

CASE REPORT

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# Two ischemic stroke events within 48 h: a case report of an unusual presentation of thrombotic thrombocytopenic purpura

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## Abstract

**Background** Thrombotic thrombocytopenic purpura (TTP) considers a rare cause of ischemic stroke (IS). We reported a case of a newly diagnosed patient with acquired immune-mediated TTP (iTTP), in whom two IS events developed during 48 h.

**Case presentation** A 59-year-old diabetic male was presented to the hospital 24 h after symptoms onset, including left hemiparesis, dysarthria, and decreased consciousness. A brain CT scan was performed with the suspicion of acute IS, indicating infarct lesions in the right middle cerebral artery (MCA) territory. The patient was not eligible for thrombolytic therapy due to admission delay. Over the next 24 h, the patient's neurological condition deteriorated, and the second brain CT scan showed new ischemic lesions in the left MCA territory. Initial laboratory evaluation indicated thrombocytopenia without evidence of anemia. However, in the following days, thrombocytopenia progressed, and microangiopathic hemolytic anemia (MAHA) developed. The ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and inhibitors assay confirmed the diagnosis of iTTP. The patient underwent plasma exchange activity and inhibitors assay confirmed the diagnosis of iTTP. The patient underwent and pulse IV methylprednisolone. Rituximab was also added due to the refractory course of the disease. After a prolonged hospital course, he had considerable neurologic recovery and was discharged.

**Conclusions** Clinicians should consider two points. First, TTP should be considered in any patient presenting with IS and having thrombocytopenia or anemia without other symptoms of TTP. Second, worsening the patient's condition during hospitalization may indicate a new stroke and should be investigated immediately.

**Keywords** Purpura, Thrombotic thrombocytopenic, Ischemic stroke, Thrombotic microangiopathies, Anemia, Hemolytic, ADAMTS13 protein, Case report

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## Background

Coagulation disorders account for less than 5% of ischemic strokes (IS) [1]. Thrombotic thrombocytopenic purpura (TTP) is a rare, though severe, inherited or acquired disease caused by severe deficiency of the Von Willebrand factor-cleaving serine protease, ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [2]. The exact incidence and prevalence figures are not available [3]. However, various numbers have been reported, from 2.2 cases per million population per year to 3.7 [4, 5] or even up



to 13 cases per million population, according to a French national registry [6]. Patients with TTP might present with severe thrombotic events such as IS, either initially or during the treatment [7–10]. Stroke develops in 8.16% of patients admitted with TTP, according to the findings from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP) [11]. Classic clinical manifestations include pentad of fever, microangiopathic hemolytic anemia (MAHA), thrombocytopenic purpura, renal dysfunction, and neurologic symptoms [3, 12]. Laboratory findings include thrombocytopenia and evidence of MAHA, including schistocytes, reticulocytosis, indirect hyperbilirubinemia, undetectable haptoglobin, and high lactate dehydrogenase (LDH) [12]. The diagnosis is suspected based on the clinical and laboratory findings and confirmed by very low ADAMTS-13 levels [12]. Of note, in the absence of other obvious causes, evidence of MAHA or thrombocytopenia without the presence of the classic pentad is strongly suggestive of TTP, hence the importance of immediate total plasma exchange (TPE) [13].

We reported a case of a newly diagnosed patient with acquired immune-mediated TTP (iTTP), in whom two IS events developed during a period of 48 h. This circumstance is unique in several ways. To begin with, iTTP is a rare disorder. Second, stroke is considered to be an unusual inaugural presentation of TTP. Third, there are currently very few reports of new ischemic lesions during hospitalization in individuals with iTTP following the first ischemic stroke event [14, 15]. Notably, some of these patients had the congenital type of the disease, making our patient even more intriguing.

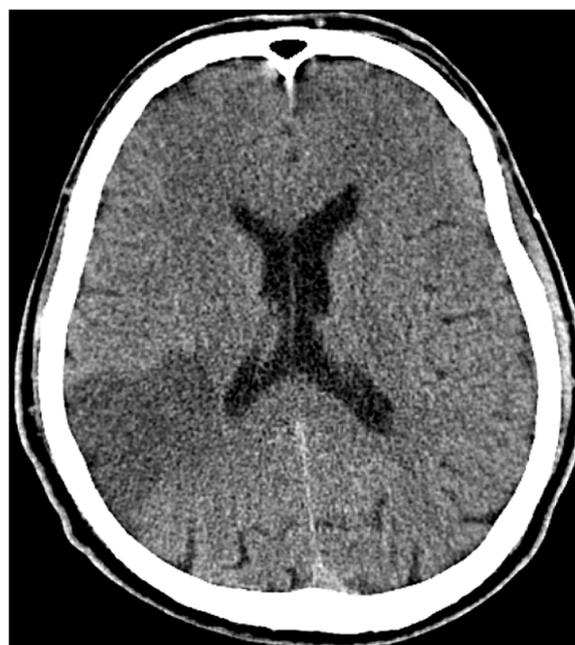
### Case presentation

A 59-year-old diabetic male was referred to our emergency room following left-sided weakness, hemifacial paresis, difficulty speaking, and drowsiness from one night before (National Institute of Health Stroke Score (NIHSS) at admission = 10). There was no history of recent head trauma. Family history of premature stroke or thrombotic events was also negative. The patient was a non-smoker, albeit an opiate user. The initial physical exam showed an elderly, confused male who could not answer the questions or follow commands cooperatively. Vitals were as follow: T = 37.4 °C, BP = 150/90 mmHG, HR = 73 bpm (beats per minute), RR = 16/minute, and O<sub>2</sub> saturation in the room air = 97%. An electrocardiogram (ECG) showed normal sinus rhythm. On initial physical examination, no signs of pallor, jaundice, petechiae, or organomegaly were evident. Except for left facial paresis, cranial nerves examination was normal. Motor examination revealed left hemiparesis, with a force of 3/5 in the left upper extremity and 4/5 in the left lower extremity.

The grimace to pinprick was reduced on the left side. The plantar reflex showed upward movement in the left side (Babinski sign).

### Investigations and treatment

The patient underwent a brain CT scan with suspicion of IS. Of note, since the patient's symptoms had been initiated more than 24 h ago, he was not eligible to receive intravenous thrombolysis (IVT) or thrombectomy [16]. The first brain CT scan showed an acute stroke in the right middle cerebral artery (MCA) territory, including the right parietotemporal lobe infarct (Fig. 1). The patient's level of consciousness deteriorated over the next 24 h, necessitating further evaluation; the second brain CT scan revealed evidence of new ischemic lesions in the left MCA territory, including the left frontal lobe (Fig. 2). Progressive thrombocytopenia was found in the patient (initial platelet count:  $77 \times 10^3/\mu\text{L}$  reduced to  $21 \times 10^3/\mu\text{L}$ ). Although the patient was not anemic at first (initial Hgb: 15 g/dL), evidence of hemolytic anemia gradually emerged, including a reticulocyte percentage of 2.6%, reduced Hgb (from 15 g/dL to 11.8 g/dL on day 6), indirect hyperbilirubinemia (total bilirubin 1.9 mg/dL increased up to 4.4 mg/dL, and indirect bilirubin 1.1 mg/dL increased up to 3.1 mg/dL), and elevated LDH (1148 U/L). Additionally, acute phase reactants, including ESR, CRP, ferritin, fibrinogen, and D-dimer, were also elevated. Troponin, coagulation tests, liver function



**Fig. 1** Brain CT scan on admission showed the right parietotemporal lobe infarct



**Fig. 2** Brain CT scan 24 h after admission showed a new infarct in the left frontal lobe

tests, lipid profile, and electrolytes were normal. Peripheral blood smear (PBS) showed occasional schistocytes. Direct and indirect Coombs tests were negative. TTP diagnosis was highly suspected based on the patient’s clinical manifestations and progressive thrombocytopenia. Therefore further evaluation was performed, indicating an ADAMTS-13 activity level of 0.3 IU/mL (our laboratory cut-off for a positive value was <0.4 IU/mL) and ADAMTS-13 inhibition screen of 18 U/mL (our laboratory cut-off for a positive value was >15 U/mL), confirming the diagnosis of iTTP. Other Serologic evaluations (antinuclear antibody (ANA), anti-double strands DNA antibody (anti-dsDNA Ab), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), cytoplasmic anti-neutrophil cytoplasmic autoantibody (C-ANCA), rheumatoid factor (RF), complement 3 (C<sub>3</sub>), complement 4 (C<sub>4</sub>), anticardiolipin IgM and IgG antibodies, antiphospholipid IgM and IgG antibodies, and anti-Sjögren’s-syndrome-related antigen A and B autoantibodies (SSA and SSB) were within normal limits. HIV, hepatitis B virus, and hepatitis C virus serology were also nonreactive (Table 1).

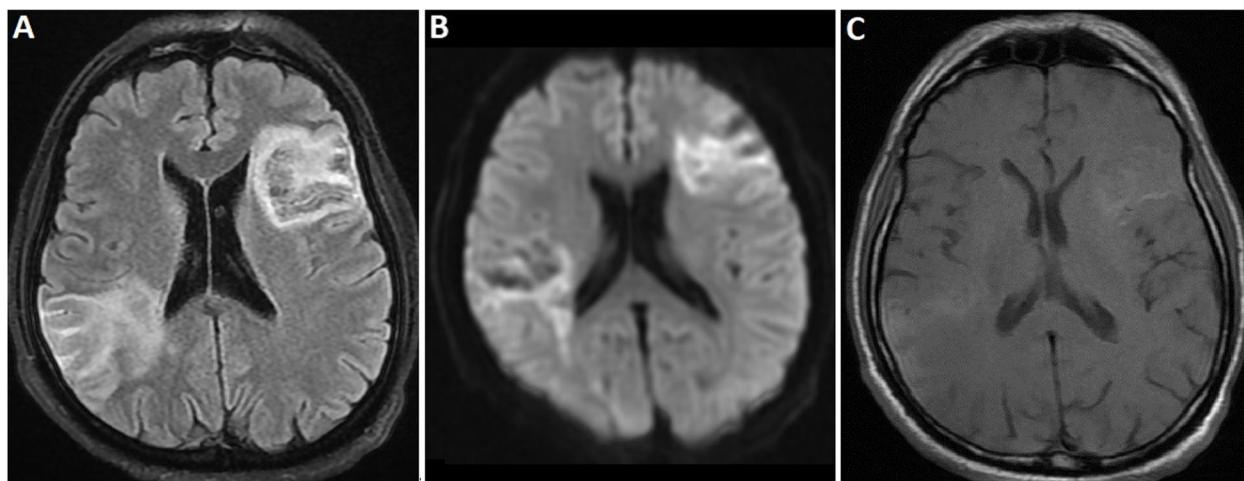
Although the cardioembolic source of stroke was suspected due to the bihemispheric infarcts, ECG Holter monitoring, trans-thoracic, and trans-esophageal echocardiography revealed no signs of arrhythmia, clot, or vegetation, and the ejection fraction (EF) was 50–55%. Brain MRI on day 8 demonstrated evidence

**Table 1** The results of patients’ laboratory evaluation at presentation, day 7 hospitalization, and discharge

Laboratory test (unit)	Initial value	Day 7 hospitalization	Discharge value
WBC (10 <sup>3</sup> /μL)	10.8		8
Hgb (g/dL)	15	12.3	12
MCV (fL)	86.5		
MCH (pg)	30.9		
Reticulocyte (%)	3.2	4	
Corrected reticulocyte (%)	1.7	2.6	
PLT (10 <sup>3</sup> /μL)	77	25	189
PT (sec)	13.1		13.1
PTT (sec)	28		26
INR	1.0		1.0
Glucose (mg/dL)	268		
HbA1c (%)	> 14	12.3	
BUN (mg/dL)	18		23
Cr (mg/dL)	0.9		0.7
Total Bilirubin (mg/dL)	1.9	4.4	1.4
Direct Bilirubin (mg/dL)	0.8	1.3	0.4
LDH (U/L)	1148		456
ESR (mm/h)	49		
CRP (mg/l)	16		
D-Dimer (μg/l)	1932		
Fibrinogen (mg/dL)	609		
Ferritin (ng/mL)	910		

WBC White blood cells, Hgb hemoglobin, MCV Mean corpuscular volume, MCH Mean corpuscular hemoglobin, PLT Platelet, PT Prothrombin time, PTT Partial thromboplastin time, INR International normalized ratio, HbA1c Glycosylated hemoglobin, BUN Blood urea nitrogen, Cr Creatinine, LDH Lactate dehydrogenase, ESR Erythrocyte sedimentation rate, CRP, C reactive protein

in favor of subacute infarctions with restriction and mild hemorrhagic transformation in the right parietotemporal, left frontal lobe, and left centrum semiovale (Fig. 3). There was no evidence of venous thrombosis or vascular lesions on magnetic resonance angiography (MRA) and magnetic resonance venography (MRV). Since malignant bone marrow infiltration is one of the main differential diagnoses in a patient with MAHA and thrombocytopenia [14], hematology was consulted. They asked for a bone marrow aspiration and biopsy (day 8), which showed normocellular marrow with increased erythroid series. Informed consent was obtained, and the patient underwent therapeutic plasma exchange (TPE) on day 8 with iTTP diagnosis. Consequently, the patient’s level of consciousness improved so that he was completely alert



**Fig. 3** Brain MRI on day 8 showed subacute infarctions with restriction and mild hemorrhagic transformation in the right parietotemporal, left frontal lobe, and left centrum semiovale; A: Diffusion-weighted imaging (DWI); B: Fluid attenuated inversion recovery (FLAIR); C: T1-weighted

and responsive 9 days after TPE (day 17 hospitalization). The platelet count also gradually increased from  $21 \times 10^3/\mu\text{L}$  up to  $91 \times 10^3/\mu\text{L}$  a week after TPE initiation, although it again started to decrease. Hence, pulse IV methylprednisolone therapy was added on day 17 of hospitalization for 3 days, followed by oral prednisolone (1 mg/kg). Rituximab ( $750 \text{ mg/m}^2$ ) was also initiated on day 30 of hospitalization. The patient’s clinical condition, as well as the MAHA, gradually improved

(NIHSS at discharge = 3), and the PLT count reached  $189 \times 10^3/\mu\text{L}$  at discharge (48 days of hospitalization, including 17 days at the stroke care unit (SCU), 5 days at the neurology ward, and 26 days at the hematology ward). During the follow-up, the neurological symptoms progressively improved, and he did not experience further relapses or report adverse effects. (modified Rankin Scale = 1, 75 days after discharge). The patient’s timeline is shown in Table 2.

**Table 2** An overview of the patient’s timeline during hospitalization

Day 0	Initiation of stroke-related symptoms
Day 1	Admission to the hospital The first brain CT showed the right parietotemporal lobe infarct Detection of thrombocytopenia
Day 2	Worsening of patient’s neurological condition
Day 6	The second brain CT showed a new infarct in the left frontal lobe Decrease in hemoglobin $\leq 13 \text{ g/dL}$ Evidence of MAHA
Day 7	ADAMTS-13 activity and inhibitors assay
Day 8	Brain MRI showed subacute infarctions with restriction and mild hemorrhagic transformation in the right parietotemporal, left frontal lobe, and left centrum semiovale Bone marrow aspiration and biopsy Initiation of therapeutic plasma exchange
Day 15	Platelet count reached $91 \times 10^3/\mu\text{L}$
Day 17	Considerable improvement neurologically Platelet count started to decrease again Initiation of pulse IV methylprednisolone
Day 20	Initiation of oral prednisolone
Day 30	Rituximab was added
Day 48	Discharged

MAHA Microangiopathic hemolytic anemia, ADAMTS-13 A disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13, IV Intravenous

## Discussion

In this study, we reported a 59-year-old male presented with hemiparesis, dysarthria, and decreased consciousness who developed two ischemic stroke events during 48 h, which is extremely rare. The results of neuroimaging revealed evidence of infarction in the right (at admission) and left (24 h after admission) MCA territories, respectively. Initial laboratory findings indicated progressive thrombocytopenia. However, MAHA was not found at presentation. Further evaluations, including measurement of ADAMTS-13 activity level and ADAMTS-13 inhibitor, confirmed the diagnosis of iTTP. The patient underwent therapeutic plasma exchange and pulse IV methylprednisolone therapy. Rituximab was also given since it could reduce relapses, and is increasingly recommended for use in refractory cases [17, 18]. Notably, studies showed that although iTTP considers an autoimmune disease, ADAMTS-13 inhibitors are not easily detectable in many patients [19], which was not the case in our patient. Similar to the prolonged course of treatment in our patient, studies showed that high titers of inhibitors of ADAMTS-13 are associated with delayed response to therapy, high risk of complications, and higher rates of refractory disease and relapses [19, 20]. Of note, while there are reports of patients with TTP who presented with IS as an atypical presentation [15, 21], there are very few reports of new ischemic lesions during hospitalization following the first ischemic stroke event [14, 15]. One was a 70-year-old female who presented with confusion, fever, and gastrointestinal symptoms who deteriorated neurologically during hospitalization, and the brain MRI revealed multiple acute and subacute infarcts in both cerebral hemispheres, midbrain, and right cerebellum. The patient had a history of hypertension, diabetes, rheumatoid arthritis, two miscarriages complicated by disseminated intravascular coagulation, two transient ischemic attacks, and a left occipital infarct and she was diagnosed with congenital TTP [14]. Another one was a 43-year-old female who was admitted with left hemiparesis, homonymous hemianopia, and dysarthria. The first brain CT showed an acute stroke in the right MCA territory, and follow-up MRIs during the first week of her hospitalization demonstrated new ischemic lesions in various territories [15].

TTP is a relapsing and life-threatening condition characterized by clot formation in small blood vessels [22]. Clinical manifestations vary from mild nonspecific symptoms to severe organ damages, including kidney and brain, and death [3]. Neurologic involvements, such as headaches, confusion, focal neurologic deficit, etc., are common as the initial presentation of TTP usually as a result of diffuse microthrombi formation in the microvasculature of the central nervous system (CNS),

resulting in transient or permanent ischemic brain damage [3, 7–9, 23]. However, TTP considers a rare cause of ischemic stroke [15], although there are similar cases in the literature of patients being diagnosed with TTP after a cerebrovascular accident [9, 21, 24–26]. A recent study on patients with TTP who presented with neurological symptoms suggested that old age, hypertension, smoking, and high plasma concentrations of anti-ADAMTS-13 IgG may be the risk factors for developing cerebral infarction in these patients [27]. Furthermore, they reported no association between iTTP stroke and diabetes, however, our patient was diabetic [27]. Additionally, it is suggested that decreased level of ADAMTS-13 is associated with stroke recurrence after remission [28], hence the importance of patients' follow-up.

A literature review conducted in 2018 reported 17 cases of IS due to iTTP [15]. Interestingly, none of the patients showed the classical TTP pentad, and wide non-specific heterogeneity in clinical manifestations was observed [15]. The combination of thrombocytopenia and hemolysis was found in less than half of the patients (41%). In 41% of cases, the stroke was multifocal and included major artery strokes, with proximal occlusion in 3 cases. Considerably, refractory and relapsing forms were observed in nearly half of the patients (47%). They reported small and large artery strokes in these patients, with the majority being multifocal and without a specific pattern [15]. These findings confirm the claim that although TTP is classified as a thrombotic microangiopathic condition, which results in small vessels obstruction, it should also be considered in patients with proximal intracranial artery occlusion [9, 15, 24, 29].

## Conclusion

In alignment with previous studies, this study showed that although TTP is considered an uncommon cause of ischemic stroke, it should be considered in every IS patient with isolated anemia or thrombocytopenia even in the absence of other classic symptoms or laboratory findings. This study also suggests that clinicians should consider the possibility that worsening of the patient's clinical condition could be attributed to emerging of new infarcts, emphasizing the importance of early diagnosis and treatment of iTTP to prevent multiple infarcts and a poor prognosis.

## Abbreviations

ADAMTS-13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ANA	Antinuclear antibody
Anti-dsDNA	Anti-double strands DNA
Bpm	Beats per minute
C-ANCA	Cytoplasmic antineutrophil cytoplasmic autoantibody
CNS	Central nervous system

C3	Complement 3
C4	Complement 4
ECG	Electrocardiogram
EF	Ejection fraction
HCUP	Healthcare cost and utilization project
Hgb	Hemoglobin
IS	Ischemic stroke
iTTP	Immune-mediated thrombotic thrombocytopenic purpura
IVT	Intravenous thrombolysis
LDH	Lactate dehydrogenase
MAHA	Microangiopathic hemolytic anemia
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRV	Magnetic resonance venography
NIHSS	National institute of health stroke score
NIS	Nationwide inpatient sample
P-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PBS	Peripheral blood smear
RF	Rheumatoid factor
SSA	Sjögren's-syndrome-related antigen A
SSB	Sjögren's-syndrome-related antigen B
TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura

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### Authors' contributions

HA and MG provided the patient with appropriate treatment according to the guidelines. SH collected the data and had a major role in the patient's treatment. MJ assisted with the patient's follow-up and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

### Declarations

#### Ethics approval and consent to participate

This study was conducted at an academic hospital complex affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran, and approved by the ethics committee of the university. Written informed consent was obtained from the patient. This study was conducted according to the Declaration of Helsinki [30].

#### Consent for publication

The patient provided written informed consent for the submission and possible publication of this manuscript. During the patient's hospitalization, consent for treatment was also obtained in the usual manner.

#### Competing interest

There are no conflicts of interest.

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