CLINICAL VIGNETTE

Immune Thrombocytopenia Induced by COVID-19 Infection

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Case Description

A 28-year-old man with a history of Hodgkin's lymphoma status post stem cell transplant presented with thrombocytopenia. The patient was diagnosed 8 years ago with nodular sclerosing Hodgkin's lymphoma, underwent autologous stem cell transplant 7 years ago, and had been in remission ever since. He had not been vaccinated against COVID-19. Six weeks prior to admission, he was exposed to COVID-19 and developed cough and rhinorrhea. He was not tested at that time but started taking hydroxychloroquine and azithromycin. About 3 weeks prior to admission, he began noticing blood mixed in with his mucus as well as bleeding in his buccal mucosa. He also developed a widespread rash with tiny red spots throughout his skin. One week prior to admission, he presented to a local hospital and was found to have a platelet count of 1 x 10^9/L and then 0 on repeat check. He was given 2 units of platelets and started on dexamethasone. COVID-19 test was negative. Complete blood count revealed a white blood cell count of 8.4 x 10^9/L and a hemoglobin of 15.4 g/dl. Petechiae were reported on exam. He underwent a bone marrow biopsy, which showed megakaryocytes without recurrence of his lymphoma. He had refractory thrombocytopenia and was transferred to our hospital for further management.

On admission, the patient's platelet count was 1 x 10^9/L. He was diagnosed with presumed COVID-19 induced immune thrombocytopenia (ITP), previously known as idiopathic thrombocytopenic purpura. COVID-19 nasopharyngeal PCR was negative, but his COVID-19 IgG was positive, suggesting a prior infection. Other viral studies including Hepatitis C and HIV were negative. He received platelet transfusions on hospital days 1, 2, and 4 with only small transient small increases in platelets, consistent with active platelet consumption (Figure 1). He underwent a variety of treatments including dexamethasone 40mg daily for 3 days, intravenous immunoglobulin (IVIG) courses twice during admission, rituximab weekly for 4 weeks, romiplostim once, eltrombopag throughout most of his hospitalization, and methylprednisolone 1 gram daily for 3 days. He had very refractory thrombocytopenia with platelet counts <10 x 10^9/L for the majority of his admission. Surgery was consulted for consideration of splenectomy. On hospital day 28, his platelets improved to 92 x 10^9/L and he was discharged.

Discussion

ITP is caused by autoimmune destruction of platelets that typically leads to severe thrombocytopenia. It is can occur spontaneously as primary ITP or as secondary ITP in association with other conditions such as systemic lupus erythematosus, antiphospholipid syndrome, chronic lymphocytic leukemia, HIV, hepatitis C, cytomegalovirus, varicella zoster, and *Helicobacter* pylori (Figure 2).[1] Testing for these infections is recommended as part of the evaluation of new-onset ITP. Drug-induced immune thrombocytopenia can be caused by a variety of agents, notably beta-lactam antibiotics, phenytoin, rifampin, trimethoprim-sulfamethoxazole, vancomycin, and quinine. Drug-induced ITP usually improves with cessation of the offending drug.

Recently, COVID-19 has been implicated in triggering ITP in both adults and children.[2-5] Given that our patient had not taken medications that typically cause ITP and had refractory thrombocytopenia long after the cessation of any drugs, the most likely diagnosis was viral-induced ITP. He had a positive COVID-19 IgG, was not vaccinated, and had known exposure to COVID-19 from his family, so this was thought to be the most likely inciting factor. In a systematic review of 45 patients with presumed ITP due to COVID-19, the median days from onset of COVID-19 symptoms to ITP was 13, similar to the time course in our patient.[6] Seven percent of patients in the study did not have COVID-19 symptoms but tested positive for the virus, which underscores the need for COVID-19 testing in all patients presenting with ITP during the pandemic.

There is little randomized data regarding the best treatments for ITP. Glucocorticoids are considered the backbone of first-line treatment. A meta-analysis of randomized controlled trials comparing dexamethasone 40mg daily for 4 days with prednisone 0.5-2.0 mg/kg daily for 14-28 days followed by taper reported greater platelet count response rate at 14 days in the dexamethasone group (79% vs 59% p=0.04).[7] However, at 6 months, there was no significant difference between groups (54% vs 43%, p=0.44). Thus, the 2019 American Society of Hematology guidelines endorse either dexamethasone or prednisone as first-line treatment for new-onset ITP.[8] The recommended threshold for treatment in patients who are asymptomatic or have minor bleeding is a platelet count <30 x 10^9/L. Observation is recommended for patients without significant bleeding or comorbidities and a platelet count >30 x 10^9/L. Elderly patients have a higher rate of intracranial hemorrhage, so treatment should be considered at higher platelet levels.

There is even less robust data about secondary treatments for ITP. IVIG can be helpful in elevating platelets acurately in the setting of significant bleeding. The American Society of Hematology guidelines recommend eltrombopag, romiplostim, rituximab, and splenectomy as acceptable treatments for thrombocytopenia refractory to glucocorticoids at 3 months. The guidelines emphasize need for shared decision-making with patients, weighing potential risks of these treatments with the benefit of resolution of thrombocytopenia. Our patient received more rapid administration of these second-line agents, due to the severity of thrombocytopenia with most platelet counts 1-3 x 10^9/L during his month-long hospitalization. It can take weeks to months to see a response to treatment in severe cases such as this one.

Conclusion

COVID-19 infection can cause serious side effects including ITP, which can be very refractory to treatment. Continued vaccination efforts and exposure mitigation are important public health measures to prevent morbidity and mortality. A new diagnosis of ITP warrants COVID-19 testing as it may occur in asymptomatic patients. Treatments for ITP include removal of any offending drugs, high dose steroids, IVIG, rituximab, thrombopoetin receptor agonists, and splenectomy. Treatment for ITP is recommended for patients with platelet counts <30 x 10^9/L, major bleeding, or with significant comorbidities. It is prudent to allow weeks to months for medical treatments to take effect prior to proceeding with splenectomy in order to mitigate the risks of this surgery, especially in the setting of severe thrombocytopenia.

Figures

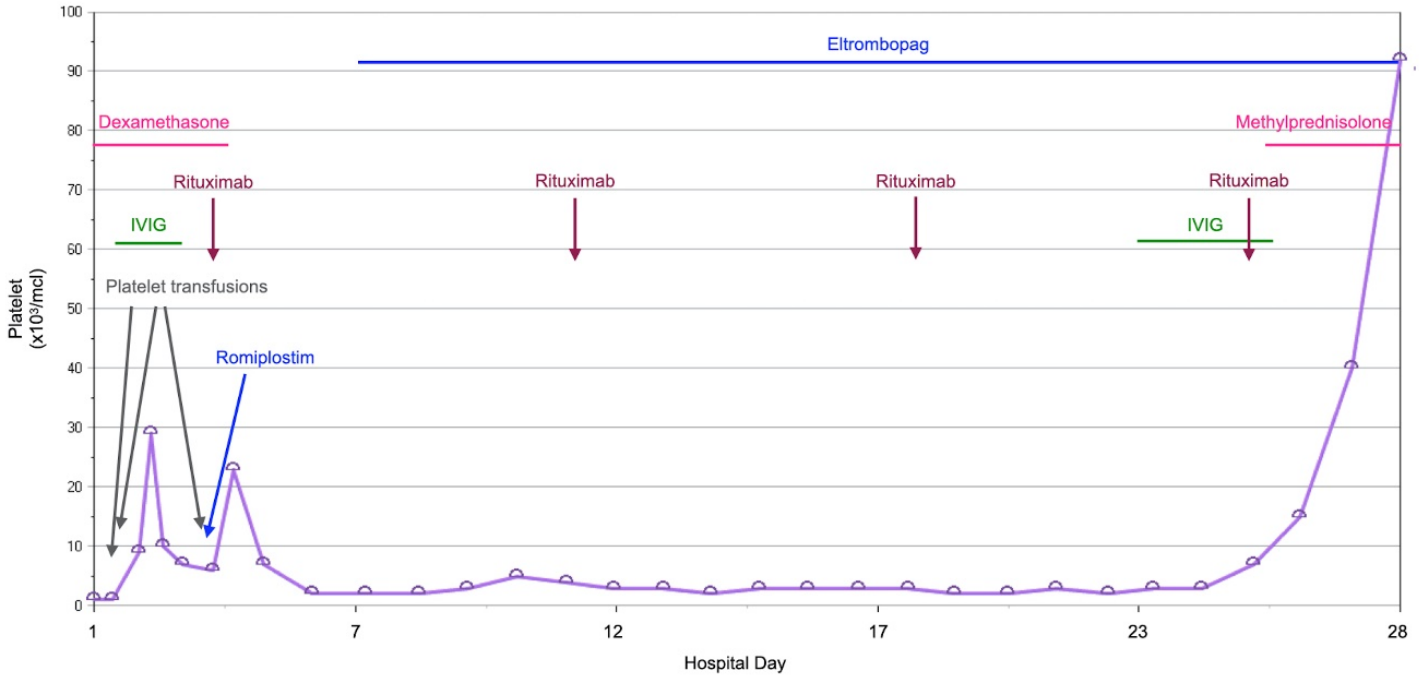

Figure 1. Platelet counts and treatments throughout the patient's hospitalization.

Primary	Secondary	Drug-Induced
Occurs spontaneously without associated condition	Autoimmune - systemic lupus erythematosus, antiphospholipid syndrome,	Antibiotics - beta lactams, vancomycin, trimethoprim-sulfamethoxazole, rifampin
	Hematologic - Chronic lymphocytic leukemia, common variable immunodeficiency	Antiepileptics - phenytoin, carbamazepine
	Viruses - COVID-19, HIV, Hepatitis C, CMV, varicella	Quinine
	Helicobacter Pylori	

Figure 2. Immune Thrombocytopenia (ITP) classification. Types of ITP as well as the most common offending drugs and associated conditions are indexed.

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