EBMT

CORRESPONDENCE

Severe acute interstitial lung disease after BNT162b2 mRNA COVID-19 vaccination in a patient post HLA-haploidentical hematopoietic stem cell transplantation

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TO THE EDITOR:

Patients with hematological diseases are more likely to develop a severe form of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The BNT162b2 mRNA COVID-19 vaccine reportedly has a good efficacy rate and is used globally to reduce disease severity and mortality. Severe adverse events due to vaccines have rarely been reported, even in patients with hematological malignancies. However, atypical adverse events may occur depending on the underlying disease and its treatment. Here, we present a case of severe acute interstitial lung disease (ILD) after two BNT162b2 mRNA COVID-19 vaccine doses in a patient with myelodysplastic syndrome (MDS) who underwent human leukocyte antigen (HLA)-haploidentical hematopoietic stem cell transplantation (HSCT). This is a rare case of a severe post-HSCT immune reaction after COVID-19 vaccination.

A 72-year-old man with a history of heavy smoking of 20–40 cigarettes per day for 50 years presented with MDS with multilineage dysplasia 1.3 years earlier after presenting with pancytopenia. He was considered high risk for MDS according to the Revised International Prognostic Scoring System and subsequently progressed to MDS with excess blasts-2 with an increased blast number in the bone marrow. Therefore, without prior treatment, the patient underwent HLA-haploidentical peripheral blood HSCT (the transplantation day was day 0). The donor was his 35-year-old daughter, who neither had a history of COVID-19 nor had been vaccinated against COVID-19. A reduced-intensity conditioning regimen of fludarabine, busulfan, and total-body irradiation was used, and post-transplant cyclophosphamide, tacrolimus (TAC), and mycophenolate mofetil were used for graft-versus-host disease (GVHD) prophylaxis. Neutrophil, erythrocyte, and platelet engraftments were achieved on days 15, 23, and 28, respectively. The patient developed acute skin GVHD (stage 3, grade III) and was administered prednisolone on day 70. GVHD improved quickly, prednisolone was discontinued on day 182 after tapering, and TAC was discontinued on day 266. During that time, he maintained MDS remission with no chronic GVHD. He had quit smoking before the HSCT.

The patient received the first BNT162b2 mRNA COVID-19 vaccine dose on day 288 post-HSCT and did not experience any adverse reactions. On day 309, after receiving the second dose, he developed fever and generalized malaise. Without seeking medical advice, the patient took acetaminophen orally, which only provided partial relief. By the 7th day after receiving his second vaccine, he was hospitalized for fever and dyspnea. On admission, the patient was fully conscious and had no cough or sputum but had fever (37.7 °C) and decreased oxygen saturation (88% on 10 L oxygen/minute). Chest radiography showed infiltrative shadows in the entire right and left lower lung fields, but no cardiomegaly or pulmonary congestion was noted. Chest computed tomography showed extensive ground-glass opacities in both lungs and traction bronchiectasis, mainly in the right lung, suggesting acute ILD (Fig. 1). Blood test results revealed elevated lactate dehydrogenase (418 U/l), C-reactive protein (7.52 mg/dl), surfactant protein A (210.2 ng/ml), and surfactant protein D (227.0 ng/ml) but no elevation of Krebs von den Lungen-6 (KL-6, 483 U/ml). Myocardial enzymes, such as creatine kinase (42 U/l) and troponin I, were within normal limits (Table 1). No other symptoms were suggestive of chronic GVHD. The quantitative test for SARS-CoV-2 antigen using a nasopharyngeal swab was negative. Bronchoalveolar lavage and lung biopsy could not be performed. However, all other serological markers of infection, such as beta-D glucan and cytomegalovirus antigen C7HRP, and blood cultures were negative.

A diagnosis of acute ILD was made, and we immediately initiated pulse corticosteroid therapy with methylprednisolone (1000 mg/day for 3 days). We also started TAC at a dose of 0.03 mg/kg in parallel with methylprednisolone in preparation for a possible immune response like GVHD. After treatment, the patient's respiratory condition, symptoms, and imaging findings improved quickly; therefore, we tapered off methylprednisolone. Two weeks after admission, a spirometry test result showed a decrease in vital capacity, and a blood test result revealed an increase in KL-6 (1021 U/ml), which strongly suggested residual ILD. However, a serum test for anti-spike immunoglobulin G antibodies using the Abbott immunoassay (Abbott Laboratories, Illinois, USA) performed at the same time, 3 weeks after the second dose of vaccination, revealed a value of 1.2×10^4 AU/ml (positivity cut off ≥50 AU/ml).

The patient then developed mediastinal emphysema 3 weeks after admission, which improved spontaneously after ~2 weeks, with no symptoms present. As per the latest follow-up, he has not had any subjective symptoms after starting corticosteroids and TAC. He is maintained on small doses of corticosteroids and TAC and has not had any further exacerbations.

This is a suspected case of vaccine-related ILD. Due to the lack of details about his condition a week after the second vaccination and because some examinations could not be performed, suggesting that the vaccine caused ILD in this patient is inconclusive. However, the patient developed fever and malaise followed by dyspnea on the day of the second dose of vaccination. Furthermore, the lack

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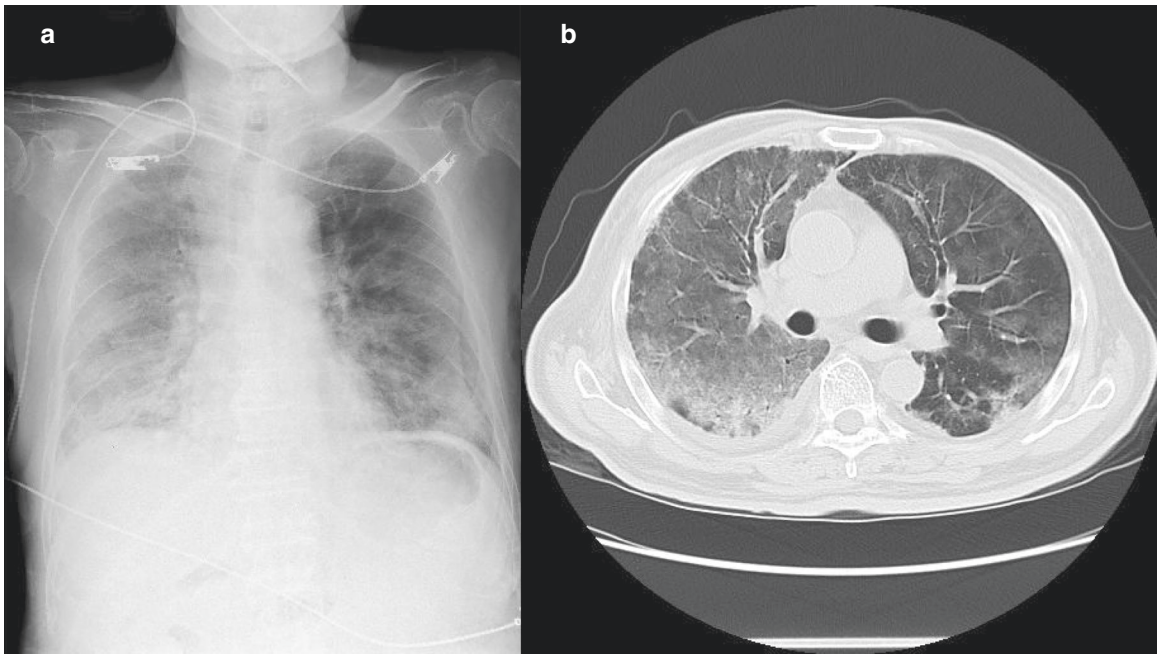

Fig. 1 Chest radiography (**a**) and computed tomography (**b**) on admission.

Table 1. Partial results of blood analysis at admission day.

White blood cell	11,420/μL	C-rective protein	7.53 mg/dL
Neutrophil	71.1%	Procalcitonin	0.07 ng/mL
Lymphocyte	24.8%	β-D glucan	<3.3 pg/mL
Monocyte	2.5%	Cytomegalovirus-antigen C7HRP	Negative
Eosinophil	1.3%		
Basophil	0.3%	Surfactant-protein A	210.2 ng/mL
Hemoglobin	11.5 g/dL	Surfactant-protein D	227.0 ng/mL
Hct	35.2%	Krebs von den Lungen-6	483 U/mL
MCV	106.0 fL		
MCHC	32.6 g/dL	Prothrombin time (PT)	12.3 s
Platelet	20.8×10^4/μL	PT acitivity percentage	91.2%
		Activated partial thromboplastin time	31.3 s
Lactate dehydrogenase	418 U/L	Fibrinogen	429 mg/dL
Creatine kinase	24 U/L	Fibrin degradation product	5.50 μg/mL
Troponin I	<10.0 pg/mL	D-dimer	2.09 μg/mL

of an underlying respiratory disease and absence of other triggering drugs strongly suggest vaccines are related to ILD development. Although there are a few case reports of new-onset or acute exacerbation of ILD after COVID-19 vaccination [1–3], this is an extremely rare adverse event compared to the number of vaccinations worldwide. Therefore, the risk factors for vaccine-related ILD are still unclear, but when considered as drug-induced ILD, older age and smoking history may be risks in this case [4].

On the other hand, this case can be considered a new onset of chronic GVHD because the clinical course was consistent with cryptogenic organizing pneumonia, a type of chronic lung GVHD. Reportedly, patients with HSCT who have COVID-19 are likely to experience a more severe illness and poorer prognosis than COVID-19 patients without any underlying disease [5], suggesting that COVID-19 vaccination for HSCT recipients is vital. Several reports have shown that the vaccine has good efficacy and safety in HSCT patients, although there is a tendency for less antibody production in certain groups [6–8]. However, a small percentage of new-onset or worsening chronic GVHD after COVID-19 vaccination have been reported [8, 9]. A prospective clinical trial reported one case of severe bronchiolitis obliterans organizing pneumonia after COVID-19 vaccination in a patient with HSCT [10]. Older recipient, HLA-haploidentical donor, female donor to male recipient, peripheral blood stem cell transplantation, and prior acute GVHD were identified as risk factors in the patient's clinical course [11]. In addition, the patient was vaccinated shortly after immunosuppressive drugs for skin GVHD discontinuation to increase the vaccine's efficacy. While this may have resulted in antibody production, it may also have triggered an overactive immune response and, in combination with other risk factors, may have led to ILD development.

This case was considered a vaccine-related ILD based on the symptoms' onset timing. However, vaccine as the cause of ILD or GVHD cannot be ascertained since this is only a case report, and there are no placebo-controlled studies. Although the mechanism of this event is also speculative, some studies have suggested that

molecular mimicry in other vaccines may cause immune cross-reactivity, leading to autoimmune diseases [12]. We emphasize that COVID-19 vaccination is highly beneficial in patients with HSCT. However, vaccination may be considered cautiously in active GVHD or shortly after discontinuation of immunosuppressive drugs.

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AUTHOR CONTRIBUTIONS

TU and TO wrote the manuscript. YS, YO, and YU contributed to the collection of clinical information. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

PATIENT CONSENT

The patient has provided informed consent for the publication of this case presentation.

ADDITIONAL INFORMATION

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