

Immune Thrombocytopenia (ITP) in a Pediatric Patient Positive for SARS-CoV-2

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Immune thrombocytopenia (ITP) is a potential presentation of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing should be considered in these patients to allow for appropriate hospital triaging and isolation to limit community spread and health care worker infection during epidemics or pandemics. ITP is characterized by isolated thrombocytopenia. Approximately two-thirds of children with primary ITP have a history of a viral infection during the previous month.^{1,2} Viruses commonly identified as triggers include cytomegalovirus, hepatitis C, herpes, varicella zoster, Epstein-Barr, influenza, and HIV.³⁻⁷ In this case report, we describe the first documented case of a pediatric patient with ITP who tested positive for SARS-CoV-2. This case raises awareness of ITP as a possible pediatric presentation of coronavirus disease.

abstract

PATIENT PRESENTATION

A 10-year-old previously healthy girl presented to the emergency department for one day of rash. The rash spread from her bilateral lower extremities to her chest and neck over 24 hours. On the morning of presentation, she developed purple lesions in her mouth and new bruises. The patient had a mild illness 3 weeks ago with 2 days of fatigue, nonproductive cough, and fever to 38.3°C in the setting of a known severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure. She then felt completely well for 2.5 weeks until she developed the rash. She denied fever, cough, difficulty breathing, chest pain, abdominal pain, gum bleeding, dysuria, easy bruising or bleeding, weight loss, decreased appetite, or enlarged lymph nodes. She took no medications, had no allergies,

and had no family history of hematologic or autoimmune disorders.

The patient's vital signs were temporal temperature 37.3°C, heart rate 90 beats per minute, respiratory rate 20 breaths per minute, blood pressure 120/77 mm Hg, and oxygen saturation 100% on room air. On physical examination, the patient was a well-appearing, conversant girl, with oral examination notable for wet purpura (Fig 1). Skin examination showed petechiae concentrated on her lower extremities, chest, and neck (Figs 2 and 3) and ecchymoses in the popliteal regions and shins. Cardiac, pulmonary, abdominal, neurologic, and lymph node examinations were normal. Testing revealed normal partial thromboplastin time, prothrombin time, international normalized ratio, and electrolytes. Complete blood count showed low white blood cell count ($3.9 \times 10^9/L$

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Dr Tsao drafted the initial manuscript; and all authors conceptualized and designed the case report, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: <https://doi.org/10.1542/peds.2020-1419>

Accepted for publication May 18, 2020

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To cite: Tsao HS, Chason HM, Fearon DM. Immune Thrombocytopenia (ITP) in a Pediatric Patient Positive for SARS-CoV-2. *Pediatrics*. 2020; 146(2):e20201419

[56% neutrophils, 38% lymphocytes, 6% monocytes]), normal hemoglobin (13.4 g/dL), normal hematocrit (39.3%), and low platelets ($5 \times 10^9/L$). Reverse transcriptase–polymerase chain reaction testing was positive for SARS-CoV-2. A respiratory pathogen panel was positive for rhinovirus/enterovirus, and negative for adenovirus, coronavirus (types 229E, HKU1, NL63, OC43), human metapneumovirus, influenza A and B, parainfluenza virus 1 to 4, respiratory syncytial virus A and B, *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Given the patient's severe thrombocytopenia and wet purpura in the setting of suspected immune thrombocytopenia (ITP), her risk for severe bleeding was significant, and she was admitted to the hematology service. She received 400 mg acetaminophen and 30 mg (1 mg/kg) diphenhydramine as pretreatment, followed by 30 g (1 g/kg) intravenous immunoglobulin (IVIg). She was discharged from the hospital the next morning.

She had telehealth visits with the hematology and infectious disease providers 2 days after being discharged. During these 2 days, she took acetaminophen every 6 hours and diphenhydramine every 12 hours. Her rash and oral lesions improved within 48 hours after IVIg administration. However, she developed a temperature to 37.9°C, decreased appetite, headache, nausea, 2 episodes of emesis, and abdominal pain likely secondary to IVIg.

At the hematology telehealth visit 2 weeks after hospital discharge, her symptoms had completely resolved. Her repeat complete blood count was normal (white blood cell count: $6.1 \times 10^9/L$; platelets: $320 \times 10^9/L$). She had a mild transaminitis (alanine aminotransferase: 56 IU/L; aspartate aminotransferase: 28 IU/L) likely secondary to viral illness that will be rechecked in 2 months. She had



FIGURE 1
Wet purpura on oral mucosa.

a negative direct antiglobulin test. Given that she was >6 years old and at higher risk for underlying autoimmune disease with her first ITP presentation, antinuclear antibodies (ANAs) were sent and were reactive with borderline positive titers (1:40) in a speckled pattern. As many as 31.7% of healthy adults have positive 1:40 ANA titers.⁸ The patient's single positive ANA in the absence of family history of autoimmune disorders is likely not significant and does not suggest increased risk of future autoimmune disease. The ANA will be trended during a follow-up visit.

DISCUSSION

In this case, we illustrate the presentation, clinical course, follow-up, and public health implications of



FIGURE 2
Petechiae on chest and neck.



FIGURE 3
Petechiae and ecchymoses on shins.

the first documented case of ITP in a pediatric patient who tested positive for SARS-CoV-2. We also describe the presentation, workup, and treatment options of ITP in children.

ITP is a disease characterized by isolated thrombocytopenia of $<100 \times 10^9/L$ platelets.⁹ Although some causes of ITP are unknown, established triggers include a previous viral, immunologic, or environmental inciting event. The pathogenesis of ITP is not fully understood. However, the thrombocytopenia is hypothesized to come from 3 mechanisms: autoantibody-mediated decreased platelet production, autoantibodies directed against platelet membrane antigens that cause increased splenic clearance of platelets and shortened platelet half-life, and deficient platelet formation in the bone marrow.

ITP classically presents with a petechial rash, bruising, and/or bleeding in an otherwise well-appearing child without systemic symptoms. Mucosal bleeding occurs in 40% of patients with ITP.¹⁰ Acute ITP typically occurs after a viral illness, and platelet counts often spontaneously recover within weeks

to months.¹¹ Chronic ITP occurs when thrombocytopenia persists for >12 months.^{9,12} The peak incidence of ITP in children is at 5 or 6 years old.⁹ Most children, with or without treatment, recover from ITP within 3 to 6 months of initial presentation.^{1,13} Approximately 10% to 20% of children with acute ITP develop chronic ITP. Risk factors include older age, insidious symptom onset, higher platelet count at time of diagnosis, and lack of preceding infection or vaccination.^{12,14,15}

Two-thirds of children with a new ITP diagnosis had a viral illness during the past month.^{1,2} The most common viruses that have been identified as potential ITP triggers include cytomegalovirus, hepatitis C, herpes, varicella zoster, rubella, Epstein-Barr virus, influenza, and HIV-1 virus.³⁻⁷ It has been postulated that molecular mimicry between viral antigens and host proteins results in viral-mediated ITP.⁴

According to a consensus report by Provan et al,¹⁶ the initial investigation for ITP should include a thorough history, physical examination, complete blood count and peripheral blood smear review, direct antiglobulin test (to exclude autoimmune hemolytic anemia), and baseline immunoglobulin levels (to exclude common variable immunodeficiency). Bone marrow aspiration, biopsy, and cytogenetics are not required unless there are abnormal or potentially malignant cells on the blood smear; abnormalities in the hemoglobin and/or white cell count (with the exception of microcytic anemia), hepatosplenomegaly, adenopathy, or failure to respond to standard ITP therapy. Patients with mild bleeding may be managed with supportive care and close follow-up. Intervention is indicated if the patient has moderate or severe bleeding, overt mucosal bleeding, bleeding leading to hemoglobin decrease of >2 g/dL,

suspected internal hemorrhage, or concerning social issues (noncompliance, behavioral issues, or limited access to health care). Initial ITP treatment options include steroids, IVIG, and less commonly anti-D. Steroids have platelet count response rates of 69% to 96.5%. Platelet count recovery with IVIG occurs in >80% of children with ITP but is associated with headache, nausea or vomiting, and fever or chills, similar to the patient in this case. Anti-D can transiently increase platelet counts in patients who are Rh positive, have a negative direct antiglobulin test result, hemoglobin of >9 g/dL, and no previous splenectomy. Treatment options for children with chronic ITP include thrombopoietin receptor agonists (eltrombopag and romiplostim), rituximab, and mycophenolate mofetil. Splenectomy is rarely indicated.

There has been one case report describing a temporal association between coronavirus disease (COVID-19) and ITP in a 65-year-old woman with hypertension and autoimmune hypothyroidism who presented with 4 days of fatigue, fever, cough, and abdominal discomfort. She had positive SARS-CoV-2 testing on admission. On day 4 of hospitalization, she developed lower-extremity purpura and epistaxis. Laboratory work showed isolated thrombocytopenia suggestive of ITP. Her course was complicated by a subarachnoid microhemorrhage. Treatment included IVIG, a platelet transfusion administered with prednisolone, and eltrombopag. Her platelet counts and purpura resolved by day 13 of hospitalization.¹⁷ Although intracranial hemorrhage is more commonly a complication of adult ITP, it occurs in <1% of children with ITP.^{1,16} This case report presents a novel association of ITP with SARS-CoV-2 in a pediatric patient, which is especially important given

the different presentation of ITP in children compared with adults.

The patient in this case report had a viral illness 3 weeks before presentation, severe thrombocytopenia out of proportion to her mild leukopenia without neutropenia or lymphopenia, rapid response to IVIG with normalization of blood counts within 2 weeks, and negative family history for hematologic or autoimmune disorders, which is most indicative of severe thrombocytopenia from primary ITP and mild leukopenia from viral suppression. Differential diagnoses for hemorrhagic diathesis, leukopenia, and thrombocytopenia that are possible but less likely include infection-associated thrombocytopenia (such as from hepatitis C,¹⁸ HIV,¹⁹ or parasitic infections^{20,21}) or secondary ITP from autoimmune syndromes (such as Evans syndrome,²² autoimmune lymphoproliferative syndrome,²³ or lupus), hematologic malignancies, medications, and infections (such as from hepatitis C, HIV, and *H pylori*^{24,25}). The clinical history, responsiveness to primary ITP therapies, and pathophysiology of these diagnoses is different from primary ITP. Primary ITP is therefore often a diagnosis that is substantiated retrospectively based on long-term follow-up to document the course of symptoms and resolution of bloodwork abnormalities.

With this case, we underscore the need for clinicians to be mindful of high SARS-CoV-2 co-infection rates and mild COVID-19 symptomatology in children. Preliminary data has described co-infection rates with other respiratory pathogens of $\leq 24.5\%$.²⁶⁻²⁸ Consistent with these data, the patient in this case tested positive for rhinovirus/enterovirus and SARS-CoV-2. In a case series of 2135 pediatric patients with COVID-19 in China, among 6- to 10-year-old

children, 5.8% were asymptomatic and 53.5% had mild disease.²⁹ The patient in this case report had mild symptoms consistent with literature describing less severe COVID-19 symptomology in children compared with adults.³⁰

This case report describes the presentation and response to treatment of ITP in a pediatric patient who tested positive for SARS-CoV-2 and suggests that ITP may be associated with SARS-CoV-2. It is

important for health care providers to be aware of ITP as a possible presentation of COVID-19 and to consider viral testing in these patients for appropriate triaging and isolation to limit community spread and health care worker infection during epidemics or pandemics.

ACKNOWLEDGMENTS

We thank pediatric hematologist oncologist Dr Bradley DeNardo for his

invaluable input and perspective on this case report.

ABBREVIATIONS

ANA: antinuclear antibody
COVID-19: coronavirus disease
ITP: immune thrombocytopenia
IVIG: intravenous immunoglobulin
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics originally published online May 21, 2020; originally published online May 21, 2020;

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