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Case Report

Immune Thrombocytopenic Purpura Secondary to Coronavirus Infection

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Abstract

Our patient is a 2-year-old previously healthy boy presenting with fever and a generalized rash. A completed blood count at his initial presentation showed a platelet count of 29,000 cu.mm. He was found to have coronavirus 229 E on the respiratory viral panel by multiplex PCR.

Keywords: Immune Thrombocytopenic Purpura (ITP); Coronavirus Infection; Epstein-Barr Virus

Introduction

Immune thrombocytopenia (ITP) of childhood is characterized by isolated thrombocytopenia (platelet count < 100,000 cu.mm, with normal white blood cell count and hemoglobin). The cause of ITP remains unknown in most cases, but it can be triggered by a preceding viral infection. Viral infections, such as infectious mononucleosis (Epstein-Barr virus), cytomegalovirus, hepatitis C, and HIV-1, can cause thrombocytopenia. However, little is known about immune thrombocytopenic purpura secondary to coronavirus infection.

Case Presentation

M.A. is a previously healthy 2-year-old boy who was referred by his primary pediatrician to the Emergency Department at the American University of Beirut Medical Center with the chief complaint of a rash and fever of 2 days duration.

His palms and soles were erythematous, then papules appeared on the dorsum of the hands, feet and abdomen then spread to the face, ears, trunk, and extremities. Rash was followed by fever 12 hours later; fever started as low grade of 38.5°C then reached 39.5°C the next day and responded to antipyretics.

On review of systems, he had also developed bilateral erythematous conjunctivae, with no discharge. He had been having chronic cough all throughout the winter season with no increase in intensity.

On initial assessment, his vitals were stable, with a temperature of 37.9˚C. He appeared well, not in distress and mildly irritable. He had palpable bilateral shotty cervical and inguinal lymph nodes. He had diffuse erythematous target-like macules and plaques on all extremities (Figure 1), trunk, abdomen (Figure 2) and face, sparing the palms and soles. His lips were edematous (Figure 3) and he had petechiae on his soft palate with bilateral exudative tonsils. The sclera were erythematous. Chest auscultation was clear. His abdomen was soft, spleen and liver were nonpalpable. His ankles were edematous. Neurological exam was unremarkable.

Figure 1

Figure 2

Figure 3

Investigations

A rapid strep test was negative. His white blood cell count was 6,500 cu.mm with a differential of 43% neutrophils and 46% lymphocytes, hemoglobin of 12.4 g/dl and platelets of 29,000 cu.mm; peripheral smear showed: reactive lymphocytes, slight anisocytosis, polychromasia, few ovalocytes and stomatocytes, rare echinocytes and acanthocytes, rare tear drop red blood cells (RBC) seen and rare large platelets. He had a C-reactive protein (CRP) level of 79 (N: 0.0 - 2.5 mg/L) and albumin level of 26 g/L. Blood levels of electrolytes, urea nitrogen, creatinine, lactate dehydrogenase calcium, bilirubin and results of liver enzymes tests were normal. Coagulation profile showed prolonged international normalized ratio: 1.5 and Partial thromboplastin time 35.7 sec (control: 32.5) that were not corrected with mixing studies. Fibrinogen was in the normal range, but D-Dimers were 4,662 (: <= 255 ng/mL). There were 8 - 10 RBCs per high power field in his urine with 2+ hemoglobin. Immunology workup that included antinuclear antibodies and anti-double stranded DNA were negative. Infection workup for parvovirus, cytomegalovirus, Epstein-Barr virus and mycoplasma was negative as well. Blood, throat and urine cultures retrieved and were sterile. Respiratory panel PCR collected from a nasal wash was positive for coronavirus 229E. All other pathogens were negative (Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza virus A and B, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Parainfluenza virus 1, 2, 3 and 4, Respiratory Syncytial Virus A/B, *Bordetella parapertussis* (IS001), *Bordetella pertussis* (ptxP), *Chlamydophila pneumoniae*, and *Mycoplasma pneumonia*).

Treatment

The patient was admitted for intravenous hydration, supportive care and monitoring.

Outcome and follow-up

The next day, the rash spread to the face with some resolution on the dorsum of the feet. Repeat complete blood count (CBC) showed an increase in platelets count to 52,500 cu.mm. After 48 hours, he became afebrile, and his rash started to resolve from his extremities. His activity was back to normal. Platelets count increased to 85,000 cu.mm and the CRP decreased to 36 mg/L.

The patient was discharged 3 days later on no medications.

Discussion

Immune thrombocytopenic purpura (ITP) is an acquired form of isolated thrombocytopenia caused by antibody production against platelet antigens, mainly GbIIb/IIIa [1]. These antibodies may also be targeting other antigens but in less proportions, against GbIb/XI, Gb Ia, IIa. The main culprits in this disease are these autoantibodies. The autoantibodies attach to the platelets, opsonizing them thus leading to immune clearance by splenic macrophages. The same autoantibodies hit megakaryocytes and severely affect their function. Thus, ITP is not only a problem of platelet destruction but also of platelet production. These antibodies, however, are detected in 50 percent of patients [2]. The simplistic concept of antibody-mediated platelet destruction has long been challenged. A new and more elaborate scenario seems to be at play as T-Cells, B-Cells and immune tolerance have been identified as key players in the overall pathogenesis of the disease. T cells in particular seem to be an important factor in ITP, as B-cell driven autoantibody production is driven by CD4+ T-cells [3]. The clear mechanism of activated T-cells is still elusive. *In vitro*, they are activated by fragments of GbIIb/IIIa, not by the whole protein. This has led to the hypothesis that exposure of these protein fragments, instead of the whole protein, to the immune system during infection may explain the development of these T-cells [4].

Failure of immune tolerance is also emerging as part of the intricate process of ITP. Anti-GbIIb/IIIa have been identified in serum of healthy individuals [5]. Furthermore, patients with ITP have decreased levels of CD4+ CD25+ T regulatory cells compared to healthy individuals [6]. Macrophages FC-gamma receptors (FCγR) have also been implicated in this loss of immune tolerance. Human macrophages normally express several FCγR, including FCγR1, FCγRIIa which are deemed to be activating receptors and FCγRIIb which is inhibitory [7]. Patients with ITP have a ratio of these receptors skewed towards the activating receptors and a decrease in the inhibitory receptor signaling.

Several viruses have been described in the literature as culprit agents in ITP. Lee., *et al.* 2009 reported the case of a 14-year old male patient who developed ITP after contracting the influenza virus in the 2009 H1N1 pandemic [8]. Tilden., *et al.* 2015 also described ITP in a 27-year-old man caused by Epstein-Barr virus and the authors mentioned 11 other cases in the literature with EBV-associated ITP [9]. Flores., *et al.* 2015 also described cytomegalovirus associated-ITP in a 37-year old female patient [10]. We carried out a thorough literature review about coronavirus-associated ITP and we failed to find similar cases. Hence, we hope this report will add to the list of culprit viruses described to be associated with ITP.

ITP remains a diagnosis of exclusion and chronic ITP has been described in multiple viral infections [11]. A diagnosis can be made with a low platelet count (usually less than 100,000 cu.mm), a normal CBC otherwise, and no secondary cause of thrombocytopenia such as liver disease, human immunodeficiency virus, Hepatitis C virus, autoimmune or immunodeficiency disorders including Systemic Lupus Erythematosus and bone marrow diseases. Drugs (prescription or nonprescription, quinine or tonic water) or family history (inherited thrombocytopenia) are crucial factors to be excluded for the diagnosis of ITP [12].

In terms of management, key factors for the treatment of ITP are multiple but one paradigm emerges as the most important: treatment is always tailored to the individual patient. The platelets count, although counterintuitive, is the least important factor for treatment decision unless it is less than 10,000 cu.mm. If the platelets number is above 10,000 cu.mm, other factors come into play, such as active bleeding, age, lifestyle (patient sedentary or practices contact sport), and other risk factors that may impair diathesis (uremia, chronic liver disease, adverse effects of medications) [13].

Conclusion

Thus, a diagnosis of ITP does not necessarily automatically equate with offering patient therapy. In a big European registry study including 610 patients diagnosed with ITP from 5 countries, 40 percent of patients did not require treatment, and of the remaining 60 percent, almost 75% needed limited treatment. Only about 15-20% had severe problems and required multiple visits [14].

Learning Points

- Corona virus infection can be associated with immune thrombocytopenic purpura (ITP).
- Pharmacological treatment is not the mainstay for ITP management.
- Viral panel by multiplex PCR, although not necessary to make a diagnosis, may be a useful tool in determining the etiology of ITP.

Patient's Perspective

"As the patient's mother, dealing with his case was not an easy experience. [His] medical condition and the spreading rash on [his] body were frightening to us, as parents. We were even more worried when the platelets count was low. The hardest phase was the waiting and having to listen to the various medical opinions while taking medical decisions. Yet, the follow-up and continuous checkups done by the medical team have made it easier to me. As a mother, I had to rely on the advice given by his attending physician, her objective judgement and the level of trust achieved as my son's primary doctor".

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