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CASE REPORT

Successful Systemic Lysis Therapy of a Floating Carotid Thrombus in an Acute Stroke Patient with Known Immune Thrombocytopenia (ITP) on Ongoing Eltrombopag Therapy and Acute COVID-19 Infection: a Case Report

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Abstract

Patients with immune thrombocytopenia (ITP) under eltrombopag therapy are vulnerable to thrombotic disbalance, both due to the disease itself and therapy-related hypercoagulability. Vascular events such as the development of a free-floating carotid thrombus are known rare complications of acute COVID-19 infections due to endothelial inflammation and presumptive underlying hypercoagulable state. In patients at risk, the onset of new focal neurological symptoms should prompt immediate angiographic diagnostics and, if necessary, appropriate treatment. Here, we report a case of a 38-year-old female with a medical history of ITP and the presence of COVID-19 infection presenting an acute sensorimotor hemiparesis of the right side while on eltrombopag therapy. Initial CT angiography revealed a free-floating thrombus in the left common carotid artery. Upon admission, the patient's platelet count was significantly elevated at 896×10^9/l. After systemic lysis therapy, the thrombus was fully dissolved. Follow-up diffusion-weighted imaging revealed multilocular cortical infarction of the left MCA territory. The patient soon recovered and was discharged with residual mild sensorimotor deficits in the right arm. Eltrombopag was paused at admission, and the patient's platelet count was quickly returning to normal. She was discharged with a daily intake of acetylsalicylic acid, a reduced daily dose of eltrombopag, and weekly monitoring of her platelet count for the next three months. This unique case highlights the need for caution in patients at vascular risk who contract COVID-19 and discusses thrombocytic derailment under thrombopoietin receptor agonist therapy in the context of an acute COVID-19 infection.

Keywords Stroke · Systemic lysis · Immune thrombocytopenia (ITP) · Thrombopoietin receptor agonist (TPO-RA) · Eltrombopag · COVID-19 infection

Abbreviations

ITP	immune thrombocytopenia
TPO-RA	thrombopoietin receptor agonist
NIHSS	NIH Stroke Scale
mRS	modified Rankin Scale
CT	computer tomography
CTA	CT angiography
CCA	common carotid artery
ICA	internal carotid artery
rt-PA	recombinant tissue plasminogen activator
MCA	middle cerebral artery

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Introduction

Vascular complications are a significant risk factor and prognostic indicator of COVID-19 infections [6]. Although rare, a free-floating carotid thrombus is a variant of these complications and requires immediate management to prevent further cerebral infarction [4, 13]. Patients with a pre-existing disbalance of their hemostatic state, such as those with

immune thrombocytopenia (ITP) undergoing thrombopoietin receptor agonist (TPO-RA) therapy, are at a significantly higher risk of thromboembolic events than the general population [12]. ITP is an autoimmune disease characterized by antibodies targeting platelet surface structures, which results in a reduced platelet count and an increased tendency to bleed, accompanied by spontaneous purpura and petechiae. Medical treatment for ITP consists of immunosuppressants and TPO-RAs such as romiplostim and eltrombopag, which promote megakaryocyte differentiation, proliferation, and platelet production [8]. In contrast to most patients with COVID-19-associated thrombocytopenia, ITP patients with and without TPO-RA therapy show a paradoxical increase in platelet count during COVID-19 infection [5].

Case Report

Here, we report a case of a 38-year-old female smoker with a medical history of ITP who contracted COVID-19 and subsequently suffered an acute left hemispheric stroke while receiving eltrombopag therapy at a dose of 75 mg/24 h. The patient was diagnosed with ITP at the age of three years and underwent a splenectomy at six years old. Nine years prior to admission, the patient had switched TPO-RA therapy from romiplostim to eltrombopag. The patient was naïve to any anticoagulation or platelet agglutination inhibitor. On admission day, the patient woke up with dysarthria and a mild distal sensorimotor hemiparesis of the right side, NIH Stroke Scale (NIHSS) 4, modified Rankin Scale (mRS) 2.

At admission, platelet count was significantly increased at 896×10^9/l, and anemia with hemoglobin 8.1 g/dl and leukocytosis 16.5×10^9/l were also apparent. Eight days prior to the onset of symptoms, the platelet count was measured at 26×10^9/l. Initial brain imaging by computer tomography (CT) was unremarkable, but CT angiography (CTA) of the head and neck revealed a nearly occluding intraluminal thrombus (0.7×0.9 cm) in the distal left common carotid artery (CCA) extending into the carotid bifurcation and left internal carotid artery (ICA), leading to a >80% stenosis as per NASCET criteria. A second thrombus was detected within the left ICA ($0.3 \times 0.3 \times 0.4$) without stenotic effect (Fig. 1A). Due to the risk of further embolization of more distal regions by mechanical intervention, a systemic lysis therapy with 70 mg recombinant tissue plasminogen activator (rt-PA) was immediately initiated at a body weight

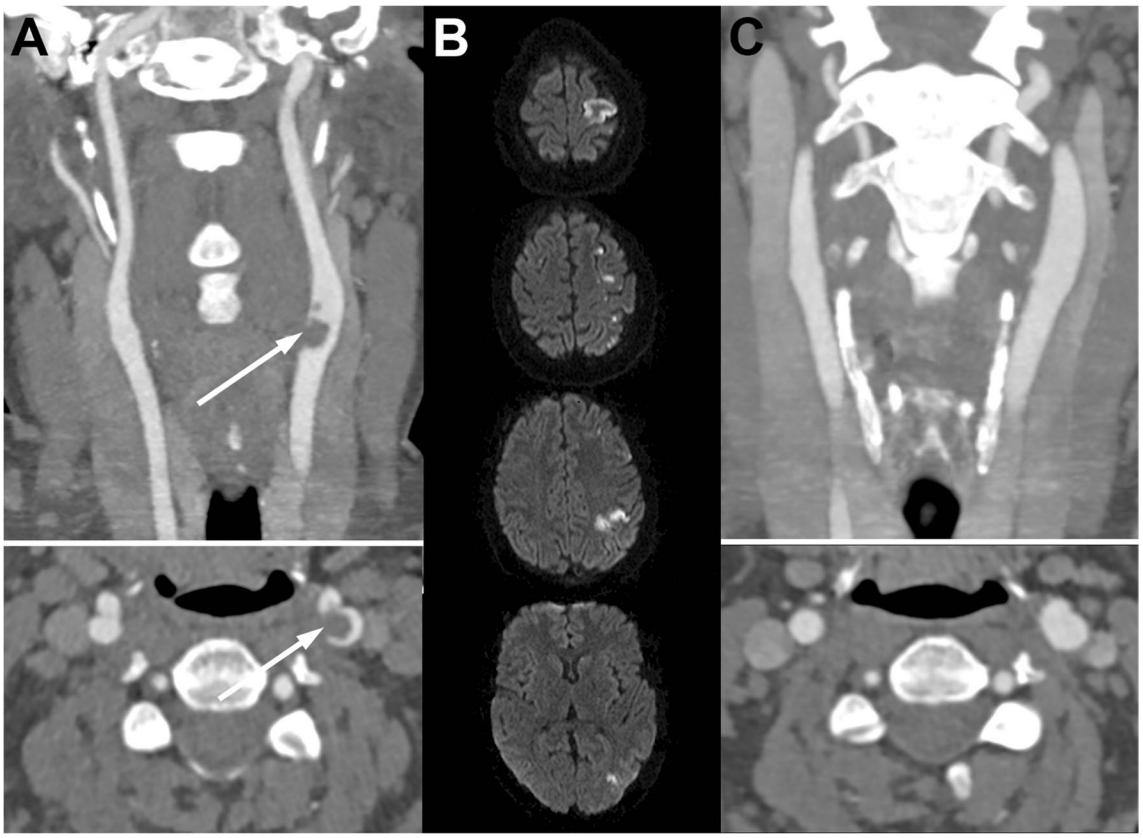

Fig. 1 CT Angiography shows the free-floating thrombus of the left common carotid artery before (**A**) and after (**C**) systemic thrombolytic therapy at a three-day follow-up. Diffusion-weighted imaging showed multilocular cortical ischemic areas in the left ACM territory caused by ruptured thrombus material (**B**)

of 78 kg (receiving 0.9 mg/kg dose), followed by continuous anticoagulation with heparin 24000 IE/24 h after 24 h. Diffusion-based imaging revealed multilocular cortical ischemic areas in the left middle cerebral artery (MCA) territory (Fig. 1B). CT angiographic follow-up imaging three days after admission showed complete lysis of the thrombotic material in the left CCA and ICA bifurcation (Fig. 1C). Eltrombopag was paused upon admission and resumed at a reduced dosage of 25 mg/24 h after the patient's platelet count reached a cut-off platelet count $<500 \times 10^9$/l, which occurred five days after stroke onset.

At discharge, the patient showed very mild sensorimotor paresis of the right side, NIHSS 2, mRS 1. The patient was discharged with lifelong secondary prophylaxis of acetylsalicylic acid 100 mg/24 h and Simvastatin 40 mg/24 h. No antiviral treatment was administered due to the absence of pulmonary symptoms and the fact that the COVID-19 infection had been progressing for 10 days before admission. The patient's platelet count was monitored daily after discharge. Two months after discharge, the patient's platelet count remained unstable, ranging between 5 and 419×10^9/l (Fig. 2). As a result, the referral doctor adjusted the patient's eltrombopag dosage, and acetylsalicylic acid was temporarily paused.

Discussion

The presented case exemplifies the neurological complications that hematological patients dealing with multiple risk factors for developing a thrombosis can experience. Moreover, the complex interplay between thrombocyte stimulation by a TPO-RA and a viral infection as a potential trigger for hypercoagulability should raise concerns at the onset of prompt focal deficits.

In the presented case, systemic lysis therapy effectively dissolved a thrombus in a carotid artery, leading to the patient's swift recovery without any significant adverse effects. The systemic lysis approach was preferred over carotid thromboendarterectomy and percutaneous transluminal angioplasty (PTA) with direct clot aspiration or a stent retriever due to the risk of the thrombus spreading to more distal regions. Although previous data indicate that neither medical nor interventional treatment is superior to the other in treating free-floating thrombus of the carotid artery [1], authors report the effectiveness of recombinant-plasminogen activator in dissolving embolic occlusions predominantly derived from fibrin-rich-clotted platelet material at the presence of COVID-19-associated-dysregulated platelet homeostasis [7].

The post-stroke procedure included the initiation of the platelet agglutination inhibitor with acetylsalicylic acid and, after a brief interruption, a continuation of eltrombopag at a reduced daily dosage of 25 mg/24 h, with weekly platelet count control for the next three months. Although recent guidelines published for ITP are not specific regarding the risk-benefit ratio in adapting eltrombopag and starting with acetylsalicylic acid [10], eltrombopag was interrupted in other cases of thromboembolic events under eltrombopag in ITP after a COVID-19 infection while a stable platelet count was observed [2].

ITP patients undergoing TPO-RA therapy have a low but significant risk of developing thromboembolic events compared to the general population [14], and thromboembolic events occur independently of the patients' platelet count or of the duration of eltrombopag intake. While most patients who develop embolic events show a reduced platelet count, some rare cases report thromboembolic events with normal or even elevated platelet numbers, as observed in the present

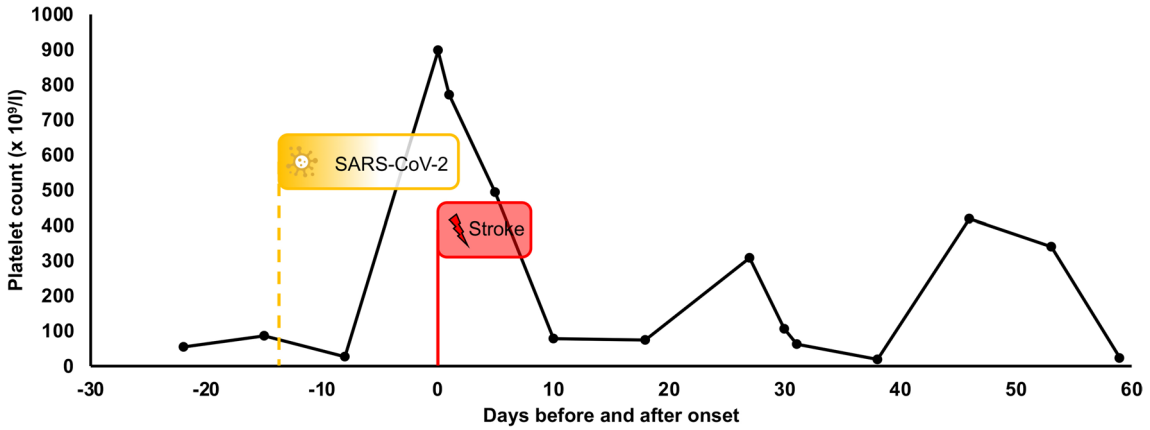

Fig. 2 Course of stroke, platelet count, and COVID-19 disease progression. SARS-CoV-2 infection was associated with fever and overall weakness for 5 days (full bar). At admission, the platelet count was 892×10^9/l, and the patient tested positive for COVID-19 without any related pulmonary symptoms (transparent bar). The patient had her first positive SARS-CoV-2 test 14 days before the stroke onset

Table 1 Clinical Features of the 13 cases of chronic ITP under TPO-R who developed a COVID-19 Infection-associated thrombocytosis, including the present case

No.	Age (years)	Sex	Severity of COVID-19 infection	Type of TPO-RA	Dosage of TPO-RA	Platelet count baseline	Platelet count peak	Days of platelet Peak after COVID-19 onset	Thromboembolic event/bleeding	Reference
1	28	F	Mild	Eltrombopag	40.2 mg/day	100×10^9/l	467×10^9/l	7	No	Pantic et al. [11]
2	39	F	Mild	Eltrombopag	75 mg/day	26×10^9/l	896×10^9/l	14	Carotid thrombus, stroke	Our case
3	45	F	Mild	Eltrombopag	25 mg/day	41×10^9/l	260×10^9/l	7	No	Pantic et al. [11]
4	61	M	Moderate	Eltrombopag	36.1 mg/day	171×10^9/l	324×10^9/l	21	No	Pantic et al. [11]
5	74	M	Severe	Eltrombopag	26.1 mg/day	92×10^9/l	160×10^9/l	5	DIC, death	Pantic et al. [11]
6	79	N.A.	MILD	Eltrombopag	N.A.	110×10^9/l	$> 300 \times 10^9$/l	N.A.	N.A.	De la Cruz-Benito et al. (2020)
7	79	F	Moderate	Eltrombopag	12.5 mg/day	15×10^9/l	183×10^9/l	20	No	Maekura et al. [9]
8	84	N.A.	Moderate	Eltrombopag	N.A.	$< 300 \times 10^9$/l	$> 600 \times 10^9$/l	N.A.	N.A.	De la Cruz-Benito et al. (2020)
9	19	F	Mild	Romiplostim	6.5 µg/kg/week	44×10^9/l	768×10^9/l	7	No	Pantic et al. [11]
10	47	F	Severe	Romiplostim		185×10^9/l	666×10^9/l	11	Pulmonary embolism	Pantic et al. [11]
11	56	N.A.	Severe	Romiplostim	N.A.	86×10^9/l	575×10^9/l	7	N.A.	De la Cruz-Benito et al. (2020)
12	72	M	Mild	Romiplostim	2.5 µg/kg/week	115×10^9/l	355×10^9/l	7	No	Pantic et al. [11]
13	76	F	Mild	Romiplostim	N.A.	N.A.	N.A.	N.A.	Intracranial hemorrhage, death	De la Cruz-Benito et al. (2020)

Determination of COVID-19 severity: "mild" illustrates no oxygen therapy requirements or asymptomatic course; "moderate" indicates oxygen therapy on hospitalization; "severe" implies ventilator management or ICU management

No., number; *N.A.*, not available

case with a significant thrombocytosis [3]. Bussel et al. [3] further identified at least one risk factor in each ITP patient with thromboembolic events; however, there was no consistent factor apparent in the majority of thromboembolic cases. As such, the present case suggests close monitoring of ITP patients' platelet count and signs of thromboembolic events during a presumptive temporal hypercoagulability as triggered by an acute COVID-19 infection, given that previous case reports and studies on COVID-19 patients with free-floating thrombus material indicate that a single risk factor and a COVID-19-related hypercoagulable state can trigger the development of a thrombus [4].

The complex mechanisms leading to COVID-19–associated thromboembolic events are not fully understood. However, an underlying hypercoagulable state in COVID-19 involves a prothrombotic malfunction of the endothelium, which involves the loss of glycocalyx, cytoprotective signaling, and antithrombotic effectors to instead promote fibrin formation, platelet adhesion, and complement activation [6]. The reported patient developed thrombocytosis, while most patients with COVID-19-associated thromboembolic events are usually associated with mild-to-severe thrombocytopenia [15].

The phenomenon of thrombocytosis following COVID-19 infection in ITP patients receiving TPO-RA therapy has been described in a few cases before (Table 1) [5, 9, 11]. Similar to our case, Pantic et al. reported severe thromboembolic complications in their patient cohort associated with post-COVID-19 thrombocytosis approximately seven days after COVID-19 onset. Although the specific cause for the acute thrombocytosis in these patients is unclear, COVID-19-associated lymphopenia has been suggested as a possible trigger. A reduced number of auto-reactive lymphocytes may lead to inhibition of ITP-related platelet destruction, and TPO-RA may promote reactive thrombocytosis due to ongoing stimulation of thrombopoiesis [5]. Maekura et al. [9] suggested an association between elevated platelets in chronic ITP patients and the development of SARS-CoV-2 neutralizing antibodies after a COVID-19 infection. Four out of 13 cases, including our case, revealed severe thromboembolic complications during elevated platelet counts after COVID-19 infection in ITP patients. The severity of the COVID-19 infection does not appear to be related to the relative increase in platelet count in the reviewed cases.

As a single case report, the findings cannot be generalized. Furthermore, compliance with eltrombopag dosage was based on self-report by the patient and was not validated by serological measurements. Prospective studies are needed to further systemically assess a potential association between COVID-19 infection, chronic ITP under TPO-RA therapy, and early thrombocytosis after COVID-19 onset.

Overall, the findings of this case suggest that acute infection with SARS-CoV-2 promotes a hypercoagulable state with platelet disbalance in ITP patients receiving eltrombopag therapy. In the rare event of ischemic stroke in a patient with ITP and COVID-19 exhibiting a free-floating thrombus of the carotid, systemic lysis therapy can successfully and safely dissolve thromboembolic material and prevent further ischemic lesions. A slight reduction of the daily dosage of TPO-RA as well as the initiation of an antiplatelet aggregation may be a feasible strategy for secondary stroke prophylaxis in these patients.

Data availability All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Code Availability

Not applicable.

Authors' Contribution L.C. Adam treated the patient, wrote the manuscript, and created the figures.

M. Burgstaller treated the patient and supervised the manuscript.

U. Taetweiler gave input during patient treatment and supervised the manuscript.

J. Mueller supervised the manuscript.

Declarations

Ethics Approval The case report was written according to the CARE guidelines.

Informed Consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest The authors declare no competing interests.

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