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American Journal of Emergency Medicine 56 (2022) 395.e1–395.e3

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Severe immune thrombocytopenia following COVID-19 vaccination (Moderna) and immune checkpoint inhibitor

Kah-Meng Chong, MD [a], Ching-Yao Yang, MD [b], Chien-Chin Lin, MD [c,d,e], Wan-Ching Lien, MD, PhD [a,*]

[a] Department of Emergency Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[b] Division of Pulmonology, Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[c] Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[d] Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[e] Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 6 October 2021
Received in revised form 14 March 2022
Accepted 14 March 2022

Keywords:
COVID-19
Moderna vaccine
mRNA-based vaccine
Immune thrombocytopenia
Immune checkpoint inhibitors

ABSTRACT

Safe and effective prophylactic vaccines are urgently needed to contain the coronavirus disease 2019 (COVID-19) pandemic. However, several vaccination-related adverse effects have been reported. Here, we report a rare case of severe immune thrombocytopenia occurring 3 days after receiving the mRNA-1273 (Moderna) COVID-19 vaccine in an Asian woman with a history of refractory lung adenocarcinoma treated with durvalumab, an immune checkpoint inhibitor. Treatment with platelet transfusion (12 units) and oral prednisolone (1 mg/kg per day) significantly improved her hemoptysis with thrombocytopenia. To the best of our knowledge, this is the first case of ITP following Moderna inoculation among Asians. This study highlights a potential adverse effect of mRNA-based COVID-19 vaccines in cancer patients receiving immune checkpoint inhibitors.

1. Introduction

Severe adverse effects following the coronavirus disease 2019 (COVID-19) vaccination include vaccine-induced thrombotic thrombocytopenia [1] and myocarditis [2]. Here, we report a rare case of severe immune thrombocytopenia (ITP) occurring 3 days after receiving the mRNA-1273 (Moderna) COVID-19 vaccine in an Asian woman treated with an immune checkpoint inhibitor (ICPi).

2. Case report

A 75-year-old woman visited the emergency department because of hemoptysis for 3 days after receiving the first dose of the Moderna COVID-19 vaccine. She had a history of refractory lung adenocarcinoma and had undergone ICPi therapy with durvalumab for 2 months. The last cycle of durvalumab was administered 4 days prior to vaccination, with a normal platelet count (Fig. 1 and Table 1). She denied any hematologic disorders or heparin exposure.

Upon arrival, her vital signs were as follows: body temperature, 37 °C; pulse rate, 77 beats per minute (bpm); respiratory rate, 20 bpm; blood pressure, 162/72 mmHg; and oxygen saturation, 98% on room air. Physical examination revealed no petechiae or ecchymoses. Laboratory data revealed a markedly reduced platelet count ($7 \times 10^3/\mu L$). A peripheral blood smear revealed no platelet clumping or morphological abnormalities. The hemolytic profile was unremarkable. The coagulation profile showed mildly elevated fibrinogen levels (389.6 mg/dL) with normal prothrombin time and activated partial thromboplastin time. Reverse transcriptase-polymerase chain reaction (RT-PCR) for COVID-19 was undetected.

With a tentative diagnosis of ITP, she underwent transfusion with 12 units of platelets and treatment with oral prednisolone (1 mg/kg per day). Serological tests for cytomegalovirus, Epstein-Barr virus, hepatitis C virus, and human immunodeficiency virus were negative, except that the hepatitis B virus profile was compatible with a previous infection. In addition, blood tests for antinuclear antibodies, complement proteins, rheumatoid factor, lupus anticoagulant, and anti-ß2-glycoprotein were negative.

Her hemoptysis subsided on the 4th day with an increase in platelet count to $173 \times 10^3/\mu L$, and she was discharged on the 5th hospitalization day with continued oral prednisolone therapy. However, she was followed up at the outpatient clinic, and her platelet count remained stationary. Therefore, the ICPi therapy was discontinued and replaced with navelbine chemotherapy. A second dose of the Moderna vaccine

* Corresponding author at: Department of Emergency Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan. Add: No.7, ZhongShan South Road, ZhongZheng District, Taipei City 100, Taiwan.
E-mail address: dtemer17@yahoo.com.tw (W.-C. Lien).

https://doi.org/10.1016/j.ajem.2022.03.030
0735-6757/

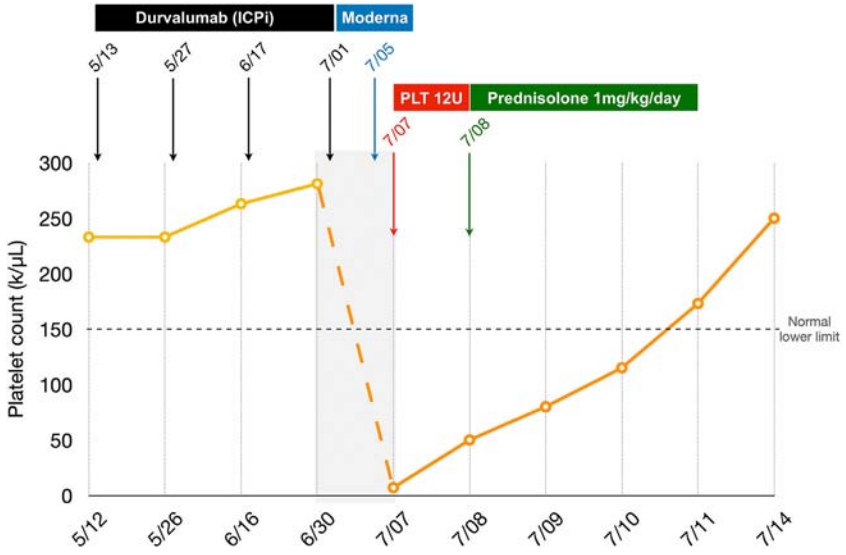

Fig. 1. Temporal relationship of observed thrombocytopenia with medical treatments.

was not suggested because of her experience of severe thrombocytopenia.

3. Discussion

The diagnosis of ITP is primarily based on the exclusion of other potential etiologies. In this patient, other causes of thrombocytopenia, autoimmune diseases, and infections were excluded. Bone marrow examination was unnecessary based on her typical presentation [3] and excellent response to ITP-directed therapy [4]. Thrombotic thrombocytopenic purpura and vaccine-induced thrombotic thrombocytopenia were not suspected because of the absence of hemolysis and thromboembolism, respectively.

Vaccine-related ITP has been associated with various vaccinations [5]. Although several cases of secondary ITP following mRNA-based COVID-19 vaccines (Pfizer/BioNTech and Moderna) have been recently reported, most of them occurred in Western countries [6-13]. The onset of ITP varies greatly from hours [7], 2–3 days [8-12], and 2 weeks [13]. Although the occurrence is rare, with an incidence rate of 0.80 per million doses, 13 cases of ITP were reported after the Moderna vaccine in

Table 1
Trends of the patient's hemogram before and after the onset of thrombocytopenia

Date	5/12	5/26	6/16	6/30	7/07 #1	7/08 #2	7/09	7/10	7/11 #3	7/14 #4
WBC (x10^3/μL)	6.77	5.36	8.52	6.63	5.87	4.04	17.81	18.88	9.07	10.56
RBC (x10^6/μL)	4.68	4.56	4.79	4.58	4.62	4.61	4.06	4.02	4.48	4.76
HB (g/dL)	15.1	14.8	15.2	14.5	14.7	14.7	12.9	12.8	14.4	15.1
HCT (%)	44.9	43.2	44.9	43.3	43.2	42.7	38.4	37.6	41.9	44.7
MCV (fL)	95.9	94.7	93.7	94.5	93.5	92.6	94.6	93.5	93.5	93.9
MCH (pg)	32.3	32.5	31.7	31.7	31.8	31.9	31.8	31.8	32.1	31.7
MCHC (g/dL)	33.6	34.3	33.9	33.5	34.0	34.4	33.6	34.0	34.4	33.8
PLT (x10^3/μL)	233	233	263	281	7*	50*	80*	115*	173	250
RDW-CV (%)	13.2	12.9	12.7	12.9	13.0	12.7	12.8	13.1	13.0	13.6
Blast (%)	0	0	0	0	0	–	–	–	–	0
Promylelocyte (%)	0	0	0	0	0	–	–	–	–	1.0
Myelocyte (%)	0	0	0	0	0	–	–	–	–	3.8
Metamyelocyte (%)	0	0	0	0	0	–	–	–	–	0
Bands (%)	0	0	0	0	0	–	–	–	–	0.9
Neutrophil (%)	53.0	68.6	68.8	60.7	66.5	–	–	–	–	73.3
Eosinophil (%)	3.1	3.2	2.7	3.5	1.6	–	–	–	–	1.9
Basophil (%)	0.6	0.4	0.5	0.8	0.4	–	–	–	–	0
Monocyte (%)	8.0	6.9	7.5	7.4	7.6	–	–	–	–	4.8
Lymphocyte (%)	35.3	20.9	20.5	27.6	23.9	–	–	–	–	14.3
Aty Lymphocyte (%)	0	0	0	0	0	–	–	–	–	0
Plasma Cell (%)	0	0	0	0	0	–	–	–	–	0
Normoblast (%)	0	0	0	0	0	–	–	–	–	0

* Laboratory data abnormality suggesting thrombocytopenia.
– Laboratory data were not available.
#1 Laboratory data were assessed upon the patient's arrival at the emergency room.
#2 Laboratory data were checked 2 h after transfusion with 12 units of platelets on the first hospitalization day.
#3 Laboratory data were examined before discharge on the 4th hospitalization day.
#4 Laboratory data were assessed at the outpatient department.

the Vaccine Adverse Event Reporting System (VAERS) of the United States [14].

In addition, thrombocytopenia can occur as a rare immune-related adverse event (IrAE) of the ICPi therapy [15,16]. ITP secondary to ICPi has been reported with ipilimumab [17], nivolumab [18], and pembrolizumab [19]. However, evidence of durvalumab-induced ITP is limited [15,20,21]. A recent Asian cohort receiving ICPi reported that thrombocytopenia developed in only one of 141 patients [21]. Typically, IrAEs occur 1–2 weeks after initial exposure or earlier after repeated exposure to durvalumab [15]. In our case, ITP might be associated with the short interval between exposure to durvalumab and Moderna vaccination because both the ICPi therapy and COVID-19 vaccination could stimulate the body's immune response [22].

The ethnic difference in the development of thrombocytopenia in patients receiving ICPi remains undetermined, although the estimated frequency of thrombocytopenia associated with ICPi is 1% in Western countries [23], slightly higher than that in an Asian cohort (0.6%) [21]. In addition, data on mRNA-based COVID-19 vaccine-induced ITP are limited. A review of the literature revealed 13 cases of ITP after receiving the Moderna vaccines in the United States [14]. In contrast, only one Asian male with previous ITP developed thrombocytopenia after receiving the Pfizer/BioNTech vaccine [24]. However, the vulnerability of different ethnic groups to COVID-19 vaccine-induced ITP remains inconclusive.

To date, this is the first case of new-onset ITP among Asians after the Moderna vaccine. In addition, this is the first reported case of severe ITP following an mRNA-based COVID-19 vaccine in a patient treated with ICPi therapy. We report this case to remind physicians to be aware of the occurrence of thrombocytopenia in patients receiving ICPi therapy and the recent COVID vaccine, although it could be rare among Asians.

Source(s) of support

Not applicable.

CRediT authorship contribution statement

Kah-Meng Chong: Conceptualization, Writing – original draft, Writing – review & editing. **Ching-Yao Yang:** Supervision, Investigation. **Chien-Chin Lin:** Supervision, Investigation. **Wan-Ching Lien:** Writing – review & editing, Conceptualization.

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