

Immune Thrombocytopenic Purpura (ITP) Triggered by COVID-19 Infection and Vaccination

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Immune thrombocytopenia (ITP) is an autoimmune condition caused by the inhibition of platelet production and circulation by autoantibodies. It presents clinically as minor to major bleeding secondary to the thrombocytopenia [1]. The most common form of ITP is idiopathic, but it has been described following various infections and drugs, and most recently, vaccinations [1].

Since the beginning of the coronavirus disease-2019 (COVID-19) pandemic in December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was postulated as a potential trigger to numerous autoimmune disorders [2]. Specifically ITP has been reported following SARS-CoV-2 infection [3]. Different vaccines against the infection were given worldwide in an attempt to control the SARS-CoV-2 pandemic, raising the question of whether ITP may also result from COVID-19 vaccination, in addition to the infection.

COVID-19 AND ITP

The development of autoimmune manifestations following different viral in-

fections may occur through multiple potential mechanisms, including molecular mimicry between human cells and specific viral components leading to antigenic cross-reactivity [1] and the ability of some viruses to induce hyper-stimulation of the immune response [4]. Both mechanisms seem to contribute greatly to the development of an autoimmune response following SARS-CoV-2 [2]. Thus, as could be predicted, COVID-19 was found to be associated with numerous autoimmune manifestations, including the production of various pathological autoantibodies, new onset of some autoimmune diseases, and other immune-mediated disorders.

Concerning molecular mimicry, SARS-CoV-2 had been shown to possess numerous primary sequences that are homologous to various human components [5]. These homological sequences have substantial pathological potential due to possible cross-reactivity with self-antigens, which could lead to the new onset of an autoimmune response. Hyperstimulation of the immune response generated by the SARS-CoV-2 could escalate this pathological potential of autoimmunity [2].

Thrombocytopenia has been frequently described in COVID-19 patients and identified in up to 36% [6]. Although most COVID-19 patients develop merely mild thrombocytopenia, some have been documented with a severe presentation. Thrombocytopenia in COVID-19 patients may be caused by various factors leading

to shortened survival time of platelets and reduction in their production from megakaryocytes. As SARS-CoV-2 infection is associated with many immune-mediated manifestations, including blood-related disorders, ITP is an essential segment of the severe thrombocytopenia presentation of COVID-19 patients.

Since the first ITP in COVID-19 patients was published, many additional cases have been documented [3,7,8]. Nevertheless, numerous similar cases might have been unrecognized or fallen under the radar. In April 2020, the *New England Journal of Medicine* published one of the first ITP case reports on a patient with COVID-19 [3], which had a classical presentation of viral-induced ITP. The patient had been admitted to the hospital due to COVID-19 with a normal platelet level, yet the platelet level had decreased rapidly throughout her stay, reaching 1000 per cubic millimeter and accompanied by lower extremity purpura. On day 9 of admission, a subarachnoid microhemorrhage in the right frontal lobe was identified. Due to sufficient treatment, the patient recovered on day 13, when platelet count was 139,000 per cubic millimeter, and the purpura had disappeared. Noteworthy, this patient had autoimmune hypothyroidism in her medical history with increased thyroid peroxidase antibody levels in her addition [6].

Similar to the previous presentation, in this issue of the *Israel Medical Association Journal (IMAJ)*, Kupietzky et al. [9] docu-

mented an additional case of ITP secondary to SARS-CoV-2 infection in a 70-year-old patient with no medical history of autoimmune diseases or hematological disorders. The patient had developed sudden and severe thrombocytopenia in the recovery stages of severe COVID-19. Possible causes of thrombocytopenia such as viral, bacterial, and hypercoagulation disorders were all negative, except for the existence of anticardiolipin IgM autoantibodies (11.6 μ /ml). Thus, a diagnosis of ITP secondary to SARS-CoV-2 infection had been made. Platelet count had reached 3000 per cubic millimeter under treatment with hydrocortisone, with no signs of signs of bleeding or thrombosis. After further treatment of intravenous dexamethasone and immune globulin (IVIG), platelet count had improved to 14,000 per cubic millimeter and the patient had been discharged. Following one month of ambulatory hematologic follow-up and prednisone treatment, platelet count had reached normal levels above 150,000 per cubic millimeter.

ITP secondary to some viral infections is a well-established autoimmune manifestation. For example, a study including 3440 patients infected with hepatitis C virus (HCV) had shown a significant association between the virus and ITP development, based on the presence of antiplatelet antibodies ($P < 0.00001$) [10]. Another well-characterized cause of ITP occurs in human immunodeficiency virus (HIV) infection [11]. Thus, it should not be surprising that SARS-CoV-2 could possess the ability to trigger ITP in infected patients.

VACCINES, COVID-19 VACCINES, AND ITP

In parallel to ITP following SARS-CoV-2 infection, in this issue of *IMAJ* Ganzel and colleagues [12] reported a 53-year-old man who was admitted to the emergency department with epistaxis and thrombocytopenia that appeared 2 weeks after the first dose of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine (Pfizer Inc, USA; BioNTech SE, Germany). In addition to the vaccination, he had recently been treated with levofloxacin for

otitis one week before his hospitalization. According to his physical examination and laboratory results, an ITP diagnosis was made. No infectious or autoimmune causes for ITP were found and he was treated with steroids with good response and the platelets count was normalized. This finding raises the question whether COVID-19 vaccination could also lead to ITP?

ITP has been described as induced by vaccination. Many mechanisms may be involved in the pathogenesis, including molecular mimicry, epitope spreading, and polyclonal activation. In addition, the presence of adjuvants in vaccine compositions, such as aluminum, to enhance the immune response, is also believed to be an important example of the environmental factors involved in the mosaic of autoimmunity [13]. The aluminum, in addition to other metals, silicone, and tattoo, as well as others adjuvants, can trigger autoimmune/inflammatory syndrome by adjuvants (ASIA), a group of autoimmune defined conditions and immune reactions that flourish after the exposure to these molecules [13]. ITP has been described as one of these disorders. In fact, approximately 45% of drug-induced ITP that was included in a French study were post-vaccinal [14].

Most of the cases of post-vaccine ITP described were mild. Rare instances of severe ITP responded well to treatment with IVIG treatment. ITP had been associated with different vaccines. The most described vaccine is measles-mumps-rubella (MMR), but many others were also reported, including influenza, hepatitis B virus (HBV), human papilloma virus (HPV), diphtheria-tetanus acellular pertussis (DTap), polio, pneumococcus, *Haemophilus influenzae*, and varicella-zoster [15].

The fact that ITP developed after vaccines both with and without adjuvants points to a possible molecular mimicry mechanism between the vaccine antigens and the human molecules. Indeed, the influenza vaccine, for example, which was associated with ITP, contains hemagglutinin as its main antigen, a molecule that

can bind receptors present in platelet surface, possibly explaining the platelet as targets to the autoantibodies in ITP [16].

Regarding ITP following the COVID-19 vaccines, we found one case report of ITP following the mRNA=1273 (Moderna) COVID-19 vaccine [17] and one case following the Pfizer-BioNTech BNT16B2b2 mRNA vaccine [18]. When looking for ITP as an adverse effect of COVID-19 vaccines in the Vaccine Adverse Event Reporting System (VAERS) database, an international program for control of vaccine adverse effects and safety by the U.S. Food and Drugs Administration (FDA) and U.S. Centers for Disease Control (CDC)—66 cases of ITP were reported (32 after the Moderna vaccine and 34 after Pfizer vaccine: CDC WONDER online database. Available from <http://wonder.cdc.gov/vaers.html>; accessed in 16 April 2021). Wise [19] mentioned 150 cases of thrombocytopenia after coronavirus vaccine [19]. Still calculated incidence per year of ITP following COVID-19 vaccination seems to be lower than the idiopathic ITP incidence in the United States, suggesting that either the vaccine is a rare but possible trigger to the disease or those cases were simply coincidental.

Both the Moderna and Pfizer COVID-19 vaccines are messenger-RNA (mRNA) vaccines that do not contain aluminum as part of their components. The RNA encoding for the SARS-CoV-2 protein is protected from degradation when in the blood, but once in the host cell, is transcribed into the S protein creating a immune response against it.

Naturally, molecular mimicry and cross-reaction are probably involved in the pathogenesis of ITP following immunization against COVID-19 since, as previously mentioned, the SARS-Cov-2 infection was already shown to trigger autoimmune responses. However, other mechanisms could explain this association.

An effective type I interferon reaction was already shown to be created in response to m-RNA vaccines. This response is also involved in inflammation and autoimmune processes. This result occurs

because despite the lysosome protection conferred to mRNA, it can be easily recognized by pattern recognition receptors (PRRs) after its entrance in the cell, enhancing numerous pro-inflammatory cascades, including the type 1 interferon response [20].

There is scarce reporting in the literature to explain if and how COVID-19 vaccines could induce ITP. Certainly, the benefits of the COVID-19 mass immunization overcome the risks, but clinicians should be aware of the possibility of this association to promptly treat it if needed.

CONCLUSIONS

COVID-19 is associated with numerous autoimmune manifestations, including the production of pathological various autoantibodies, new onset of some autoimmune diseases, and other immune-mediated disorders. Some of these manifestations include blood-related disorders such as ITP [2,3,7,8]. Important to note, thrombocytopenia had been frequently described in COVID-19 patients, identified in up to 36% [6]. Although most COVID-19 patients develop mild thrombocytopenia, some have been documented as presenting with a severe presentation. ITP holds an important segment of the severe thrombocytopenia presentation by COVID-19 patients.

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Words are a kind of natural resource; it is impossible to have too many of them.

Robert Watson Claiborne, Jr. (1919–1990), American writer, folk singer, and labor organizer

Capsule

Taking machine learning to heart

Both children and adults can have cardiac problems. Congenital problems predominate in childhood, whereas adults are more likely to present with conditions associated with age. In both cases, however, accurate diagnosis depends on access to healthcare and the availability of trained specialists. In two recent studies, **Arnaut** et al. and **Yao** et al. showed how machine learning can supplement specialist care in both pediatric and adult cardiology settings. **Arnaut** and colleagues analyzed fetal ultrasound images

to detect congenital heart disease. **Yao** et al. used machine learning in conjunction with electrocardiogram imaging to detect adults with low ejection fraction (a measure of the amount of blood that the heart succeeds in pumping), which is a risk factor for subsequent heart failure. In each case, the technology should help to improve diagnostic accuracy and access to appropriate treatment.

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