection during treatment with nivolumab and ipilimumab. Fever is a common event in cancer patients, especially in COVID-19-infected patients, but when fever develops during cancer immunotherapy, CRS should always be kept in mind.

KEYWORDS

cancer immunotherapy, cytokine release syndrome, immune-related adverse events, SARS-CoV-2

INTRODUCTION

Cytokine release syndrome (CRS) is a systemic inflammatory disease characterized by a massive release of cytokines, and triggered by a variety of factors such as infections and certain drugs. The clinical picture of CRS is a systemic inflammatory disease that begins with fever, and severe cases manifests hypotension, hypoxia, organ dysfunction requiring urgent treatment. Interleukin-6 (IL-6) is known to play an important role in the pathogenesis of CRS, and although immunosuppressive drugs such as corticosteroids have been used, therapies that suppress IL-6 are now being applied clinically.[1–5]

COVID-19 is now a global pandemic. COVID-19 patients are known to have elevated IL-6 levels. Up to 20% of COVID-19 patients develop acute respiratory distress syndrome, suggesting CRS.[1,2,6]

Immune checkpoint inhibitors (ICIs) are the latest breakthrough in the treatment of patients with advanced tumors. Immune-related adverse events (irAEs) can develop with ICIs, and ICI-related CRS has been recognized as an irAE.[7,8] Herein, we report a case of CRS acompanied with COVID-19 infection during treatment with ICIs.

CASE REPORT

A 70-year-old Japanese man visited our hospital. He had undergone thoracoscopic surgery 2 years prior to admission

and had been diagnosed with left upper lobe lung adenocarcinoma pT3N0M0, stage IIB. Five months prior to admission, he had received the second dose of COVID-19 vaccine with no adverse reactions. Around the same time, the lung adenocarcinoma recurred in the right upper lobe with a PD-L1 expression level of 30%. The tumor was negative for driver genes, and the patient was started on nivolumab plus ipilimumab combined with two cycles of carboplatin and pemetrexed. After two and four cycles of therapy, chest contrast-enhanced computed tomography (CT) showed that the tumor had decreased in size (Figure 1). Three months prior to admission, the patient developed grade 2 hypophysitis (isolated adrenocorticotropic hormone deficiency), an irAE. Immunotherapy was held for 1 month and the patient was treated with corticosteroids. One and a half months prior to admission, immunotherapy was resumed. After confirmation of tumor regression and no evidence of pneumonitis and colitis on the contrast-enhanced CT, the patient was administered nivolumab (Figure 1). Three days after administration, the patient had diarrhea more than 10 times a day. The next day, the patient presented with diarrhea and fever. Although the patient had no respiratory symptoms, he underwent polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 and was diagnosed with COVID-19. CT showed no evidence of pneumonia, but there was bowel edema (Figure 1). The COVID-19 infection was considered mild because the patient had no respiratory symptoms and no pneumonitis on CT. The patient was diagnosed with COVID-19 infection accompanied by severe colitis and admitted to the intensive

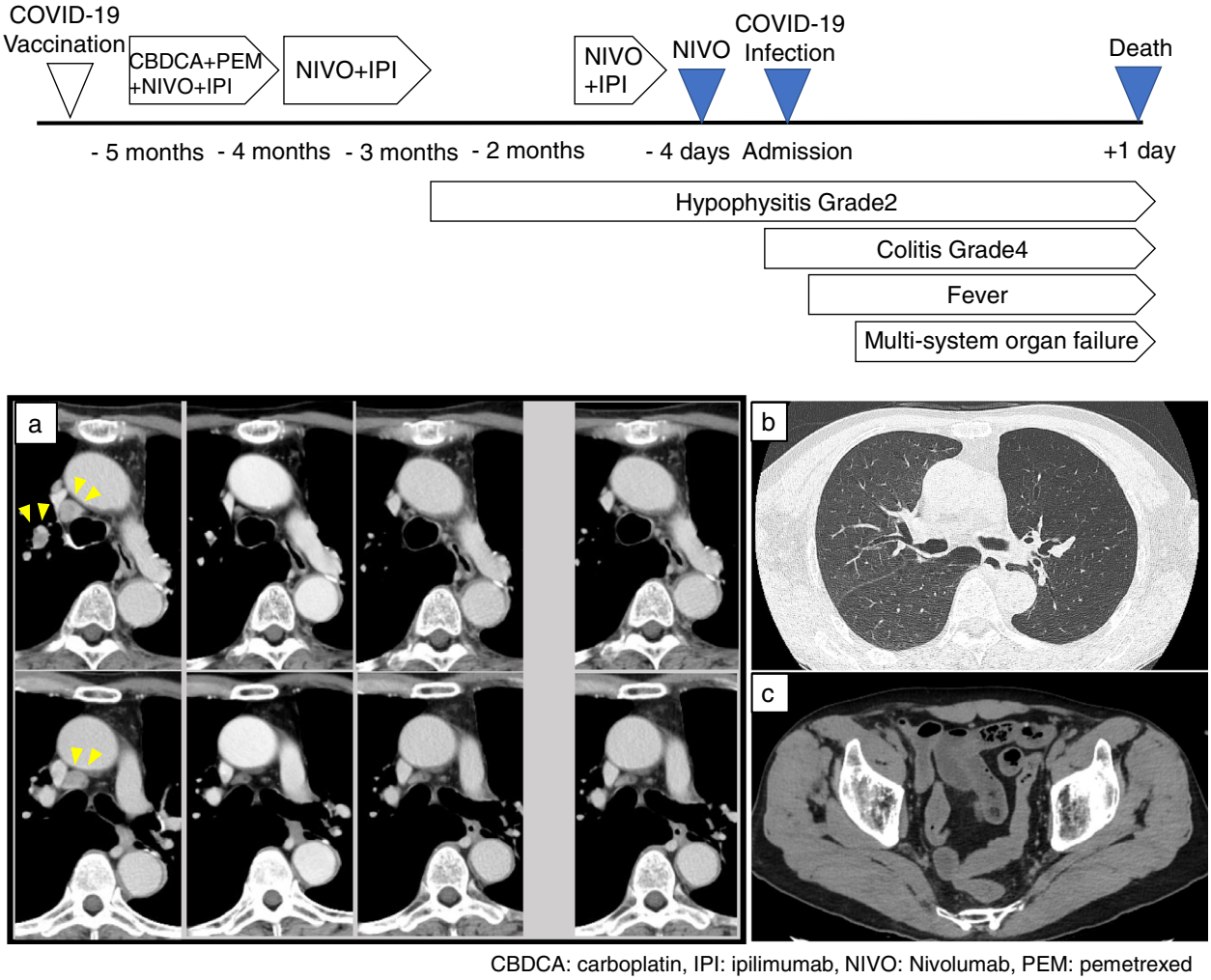

FIGURE 1 Clinical course of lung adenocarcinoma. Lung adenocarcinoma recurred 5 months prior to admission, and nivolumab plus ipilimumab was started combined with two cycles of carboplatin and pemetrexed. After two and four cycles of therapy, contrast-enhanced computed tomography (CT) showed that the tumor had decreased in size. Three months prior to admission, the patient developed grade 2 hypophysitis (isolated adrenocorticotropic hormone deficiency) as an immune-related adverse event. Immunotherapy was stopped, then restarted a month and a half later. CT showed no tumor regrowth just 4 days prior to admission. The final dose of nivolumab was administered on this day. Four days after resuming treatment with nivolumab, the patient returned with diarrhea and high fever. The patient was diagnosed with COVID-19 infection and suggested cytokine release syndrome. Findings of thin-section computed tomography. (a) Transition of CT findings over time. The lung adenocarcinoma shrank after the start of treatment and did not regrow. (b) Chest CT on admission. There was no evidence of pneumonia or acute respiratory distress syndrome which would indicate COVID-19 infection in the lung fields. (c) Abdominal CT on admission. Bowel edema suspicious of colitis was present

TABLE 1 Results of laboratory tests

	Four days before admission	Upon admission
WBC (/μl)	6.0×10^3	9.1×10^3
Neutrophils (%)	57.0	83.3
Lymphocytes (%)	25.5	9.9
Monocytes (%)	9.6	6.6
Basophils (%)	0.7	0.2
Eosinophils (%)	7.2	0.0
RBC (/μl)	4.21×10^6	4.76×10^6
Hemoglobin (g/dl)	12.4	13.9
Platelets (/μl)	2.0×10^5	1.3×10^5
AST (U/l)	22	904
ALT (U/l)	11	179
LDH (U/l)	188	1616
γ-GTP(U/l)	31	35
Total protein (g/dl)	7.4	7.2
Albumin (g/dl)	4.1	3.8
Total bilirubin (mg/dl)	0.8	0.7
BUN (mg/dl)	24	52
Creatinine (mg/dl)	1.22	4.73
CK (U/l)	76	57 864
CK-MB (U/l)	-	101
Sodium (mmol/l)	141	134
Potassium (mmol/l)	4.8	5.7
Chloride (mmol/l)	105	101
D-dimer (μg/ml)	-	46.4
Procalcitonin (ng/ml)	-	29.05
Lactate (mmol/l)	-	4.97
Glucose (mg/dl)	103	87
CRP (mg/dl)	0.25	10.29

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; γ-GTP, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; RBC, red blood cells; WBC, white blood cells.

care unit. On admission, his body temperature was 39°C, blood pressure was 120/40 mmHg, and pulse was 110/min. He did not require treatment with oxygen or a vasopressor. Although intensive care was performed, including hydration, high dose corticosteroids, and antibiotics, the patient suddenly went into cardiopulmonary arrest 3 h after admission. Remdesivir was planned but had not yet been administered. A total of 27 min of cardiopulmonary resuscitation and one electrical defibrillation were performed, and the patient was returned to spontaneous circulation. His laboratory tests submitted before the sudden change showed increased C-reactive protein and suggested multisystem organ failure (Table 1). An additional examination revealed an abnormally high IL-6 level of 69 586 pg/ml. Accordingly, we diagnosed CRS due to systemic symptoms with inflammation and elevated IL-6. Despite all efforts, he died the day after admission. Blood cultures were later confirmed negative.

DISCUSSION

This is the first report of a patient with CRS acompanied with COVID-19 infection during treatment with ICIs. It is not clear whether COVID-19 infection or ICIs were the cause of CRS, but it was determined that CRS was triggered by COVID-19 infection because it coincided with the timing of COVID-19 infection. IrAEs have been suggested to reflect the favorable therapeutic efficacy of ICI treatment, but can sometimes be life-threatening.[7,9–11] In addition, irAEs can be triggered by infections.[12,13] In the present case, the patient developed an irAE and showed a favorable response to immunotherapy. The CRS in this case may have been an irAE triggered by infection. Especially in cases of favorable tumor response, it is unfortunate that complications can lead to a poor prognosis.

ICIs are known as a cause of CRS in various types of cancer, and patients who received ICIs have been reported to develop CRS at a ratio of 0.06%–0.14%.[8] Several ICIs are

TABLE 2 Previously reported CRS cases induced by nivolumab plus ipilimumab

Authors	Age/sex	Primary cancer	IL-6 level (pg/ml)	Immunosuppressive therapy	Outcome
Urasaki et al.[13]	46/F	Renal cell carcinoma	No date	Tocilizumab MMF IVIg	Recovered
Ohira et al.[14]	70/M	Renal cell carcinoma	467	mPSL/PSL MMF IVIg	Recovered
Kunimasa et al.[15]	64/F	Lung cancer	25 100	Tocilizumab Infliximab mPSL/PSL MMF	Recovered
Present study	70/M	Lung cancer	69 586	Hydrocortisone 100 mg	Death

Abbreviations: IL-6, interleukin-6; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PSL, prednisolone.

linked to CRS, including anti-programmed cell death protein-1/ligand-1 antibodies, and anticytotoxic T lymphocyte antigen-4 antibodies. Because of the progressively increasing use of ICIs, CRS induced by ICIs is becoming more easily recognized and diagnosed.[8,14–16]

Previously reported CRS cases induced by nivolumab plus ipilimumab are summarized in Table 2. IL-6 values varied from case to case, but the patient described herein had the highest value. In all previous cases, immunosuppressive therapy had been used with favorable outcomes. The addition of immunosuppressive therapy such as an IL-6 blocker or IL-6 receptor antagonist may improve the prognosis of patients with CRS.

Fever is a common event in cancer patients, especially in COVID-19-infected patients, but when fever develops during cancer immunotherapy, CRS should always be kept in mind.

CONFLICT OF INTEREST

KA reports receiving personal fees from AstraZeneca, MSD, Bristol Myers Squibb, Ono Pharmaceutical, Takeda Pharmaceutical, Pfizer and Chugai Pharmaceutical. TT reports receiving personal fees from AstraZeneca, Bristol Myers Squibb, MSD, Novartis and Chugai Pharmaceutical. The remaining authors have no conflicts of interest to disclose.

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