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COVID-19-associated immune thrombocytopenia

Mara-Andrada Plesu[1], Gabriel Cristian Bejan[2], Ioana Veronica Grajdeanu[2], Anca Angela Simionescu[3,4], Ana Maria Alexandra Stanescu[2]

[1]Private Medical Practice Dr. Ioana Veronica Grajdeanu, Bucharest, Romania
[2]Department of Family Medicine,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Obstetrics and Gynecology,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4]Filantropia Clinical Hospital, Bucharest, Romania

ABSTRACT

The coronavirus disease 2019 (COVID-19) is a contagious respiratory tract infection caused by the beta-coronavirus SARS-CoV-2. The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020. Since the COVID-19 pandemic started, more than 166 million patients have been tested positive worldwide with more than 3.4 million related deaths recorded. COVID-19 has a wide range of signs and symptoms. Hematological changes such as lymphopenia, thrombocytopenia, and coagulation disturbances are not unusual in patients with COVID-19. However, the mechanisms causing these changes are partially comprehended. Immune thrombocytopenia was identified to be among the hematologic autoimmune diseases seen in patients infected with SARS-CoV-2. This review summarizes the evidence on COVID-19-associated immune thrombocytopenia and the underlying mechanisms involved in its development.

Keywords: thrombocytopenia, immune thrombocytopenic purpura, COVID-19, SARS-CoV-2, coronavirus

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a contagious respiratory tract infection caused by the beta-coronavirus SARS-CoV-2. It was first identified in Wuhan, the largest metropolitan area in China's Hubei Province, in late 2019, when a series of pneumonia cases of unknown cause emerged [1]. The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020 [2]. Since the COVID-19 pandemic started, more than 166 million patients have been tested positive worldwide with more than 3.4 million related deaths recorded [3].

SARS-CoV-2 infection tends to affect people of all ages, but the clinical manifestations vary depending on their age. Many infections, primarily in children and young adults, are asymptomatic or mild, but severe illness, respiratory failure, and death are more frequent in the elderly and/or people with comorbidities [4].

COVID-19 has a wide range of signs and symptoms. The most common symptoms at onset of illness are fever, fatigue and cough, but also myalgia, anorexia and in severe cases dyspnea. Headache, dizziness, sore throat, and chest pain are less common symptoms, as are gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting [4-6]. Also, a significant number of patients complained of olfactory and taste disturbances. Anosmia and ageusia are nonspecific symptoms that may be the first or only sign of the condition [7,8].

Most patients reported symptoms of disease, after an incubation period of 1-14 days (typically about 5 days); dyspnea and pneumonia occurred within a median of 8 days from disease onset [8].

Corresponding author:
Gabriel Cristian Bejan
E-mail: cristian.bejan@umfcd.ro

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TABLE 1. *Reported COVID-19 induced immune thrombocytopenia cases*

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombo-cytopenia	Platelet count in evolution, cells/μL	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #1 Zulfiqar et al (26)	65 yo, female	hypertension, autoimmune hypothyroidism	On presentation: 4-day history of fatigue, fever, dry cough, abdominal discomfort; diminished breath sounds bilaterally with bibasilar rales	On day 4: lower-extremity purpura, epistaxis On day 9: right frontal headache, (head CT scan: subarachnoid microhemorrhage in the right frontal lobe)	CT scan: ground-glass opacities in the lower zones	4	On presentation: 183000; On day 4: 66000; On day 5: 16000; On day 7: 8000; Nadir: 1000	Elevated CRP levels (55mg/l), LFTs showed cholestasis; Increased fibrinogen level	Increased thyroid peroxidase antibodies; antiplatelet negative factor 4, antiplatelet antibodies, and antinuclear antibodies	IVIG 1g/kg – 2 doses; platelet transfusion; prednisolone (100mg); eltrombopag (75mg/day)	intravenous amoxicillin–clavulanic acid; LMWH; oxygenation therapy	On day 10: platelet count increased to 139,000 cells/μL, the headache had resolved, the purpura had disappeared Discharged
Patient #2 Murt et al (27)	41 yo, male	unremarkable	cough and runny nose 15 days ago	On presentation: petechiae; nasal bleeding; purpuric rash;	CT scan: bilateral ground glass opacities	On presentation	Nadir: 9000	Negative viral hepatitis panel and rheumatological markers	Negative	IVIG 1g/kg – 2 doses	Favipiravir	Pneumonia gradually resolved in 5 days; 2 days after treatment platelet count increased to: 54,000 cells/μL; At 4-weeks follow-up 50-100,000 cells/μL; discharged
Patient #3 Bomhof et al (28)	59 yo, male	stage IV neuroendocrine tumor (NET) of the small bowel	coughing and fever 10 days before presentation; contact with a positive case	On presentation: oral mucosal petechiae, spontaneous skin hematomas	NR	On presentation	Nadir: 3,000	NR	Positive platelet autoantibodies	platelet transfusion, without increment; IVIG 1g/kg – 2 doses; dexamethasone	NR	Platelet count increased to 47,000 cells/μL, then dropped to 19,000 cells/μL when dexamethasone was started leading to a platelet count of 51,000 cells/μL on day 27; discharged
Patient #4 Bomhof et al (28)	66 yo, female	hypertension	4 weeks before admission: fever, dyspnea and coughing, followed by diarrhea and vomiting for several days	On presentation: petechiae, spontaneous epistaxis and increased blood loss from hemorrhoids since 3 weeks	NR	On presentation	Nadir: 2,000	NR	Negative platelet autoantibodies	platelet transfusion – 1 unit (no response); dexamethasone 40mg/day – 4 days (no response); IVIG – on day 6 (responsive)	NR	Platelet count increased to 32,000 cells/μL on day 22; discharged
Patient #5 Bomhof et al (28)	67 yo, male	Hypertension, diabetes mellitus	On presentation: fever, coughing and dyspnea since 9 days; Day 2: respiratory failure, ICU admitted; Day 3: intubated	Intracerebral bleeding	CT scan: bilateral infiltrates; segmental pulmonary embolism (on day 10)	9	Day 10: 112,000; On day 12: 3,000 (nadir)	NR	NR	platelet transfusions	unfractionated heparin	Platelet count did not increased on platelet transfusions; on intracerebral bleeding within 24 hours; exitus
Patient #6 Deruelle et al (29)	41 yo, male	Hypertension, obesity	On presentation: acute respiratory failure; fever, cough, and dyspnea for the previous 13 days	On day 10: mild bleeding in endotracheal tube secretions	CXR: mild ARDS, bilateral opacities	8	On presentation: 261,000; On day 10: 24,000; On day 14: 19,000; On day 19: 56,000	increased CRP, ferritin, fibrinogen, mild liver cytolysis; highly elevated d-Dimers;	Negative anti-PF4 antibodies, antinuclear factors	On day 14: methyl-prednisolone 1 mg/kg/day; On day 20: IVIG 1g/kg	mechanical ventilation, neuromuscular blocking agents, LMWH, danaparoid sodium, cefotaxime	Two days after the IVIG infusion, the platelet count returned to normal; discharged on day 38
Patient #7 Ahmed et al (16)	50 yo, male	No known prior comorbidities	Asymptomatic, contact with a positive case	On presentation: epistaxis, generalised petechial rash, oral blisters	CXR: normal	On presentation	Nadir: 0 (day 1)	Normal -urea and electrolytes, LFTs, haemolysis screen, coagulation profile, viral serology	Negative	IVIG 1 g/kg – 2 doses;	tranexamic acid; nasal packing	Two days after the IVIG infusion, the platelet count increased to 11,000 cells/μL, and then to 25,000 cells/μL in the next 24 hours; At 2-weeks follow-up: 103,000 cells/μL; discharged

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombo-cytopenia	Platelet count in evolution, cells/μL	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #8 Ahmed et al (16)	49 yo, female	No known prior comorbidities	No chest symptoms	On presentation: generalised bruises, gum bleeding for the past 3 days	CXR: normal	On presentation	Nadir: 4,000	Normal -urea and electrolytes, LFTs, coagulation profile; negative viral serology	Negative	IVIG 1 g/kg – 1 dose;	NR	Two days after the IVIG infusion, the platelet count increased to 18,000 cells/ μL, then to 52,000 cells/ μL over the next 48 h; discharged
Patient #9 Ahmed et al (16)	96 yo, female	atrial fibrillation, ischaemic heart disease, chronic kidney disease	On presentation: shortness of breath, bilateral coarse crepitations	NR	CXR: bilateral patchy consolidation	5	On presentation: 109,000; Day 5: 3,000	Normal LFTs, coagulation profile & bone profile; negative viral serology	NR	IVIG 0.4 mg/kg - 5 days	oxygenation therapy	Platelet count started improving after the IVIG treatment: 16,000 cells/ μL; Clinical deterioration, with increasing oxygen requirements; exitus
Patient #10 Humbert et al (30)	84 yo, male	polymyalgia rheumatica, essential tremor	On presentation: 10-day history of cough and progressively worsening dyspnea; bilateral crackles on auscultation	On day 6: sudden onset of spontaneous macroscopic hematuria and bilateral epistaxis	CT scan: diffuse ground-glass opacities and condensations involving more than 50% of pulmonary parenchyma; sub-segmental pulmonary embolism	6	On presentation: 330,000; On day 6: 4,000 (nadir)	Increased fibrinogen	Negative ENA, ANCA, and platelet antibodies; positive lupus anticoagulant antibody	prednisone 1 mg/ kg/day; IVIG 1 g/kg – 1 dose	oxygenation therapy; ceftriaxone; rivaroxaban; hydrocortisone	Two days after the IVIG infusion, the platelet count increased to 57,000 cells/ μL, and at one week it was at 155.000 cells/μL;
Patient #11 Levesque et al (31)	53 yo, male	hypertension, dyslipidemia, type 2 diabetes	On presentation: 3-day history of dyspnea, dry cough and fever;	On day 20: abnormal bleeding from the tracheotomy site; On day 39: small spontaneous intraventricular hemorrhage	NR	20	On presentation: 224,000; On day 20: 23,000	Decreased hemoglobin concentration, lymphopenia; increased creatinine, mildly elevated liver enzymes; negative viral serology	anti-PF4 antibodies weakly positive	IVIG 1 g/kg – 2 doses; intravenous dexamethasone 40 mg/day – 4 doses; platelet and red blood cell transfusions; intravenous tranexamic acid; romiplostim; vincristine	mechanical ventilation; ceftriaxone, azithromycin; unfractionated heparin; renal replacement therapy; piperacillin–tazobactam and cefazolin	Complications: ARDS, AKI, methicillin-sensitive staphylococcus aureus ventilator-associated pneumonia and ICU-acquired neuromyopathy. The platelet count started to increase on ITP day 11 and reached 178,000 cells/ μL, 14 days after first dose of IVIG
Patient #12 Tang et al (32)	41 weeks pregnant female	No significant past medical history	On presentation: sore throat, but no other flu-like symptoms	NR	CT scan: i nfiltrates in the left lower lobe with ground-glass opacities	On presentation	On presentation: 16,000; 2 weeks earlier: 98,000; Day 8: 1,000	NR	Positive platelet auto-antibodies against glycoprotein V	IVIG – 2 days; 2 units of donor thrombocytes	Epidural anesthesia was complicated by hypotension; an urgent caesarian section was performed	Discharged without flu-like symptoms and with stable platelet counts of 82,000 cells/μL that normalized 3 weeks later (315,000 cells/μL)
Patient #13 Tsao et al (33)	10 yo, female	No significant past medical history	3 weeks prior to presentation: 2 days of fatigue, non-productive cough and fever, in the setting of a known SARS-CoV-2 exposure	On presentation: one day of rash; mouth oral examination notable for wet purpura; petechiae concentrated on her lower extremities, chest and neck; ecchymoses in the popliteal regions and shins	NR	On presentation	On presentation: 5,000	Respiratory pathogen panel: positive for rhinovirus/ enteroviru	antinuclear antibodies (ANA) reactive, borderline positive	IVIG 30g (1 g/kg)	400 mg acetaminophen; 30mg (1 mg/kg) diphenhydramine as pretreatment	Discharged; rash and oral lesions improved within 48 hours after IVIG administration; 2 weeks after hospital discharge, her symptoms had completely resolved

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombo-cytopenia	Platelet count in evolution, cells/μL	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #14 Martincic et al (34)	48 yo, male	type 2 diabetes, obesity, obstructive sleep apnea	On presentation: 3-day history of progressive dyspnea, cough, fever, headache, muscle soreness; respiratory rate: 42 breaths/minute; oxygen saturation: 60%; transferred to the ICU	On day 9: macroscopic hematuria after a non-traumatic re-insertion of a urinary catheter; minor bleeding from oral mucosa and blood clots in gastric residual volume	CXR: diffuse bilateral consolidations	Day 9	Day 9: 96,000; Day 12: 2,000 (nadir)	Increased WBC count; increased levels of CRP, fibrinogen, D-dimers; negative viral serology	Direct Coombs test: positive for IgG, indirect Coombs test: negative. Heparin-induced thrombocytopenia (HIT) antibodies: negative	Transfusion of 1 unit (325 ml) of pooled platelet concentrate; IVIG 1 g/kg – 2 doses concomitantly with intravenous dexamethasone 40 mg/day	mechanical ventilation; lopinavir/ritonavir; hydroxychloroquine sulphate; piperacillin/ tazobactam; low-dose noradrenalin, nadroparin	One-hour post transfusion platelet count increased from 4,000 cells/μL to 9,000 cells/μL; The platelet count increased to 185,000 cells/μL on the third day of treatment. The platelet count remained normal during the rest of the hospitalization.
Patient #15 Levraut et al (35)	63 yo, female	autoimmune hypothyroidism, stroke	On presentation: 7-day history of asthenia, fever, dry cough, and headaches; bilateral crackles of lung bases; contact with a positive case	On day 26: lower limb purpura; bruises of both arms and legs	CT scan: bilateral and subpleural frosted glass beaches;	Day 26	Day 26: 3,000	Persistent lymphocytopenia; tested negative for the nasal SARS-CoV-2 RT-PCR	Antinuclear antibodies with a nucleolar coloration; direct antiglobulin test and antiphospholipid antibodies negative	IVIG 1 g/kg – 2 doses	Azithromycin 500 mg/day -6 days; hydroxychloroquine 600 mg/day - 12 days	Platelet levels progressively increased to 38, 000 cells/ μL, 95,000 cells/μL, and 145,000 cells/μL on days 29, 31, and 33. Purpura of lower limbs and bruises totally disappeared. Discharged on day 33.
Patient #16 Molinaro et al (36)	19 yo, female	No significant past medical history	On presentation: fatigue, ageusia; known SARS-CoV-2 exposure; fever for a few days 2 weeks earlier	On presentation: diffuse petechial rash	CXR: normal	On presentation	On presentation: 2,000 (nadir)	Leukocytosis, lymphocytosis; elevated AST, ALT and serum LDH levels	Positive anti-nuclear antibodies (ANA), positive Connective Tissue Disease (CTD) screen	IVIG 400 MG/KGBW; methyl-prednisolone 1 MG/KGBW for 5 days	Hydroxychloroquine and antiretroviral agents were also administered	Platelet count increased to 7,000 cells/ μL (day 3), to 40,000 cells/ μL (day 4, and to 98,000 cells/μL (day 5). Parient discharged

ag), and platelet transfusions. In several of the cases documented, intravenous immunoglobulin administration resulted in a favorable response relatively fast (Patient #2, #7, #8, #13, #15) [16,27,33,35]. IVIG was administered for Patient #3 due to active bleeding and the relative contraindication of glucocorticoid medication, which may interact with his prior treatment (somatostatin analog therapy for the neuroendocrine tumor), and for Patient #4 due to dexamethasone treatment failure [28].

Glucocorticoids comprise the main therapy of ITP [40]. However, glucocorticoids are considered unsafe for patients with COVID-19 infection as they inhibit immune responses and clearance of the novel coronavirus [9,42].

Thrombopoietin receptor agonists have made a significant contribution to the treatment in patients with immune thrombocytopenia, which are refractory to first-line agents. About 30% of patients have shown a steady rise in platelet counts after treatment [43]. Because TPO-RA therapy has demonstrated that the risk of venous thromboembolism has increased in selected patients, it should be used judiciously in COVID-19 infection [44].

CONCLUSIONS

Several hematological abnormalities that might lead to life-threatening bleeding complications were identified in COVID-19. Such manifestations must be included in the clinical evaluation of patients infected by SARS-CoV-2. Since the outbreak of the pandemic, there were several case reports of immune-mediated thrombocytopenia linked to COVID-19. Thrombocytopenia may be attributed to different reasons and promptly diagnosis of the immunological cause is essential, so that proper immunosuppression may be initiated on time. Failure of timely recognition may eventually result in serious complications. The management of ITP should be decided upon the balance of the bleeding risk due to immune thrombocytopenia versus the prospective complication of COVID-19-infection due to immunosuppressive treatment.

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