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LETTER TO THE EDITOR

Immune thrombocytopenia secondary to COVID-19 infection: Report of two cases

To the Editor:

Immune thrombocytopenia (ITP) is well described in childhood, affecting approximately 1.9–6.4 /100,000 children per year.[1] It has been linked to vaccinations and viral infections occurring approximately 1–3 weeks earlier. Recovery time is usually less than 3 months. The suggested management is "watch and wait," but in cases with active mucosal bleeding treatment with corticosteroids and/or intravenous immunoglobulin (IVIG) is recommended.[2]

Infection with the severe acute respiratory syndrome–corona virus-2 (SARS-CoV-2) could represent a novel cause of secondary immune phenomena including thrombocytopenia.[3] Although in adults cases suspicious of ITP have been reported in the setting of corona virus disease 2019 (COVID-19),[4–6] similar reports in pediatric patients are scarce.[7]

Herein, we describe two pediatric patients with ITP, temporally and possibly causally, related to a preceding, real-time polymerase chain reaction (RT-PCR) confirmed, COVID-19 infection, presenting in two tertiary hospitals when the second wave of the pandemic swept northern Greece in late 2020.

Patient 1: A 15-year-old male presented with epistaxis, petechiae, and bruises that had commenced 7 days earlier. On admission, he was hemodynamically stable, with unremarkable physical examination apart from the bruises and petechiae. Blood tests revealed severe thrombocytopenia (platelets = 1000/μL), whereas the rest of the full blood count was normal (hemoglobin = 16 g/dl, white blood cells [WBC] = 7070/μl, N: 72.7%, L:19%, M: 7.5%). Liver and renal function and coagulation tests were normal. Serology for viruses commonly associated with ITP (Epstein–Barr virus [EBV], seasonal influenza, adenovirus, hepatitis C, Varicella Zoster virus [VZV], and cytomegalovirus [CMV]) was negative. His RT-PCR for SARS-CoV-2 was negative. He had no past medical or family history of autoimmunity or previously abnormal laboratory tests. Interestingly, he reported a history of an asymptomatic, RT-PCR-confirmed, COVID-19 infection 5 weeks earlier requiring no treatment or hospitalization. Due to the very low platelet count, he was treated with IVIG (1 g/kg), with a good clinical and laboratory response. He was discharged four days later with a platelet count of 49,000/μl, which gradually increased to 110,000/μl during 12 weeks of follow-up.

Patient 2: A 3-year-old female child was referred to the pediatric A&E because of thrombocytopenia. Disease onset was 3 days earlier, with low-grade fever for 24 h, epistaxis, and melaena (due to nasal bleeding). On admission she was hemodynamically stable and in good clinical condition. Physical examination revealed approximately 10 ecchymoses (<3 cm) in several parts of her body but was otherwise unremarkable with no organomegaly or lymphadenopathy. She had one further episode of nasal bleeding upon admission. Laboratory findings revealed moderate thrombocytopenia (platelets = 26,000/μl) with normal hemoglobin = 10.4 g/dl, WBC:6950/μl (N:46%, L: 39%, M:11%), coagulation and biochemistry. Viral infections known to trigger ITP (EBV, CMV, Herpes Simplex virus, Hepatitis C, adenovirus, seasonal influenza, and VZV) were excluded with serologic tests, whereas RT-PCR for SARS-CoV-2 was negative. Of note, she had a history of RT-PCR-confirmed COVID-19 infection 3 weeks earlier, with mild pyrexia and fatigue for 48 h, not requiring hospitalization. No medical or family history of autoimmunity or previous abnormal laboratory tests was reported. Because of the continuing epistaxis, IVIG was administered (1 g/kg), with immediate clinical and laboratory improvement. She had no further bleeding episodes, her platelet count increased to 100,000/μl and she was discharged 2 days later. During 12 weeks of follow-up, her platelet count gradually increased to 236,000/μl and remained stable.

Our hypothesis is that in these patients ITP is possibly related to SARS-CoV-2 based on the serological exclusion of other viral infections, and the evidence of preceding COVID-19 infection (asymptomatic-first patient/mild-second patient), which were molecularly confirmed 3–4 weeks prior to manifestation of thrombocytopenia.

There is a growing body of literature regarding the clinical and laboratory manifestations of COVID-19 infection in children. The vast majority of reports refer to the period of acute infection, when leukopenia and anemia can be present, although most children have normal counts.[8] Thrombocytopenia has been reported in relation to severe disease or to the multisystem inflammatory syndrome.[8] As the infection runs a mild course in children and adolescents, follow-up with blood tests or physical examination is not advised unless clinically indicated. Since the beginning of the pandemic >3.9 million pediatric cases of SARS-CoV-2 infection have been recorded in the United States alone,[9] however no severe hematologic sequalae were reported.

Up to date, only three patients <18 years old with ITP after COVID-19 have been reported. All of them were pre-adolescents/adolescents, with platelets <10,000/μl, no active bleeding, and were treated with IVIG or corticosteroids with adequate clinical/laboratory response.[7,10,11] One of the patients presented herein is 3.5 years old, the youngest reported to date.

In addition, there are reports of thrombocytopenia cases temporally related to COVID-19 vaccination, raising the question of a possible association. Vigilance is advised among clinicians, as it is still unclear whether this relationship is coincidental or causal.[12,13,14]

The experience to date is that COVID-19 is associated with immune phenomena via the production of cytokines and autoantibodies, therefore manifestations such as myositis, arthritis, hemolytic anemia, thrombocytopenia, and acute demyelination could be expected after COVID-19.[3] Given these special characteristics of the SARS-CoV-2, it is plausible that it could also trigger childhood ITP, behaving in a way similar to other viruses.

Possible pathogenetic mechanisms are similar to other postinfectious and postvaccination ITP, depend on the phase of COVID-19 infection, and include (1) reduced platelet production due to destruction of the bone marrow progenitor cells by the cytokine storm or due to reduced thrombopoietin caused by direct liver damage and (2) increased platelet destruction via production of cross-reacting autoantibodies (via molecular mimicry). During the acute phase of COVID-19 infection, thrombocytopenia has been attributed to platelet consumption due to lung microthrombi.[6,15,16]

We report these cases to raise awareness among pediatricians and pediatric hematologists to look for evidence of SARS-CoV-2 infection in the period immediately before ITP in order to increase our understanding of the condition.

In addition to the previous reports, these patients offer further evidence that ITP could be secondary to COVID-19, similarly to other infections and vaccinations, but unlike other coronaviruses. Additional research is warranted to investigate whether infection with SARS-CoV-2 represents a frank cause of ITP or other immune cytopenias to decipher the role of predisposing factors and to determine whether the clinical course in these patients is the same as post other causes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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