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## Immune-Mediated Thrombocytopenia Associated With Ad26.COV2.S (Janssen; Johnson & Johnson) Vaccine

### *To the Editor:*

Immune thrombocytopenia (ITP) is an acquired coagulopathy caused by antibody-mediated platelet destruction. Patients may be asymptomatic or may present with mucocutaneous to life-threatening bleeding.<sup>1</sup> Vaccines such as influenza, MMR, hepatitis B, and diphtheria-tetanus-pertussis have been reported to cause ITP.<sup>2</sup> Approximately 40 cases of ITP were reported to the Vaccine Adverse Event Reporting System after receiving the Pfizer and Moderna COVID-19 vaccines by the end of January 2021.<sup>3</sup> It is unknown whether these cases include those with pre-existing thrombocytopenia. Here, we present a case report of an elderly woman presenting with life-threatening thrombocytopenia after receiving the Ad26.COV2.S (Janssen; Johnson & Johnson, New Brunswick, NJ) vaccine. To the best of our knowledge, this is the first publication of isolated severe thrombocytopenia in a patient with no pre-existing risk factors after receiving the Ad26.COV2.S vaccine.

A 63-year-old woman with a medical history of cervical cancer status after total hysterectomy, presented to the hospital with complaints of bleeding from her gums for the past 3 days. Seventeen days before presentation, the patient had received the Ad26.COV2.S (Janssen; Johnson & Johnson) vaccine. She did not experience any major side effects after her vaccination except for muscle soreness at the administration site. She did not have fever, chills, shortness of breath, or recent infections. A week later, she went for a routine dental checkup which was unremarkable. She started experiencing bleeding in her gums 3 days before presentation. She later had sudden onset nose bleeds which prompted her to go to the emergency department.

On presentation to the emergency department, the patient was hemodynamically stable and afebrile. Her bleeding had resolved. Complete blood count showed hemoglobin 12.2 g/dL, hematocrit 36.3%, white blood

cell count  $10.9 \times 10^3$  cells/uL, and significant severe thrombocytopenia  $2 \times 10^9$ /L. Her international normalized ratio was 1.02, with a prothrombin time of 13.5 seconds and a partial thromboplastin time of 27.0 seconds. Hemolytic workup was completed with lactate dehydrogenase 150 U/L, haptoglobin 192 mg/dL, and D-dimer 0.76.

On admission, she received 2 units of platelets. She was also given a one-time dose of prednisone 60 mg orally. Her repeat platelet count posttransfusion improved to  $14 \times 10^9$ /L. Hematology was consulted and recommended starting the patient on immune globulin (human) infusion intravenously and dexamethasone 20 mg daily.

Throughout admission, the patient's platelet count steadily increased. She did not have further bleeding episodes and did not require additional platelet transfusions. Testing for HIV and hepatitis B and C was negative. Heparin-induced platelet IgG antibody was negative. Imaging including ultrasound Doppler of the abdomen/pelvis, ultrasound Doppler of upper and lower extremities, magnetic resonance venogram of the head, and computed tomography angiography of the thorax showed no evidence of thrombosis. The patient remained hemodynamically stable throughout admission with no signs of active bleeding. She was ultimately deemed stable for discharge 5 days after admission, with a platelet count of  $252 \times 10^9$ /L.

Immune thrombocytopenia purpura (ITP) is a diagnosis of exclusion characterized by a decrease in platelet count and prolonged bleeding time secondary to impaired platelet production or destruction of circulating platelets. Patients are commonly asymptomatic; however, based on the severity of thrombocytopenia, clinical features include easy bruising, petechiae, bleeding gums, hematuria, or melena. ITP is often triggered idiopathically; however, other triggers include previous viral or bacterial infections, lymphoma or

leukemia, or autoimmune diseases. Vaccines such as influenza, MMR, hepatitis B, HPV, varicella, and diphtheria-tetanus-pertussis (DPT) have also shown an increased risk of ITP.<sup>4</sup> The main mechanism of action is a cross-reaction between platelet antibodies and platelet antigens, such as GP Ib/IX, GP Ia/IIa, and GP VI. There may also be antigen responses to vaccine adjuvants, constituents and preservatives or by molecular mimicry, epitope spreading, and polyclonal activation.<sup>5</sup>

A causal or coincidental relationship between thrombocytopenia and COVID-19 vaccination is yet to be determined. As per the US FDA and CDC and Prevention, the incidence of ITP after COVID-19 vaccination was not greater than that of the general population.<sup>4</sup> However, a prospective study published in the British Journal of Hematology found that vaccination can cause exacerbation in those with chronic ITP in up to 12% of patients.<sup>6</sup>

Another entity that can manifest is vaccine-induced thrombotic thrombocytopenia (VITT) and has been reported in approximately 3.2 cases per million after administration of Ad26.COV2.S vaccine.<sup>7</sup> VITT is pathogenically linked to autoimmune heparin-induced thrombocytopenia with the demonstration of antiplatelet factor 4 antibodies.<sup>7</sup> VITT is associated with propensity for cerebral and/or splanchnic vein thrombosis, consumptive coagulopathy, and poor outcomes.<sup>7</sup> Given the high rate of mortality associated with VITT, it is important to rule this out in patients with thrombocytopenia after COVID-19 vaccination.

The treatment of immune thrombocytopenia includes corticosteroids, intravenous immunoglobulin, and IV Rh Anti-D. Second-line pharmacotherapy such as dapsone and rituximab is also commonly used. In cases of severe life-threatening hemorrhage, surgical intervention with splenectomy is suggested.<sup>8</sup> Most reported cases of ITP after COVID-19 vaccination have a response to corticosteroid and Intravenous Immunoglobulin usage.<sup>9</sup>

The SARS COVID-19 pandemic has catalyzed the development of a multitude of highly effective vaccines. Minor side effects of COVID-19 vaccination have included pain at the injection site, ipsilateral axillary lymph node enlargement, fever, fatigue, and headache.<sup>10</sup> Major side effects include rare cases of anaphylaxis and thrombosis with thrombocytopenia.<sup>7,11</sup> To the best of our knowledge, this is the first case of an individual with no other identifiable cause experiencing ITP after receiving the Ad26.COV2.S (Janssen; Johnson & Johnson) vaccine. The possibility of vaccination-triggered de novo ITP cannot be excluded; however, the abrupt occurrence 17 days after vaccine administration and a severe drop in platelets to  $2 \times 10^9/L$  raise concern for drug-induced thrombocytopenia. With

widespread distribution and administration of the COVID-19 vaccine, additional surveillance and analysis of data are needed to determine the true correlation or causation of severe thrombocytopenia after vaccination.

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## Pembrolizumab-Induced Myocarditis Leading to Persistent Atrial Arrhythmias and a Cascade of Complications: A Therapeutic Dilemma

*To the Editor:*

### CASE REPORT

A 73-year-old man with a past medical history of hypertension, hyperlipidemia, tobacco use, coronary artery disease status after stent placement in all 3 main coronary arteries in 2013, stage IV adenocarcinoma of the lung, and paroxysmal atrial fibrillation (AF) on apixaban 5 mg twice daily presented to the emergency department after a fall. He was diagnosed with right upper lobe lung adenocarcinoma 1-year ago and underwent cyberknife radiation treatment. He was later found to have brain metastasis and underwent cyberknife radiation to a solitary brain lesion, followed by immunotherapy with an immune checkpoint inhibitor (ICI), pembrolizumab. One week later, he felt lightheaded and had an episode of syncope in his garage and eventually presented to the emergency department by emergency medical services with a heart rate (HR) of 120 beats/min. An electrocardiogram showed AF with a rapid ventricular response. He was started on a diltiazem drip and given one dose of oral metoprolol tartrate 50 mg, and of note, he continued his home dose of apixaban. The patient had a difficulty to control AF and developed hypotension and underwent transesophageal echocardiography-guided cardioversion. Normal sinus rhythm was achieved, but he had early recurrence of AF. He was started on sotalol 80 mg twice a day, and although his HR was controlled, he developed respiratory distress requiring oxygen supplementation with an FiO<sub>2</sub> of 40%.

During next 5 days (days 2–6), the patient developed worsening hypotension (82/49 mm Hg) on rate control medications, and diltiazem was discontinued. Patient's platelet count dropped from 140,000 to 30,000. Patient did not receive any heparin and had no signs of infection, and his thrombocytopenia was attributed to

pembrolizumab and was started on 1 mg/kg of methylprednisolone with improvement in his thrombocytopenia over the next several days.

The patient's respiratory status slowly improved, and he was weaned to nasal cannula oxygen supplementation, and attempts to achieve normal sinus rhythm through cardioversion 2 more times were unsuccessful.

On days 7–11 of admission, echocardiogram was repeated that revealed a soft tissue density within the pericardial space. A subsequent computed tomography scan showed a large amount of epicardial fat and lipomatous hypertrophy of the interatrial septum, raising a concern for myocarditis. The patient's erythrocyte sedimentation rate was elevated to 47, and his C-reactive protein was elevated to 11.9. The patient was still requiring 6 L of oxygen supplementation on nasal cannula, so an infectious sputum workup was pursued, which was positive for *Pneumocystis jirovecii* pneumonia by polymerase chain reaction testing. The patient was started on atovaquone 750 mg twice a day (due to allergy to trimethoprim sulfamethoxazole). A cardiac magnetic resonance imaging (MRI) was performed and had increased signal intensity of the apical myocardium with midwall late gadolinium enhancement involving the apical septum and lateral wall, suggesting a myocardial inflammatory process. He was treated with steroids with 1 mg per kg of prednisone for 1 week, which was tapered over a course of 21 days, which would later show myocardial inflammation resolution on outpatient repeat cardiac MRI after discharge. As the patient developed myocarditis and cardiac arrhythmias (both tachycardia and bradycardia), the patient did not receive a second dose of pembrolizumab.

On day 15 of admission after adequate rate control, blood pressure control, and oxygen supplementation, the patient was discharged to a subacute rehabilitation facility (in AF) on metoprolol 12.5 mg twice daily, amiodarone 200 mg daily, 2 L of oxygen supplementation at rest, the remainder of his home medications,