Immune thrombocytopenia during the COVID-19 pandemic

Given past experience with widespread viral infections, for example influenza, we expected that SARS-CoV-2 would create a large number of *de novo* cases of immune thrombocytopenia (ITP). Perhaps a silver lining on the cloud of SARS-CoV-2 is that for patients with ITP, the virus is not having a major effect, as evidenced by few reports of ITP in conjunction with SARS-CoV-2 infection.

We performed a retrospective review of patients ≥18 years diagnosed with COVID-19 and ITP seen at New York Presbyterian–Weill Cornell Medicine (NYP-WCM) or Shandong Provincial Chest Hospital–Shandong University (SPCH-SDU) from February to August 2020. Ten patients from NYP-WCM and two from SPCH-SDU were identified (Table I). The study was approved by the Institutional Review Board of NYP-WCM and the Medical Ethical Committee of SPCH-SDU.

There were 10 patients with pre-existing ITP and two with presumed new SARS-CoV-2-associated ITP (Table I). Patient 8 was diagnosed with ITP during hospitalization for COVID-19 and Patient 10 developed isolated ITP six weeks following SARS-CoV-2 infection; neither had a prior history of thrombocytopenia. For those with pre-existing ITP, SARS-CoV-2 infections were managed as outpatients ($n = 3$), ER visits ($n = 2$), and hospitalizations ($n = 5$).

During active COVID-19, five patients required ITP treatment for platelet nadirs of 8–33 $\times$ 10^9/l. Patient 7 received platelet transfusion, steroids and intravenous immunoglobulin (IVIg). Patients 1 and 9 received IVIg alone. Patient 1 had been on weekly romiplostim, twice daily mycophenolate mofetil (MMF) and IVIg as needed since 2017. She had fevers, fatigue, body aches and was ITP-Bleeding Assessment Tool: Skin 1 (petechiae), Mucosae 1 (epistaxis).[1] Due to morbid obesity, limited mobility, and advanced age, she received weekly home infusions of IVIg 80 g for counts <10–20 $\times$ 10^9/l. Patient 9, on prednisone 15 mg daily for platelets 20–30 $\times$ 10^9/l, was hospitalized at SPCH-SDU. He received IVIg 10 g daily for two days with platelet improvement from 18 to 28 $\times$ 10^9/l.

Patient 8 received inpatient IVIg 15 g daily for three days, methylprednisolone 80 mg BID, and convalescent plasma for SARS-CoV-2-associated ITP with platelets increasing from 33 to 83 $\times$ 10^9/l. Several weeks following SARS-Cov-2 diagnosis, Patient 10 received IVIg with steroids for *de novo* ITP with platelet improvement from 6 to 82 $\times$ 10^9/l. Patient 7 had chronic ITP with platelets of 8 $\times$ 10^9/l requiring platelet transfusions. In the setting of multiorgan failure, he declined additional treatment and passed away.

Two patients received steroids alone for exacerbations of known ITP during infection with SARS-CoV-2. Patient 11's platelets dropped from 60–70 to 23 $\times$ 10^9/l two weeks after diagnosis. His platelets improved to 180 $\times$ 10^9/l on prednisone 20 mg daily. Patient 4's platelets dropped from a baseline of 60–70 to 26 $\times$ 10^9/l. She received dexamethasone 40 mg for four days with platelets rising to 105 $\times$ 10^9/l.

Five patients (Patients 2, 3, 5, 6, 12) did not modify their ITP treatment despite COVID-19. Three (Patients 2, 3, 6) were on treatment (eltrombopag, steroids, rituximab, respectively). Patient 5 was discharged from the ER with haematology follow-up for platelets 26 $\times$ 10^9/l and Patient 12 was diagnosed with SARS-Cov-2 on routine screening for caesarean section with platelets 94 $\times$ 10^9/l.

Patients 3, 4, 6, 8 were hospitalized and received prophylactic anticoagulation with enoxaparin 40 mg SC daily (NYP-WCM) or nadroparin 3 800 U SC daily (SPCH-SDU) without bleeding events. Patient 6 developed deep vein thrombosis (DVT) and pulmonary embolus (PE) despite prophylactic enoxaparin. He received therapeutic heparin and was discharged on apixaban. Patient 2 presented with a new headache due to cerebral venous sinus thrombosis and was discharged on apixaban.

Treatments of ITP, ongoing or newly initiated, can impact the course and outcome of SARS-CoV-2. Thrombosis is a major concern in patients with SARS-CoV-2 infection[2,3] and immunosuppression could worsen infection. The American Society of Hematology offers recommendations limited by data to expert opinion[4] for ITP management in SARS-CoV-2 infection.

IVIg is not immunosuppressive, rapidly increases platelets, and has anti-inflammatory effects. To avoid prolonged visits and SARS-CoV-2 exposures, home administration (like Patient 1) is useful. Steroids may risk increasing viral susceptibility early in infection; however, published reports and our own experience suggest steroid use does not often lead to worse outcomes in COVID-19.[5–7]

No consensus exists regarding increased severity of COVID-19 infection in patients who have received rituximab or are on other chronic immunosuppressants.[8–10] Anti-CD20 agents impair humoral responses to *de novo* infections and vaccines for at least 4–6 months. We agree with avoiding immunosuppressives or rituximab during the COVID-19 pandemic pending reasonable alternatives.[11] We also caution use of splenectomy due to increased thrombotic risk and risk of overwhelming sepsis.

British Journal of Haematology, 2021, **193,** 1093–1095
First published online 14 April 2021
doi: 10.1111/bjh.17457

Table I. Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age (years)	89	53	38	54	20	61	88	65	50	73	72	38
Gender (M/F)	F	F	F	F	F	M	M	M	M	M	M	F
Body mass index (kg^2/m)	42·3	24·5	32·8	64·5	23·4	23·8	22·4	24·6	22·4	26·2	28·3	25·3
Comorbidities	Multiple sclerosis, hypertension, hyperlipidaemia, hyperthyroidism	Hypothyroidism	None	Asthma	McCune–Albright syndrome	Warm autoimmune haemolytic anaemia, hypertension	Low-grade B-cell lymphoma	None	None	Celiac disease, hypertension, hyperlipidaemia	Ankylosing spondylitis, hypertension, hyperlipidaemia	Autoimmune gastritis, Hashimoto's thyroiditis
ITP (*de novo*/ existing)	Existing	Existing	Existing, pregnancy-associated	Existing	Existing	Existing	Existing	*De novo*	Existing	*De novo*	Existing	Existing
Distant ITP treatments	Azathioprine, steroids, rituximab, eltrombopag	Rituximab, steroids, splenectomy	Steroids, IVIg during pregnancies	Steroids	IVIg, steroids	Steroids, IVIg, romiplostim, rituximab	None	None	Steroids, IVIg, recombinant thrombopoietin	None	Steroids	None
ITP treatment prior to COVID19 hospitalization	Romiplostim, mycophenolate mofetil, IVIg PRN	Eltrombopag	Prednisone 30 mg	None	None	Rituximab	None	None	Prednisone 15 mg	None	None	None
COVID19 hospitalization type	Outpatient	ER	Floor, non-ICU	Floor, non-ICU	ER	Floor, non-ICU	Floor, non-ICU	Floor, non-ICU	Floor, non-ICU	Outpatient¶	Outpatient	Labour & delivery**
Hospitalization length (days)	N/A*	2	3	4	<1	7	4	26†	21†	N/A	N/A	N/A
Oxygen requirement	N/A	None	Nasal cannula	Nasal cannula	None	Nasal cannula	Nasal cannula	High flow nasal cannula	Nasal cannula	N/A	N/A	None
Thrombosis?	No	Cerebral venous sinus thrombosis	No	No	No	Pulmonary embolus, deep vein thrombosis	None	None	None	None	None	None
Platelet nadir ($\times 10^9/l$)	8	158	112	26	26	137	8	33	18	6	23	94
ITP rescue treatment	IVIg	None	None	Dexamethasone 40 mg × 4 days	None	None	Platelet transfusion	Methylprednisolone 80 mg BID with taper, IVIg	IVIg	IVIg, solumedrol	Prednisone 20 mg	None
Platelets ($\times 10^9/l$) on discharge or after outpatient treatment	N/A	158	236	105	26	346	13‡	83	28	82	180	N/A
Prophylactic anticoagulation	No	No	Yes	Yes§	No	Yes	No	Yes	No	No	No	No

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin.

*No hospitalization for COVID-19 or ITP, treated at home.

†Per institutional policy, discharge pending negative nucleic acid testing.

‡Deceased without escalation of care per patient's wishes.

§Anticoagulation started when platelets were >50 × 10^9/l.

¶No hospitalization for COVID-19, hospitalized two months after COVID-19 diagnosis for *de novo* ITP.

**Diagnosed with COVID19 on screening prior to admission to Labour & Delivery for planned caesarean section.

The risk of thrombotic events with SARS-CoV-2 is well documented[2,3] and prophylactic anticoagulation is recommended in hospitalized patients including those with ITP.[4,12,13] Cases of thrombosis in COVID19-infected ITP patients have been reported, including two patients included in this report.[5,7,14] Patient 6 developed DVT/PE despite prophylactic anticoagulation. Although an advantage of thrombopoietin receptor agonists (TPO-Ras) would be absence of immunosuppression, caution is recommended during the COVID19 pandemic in patients with additional thrombotic risk factors such as post-splenectomy and platelet counts $>100 \times 10^9$/l (Patient 2).

Follow-up information through February 2021 is available for seven patients (Patients 1, 2, 3, 6, 8, 9, 10). None required hospitalization for recurrent ITP flares. Both patients with presumed new SARS-CoV-2-associated ITP (Patients 8, 10) maintain normal platelet counts without platelet-specific treatment. Patient 8 did not require treatment beyond IVIg and steroids received during hospitalization. Patient 10 was successfully tapered off steroids in October 2020.

The starting platelet counts in our 12 patients were somewhat higher than in the 14-patient French series[6] which had a high percentage of *de novo* cases whereas 10 of our 12 involved pre-existing ITP. As with ITP in the absence of SARS-CoV-2 infection, treatment needs to be individualized. Steroids, IVIg, rituximab, immunosuppressives, splenectomy and TPO-RAs are discussed above and considerations based on experience applicable to SARS-CoV-2 infection emphasized. Ongoing experience continues to be gathered to better inform care to SARS-CoV-2 infected ITP patients.

Acknowledgements

EL, XL, MH, JB performed the research and analyzed the data, EL and JB wrote the paper, XL and MH revised the paper. All authors approved the final manuscript.

Conflicts of interest

EL, XL and MH have no disclosures. JBB has served on advisory boards and/or consulted for Amgen, Novartis, Dova, Rigel, UCB, Argenx, Momenta, Regeneron, RallyBio, and CSL-Behring.

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