Case Report

Cytokine release syndrome in a patient with non-small cell lung cancer on ipilimumab and nivolumab maintenance therapy after vaccination with the mRNA-1273 vaccine: a case report

Toshiyuki Sumi[1,2]^, Yuta Koshino[1,2], Haruhiko Michimata[1,2], Daiki Nagayama[1,2], Hiroki Watanabe[1], Yuichi Yamada[1], Hirofumi Chiba[1]

[1]Department of Pulmonary Medicine, Hakodate Goryoukaku Hospital, Hokkaido, Japan; [2]Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine, Sapporo, Japan

Correspondence to: Toshiyuki Sumi, MD, PhD. Department of Pulmonary Medicine, Hakodate Goryoukaku Hospital, 38-3 Goryoukaku-cho, Hakodate-shi, Hokkaido 040-8611, Japan. Email: tsh715@gmail.com.

Background: Cytokine release syndrome (CRS) is caused by the release of inflammatory cytokines that appear during or immediately after administration of a therapeutic antibody and can cause a variety of symptoms. COVID-19 vaccination is effective in cancer patients and prevents breakthrough infections. The safety of vaccines during immune checkpoint inhibitor (ICI) therapy has been reported; however, multiple vaccinations have been developed in recent years, and it is unclear whether repeated vaccinations play a role in the development of CRS in patients receiving ICI.

Case Description: A 55-year-old man with stage IV non-small cell lung cancer received ipilimumab and nivolumab maintenance therapy; adverse reactions during the first and second COVID-19 vaccinations (BNT162b2) included injection site pain and slight fever; however, the day after the third COVID-19 vaccination (mRNA-1273), he developed a high fever and lost consciousness. Brain MRI showed parietal meningitis. Cytokine levels (IL-6, sIL-2R, IL-10, IFN-γ) were elevated and Grade 2 liver and renal dysfunction were also observed. As various tests ruled out infection and a PCR test for SARS-CoV-2 was negative, a diagnosis of CRS due to COVID-19 vaccination was made. After steroid therapy, his symptoms improved dramatically.

Conclusions: In this case, there was a close association between the time course after vaccination and clinical symptoms of high fever and lost consciousness. Clinicians should be aware of the possibility of vaccine-induced adverse effects such as CRS.

Keywords: Cytokine release syndrome (CRS); non-small cell lung cancer; vaccination; COVID-19; case report

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Introduction

Cytokine release syndrome (CRS) is a general term for symptoms caused by the release of inflammatory cytokines that appear during or immediately after the administration of antibody therapies. Antibody therapies can hyperactivate the immune response, resulting in the release of cytokines such as interleukins and interferons, causing chills, nausea, fatigue, headache, and other symptoms. In immune-related adverse events (irAEs) associated with anti-PD-1 monotherapy, the frequency of CRS occurrence is less than 0.01% (1).

Cancer patients infected with COVID-19 have high

^ ORCID: 0000-0002-2540-5878.

mortality rates. Coronavirus vaccines are effective in cancer patients and protect against breakthrough infection (2), and previous studies have reported on vaccine safety during immune checkpoint inhibitor (ICI) treatment (3-5). While multiple vaccine doses are now common, there have been no previous reports of CRS caused by booster vaccination with mRNA-1273 after two doses of BNT162b2, and adverse reactions were within acceptable limits (6). However, it is unclear what effect multiple doses of COVID-19 vaccine may have on the pathogenesis and frequency of CRS in patients treated with ICI.

Our patient developed CRS shortly after his third coronavirus vaccination during ipilimumab and nivolumab chemotherapy. We present the following article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-388/rc).

Case presentation

A 55-year-old man with stage IV non-small cell lung cancer was started on ipilimumab and nivolumab chemotherapy in December 2020. He showed Grade 3 (Common Terminology Criteria for Adverse Events version 5.0) skin rash during the first 2 weeks of treatment, which improved with topical and oral steroids. He was administered 20 mg hydrocortisone for Grade 2 adrenal failure and continued with maintenance therapy. The last ICI dose was administered 9 days before the patient received his third COVID-19 vaccine dose. The adverse reactions during the first and second vaccinations (Pfizer BioNTech (BNT162b2)) were limited to pain at the injection site and slight fever; however, a day after his third vaccination with Moderna COVID-19 (mRNA-1273), the patient developed a high fever (40.2 ℃) and experienced disorientation. Magnetic resonance imaging of the brain showed meningitis in the parietal region (*Figure 1A*). In addition, the levels of ferritin (1,571.7 μg /L; normal range, 39.4–340 ng/mL), inflammatory markers (C-reactive protein, 17.22 mg/L; normal range, 0–0.30 mg/L; lactate dehydrogenase, 440 U/L; normal range, 124–222 U/L), and cytokines (IL-6, 46.7 pg/mL; sIL-2R, 1,130 U/mL, IL-10, 15 pg/mL; IFN-γ, 0.3 U/mL) were upregulated. Grade 2 hepatic dysfunction and Grade 2 renal dysfunction were also observed. Blood and urine cultures were negative, spinal fluid findings did not suggest bacterial or viral infection, and a PCR test for SARS-CoV-2 was negative, leading to a diagnosis of CRS triggered by mRNA-1273 administration. Following steroid pulse therapy, symptoms and biochemical parameters improved dramatically. Subsequently, the patient was prescribed a maintenance dose of hydrocortisone and discharged from the hospital (*Figure 1B*,*1C*). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In this case, CRS was triggered by booster vaccination with mRNA-1273 during ICI therapy. Although there are no clear diagnostic criteria for CRS, an increase in IFN-γ, IL-2R, IL-18, IL-6, and IL-10 levels may aid diagnosis (1,7). During irAEs associated with anti-PD-1 monotherapy, the occurrence frequency of CRS is less than 0.01% (1). As ICI-associated CRS often occurs at a relatively early timepoint (median of 4 weeks after ICI initiation) (8), this may not be the only cause of CRS in our patient, who had been on immunotherapy for more than 1 year.

There are no previously known reports of booster vaccinations of mRNA-1273 (after two doses of BNT162b2) triggering CRS and reported adverse reactions have always been within acceptable limits (6). However, it has been suggested that COVID-19 vaccines may induce hyperprogression of an existing disease or CRS in patients undergoing ICI treatment (9). One study reported CRS occurrence due to COVID-19 vaccine administration in a patient with colorectal cancer who was being treated with PD1 antibodies (10). There was a close association between the time course after vaccination and clinical symptoms in this case as well, suggesting that the vaccine may have triggered CRS. Although tocilizumab treatment is recommended for CRS (11), this case was treated with the maximum allowable steroid doses for rapid administration. In addition, his increased IL-6 levels were not determined immediately, and this condition was being addressed for the first time.

Cancer patients infected with COVID-19 have a higher mortality rate than non-cancer patients with COVID-19. Furthermore, the risk of death increases with age, male sex, and complications/comorbidities such as cardiovascular disease (12). Coronavirus vaccination is effective in cancer patients and protects against breakthrough infections (2). As

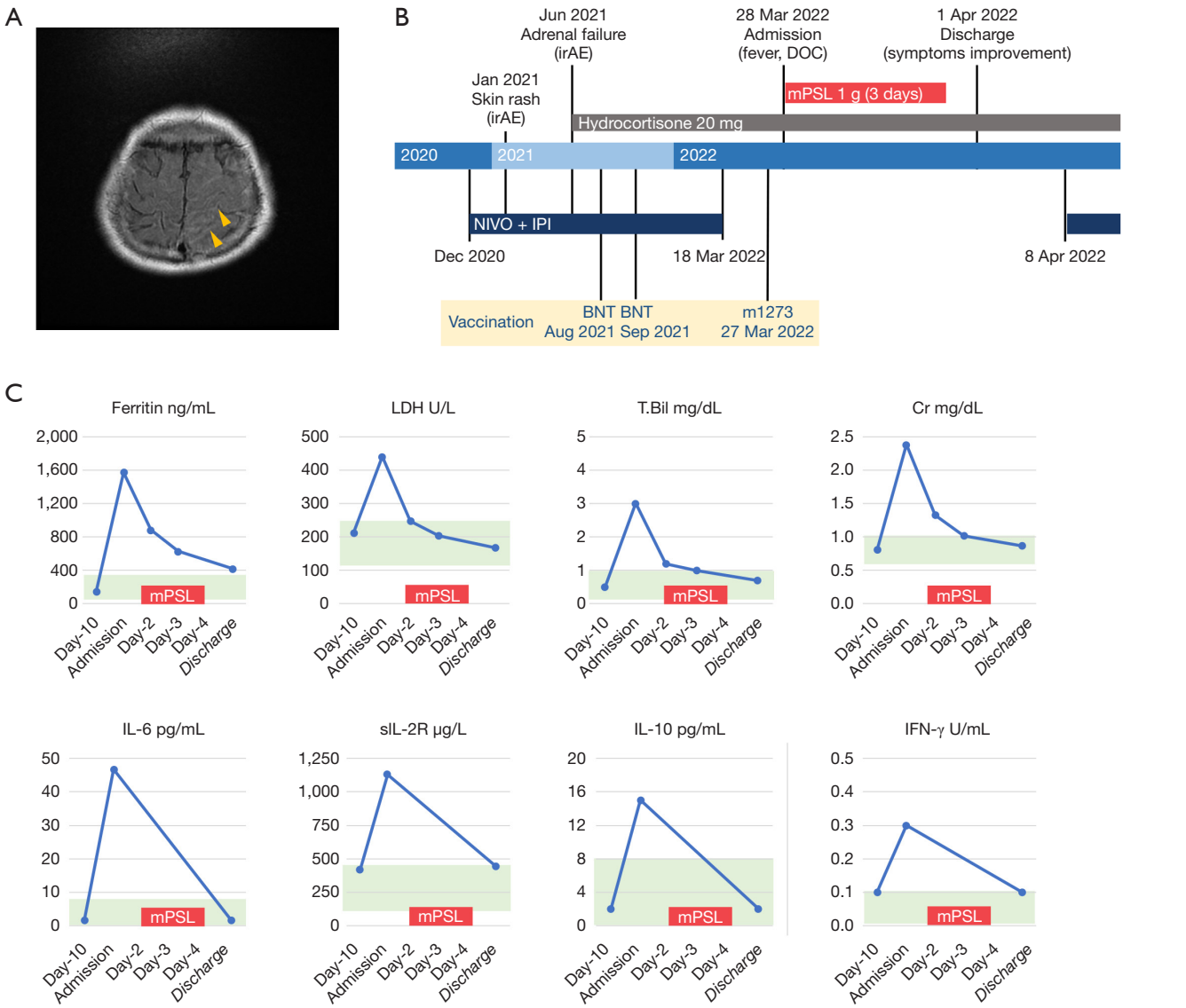

Figure 1 Image findings and clinical course. (A) Fluid attenuated inversion recovery magnetic resonance imaging showed a high intensity lesion on the cerebral surface of the left parietal lobe (indicated by orange arrowheads), suggesting meningitis. (B) Clinical timeline from the diagnosis of non-small cell lung cancer to CRS after vaccination with mRNA-1273. (C) Ferritin, LDH, total bilirubin, creatinine, and cytokines levels during the disease course. Normal ranges are indicated in green. Treatment with methyl prednisolone pulse is indicated in red. CRS, cytokine release syndrome; irAEs, immune-related adverse events; DOC, disturbance of consciousness; mPSL, methyl prednisolone; NIVO, nivolumab; IPI, ipilimumab; BNT, BNT162b2; m1273, mRNA-1273; LDH, lactase dehydrogenase; T.Bil, total bilirubin; Cr, creatinine; IL-6, interferon-6; sIL-2R, soluble interleukin-2 receptor; IL-10, interferon-10; IFN-γ, interferon-γ.

cancer patients are vulnerable to coronavirus infections, and studies have reported a short-term safety profile of vaccines during ICI treatment (3-5), vaccination is recommended in such patients. However, clinicians should be aware of the possibility of adverse effects, such as CRS. A prospective study is currently ongoing to determine the impact of vaccination on the development of irAEs in patients receiving immunotherapy, and the results will be closely monitored (13). We have reported these adverse events to the appropriate repositories for pharmacovigilance purposes (8).

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-388/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-388/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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