Cytokine release syndrome induced by immune checkpoint inhibitor treatment for uterine cervical cancer recurrence: A case report

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Abstract. Cytokine release syndrome (CRS) is a systemic inflammatory condition caused by an excessive immune response and cytokine overproduction. CRS is a life-threatening condition that is often associated with chimeric antigen receptor T-cell therapy. Despite the increased use of immune checkpoint inhibitors (ICIs), ICI-induced CRS remains rare. The present study describes a case of CRS that occurred after the administration of ICIs for recurrent adenocarcinoma of the uterine cervix. A 49-year-old woman received paclitaxel, carboplatin and pembrolizumab for recurrent cervical adenocarcinoma. On day 27 of the third cycle, the patient was admitted with a fever and suspected pyelonephritis. The following day, hypotension, upper respiratory symptoms and myalgia of the extremities were noted, and the left ventricular ejection fraction (LVEF) was decreased to 20%. Multiorgan failure (MOF) occurred, and the patient received ventilator support and continuous hemodiafiltration. Rhabdomyolysis, pancreatitis, erythema multiforme and enteritis were observed. CRS was diagnosed based on elevated ferritin and IL-6 levels. Steroid pulse therapy was administered; however, the MOF did not improve and the anti-IL-6-receptor monoclonal antibody tocilizumab (TOC) was administered. Subsequently, the LVEF improved to 50%, and the patient was removed from the ventilator on day 4 and from the continuous hemodiafiltration unit on day 6 after TOC administration. The patient was discharged on day 21. In conclusion, considering that ICI-induced CRS is a rare but severe complication, fever and other systemic conditions following ICI administration should be monitored.

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Introduction

Molecularly targeted drugs and immune checkpoint inhibitors (ICIs) are being introduced more frequently in the field of gynecologic oncology. Although ICIs have only recently been developed, they have been proven effective in cancer treatment. The anti-programmed death 1 (PD-1) monoclonal antibody pembrolizumab, combined with platinum-based chemotherapy, is especially useful for managing persistent, recurrent, or metastatic cervical cancers (1). Immune-related adverse effects (irAEs) commonly occur with ICI use and generally affect the skin, gastrointestinal tract, liver, lungs, thyroid gland, and adrenal cortex (2). Many irAEs are reversible and often improve with the discontinuation of ICIs. These rarely progress to fatal conditions and often respond to treatment. However, risk factors for the development of irAEs are increasingly apparent, and gynecologists lack the clinical experience of treating irAEs (3,4). Cytokine release syndrome (CRS) is a serious irAE that develops after ICI treatment. CRS is an inflammatory syndrome caused by an excessive immune response that results in cytokine overproduction. Although ICI-induced CRS is rare, the condition can be severe, rapidly exacerbated, and life-threatening (4). CRS may develop with chimeric antigen receptor (CAR)-modified T cells (CAR-Ts) for hematological malignancy; however, tocilizumab (TOC), an anti-IL-6 receptor antibody, is effective in such cases (5). In contrast, ICI-induced CRS develops less frequently, and an effective treatment has not yet been established.

Here, we report a case of CRS after ICI treatment for recurrent adenocarcinoma of the uterine cervix. Treatment for ICI-induced CRS had not yet been established; therefore, pulse steroid therapy was initiated. TOC was administered

because the CRS was resistant to treatment, and it saved the patient's life.

Case report

A 49-year-old Japanese woman with a suspected uterine cervical adenocarcinoma was admitted to the hospital of the University of Occupational and Environmental Health (Kitakyushu, Japan) in May 2021. The patient was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIB (cT2bN0M0) uterine cervical cancer and received concurrent chemoradiotherapy with weekly cisplatin. Eight months after the initial treatment, pelvic recurrence was evident. One year after the initial treatment, abdominal distention, pain, and bilateral hydronephrosis were detected. Paclitaxel, carboplatin, and pembrolizumab were administered every 3 weeks after ureteral stenting. After the first dose, the patient presented with a fever of 37˚C and Grade 2 neutropenia. No inflammatory response or systemic symptoms were observed on the first day of the second treatment cycle, which was performed as planned. On day 21 of the second treatment cycle, the patient's serum creatinine level was elevated, and pollakiuria ensued; therefore, the third cycle was postponed, and ureteral restenting was performed. On day 23 of the second treatment cycle, the patient presented to our hospital with a fever of 38˚C and right lumbar pain (Fig. 1). Laboratory data (L/D) revealed a white blood cell (WBC) count of 7,400/μg, neutrophilic sequestration of 68.2%, procalcitonin (PCT) level of 0.05 ng/dl, and C-reactive protein (CRP) content of 2.35 mg/dl; an enhanced computed tomography (CT) scan showed no obvious focus of infection. Bacteriuria was evident, indicating possible pyelonephritis; therefore, intravenous antibiotics (cefmetazole) were administered every 12 h. Several days after hospitalization, the patient experienced intermittent nighttime fever, which eventually disappeared. Blood and urine cultivation tests revealed methicillin-sensitive *Staphylococcus aureus*, and bacteremia was diagnosed in association with a uterine tract infection; therefore, the antibiotic was changed to cefazolin. After discharge on day 8, the fever disappeared and the blood test results improved. The third chemotherapy cycle was administered 40 days after the initial treatment. On day 14 of the third cycle, the patient presented with a fever of 39˚C and fatigue. L/D revealed a WBC count of 3,700/μg, neutrophilic sequestration of 55.9%, CRP of 5.26 mg/dl, and bacteriuria. The latter result suggested a relapse of pyelonephritis, and intravenous antibiotics (tazobactam and piperacillin, TAZ/PIPC) were administered empirically every 8 h. All cultivation tests (urine and blood cultures, including both aerobic and anaerobic cultures) performed at the time of admission to the hospital were negative. The patient's fever and general condition improved within one week, at which time she was discharged from the hospital. On day 27 of the third cycle, the patient was readmitted with a fever of 40˚C and fatigue. In addition, erythema of the extremities and face, and influenza-like symptoms, including headache, myalgia, arthralgia, and upper respiratory tract symptoms, were observed. L/D showed a WBC count of 3,300/μg, CRP of 12.22 mg/dl, Grade 3 liver dysfunction associated with aspartate aminotransferase, and Grade 1 thrombocytopenia and renal dysfunction associated with an elevated serum creatinine level. The patient was admitted for fever evaluation and received a course of intravenous antibiotics (TAZ/PIPC) after cultivation tests were performed.

Table I. Laboratory test results at intensive care unit admission.

Parameter	Value
Biochemistry	
Total bilirubin	0.4 mg/dl
Albumin	1.9 g/dl
Aspartate aminotransferase	438 U/l
Alanine aminotransferase	77 U/l
Lactate dehydrogenase	2,731 U/l
Amylase	151 U/l
Creatinine kinase	2,846 U/l
Blood urea nitrogen	28 mg/dl
Creatinine	1.52 mg/dl
Sodium	135 mmol/l
Chlorine	102 mmol/l
Potassium	3.1 mmol/l
C-reactive protein	13.19 mg/dl
Procalcitonin	13.00 ng/ml
Blood cell count	
White blood cell	4,300/μl
Hemoglobin	7.0 g/dl
Platelet	$4.7x10^3$/μl
Coagulation	
Prothrombin time-international normalized ratio	1.33
Activated partial thromboplastin time	52.4 sec (control: 27.5 sec)

Cultivation tests were also performed and all cultivation tests yielded negative results.

One day after hospitalization, the patient suddenly developed hypotension after a bout of diarrhea, and LD showed a PCT level of 13.00 ng/dl. Disseminated intravascular coagulation (DIC) secondary to septic shock was suspected, based on the elevated CRP level and the presence of thrombocytopenia, and the patient was admitted to the intensive care unit for circulation dynamics assessment (Table I). Steroids (prednisolone 0.5 mg/kg/day) and catecholamines were administered for shock recovery. All cultivation tests yielded negative results, and a CT scan showed only a portion of bowel edema. Therefore, bacterial infection was discounted. L/D and echocardiography revealed MOF, including liver dysfunction, heart failure [left ventricular ejection fraction (LVEF) decreased to 20%], and kidney dysfunction following rhabdomyolysis (Fig. 2). Systemic symptoms associated with irAEs were initially suspected, and the steroid dose was increased to 2 mg/kg/day (prednisolone). Chest radiography revealed a decrease in the permeability of the lower lung and cardiac enlargement, with no elevation in muscle or brain troponin or creatine kinase levels. High-flow nasal cannula oxygen therapy was initiated with a fraction of inspired oxygen (FiO_2) concentration of 100% and a flow rate of 50 l/min;

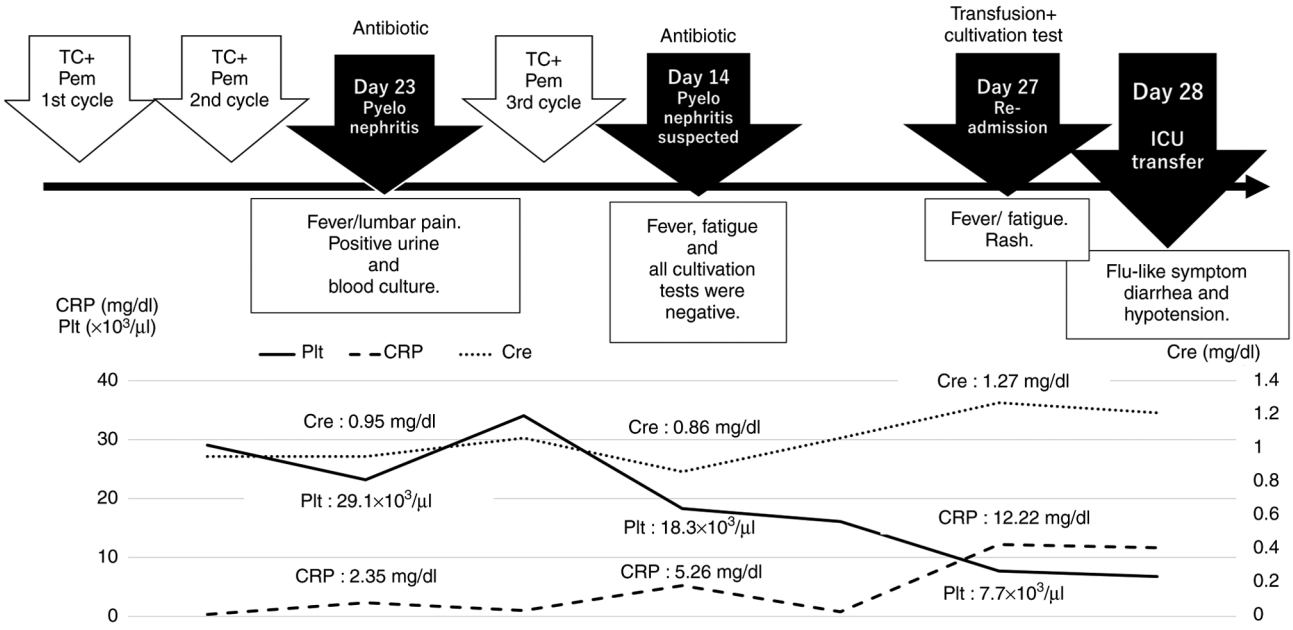

Figure 1. Events during anticancer therapy and the main data from the laboratory test. TC, paclitaxel and carboplatin; Pem, pembrolizumab; CRP, C-reactive protein; Plt, platelet; Cre, creatinine; ICU, intensive care unit.

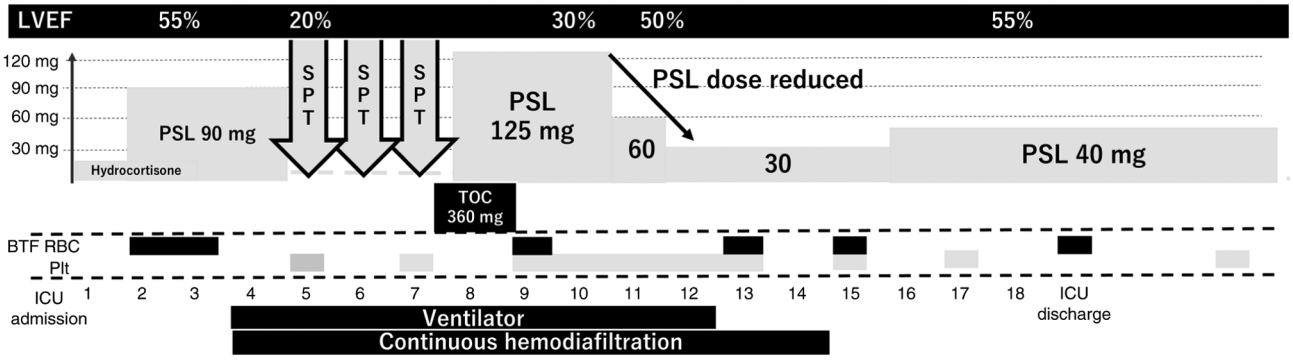

Figure 2. Course of left ventricular ejection fraction and diagram of the therapeutic process. BTF, blood transfusion; Plt, platelet; RBC, red blood cell; SPT, steroid pulse therapy; TOC, tocilizumab; LVEF, left ventricular ejection fraction; PSL, prednisolone; ICU, intensive care unit.

however, hypercarbonemia was exacerbated, and intratracheal intubation was required. Renal dysfunction resulting from rhabdomyolysis caused renal failure and progression of acidosis; therefore, continuous hemodiafiltration (CHDF) was initiated. Considering that high-dose steroid therapy had little effect and -multiorgan failure (MOF) persisted, close examination for irAEs was continued. Causes of thrombocytopenia other than DIC were considered, and pancytopenia was determined to be the principal clinical condition associated with comorbid anemia. Eventually, the patient was diagnosed with hemophagocytic syndrome associated with CRS, based on elevated serum ferritin and soluble interleukin-2 receptor levels. Steroid pulse therapy was administered for 3 of the 5 days in the ICU; however, the effect was negligible. L/D showed elevated amylase and lipase levels and a CT scan revealed acute pancreatitis. CRS continued to affect other organs; therefore, the anti-IL-6-receptor mAb, tocilizumab, was administered on the 8th day in the ICU. The steroid pulse therapy was discontinued, and the steroid dose was reduced to 3.5 mg/kg/day of prednisolone. Two days after TOC administration, L/D showed improvements in the levels of liver enzymes, creatinine kinase, and lipase. Blood pressure measurements improved and catecholamines were discontinued on the same day. The chest radiography results and oxygenation levels improved. The patient was extubated on day 4, and CHDF was discontinued after 6 days. The steroid dose was tapered from 40 to 20 mg of prednisolone by 10 mg each week to prevent irAE relapse. Thereafter, L/D showed improvement of MOF, and the patient was transferred from the ICU on the 19th day after admission. The steroid was changed to methylprednisolone for oral administration, and the dose was reduced by 2.5-5 mg/day every 2 weeks. The patient was discharged on the 31st day after admission.

Discussion

The anti-programmed death 1 (PD-1) monoclonal antibody pembrolizumab combined with platinum-based chemotherapy is effective for persistent, recurrent, or metastatic cervical cancer (1), and pembrolizumab use for the treatment of cervical cancer is widespread in Japan. The use of ICIs can result in irAEs

and concurrent systemic immune reactions. Risk factors for the development of irAEs are becoming increasingly apparent; however, the establishment of CRS in these cases is rare (3,4). In the present study, the patient was diagnosed with CRS, rhabdomyolysis, pancreatitis, enteritis, and erythema multiforme, which were identified through examination and imaging tests. In addition, hemophagocytic syndrome and myocarditis were suspected; however, these findings could not be verified without bone marrow puncture or myocardial biopsy (6,7). CRS, which has been recognized as an irAE, is mainly caused by rapid immune activation induced by CAR-Ts (5). ICI-induced CRS, particularly that involving PD-1 or PDL-1 inhibitors, is rare, and to our knowledge, PD-1 inhibitor-induced CRS in relation to uterine cervical cancer has not yet been reported. CRS is mainly driven by the T cell-derived interferon-gamma (IFN-γ), which stimulates macrophages to produce proinflammatory substances such as interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (8). The initial clinical aspects of CRS include fever of 38˚C or higher and influenza-like symptoms (headache, chills, and myalgia), after which CRS can progress to life-threatening hypovolemic shock, hypoxia, and end-organ dysfunction (5). A fever ≥38˚C is the main symptom of CRS, and hypotension and respiratory failure requiring ventilator support indicate an increased severity of the condition (5,9). In its initial phase, CRS has characteristics similar to those of severe infections, including hypovolemia and disseminated intravascular coagulation (10). In this case, CRS was not identified at the time of admission; the patient was diagnosed with septic shock resulting from pyelonephritis, and antimicrobial therapy was initiated. IFN-γ level should be used as a biomarker to differentiate CRS from infections because IFN-γ is not generally elevated in sepsis cases (4). An accurate testing approach for differentiating between these conditions is therefore required.

In this case, the patient presented with high fever and fatigue on day 14 after PD-1 inhibitor administration, and influenza-like symptoms (headache, sore throat, and myalgia) on day 28. Subsequently, acute heart failure occurred owing to low cardiac output, respiratory failure that required ventilator support, renal failure, and hypotension. Clinical symptoms matched those of Grade 4 CRS (9). The symptoms improved with steroid pulse therapy (prednisolone equivalent to 1,000 mg) and TOC (anti-IL-6 antibody) administration, and relapse was not observed once the steroids were tapered off. Relapses occur in greater than 40% of initial CRS cases (4); therefore, careful observation should be maintained after the initial signs of CRS improvement. In contrast, ICI re-administration after Grade 1 or 2 CRS with steroid therapy does not trigger relapse (4). There is no clear consensus regarding ICI rechallenge after CRS. Owing to the lack of evidence for safe rechallenge after Grade 4 CRS, the patient did not receive ICI readministration. Although steroid administration for irAEs is effective, the tumor-suppressive effect of steroid administration is controversial. The development of irAEs after ICI administration may prolong progression-free and overall survival (11); however, the need for and dosage of steroids during CRS therapy can affect tumor-suppressive outcomes (12). Excessive anti-inflammatory therapy for irAEs may lead to tumor growth and recurrence. Therefore, to prevent the relapse of irAEs or CRS, it might be safer to use anti-inflammatory therapy only during the relapse period as opposed to continuously.

Serum ferritin and soluble interleukin-2 receptor (sIL-2R) levels were measured as indicators of hemophagocytic lymphohistiocytosis (HLH), and thrombocytopenia suggestive of HLH or macrophage activation syndrome (MAS) was noted. HLH associated with rheumatic disease is termed MAS, whereas that associated with other triggers, including malignancy and infection, is called secondary HLH (sHLH) (13). In addition, CRS and HLH can overlap, and HLH can be considered a symptom of CRS after ICI administration (12,14). The diagnostic criteria for HLH include elevated serum ferritin and sIL-2R levels (7). In addition, ferritinemia of ≥10,000 μg/l has a sensitivity of 90% and a specificity of 96% for MAS, and hyper-ferritinemia may indicate CRS (4). If CRS is suspected in clinical situations, the measurement of ferritin and IL-2R levels may help in the diagnosis.

Interleukin-6 (IL-6) has been suggested as an important mediator of CRS; however, whether IL-6 levels predict CRS severity remains unclear (4,9,15). In addition, IL-6 cannot be measured in real time in a clinical setting or during treatment; therefore, its relevance in clinical diagnosis and therapeutic use is low (9). IL-6 analyses were performed three times: 2 days before TOC administration, on each administration day, and 3 days after administration. The respective values were 45.3, 48.1, and 6,380 pg/ml, and each level increased immediately after TOC administration. It is unclear whether severity in an individual patient can be predicted based on serum cytokine levels; therefore, analysis of cytokine levels may not be sufficient to evaluate therapeutic effects in clinical settings (4).

IL-6 overexpression induced by functional genetic variants in the *IL-6* gene, radiation therapy, and vaccines [e.g., the messenger ribonucleic acid (mRNA) coronavirus 2019 vaccine] trigger CRS development in patients receiving ICIs; however, the mechanism of the related CRS pathogenesis has not been elucidated (4,16). CRS is a consequence of an immune response that may cause adverse events in regions other than the tumors and target organs. Therefore, ICI re-administration after irAEs was considered after evaluating the risk of recurrence in each organ, and ICI re-administration after Grade 4 irAEs (hypotension requiring vasopressors or hypoxemia requiring ventilation with high-flow oxygen) should be permanently discontinued (17).

We encountered a case of CRS induced by ICI administration for recurrent uterine cervical cancer in which TOC was used to resuscitate the patient. The systemic manifestations of CRS varied, and it was difficult to distinguish CRS from infection or sepsis. TOC has been reported to be effective in the treatment of severe CRS, which was corroborated by the present case. Considering that ICI-induced CRS is a rare but severe complication, fever and other systemic conditions following ICI administration should be monitored. We hope this case may help gynecologist to understand ICI-induced CRS.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MS and YK collected the clinical data, wrote the manuscript and confirmed the authenticity of all the raw data. AT and MM acquired and interpreted the clinical data. SHa, YS, SHi, MH, RT, KH, HH, TU, TK, YM and KY contributed to acquisition and interpretation of data and revised the original manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of Medical Research of the University of Occupational and Environmental Health (Fukuoka, Japan; approval no. H30-160).

Patient consent for publication

Written informed consent for publication of the clinical data was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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