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Relapse of Evans syndrome following BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine: case report and literature review

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) vaccines are considered to be safe. Only few cases of vaccine-induced immune thrombocytopenia or immune hemolysis have been reported so far. Evans syndrome (ES) is a very rare syndrome characterized mainly by warm autoimmune hemolytic anemia (wAIHA) and immune thrombocytopenia (ITP).

Case presentation: We present a case of a 47-year-old male with a history of wAIHA, diagnosed in 1995 and successfully treated with glucocorticoids, with sustained remission. ITP was diagnosed in May 2016. Due to refractoriness to glucocorticoids, intravenous immunoglobulins (IVIGs), azathioprine and vinblastine, he was splenectomised in April 2017, resulting in complete remission. In May 2021, eight days after the second dose of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, he experienced mucocutaneous bleeding. Blood tests showed platelet count (PC) of 8×10^9/L, while his hemoglobin (Hb) was normal (153 g/L). He was treated with prednisone and azathioprine, without response. On day 28 after vaccine administration, weakness, jaundice and dark brown urine occurred. His laboratory tests: PC 27×10^9/L, Hb 45 g/L, reticulocytes 10.4%, total bilirubin 106.6 µmol/L, direct bilirubin 19.8 µmol/L, lactate dehydrogenase 633 U/L, haptoglobin <0.08 g/L, and positive Coombs test were consistent with ES relapse. After treatment with glucocorticoids, azathioprine and IVIGs, his blood count finally improved (PC 490×10^9/L, Hb 109 g/L) and remained stable on day 40 of hospitalization.

Conclusions: Although it is unclear whether the relationship between COVID-19 vaccination and relapse of ES in our patient is coincidental or causal, it highlights the need for monitoring of serious outcomes following vaccination.

Key words: Evans syndrome; relapse; COVID-19; vaccination.

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Introduction

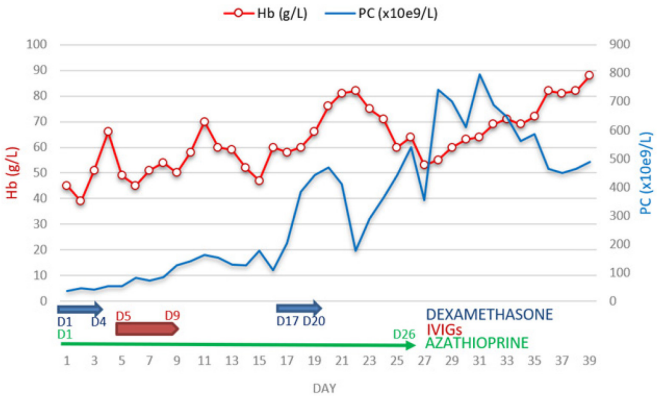
According to the World Health Organization (WHO) coronavirus disease 2019 (COVID-19) vaccines provide strong protection against serious illness, hospitalization and death. COVID-19 vaccines are considered to be safe even in pregnancy and childhood, except for occasional adverse events (AE) [1]. The most commonly reported serious complication is vaccine-induced immune thrombotic thrombocytopenia (VITT), usually seen after adenoviral vector vaccination [2]. Other hematologic complications are seldom registered, with only a few cases of immune thrombocytopenia (ITP) or warm autoimmune hemolytic anemia (wAIHA) reported so far [3-12]. Evans syndrome (ES) is a very rare condition of unknown etiology, characterized by simultaneous or sequential occurrence of two or more autoimmune cytopenias, most commonly wAIHA and ITP with or without autoimmune neutropenia, with reported incidence of 1.8 per million person-years [13-15]. The diagnosis is one of exclusion, and the possible mechanism of action involves IgG warm antibodies directed against red blood cell (RBC) surface antigens in wAIHA, and antibodies directed against GPIIb/IIIa on platelets in ITP [13,16]. We report a case of relapsing ES that occurred after the second dose of BNT162b2 (Pfizer-BioNTech) mRNA COVID-19 vaccine in May 2021.

Case presentation

A 47-year-old male presented with ecchymoses on his extremities and oral bleeding. He had a past medical history of wAIHA, diagnosed in 1995 and successfully treated with glucocorticoids, with complete and sustained remission, together with a history of ITP diagnosed in May 2016, thus fulfilling the criteria for ES. Due to refractoriness to glucocorticoids, intravenous immunoglobulins (IVIGs), azathioprine

and vinblastine, he was splenectomised in April 2017 with the consequent complete remission. Later on, in August 2017 and in June 2020, he experienced recurrences of ITP triggered by respiratory infections, and managed by short-courses of prednisone. In May 2021, eight days after the second dose of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, he noticed purpura on his extremities and bleeding from oral mucosa. His platelet count (PC) was 8×10^9/L, while his hemoglobin (Hb) was normal (153 g/L). He was initially treated in a regional medical center with prednisone and azathioprine, without response. On day 28 after vaccination, sudden weakness, jaundice and dark brown urine occurred and he was referred to our institution. On admission, he appeared pale and icteric, without bleeding or lymphadenopathy. His blood analyses showed Hb of 45 g/L, reticulocytes of 10.4% (0.12×10^{12}/L), PC of 27×10^9/L, total bilirubin - 106.6 µmol/L and direct bilirubin - 19.8 µmol/L, lactate dehydrogenase (LDH) of 633 U/L, and haptoglobin < 0.08 g/L. Both direct Coombs test (anti IgG antibody +++, anti C3 antibody -) and indirect Coombs test were positive, which is in line with wAIHA, and the diagnosis of ES was established. There were neither clinical signs, nor laboratory parameters of underlying autoimmune (rheumatoid factor negative, absence of antinuclear and anti-cardiolipin antibodies, normal complement factors; alpha beta double-negative T cells in the peripheral blood 0.34%) or malignant diseases. In addition, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, hepatitis B and C and *Mycobacterium tuberculosis* infections were ruled out. Bone marrow examination showed nonspecific reactive findings, consistent with ITP and wAIHA. On the day of admission, high dose dexamethasone was administered (40 mg i.v. daily, D1-D4) and response regarding PC was observed (53×10^9/L). As there was no improvement in Hb level (49 g/L), IVIGs were introduced (0.4 mg/kg/per day, D5-D9), resulting in sustained increase in PC (140×10^9/L), but still without significant effect on Hb level (58 g/L). Finally, after administering the second course of dexamethasone (D17-D20), and azathioprine ceased shortly after (D26), his blood count finally improved and became stable (PC 490×10^9/L, Hb 109 g/L), and he was discharged from hospital on day 40. During the hospitalization, the patient received 10 units of packed red blood cells, the last transfusion was given on D17. Hb and PC trends, as well as the response to different treatment modalities are presented in Figure 1.

Figure 1. Platelet count and hemoglobin trend.



Evolution of platelet count (PC), solid blue line, and hemoglobin (Hb), red line, and their response to the treatment since the onset of wAIHA. The X-axis represents the length of hospital days, and the Y-axes represent PC (×109/L) and Hb levels (g/L). IVIGs: intravenous immunoglobulins, wAIHA: warm autoimmune hemolytic anemia.

Discussion

COVID-19 vaccines are proven to be effective in limiting viral transmission, preventing symptomatic SARS-CoV-2 infection and severe disease in adults. Moreover, AE are mostly local, short-term and transient. That is, most people report localized injection site reactions or mild to severe systemic response, such as fatigue, myalgia, arthralgia, headache, that resolve without consequences [17]. Rarely, serious AE can occur such as deep venous thrombosis, pulmonary embolism, acute arterial thrombosis or thrombosis at unusual site in the days following vaccination. Since those AE were associated with thrombocytopenia, D-dimer elevation and normal or low fibrinogen levels, it was suggested that they should be part of VITT [18-20]. High levels of antiplatelet factor 4 antibodies were detected in almost all patients with VITT, confirming immunological hyperactivation [19]. This complication is mostly associated with viral vector vaccines [2, 18-20]. Lately, autoimmune cytopenias have been reported following COVID-19 vaccination, suggesting that the vaccine could trigger autoimmune disorder. The most commonly reported autoimmune cytopenia, usually associated with mRNA vaccines is secondary ITP. Since the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the mRNA Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines in December 2020, there have been an increasing number of reports to the Vaccine Adverse Event Reporting System (VAERS) [21,22]. The concept of immunization-induced thrombocytopenia is not new, nor is unusual at young age. Namely, ITP, either de novo or a relapse of ITP has been reported to be associated with various vaccines,

including measles-mumps-rubella (MMR), *Haemophilus influenzae*, diphtheria-tetanus-pertussis (DTP), polio and hepatitis B virus, with similar pathogenesis as in COVID-19 mRNA vaccine [23-27]. It is presumed that de novo ITP might be associated with molecular mimicry and circulating immune complexes, and that an ITP relapse is the result of pre-formed antibodies [28]. We searched VAERS database with following filters: COVID-19 vaccine, vaccine manufacturer Moderna and Pfizer/BioNTech, ≥18 years, and as adverse event used term ITP. By October 16th 2022, 385 reports of ITP were found in the United States, and 539 overall. There is no standard therapeutic approach or guideline for COVID-19 vaccine-induced ITP. Our treatment approach seems to be similar to the others, and most of the patients were treated successfully with glucocorticoids and IVIGs [5-7].

While ITP secondary to COVID-19 vaccination has already reached public attention, there have not been many cases of wAIHA reported, with only few published until now, and all of them were associated with mRNA vaccines. All cases have been successfully treated with glucocorticoids and transfusion support [3,8-12]. wAIHA has previously been described as an adverse reaction to other viral vaccines such as *Haemophilus influenza*, DTP, polio, with possible mechanism of action being molecular mimicry [29-31]. While searching VEARS using filters: COVID-19 vaccine, vaccine manufacturer Moderna and Pfizer/BioNTech, ≥18 years, and as adverse event used term warm AIHA, we found 20 reported cases of wAIHA, with 5 cases excluded (cold agglutinin disease, inadequate definition, COVID-19 infection). Only 8 cases were published so far, as to our knowledge [12].

Here, we report a case of relapsing ES that occurred after the second dose of BNT162b2 mRNA COVID-19 vaccine. Considering the temporal relationship between vaccination and the uncommon complication, we assumed that the mRNA COVID-19 vaccine might trigger a relapse of ES in our patient. There are several ES cases published as a complication of other vaccines, such as *Haemophilus influenzae* and hepatitis B vaccine [32,33]. Eighteen cases associated with SARS-CoV-2 vaccine have been reported to VAERS by October 16th 2022. Of these 18 cases, 7 were excluded (only one cytopenia present, inadequate definition, COVID-19 infection), leaving 11 cases, with 6 of them having no detailed AE description. Two case reports of new-onset ES following BNT162b2 mRNA COVID-19 vaccination have been published so far [34,35]. Although ES relapse is very common [13], it has not yet been described as an AE following Pfizer-BioNTech COVID-19 vaccination.

Conclusions

Although it is unclear whether this relationship between COVID-19 vaccination and relapse of both ITP and wAIHA is coincidental or causal, it highlights the need for monitoring and accurate management of possible vaccine life-threatening AE. In addition, the extreme rarity of these AE favors the beneficial effect of vaccine.

Authors' contributions

MC, NP, and MM designed and wrote the first version of the manuscript. MV, ZP, NS and NSV contributed to the clinical management of patient. MC, NP, MV, ZP, and NS contributed to reviewing the literature. MM and NSV supervised the study. All authors read, provided feedback and approved the final manuscript.

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