Prognosis of chronic immune thrombocytopenia in the setting of COVID-19 infection

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Abstract

Background Although several studies discussed new-onset thrombocytopenia in the setting of COVID-19 infection, the course of chronic ITP in patients with COVID-19 and the propensity to relapse remains not well addressed. **Methods** This a retrospective study that included all adult patients with the diagnosis of chronic ITP who admitted to

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This study highlights clinical presentation, management, and prognosis of all in-patients diagnosed with chronic immune thrombocytopenia (ITP) and got COVD-19 infection.

Data avalibility statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Background

Although several studies discussed new-onset Immune thrombocytopenia in the setting of COVID-19 infection, the course of chronic ITP in patients with COVID-19 and the propensity to relapse remains not well addressed.

Methods

This a retrospective study that included all adult patients with the diagnosis of chronic ITP who admitted to Cleveland Clinic Foundation hospitals between March 2020 and November 2020 with COVID-19.

Results

We screened 3,255 hospitalized COVID-19 patients and identified 30 patients with chronic ITP admitted to the hospital. Of all patients, only six (20%) were admitted to ICU. None of the patients had bleeding at the time of admission. During hospitalization, 13 (43.3%) patients developed ITP relapses. Five (38.5%) patients developed six bleeding complications, None of the bleeding events was major. Of all patients treated for ITP relapses, three patients (23%) showed complete response after different steroid treatment regimens. None of our relapsed patients required IVIG. Among patients who were treated conservatively, complete response achieved in 50% (4/8) and partial response achieved in 12.5% (1/8). Overall, seven (23.3%) death events happened. The main cause of death in all patients was acute hypoxic respiratory failure. Five (71.4%) out of the total patients who died had ITP relapses.

Conclusions

COVID-19 is associated with an increased risk of flares in patients with chronic ITP within the first week of symptoms and up to three weeks in some cases. ITP flares can be considered a poor prognostic factor. A complete response to systemic steroids is expected in the majority of cases.

Significance statement:

We investigated the clinical impacts of COVID-19 infections on the rate of disease relapses among chronic immune thrombocytopenia (ITP) patients admitted to the Cleveland Clinic enterprise. Treatment guidelines for COVID-19 associated ITP or diseases relapses are limited due to lack of experience. We also reported different treatment used in patients who relapsed and response rates to different treatment protocols, including observation, which is important to guide treatment in this unique patients population.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease defined by a platelet count less than 100×10^9/L due to immune-mediated destruction of platelets with inadequate platelet production.[1] ITP can occur as a primary in the absence of obvious underlying causes or as a secondary due to an underlying disease or a medication exposure. The majority of ITP patients are asymptomatic or present with mucocutaneous bleeding at the time of diagnosis. However, life-threatening bleeding can be the initial presentation, but still rare.[2] Diagnosis of ITP is usually made clinically by excluding other causes of thrombocytopenia. Chronic ITP is characterized by persistent thrombocytopenia for 12 months or more.[1]

Several viral agents have been previously implicated as pathogenic triggers for secondary ITP.[3] Since the identification of the novel coronavirus at the end of 2019, and thrombocytopenia was considered as a risk factor associated with poor COVID-19 outcomes.[4] Several case reports and case series of ITP secondary to COVID-19 have been published[5, 6], however, only two small-sized reports in the literature have reviewed the consequences of COVID-19 in patients previously diagnosed with chronic ITP.[4, 7] For that reason, we designed a retrospective cohort study to investigate the clinical impacts of COVID-19 infection on the admitted patients to the hospital who previously diagnosed with chronic ITP.

Methods and Materials

We conducted a multi-center, retrospective cohort study in the Cleveland Clinic Enterprise. We included all adult patients (age [?] 18 years) with the diagnosis of chronic ITP admitted between March 2020 and November 2020 with COVID-19. Diagnosis of COVID-19 was confirmed using polymerase chain reaction test (PCR). The patients were identified through a manual review of the electronic medical records. We excluded patients who were newly diagnosis with ITP secondary to COVID-19 infection, were not admitted to the hospital, or tested negative with COVID-19 from the study. We reviewed patients admitted to both regular medical floor and Intensive care units. The study was approved by the Institutional Review Board of the Cleveland Clinic.

ITP relapse was defined as recurrence of bleeding symptoms or drop in platelet count to < 100 x 10^9/L after sustaining remission for three months at least with or without treatment.[8] Partial response to treatment was defined based on platelet count of >30 x 10^9/L and doubling of the baseline value and complete response to treatment was defined based on a platelet count of >100x 10^9/L.[9]

Development of bleeding events like gastrointestinal (GIB), skin, mucocutaneous, central nervous system (CNS), genitourinary, epistaxis, hemoptysis, and muscles hematoma were investigated in the setting of COVID-19 infection. Patients with CNS bleeding or who developed hemorrhagic shock secondary to bleeding, or required blood transfusion were considered to have major bleeding events. Modified WHO bleeding scale was used to assess bleeding events severity.[10]

Results

Baseline characteristic

We screened 3,255 hospitalized COVID-19 patients and identified 30 patients with chronic ITP and had been admitted to the hospital. Of all patients, eighteen (60%) were male, and the median age was 68 year old (IQR: 64-77). Hypertension (73%) and diabetes (50%) were the most common comorbidities. At the time of COVID-19 diagnosis, nine (30%) patients had an active malignancy and three (10%) patients had a history of autoimmune diseases which were SLE, Takayasu arteritis, and Hashimoto's thyroiditis. Shortness of breath and fever were the main reasons for hospital presentation; 50%, and 30% respectively. The median platelet count at the time of admission was 120 x 10^9/L (IQR: 110-166). Of all patients, only six (20%) were admitted to ICU and four (13.3%) required mechanical ventilation. None of the patients had bleeding at the time of admission or had a splenectomy in the past.

ITP relapses and clinical manifestations

During hospitalization, 13 (43.3%) patients developed ITP relapses. The median time from COVID-19 diagnosis to the ITP relapse time was two days (IQR: 1-6). The median lowest platelet count was 60 x10^9/L (IQR: 43-74) and the median time to lowest platelet count was three days (IQR: 1.5-8.5) after COVID-19 diagnosis. Figure 1 shows platelet counts during the admission. Table 1 summarizes the clinical characteristics, treatment lines, and outcomes of all chronic ITP patients who developed relapses. Among the patients who developed ITP relapses, seven (53.8%) patients were male, and the median age was 70 year old (IQR: 67-78). Three (23.1%) patients received ITP treatment in the past during their life, one patient was on Eltrombopag, one patient was on steroids and IVIG, and the last one was on steroid, Eltrombopag, romiplostim, and IVIG. Five (38.5%) patients developed six bleeding complications, of which three (50%) were GI bleed, two (33.3%) were skin purpura and one (16.7%) was hemoptysis. None of the bleeding events were major or required blood transfusion.

Relapse treatments and outcomes

Of all patients treated for ITP relapses, three patients (23%) showed complete response after different steroid treatment regimen in the context of COVID-19 therapy, as following: methylprednisolone 40mg twice daily for 10 days, dexamethasone 6mg daily for eight days, and methylprednisolone 60mg daily for ten days. One patient (7.7%) required romiplostim 3mcg/kg for one day in addition to prednisone 5mg for seven days and dexamethasone 6mg for ten days. One patient (7.7%) achieved partial response to dexamethasone 6mg for ten days and so recommended initiating eltrombopag, however, the final decision was not to proceed with

eltrombopag because of the concern for hepatotoxicity side effect and platelet count was trending up from the nadir of 17 x10^9/L. None of our relapsed patients required IVIG. Among patients who were treated conservatively, complete response achieved in 50% (4/8) and partial response achieved in 12.5% (1/8). Of the remaining observed patients, 25% (2/8) of the patients had stable platelet count and only one (7.7%) patient had a progressive decline in platelet count and the patient opted for hospice due to life-limiting illness.

Out of all patients with chronic ITP and COVID-19 infection, seven (23.3%) death events happened. None of the patients died secondary to bleeding complications. The main cause of death in all patients was acute hypoxic respiratory failure. Five (71.4%) out of the total patients who died had ITP relapses.

Discussion

In general, SARS-CoV-2 as any viral infection could trigger the immune system to cause thrombocytopenia. Although the development of new-onset ITP in the context of COVID-19 infection has been well discussed in the literature, the chronic ITP has been rarely reported. Our study is addressing the course of chronic ITP in patients who contracted COVID-19 and admitted to the hospital. Also, the study is examining the propensity to relapse among these patients.

The incidence of ITP relapse in chronic ITP patients with COVID-19 infection was 43% in our study which is almost double what was reported before in the literature. de la Cruz –Benito et al published a case series for 8 chronic ITP patients, managed as in-patient and out-patient during the first months of the pandemic in Madrid, Spain. The author reported that 25% of chronic ITP patients had relapses, and 50% developed paradoxical thrombocytosis, including one of the relapsed patients. The author included patients without positive PCR tests and didn't report blood counts for two patients. The sharp inclining then declining in the platelet count which was reported by the author, makes it questionable if it was false reading or related to other causes of thrombocytosis. In our study, we didn't observe paradoxical thrombocytosis. Our study included larger sample size, more strict inclusion and exclusion criteria which could explain the difference in the observation between our study and de la Cruz –Benito et al. Onset time of ITP relapse in majority of cases was during the first week from COVID-19 diagnosis which is similar for what we reported in our experience with newly diagnosed ITP during the pandemic.[5]

From a clinical perspective, ITP relapses could be asymptomatic or could present with bleeding. Among the five patients who developed relapse, 38.5% presented with non-major bleeding symptoms which didn't require a blood transfusion. Half (50%) of those events were related to G.I bleeding, which is different than what was observed in COVID-19 patients who developed acute ITP, where G.I bleeding reported in 9% - 18% of the patients, while cutaneous manifestations in form of petechiae/purpura/ecchymoses consisted the majority, 46% - 49%.[5, 6]

Current guidelines recommend systemic steroids as first-line therapy for COVID-19-induced ITP and reserve IVIG as a second line when immediate platelet count elevation is required or if there is failure to respond to steroids. Although there are no data on the use of TPO-RAs in COVID-19 positive patients, the risk of hepatotoxicity and the potential for increased thrombosis remain a concern, and experts advice to weigh the risks and benefits before using it.[11] In our study, the complete response to ITP treatment has been observed in 80% (4/5) of the patients and 20% (1/5) achieved partial response. Only one patient had steroid failure and required a second-line agent, Romiplostim, which re-emphasis the cornerstone role of steroid in managing COVID-19 related ITP as recommended by expert consensus from the United Kingdom.[11] No patient received IVIG in our study. The response rate to treatment close to what reported by de la Cruz –Benito et al in their chronic ITP series, but interestingly this rate is higher than what observed in newly diagnosed ITP induced by SARS-CoV-2 infection; complete response rate 45 - 67% and partial response rate 18% - 27.3%. This might be explained by the fact that chronic ITP patients were already getting treatments for ITP.

Our study has some limitations. First, the study is retrospective in nature. Second, it was difficult to determine whether COVID-19 infections solely triggered relapses in our patients since other comorbidities

and even critical illness could have played a role in the ITP course. In conclusion, our study highlights the fact that COVID-19 is associated with an increased risk of flares in patients with chronic ITP within the first week of symptoms and up to three weeks in some cases. A complete response to systemic steroids is expected in the majority of cases.

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Author's contribution

DA, TK, SA,MA,TG,KM,HD,and AH contributed to the literature review. DA, TK, MA, HD, and AH contributed to the study design and conceptualization. DA, TK, SA, TG, and KM contributed to data collection and curation. DA, TK, and AH contributed to Data analysis and interpretation. DA, TK, SA, MA, TG, KM, HD, and AH wrote the initial draft. All authors contributed to reviewing and editing the final draft and verified the underlying data.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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