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CASE REPORT

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Cytokine release syndrome following COVID-19 infection during treatment with nivolumab for cancer of esophagogastric junction carcinoma: a case report and review

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Abstract

Background Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome characterized by fever and multiple organ failure, which is triggered by immunotherapy or certain infections. Immune checkpoint inhibitors rarely cause immune-related adverse event- cytokine release syndrome (irAE-CRS). This article presents a case report of irAE-CRS triggered by coronavirus disease 2019 (COVID-19).

Case presentation A 60-year-old man with type 2 diabetes received nivolumab treatment for esophagogastric junction carcinoma and experienced two immune-related adverse events: hypothyroidism and skin disorder. Eleven days before his visit to our hospital, he had a fever and was diagnosed with COVID-19. Five days before his visit, he developed a fever again, along with general malaise, water soluble diarrhea, and myalgia of the extremities. On admission, the patient was in a state of multiple organ failure, and although the source of infection was unknown, a tentative diagnosis of septic shock was made. The patient's condition was unstable despite systemic management with antimicrobial agents, high-dose vasopressors, and intravenous fluids. We suspected CRS due to irAE (irAE-CRS) based on his history of nivolumab use. Steroid pulse therapy (methylprednisolone 1 g/day) was started, and the patient temporarily recovered. However, his respiratory condition worsened; consequently, he was placed on a ventilator and tocilizumab was added to the treatment. His muscle strength recovered to the point where he could live at home, and was subsequently discharged.

Conclusion In patients previously treated with immune checkpoint inhibitors, irAE-CRS should be considered as a differential diagnosis when multiple organ damage is observed in addition to inflammatory findings. It is recommended to start treatment with steroids; if the disease is refractory, other immunosuppressive therapies such as tocilizumab should be introduced as early as possible.

Keywords Immune-related adverse event, Cytokine release syndrome, Immune checkpoint inhibitor

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Background

Cytokine release syndrome (CRS) is triggered by certain infections or immunotherapy, and leads to the excessive release of inflammatory cytokines as an immune response, which results in multiple organ damage [1]. The symptoms of CRS range from mild fever, myalgia, and fatigue to severe conditions including acute respiratory distress syndrome, hypotension, and disseminated intravascular coagulation syndrome [2]. While CRS is frequently associated with chimeric antigen receptor-T (CAR-T) cell therapy [3], it has also been observed after immune checkpoint inhibitor (ICI) administration [4]; tebentafusp which is a T-cell receptor–bispecific molecule that targets glycoprotein 100 and CD3 [5]; and Kaposi Sarcoma Inflammatory Cytokine Syndrome described in patients co-infected with Human Immunodeficiency Virus and Kaposi Sarcoma Herpes Virus [6]. Early diagnosis and prompt therapeutic interventions are essential to avoid the potentially fatal outcome of CRS.

Here, we present a patient who developed immune-related adverse events (irAEs) after the induction of nivolumab, an ICI, for esophagogastric junction carcinoma, and then suffered CRS triggered by COVID-19; he was successfully treated with high-dose steroids and tocilizumab.

Case presentation

A 60-year-old man with type 2 diabetes had been discharging black stools for 3 years. Two years ago, he developed chest tightness, and upper gastrointestinal endoscopy revealed a submucosal tumor-like raised lesion in the esophagogastric junction. The pathology results revealed squamous cell adenocarcinoma, and a diagnosis of cT3N3M1 stage IV esophagogastric junction carcinoma was made. S-1 plus oxaliplatin (SOX) therapy was started, and the tumor showed a tendency to shrink. However, later in the treatment course, the patient had to be treated with only S-1 owing to an allergic reaction to oxaliplatin. Although imaging tests revealed stable disease, the patient was switched to S-1 plus nivolumab 3 months before his visit to our hospital because of an increasing trend of tumor marker levels. Approximately 2 months after starting nivolumab (4 courses every 3 weeks; last dose administered 35 days before the patient's visit to our hospital), the patient developed hypothyroidism and dermatitis due to irAEs.

He presented fever of 40 °C for 11 days before visiting our hospital and was diagnosed with COVID-19. He had received five doses of COVID-19 vaccine. He had been taking ensitrelvir and was recovering at home. However, 5 days before the hospital visit, the patient developed a fever again, along with general malaise, water soluble diarrhea, and myalgia of the extremities, which made it difficult for him to move, and he called for emergency medical service. His vital signs on arrival were as follows: blood pressure, 94/73 mmHg; pulse, 132 beats per minute; respiratory rate, 25 breaths per minute; peripheral oxygen saturation, 96% without oxygenation, and body temperature, 39.3 °C. The Glasgow Coma Scale scores were as follows: eye opening, 4; verbal response, 4; motor response, 6. As mottled skin and prolonged capillary refill time were observed, and the left ventricular cavity was found to be collapsed on echocardiography, we considered septic shock and started resuscitative infusion. About 2000 mL of crystalloid fluid was administered, and vasopressors were started because his circulation was unstable. Laboratory tests showed hepatic dysfunction, renal dysfunction, rhabdomyolysis, low platelet count, and elevated ferritin level (Table 1). Computed tomography (CT) examination revealed no lung disease (Fig. 1); there were no other specific findings. The source of infection was unknown, but the patient had gingival ulceration in the oral cavity and episodes of soluble diarrhea. Therefore, we considered a bacterial infection triggered by mucosal breakdown, and cefmetazole treatment was initiated. After admission to the high care unit (HCU), the patient remained unstable and hydrocortisone was added as a treatment for critical illness-related corticosteroid insufficiency, but no improvement was observed. irAE-CRS was suspected based on the history of nivolumab use (American society for Transplantation and Cellular Therapy, ASTCT Grade 4) and steroid pulse therapy (methylprednisolone 1000 mg/day) was started (Fig. 2). The patient's organ damage showed a tendency to improve. On admission, erythema papulosum on the trunk and extremities (Fig. 3), water soluble diarrhea, and myalgia of the extremities were observed, which were consistent with irAEs. After starting steroid pulse therapy, the patient showed signs of recovery. However, on day 4, his respiratory condition deteriorated rapidly and a CT scan revealed new infiltrative shadows in the lower lobes of both lungs, which were considered to be irAE pulmonary organitis (Fig. 1). The patient was admitted to the intensive care unit (ICU) and was managed with mechanical ventilation. Owing to steroid refractoriness, tocilizumab 480 mg (8 mg/kg) was added to the treatment (Fig. 2). The antimicrobial was changed to meropenem and vancomycin. Cultures of blood and sputum samples collected on admission were negative. His respiratory condition improved over time with lung protection strategy, and the patient was extubated on day 7. The patient was transferred to the HCU on day 8, and antimicrobials were discontinued. Vasopressors were discontinued on day 10. After 3 days of steroid pulse therapy, the patient was treated with 120 mg/day methylprednisolone intravenously for 7 days, and

Table 1 Laboratory findings on emergency department arrival

	Result	Normal range		Result	Normal range
WBC	7130	3300–8600 (/μL)	PT	52.7	80–120 (%)
Neutrophilis	87.1	39.5–74.5 (%)	PT-INR	1.56	0.90–1.20
Lymphocytes	8.1	20.9–54.1 (%)	APTT	41.7	24–35 (s)
Monocytes	0.9	3.6–9.8 (%)	D-dimer	6.1	0–1.0 (μg/mL)
Eosinophils	2.6	0.0–8.1 (%)	Fib	606	200–400 (mg/dL)
Basophils	0.1	0.0–1.7 (%)	AChRAb	< 0.1	0–0.2 (nmol/L)
RBC	398	435–555 (10^4/μL)	pH	7.562	7.35–7.45
Hb	14.1	13.7–16.8 (g/dL)	PaCO2	21	36–45 (mmHg)
Ht	41.2	40.7–50.1 (%)	PaO2	89.7	86–107 (mmHg)
MCV	103.5	83.6–98.2 (fL)	HCO3-	18.5	23–28 (mmol/L)
PLT	13.1	15.8–34.8 (10^4/μL)	Lac	20	4–16 (mg/dL)
AST	119	13–30 (U/L)			
ALT	33	10–42 (U/L)			
LDH	830	124–222 (U/L)			
ALP	66	38–113 (U/L)			
γ-GTP	23	13–64 (U/L)			
CK	1150	59–248 (U/L)			
Total-bilirubin	1.9	0.4–1.5 (mg/dL)			
Total-albumin	7.1	6.6–8.1 (g/dL)			
Albumin	3.8	4.1–5.1 (g/dL)			
BUN	38	8–20 (mg/dL)			
Creatinine	2.43	0.65–1.07 (mg/dL)			
sodium	130	138–145 (mmol/L)			
Potassium	5.1	3.6–4.8 (mmol/L)			
Chloride	93	101–108 (mmol/L)			
CRP	14.27	0.00–0.14 (mg/dL)			
Ferritin	7313	10–250 (ng/mL)			
IL-2R	2730	121–613 (U/mL)			
Glucose	157	73–109 (mg/dL)			
HbA1c	7.6	4.9–6.0 (%)			
TSH	29.84	0.61–4.23 (mIU/L)			
FT4	< 0.42	0.70–1.48 (ng/dL)			
cortisol	13.7	5.0–25 (μg/dL)			
BNP	7.2	0–18.4 (pg/mL)			
Troponin I	11.4	0–26.2 (pg/mL)			

WBC white blood cell, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematocrit, *MCV* mean corpuscular volume, *PLT* platelet, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyltransferase, *CK* creatinine kinase, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *IL-2R* interleukin-2 receptor, *HbA1c* hemoglobin A1c, *TSH* thyroid stimulating hormone, *FT4* free-thyroid 4, *AChRAb* acetylcholine receptor antibody

then switched to oral prednisolone (60 mg/day), which was tapered off (total duration of steroid administration was 40 days). The patient's muscle strength recovered to the point where he could live at home, and he was discharged (hospital stay: 68 days).

Discussion and conclusions

IrAEs cause systemic inflammatory reactions similar to autoimmune diseases, with a wide range of symptoms. IrAE-CRS is a fatal condition that requires early and appropriate treatment. The incidence of irAEs is higher with combination therapy than with monotherapy, and irAEs may occur immediately or several months after therapy [7, 8]. In 2020, 80,700 irAEs related to ICIs were analyzed using the World Health Organization (WHO) database and 58 cases of CRS [9]. In this report, more than half of the 58 patients had malignant melanoma and hematological malignancies. In addition, 21 patients developed CRS with nivolumab. The median onset of CRS was 4 weeks [9]. Characteristics

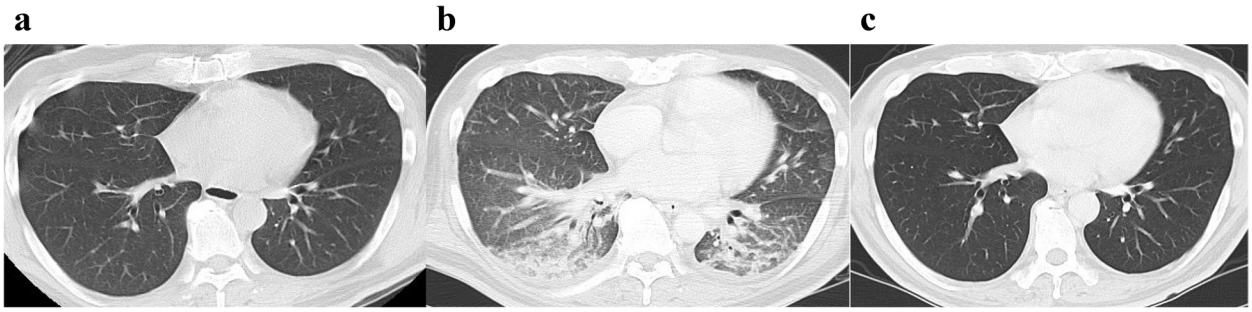

Fig. 1 Computed tomography (CT) findings of the chest. **a** on admission, **b** day 4, **c** after discharge

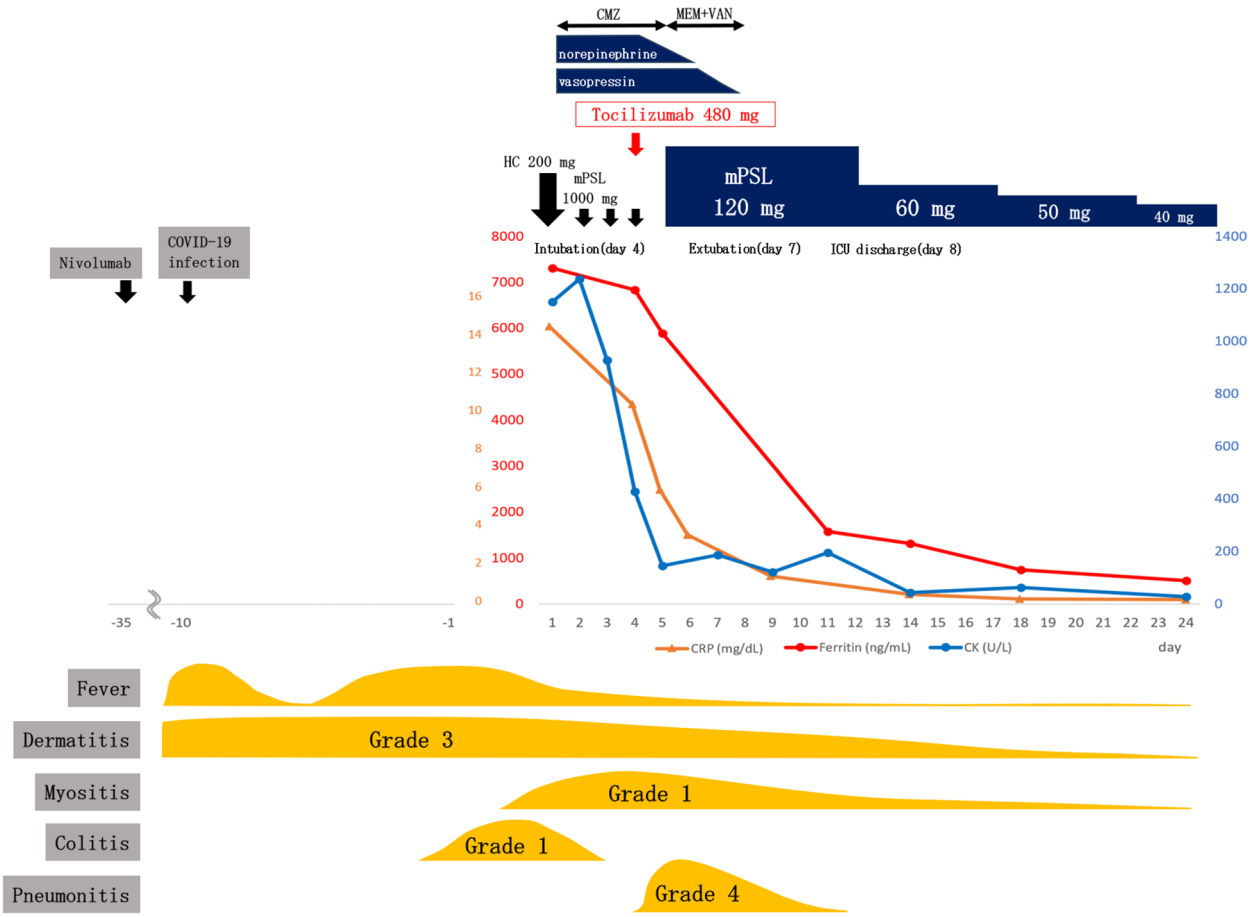

Fig. 2 Clinical course. CMZ: cefmetazole, MEM: meropenem, VAN: vancomycin, HC: hydrocortisone, mPSL: methylprednisolone, CRP: C-reactive protein, CK: creatinine kinase

of 20 cases of nivolumab-induced irAE-CRS are presented in Table 2. The patient developed irAE-CRS 35 days after the last dose of nivolumab, which is not significantly different from previously reported cases. Meanwhile, there have been no previous cases of this disease in esophagogastric junction carcinoma, thereby making this a very rare case. There were some cases of prior infection, which are discussed below.

As the initial symptoms resemble influenza-like symptoms such as fever and general malaise, the diagnosis is often delayed. Additionally, the clinical manifestations are similar to those of septic shock; therefore, it is often

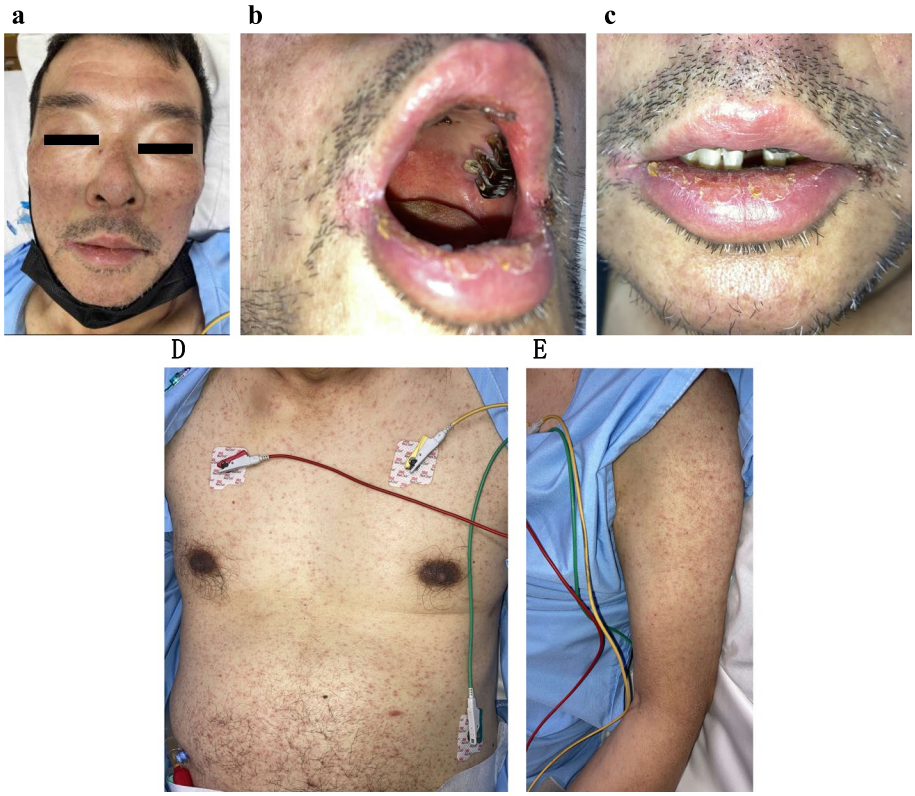

Fig. 3 Skin findings. **a** face, **b** oral cavity, **c** labia, **d** trunk, **e** upper limbs

difficult to distinguish between them in the early stages [1]. Currently, there are no established criteria for the diagnosis, and irAE-CRS should be considered when multiple organ dysfunction is observed with systemic hyperinflammation. Empiric antimicrobial therapy should be initiated while screening for infection and irAE-CRS should be treated simultaneously. Steroid is the mainstay treatment; immunosuppressive therapy in cases of steroid refractoriness has not been established. Various inflammatory cytokines are involved in CRS, with interleukin-6 (IL-6) playing a central role [7]. Moreover, low platelet count and elevated CRP and ferritin levels have been reported as surrogate indices, which may assist in CRS diagnosis [10]. Tocilizumab, an IL-6 receptor inhibitor, was originally approved for the treatment of autoimmune diseases including rheumatoid arthritis, and its indication was later expanded to CRS treated with CAR-T therapy [11]. Currently, tocilizumab is the second-line treatment for steroid-refractory irAE-CRS, but the treatment choice in the case of tocilizumab refractoriness is controversial [12].

In this case, influenza-like symptoms preceded the patient's illness. On arrival at the hospital, the patient had dermatitis (Grade 3), hypothyroidism (Grade 2), enterocolitis (Grade 1), and myositis (Grade 1), which were considered to be irAEs, as well as symptoms of hepatic and renal dysfunction. IL-6 was not measured while diagnosing irAE-CRS in this case, but it is possible to recall irAE-CRS from the history of use of ICIs, and the elevated ferritin level helped in the diagnosis. After the steroid pulse therapy, we were able to temporarily reduce vasopressor doses. However, on day 4, his respiratory condition deteriorated rapidly, and pulmonary lesions that were thought to be irAE pneumonitis were observed (Grade 4). As the patient's condition deteriorated again, tocilizumab was administered as he was refractory to steroids; the treatment was successful, and the patient recovered.

There have been several reports of prior infection contributing to the development of irAE-CRS. A case where nivolumab was administered for hemophagocytic lymphohistiocytosis with serologically confirmed Epstein-Barr virus infection developed CRS one day after administration [13]. It was considered CRS due to nivolumab treatment, as IL-10 and IFN-γ levels dramatically increased within 24 h after nivolumab administration. Yamamoto et al. reported a case of irAE-CRS triggered by viral upper respiratory tract infection [14]. In another case, a patient with lung adenocarcinoma who had been receiving nivolumab contracted

Table 2 Cases of irAE-CRS triggered by nivolumab administration

Author	Age	Sex	Cancer type	Prior infection and vaccination	Number of nivolumab cycles	Combined therapy	Time from last dose of ICIs to onset of irAE-CRS	IrAE-CRS Grade	Treatment	Outcome
Case 1 Honjo et al. [4]	52	Female	Pleomorphic carcinoma of the lung cT4N2M0 Stgae IIIB	None	4	None	14 days	4	1. mPSL 1 g (3 days) 2. mPSL 1 mg/mg → gradual decrease 3. MMF	Discharge
Case 2 Kunimasa et al. [12]	64	Female	G-CSF-producing pleomorphic carcinoma of the lung cT2aN0M1b Stage IVB	None	Unknown details	Ipilimumab	Unknown details (67 days after the first dose)	4	1. mPSL 1 g (1 day) mPSL 0.25 g (1 day) 2. Tocilizumab 3. Infliximab for irAE pneumonitis 4. MMF	Discharge
Case 3 Xu et al. [13]	3	Female	EBV-HLH	None	1	L-DEP Ruxolitinib	1 day	5	mPSL 15 mg/kg	Death
Case 4 Yamamoto et al. [14]	63	Female	Left clear cell renal cell carcinoma Stage IV	Upper respiratory tract inflammation due to viral infection	3	Ipilimumab	43 days (Prior infection 5 days before admission)	3	1. mPSL 0.5 ~ 1.0 g (3 days) 2. mPSL 1 mg/kg → gradual decrease	Discharge
Case 5 Murata et al. [15]	70	Male	Lung adenocarcinoma pT3N0M0 Stage IIB	COVID-19 infection	4	Ipilimumab	4 days	5	High-dose steroid	Death
Case 6 Sumi et al. [17]	55	Male	Non-small cell lung cancer Stage IV	Vaccination (mRNA-1273)	Unknown details	Ipilimumab	10 days (Onset of disease the day after vaccination)	1	mPSL 1 g (3 days)	Discharge
Case 7 Tanaka et al. [20]	55	Male	Lung adenocarcinoma Stage IV	None	5	Ipilimumab	20 days	4	1. mPSL 1 g (3 days) 2. mPSL 1 ~ 2 mg/kg → gradual decrease 3. IVCY 4. IVIG	Discharge
Case 8 Ntwali et al. [21]	65	Male	Gastric cancer cT3N2M1 stage IV	None	10	5-fluorouracil Oxaliplatin	During treatment cycle 10	3	HCS 100 mg/day	Discharge

Table 2 (continued)

Author	Age	Sex	Cancer type	Prior infection and vaccination	Number of nivolumab cycles	Combined therapy	Time from last dose of ICIs to onset of irAE-CRS	IrAE-CRS Grade	Treatment	Outcome
Case 9 Shiraishi et al. [22]	① 70 ② 70 ③ 44 ④ 51 ⑤ 71	① Male ② Female ③ Female ④ Male ⑤ Female	① Lung adenocarcinoma ② Lung adenocarcinoma ③ Squamous cell carcinoma Stage IVB ④ Lung adenocarcinoma ⑤ Non-small cell lung cancer Stage IV	① COVID-19 infection ② None ③ None ④ None ⑤ None	① 6 ② Unknown details ③ 1 ④ 4 ⑤ 1	① Ipilimumab ② Ipilimumab ③ Ipilimumab ④ Ipilimumab ⑤ Ipilimumab	① 3 days ② Unknown details ③ 14 days ④ 35 days ⑤ 8 days	① 5 ② 5 ③ 2 or 3 ④ 3 ⑤ 5	① Supportive care ② mPSL 1.0 g (Duration unknown) ③ mPSL 1.0 g (3 days) PSL 1 mg/kg →gradual decrease ④ mPSL 1.0 g (3 days) PSL 1 mg/kg →gradual decrease ⑤ Supportive care	① Death ② Death ③ Discharge ④ Discharge ⑤ Death
Case 10 Mosalem et al. [23]	26	Male	Recurrent/refractory classical hodgkin lymphoma Stage IIB	None	1	Brentuximab Vedotin	9 days	5	For irAE-CRA and HLH like syndrome 1. Dexamethasone 2. Tocilizumab 3. Etoposide 4. Plasma exchange for management of hypertriglyceridemia	Death
Case 11 Tsutsui et al. [24]	75	Female	Non-small cell lung cancer Stage IIB	None	Unknown details	Ipilimumab	Unknown details (9 days after the first dose)	2	1. mPSL 125 mg (3 days) 2. mPSL 1 g (3 days) 3. mPSL 1 mg/kg	Discharge
Case 12 Menakuru et al. [25]	58	Female	Metastatic melanoma Stage IV	None	4	Ipilimumab	6 days	4	1. mPSL 1 mg/kg 2. Tocilizumab 3. Etanercept	Discharge
Case 13 Deng et al. [26]	44	Female	Lung adenocarcinoma cT3N3M0 Stage IIIc	None	5	None	17 days	5	1. Dexamethasone 10 mg (7 days) 2. Gamma globulin 20 g (3 days)	Death
Case 14 Ciner et al. [27]	72	Male	Hepatic-limited metastatic colorectal cancer	None	4	5-fluorouracil Levofolinate Oxaliplatin CV301	42 days	4	HCS	Discharge

Table 2 (continued)

Author	Age	Sex	Cancer type	Prior infection and vaccination	Number of nivolumab cycles	Combined therapy	Time from last dose of ICIs to onset of irAE-CRS	IrAE-CRS Grade	Treatment	Outcome
Case 15 Ohira et al. [28]	70	Male	Renal cell carcinoma with multiple metastases pT4N1M1 Stage IV	None	2	Ipilimumab	Approximately 10 days	4	1. mPSL 0.5 g (3 days) 2. mPSL 1 mg/mg → gradual decrease 3. MMF 4. Plasma exchange 5. IVIG	Discharge
Case 16 Sindel et al. [29]	28	Female	Recurrent/refractory classical hodgkin's lymphoma Stage IV	None	1 (Administered prior to haematopoietic stem cell transplantation)	None	33 days (7 days after transplantation)	4	1. mPSL 1 mg/kg (twice a day) 2. Intravenous ascorbic acid	Discharge
Case 17 Oda et al. [30]	43	Male	Gastric adenocarcinoma with multiple metastases	None	1	None	8 days	5	1. mPSL 1 mg/mg 2. mPSL 1 g (3 days) 3. MMF	Death
Case 18 Zhao et al. [31]	25	Male	Recurrent/refractory classical hodgkin's lymphoma	None	1	None	6 days	2	Supportive care	Discharge
Case 19 Rotz et al. [32]	29	Female	Alveolar soft part sarcoma with multiple metastases	None	2	Pazopanib	4 days	2	1. HCS 2. mPSL → gradual decrease 3. Tocilizumab	Discharge
Case 20 Foran et al. [33]	7	Male	Recurrent/refractory classical hodgkin's lymphoma Stage IIIB	None	1	None	4 h	3	High-dose steroid	Discharge

mPSL Methylprednisolone, *IVCY* Intravenous cyclophosphamide, *IVIG* Intravenous immunoglobulin, *HCS* Hydrocortisone, *HLH* Haemophagocytic lymphohistiocytosis, *G-CSF* Granulocyte-colony stimulating factor, *MMF* Mycophenolate mofetil, *EBV-HLH* Epstein barr virus-haemophagocytic lymphohistiocytosis, *L-DEP* Liposomal doxorubicin, etoposide, and methylprednisolone, *CV301* Cancer vaccine 301

COVID-19 and was hospitalized [15]. Five months had passed since the initiation of nivolumab, and the final administration was four days before hospitalization. The patient suddenly went into cardiac arrest three hours after admission. IL-6 levels were abnormally high, and it was believed that CRS developed in association with COVID-19 infection. Guo et al. reported that COVID-19 infection can cause high-grade irAE [16], but this report did not include cases of irAE-CRS. Our patient had contracted COVID-19 eleven days prior to admission, and it is possible that COVID-19 triggered irAE-CRS development. There are few reported cases of irAE-CRS triggered by COVID-19 infection, and it is thought that the infection triggered immunological dysregulation, which resulted in the induction of excessive inflammatory cytokines. Meanwhile, Sumi et al. reported a case of irAE-CRS the day after COVID19 vaccination (mRNA-1273) [17]. It is of great interest that a prospective study is currently underway to determine the impact of vaccination on the development of irAE in patients receiving immunotherapy [18].

Levels of IL-6 and acute phase reactants increase in severe COVID-19 patients, which indicates the onset of CRS. In an observational study of 12 patients with hypertension, diabetes, or chronic obstructive pulmonary disease who were not administered ICI, administration of tocilizumab resulted in no cases of grade 4 CRS within 1 week, and serum markers of inflammation, including IL-6, decreased [19]. Randomized controlled trials have not been conducted, so it is unclear whether tocilizumab is effective in preventing the onset of CRS. As mentioned earlier, IL-6 was not measured in this case, but if tocilizumab had been administered from the beginning of hospitalization based on IL-6 levels, the onset of grade 4 CRS might have been prevented.

IrAE- CRS is a life-threatening disease and the nonspecific nature of the initial symptoms may delay therapeutic intervention. It is noteworthy that prior infection can be a trigger. Treatment should be initiated with steroids based on the history of ICI use. Further, immunosuppressive agents such as tocilizumab may be effective if the disease is steroid refractory. However, standard treatment for irAE-CRS has not been established, and more cases need to be accumulated.

Abbreviations

CRS	Cytokine release syndrome
irAE	Immune-related adverse event
COVID-19	Coronavirus disease 2019
CAR-T	Chimeric antigen receptor-T
ICI	Immune checkpoint inhibitor
CT	Computed tomography
ICU	Intensive care unit
HCU	High care unit
IL-6	Interleukin-6
WHO	World Health Organization

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Authors' contributions
TN prepared the original draft. TT reviewed and edited the manuscript. HK, SS, SY, and HY participated in the care of the patient. KH provided advice on treatment strategies.

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Availability of data and materials
No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The authors declare no competing interests.

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