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The Clinical Conundrum of Managing Ischemic Stroke in Patients with Immune Thrombocytopenia

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ABSTRACT: Guidelines are lacking for management of acute ischemic stroke and stroke prevention in patients with immune thrombocytopenia (ITP). Our aim is to highlight the dilemma inherent in managing patients with both significant bleeding and thrombotic risk factors. In this review, we present two patients with history of ITP who presented with acute ischemic stroke and received tissue plasminogen activator (tPA) and endovascular thrombectomy (EVT), a rare management strategy in this patient population. In addition, we identified 27 case reports of ischemic stroke in patients with ITP; none of them received tPA or EVT. Furthermore, there are 92 patients with significant thrombocytopenia with no available data regarding the cause of thrombocytopenia, who were acutely treated with tPA or EVT. Conclusive evidence cannot be determined based on these limited number of cases. Future multicenter prospective cohort studies in patients with ITP are needed to provide better evidence-based treatment plans. At present, treatment of acute ischemic stroke in patients with ITP requires close collaboration between hematology and vascular neurology experts to find a balance between the benefit and risk of hemorrhagic complications.

RÉSUMÉ : La prise en charge de patients atteints de thrombopénie immune qui ont été victimes d'un AVC ischémique : une énigme clinique. Les cliniciens sont à court de lignes directrices quand il est question de prise en charge et de prévention dans le cas de patients atteints de thrombopénie immune (TPI) qui ont été victimes d'un AVC aigu. Notre objectif est ici de mettre en évidence le dilemme inhérent à la prise en charge de patients présentant à la fois des facteurs de risque hémorragique et thrombotique importants. Nous entendons donc présenter dans cette étude deux patients ayant des antécédents de TPI qui se sont présentés dans un établissement hospitalier après avoir été victimes d'un AVC aigu et qui ont bénéficié d'activateurs tissulaires du plasminogène par intraveineuse (tPA-IV) et d'une procédure de thrombectomie endovasculaire (TE), ce qui constitue une stratégie de prise en charge inhabituelle pour ce groupe de patients. Nous avons aussi identifié 27 rapports de cas de patients atteints de TPI et victimes d'un AVC ischémique qui n'ont bénéficié ni de tPA ni d'une procédure de TE. De plus, nous nous sommes intéressés à 92 patients gravement atteints de TPI pour lesquels on ne possède aucune donnée en ce qui regarde les causes de leur maladie et qui ont été traités de manière intensive avec des tPA ou au moyen d'une procédure de TE. Chose certaine, il est impossible d'obtenir des preuves concluantes sur la base de ce nombre limité de cas. Des études de cohorte prospectives menées dans plusieurs établissements de santé et portant sur des patients atteints de TPI sont nécessaires dans le futur afin de pouvoir offrir de meilleurs plans de traitement fondés sur des données probantes. À l'heure actuelle, le traitement des AVC ischémiques chez ces patients nécessite la collaboration étroite de spécialistes en hématologie et en neurologie vasculaire afin de trouver un équilibre entre les avantages thérapeutiques et les risques de complications hémorragiques.

Keywords: Immune thrombocytopenia (ITP), Thrombocytopenia, Ischemic stroke, Thrombolysis, Endovascular thrombectomy

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Immune thrombocytopenia (ITP) is an autoimmune condition characterized by isolated severe thrombocytopenia. Hemorrhagic tendency is the main manifestation of ITP, but the risk of thrombosis in patients with ITP is thought to be 5%, predominantly causing venous thromboembolism.[1] Risk of thrombosis is similar to that associated with malignancy. There is lack of evidence on how to manage acute ischemic stroke and manage secondary prevention in patients with ITP. This is of particular importance as the standard of care for acute ischemic stroke includes a prompt initiation of reperfusion therapies and subsequent use of antiplatelets or anticoagulant agents, which can increase the risk of major bleeding. Concern for potential

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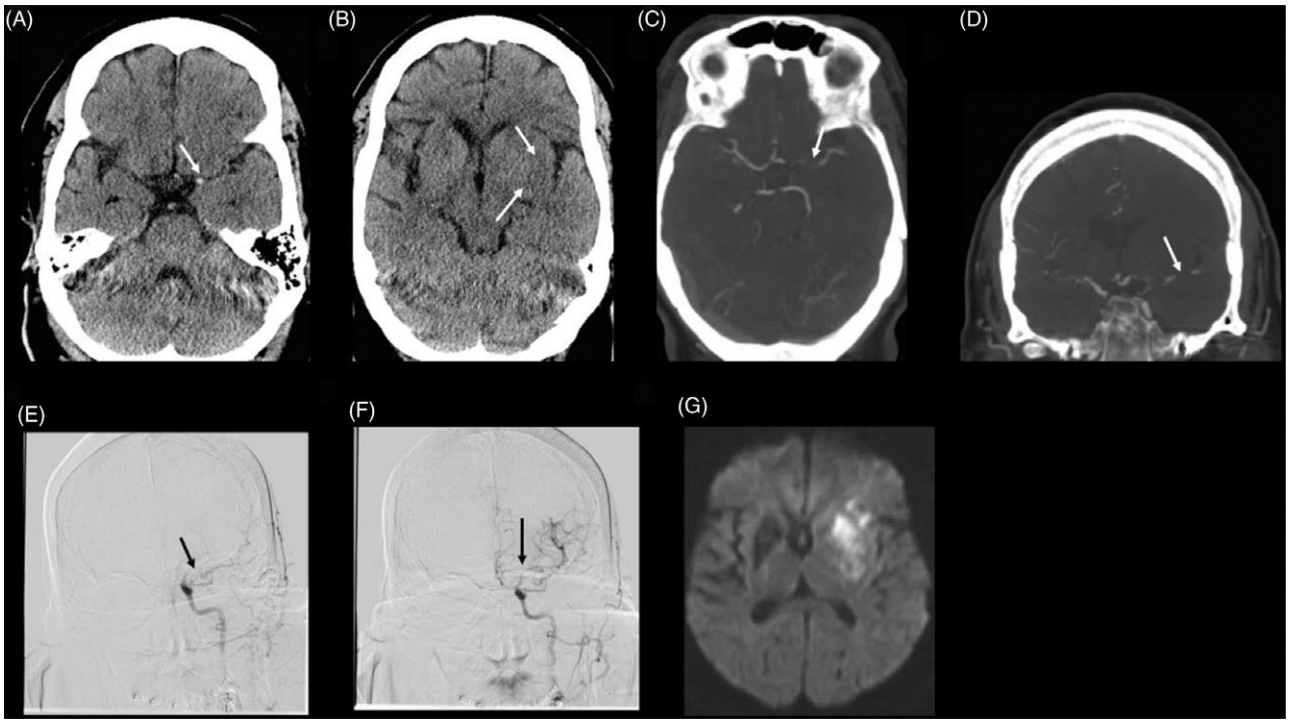

Figure 1: *Diagnostic imaging and therapeutic intervention for the first case reported. (A) Axial CT head shows left MCA hyperdense sign indicating a fresh clot. (B) Axial CT head reveals early ischemic changes in the left insula and basal ganglia as indicated by the arrows. (C and D) Axial and coronal sections of CTA show thrombotic occlusion of the left carotid terminus extending into the left M1 segment of MCA. (E) Digital subtraction angiogram further demonstrates the same finding shown in CTA. (F) Digital subtraction angiogram shows revascularization after a successful endovascular thrombectomy. (G) Diffusion weighted imaging of the brain 24 h after the ischemic stroke reveals a diffusion restriction in the left insula and basal ganglia.*

life-threatening hemorrhage in ITP patients influences decision-making in acute stroke management.

We present two patients with ITP and acute ischemic stroke who received tissue plasminogen activator (tPA) and endovascular thrombectomy (EVT). In addition, we performed a review of the literature to summarize the available evidence.

Case Series

Case 1

A 61-year- old female was brought to hospital after a witnessed sudden onset of right-sided weakness and global aphasia that started 90 min prior. She had been diagnosed with ITP more than a decade prior to her stroke onset. She had been treated with corticosteroid and intravenous rituximab, and ultimately underwent splenectomy 13 years ago. Despite this, she failed to achieve complete long-term remission. At the time of her stroke she was not on antiplatelet or ITP-specific therapy. Two months prior to stroke onset her platelet count was 28×10^9/l. Her past medical history included coronary artery disease, dyslipidemia, hypertension, breast cancer in remission for several years, and a remote pulmonary embolism which was managed with an inferior vena cava (IVC) filter and no anticoagulation. Upon arrival to the emergency room, she was in atrial fibrillation (AF) but hemodynamically stable. Her blood pressure was 165/80 mmHg and heart rate was 85 beats per minute (bpm). Blood glucose level was 6.5 mmol/l (117 mg/dl). Neurological examination revealed drowsiness, global aphasia, and right-sided dense hemiparesis. Her National Institute of Health Stroke Scale (NIHSS) was 16. Computed tomography (CT) of the head demonstrated left middle cerebral artery (MCA) hyperdense sign and early acute ischemic changes within the left basal ganglia and inferior left insula (Figure 1(A) and (B)). CT angiogram (CTA) head and neck showed thrombotic occlusion of the left carotid terminus extending into the left M1 segment of MCA (Figure 1(C) and (D)) with good collaterals and no significant atherosclerotic changes. Her platelets at presentation were 48×10^9/l. Given the significant neurological deficits, timely presentation to emergency department, and her high prehospitalization functional capacity, the decision was made with the patient's family to proceed with thrombolysis using tPA. This was followed by a single-pass successful EVT using combined approach with stent retriever and aspiration assisted by balloon guide catheter (Figure 1(E) and (F)). The door to successful recanalization time of the thrombolysis in cerebral infarction (TICI) 2B was approximately 120 min. Follow-up CT head after 24 h showed the expected evolution of ischemic stroke, but there was no hemorrhagic complication. Platelet transfusion was not considered prior to thrombolysis/EVT or required during hospital admission. Four days after thrombolysis and EVT, her NIHSS was 0 and her modified Rankin Score (mRS) was 1 for very mild short-term memory difficulties. While in hospital, she was assessed by hematology and acetylsalicylic acid (ASA) for secondary stroke prevention was recommended, but no specific immunotherapy for ITP was suggested. Further assessment and discussion of risk and benefit of anticoagulation for AF was

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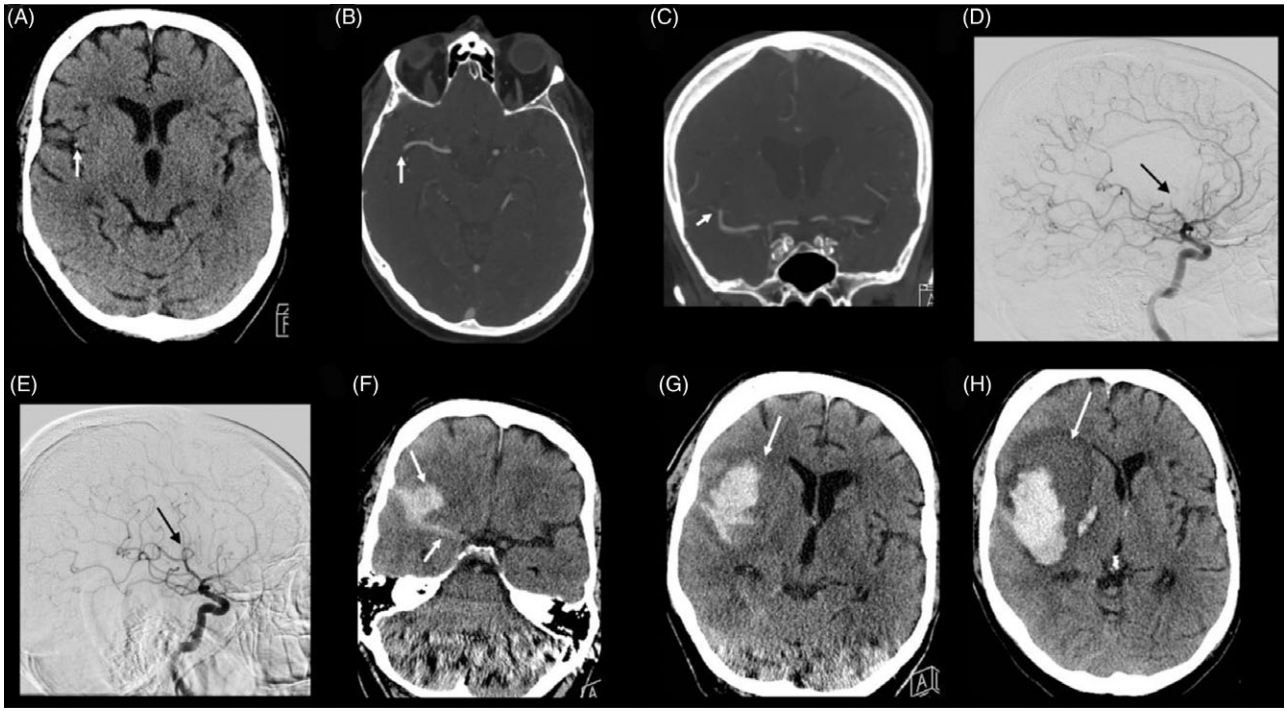

Figure 2: *Diagnostic imaging, therapeutic intervention, and follow-up scan for the second case reported. (A) Axial CT head reveals a right distal MCA hyperdense sign in the sylvian fissure correlating with right M2 occlusion. (B and C) Axial and coronal CTA show proximal occlusion of M2 segment of the MCA. (D) Digital subtraction angiogram further demonstrates the same finding shown in CTA. (E) Digital subtraction angiogram shows revascularization after a successful EVT. (F, G, and H) Axial CT head after tPA EVT reveals right frontoparietal SAH and large ICH surrounded by edema.*

arranged with outpatient hematology after discharge. At 6 months of follow-up, there was no hemorrhagic or thrombotic complication, and her mRS remained 1. Unfortunately, the patient did not return for hematology follow-up on a number of occasions to assess the risks and benefits of switching ASA to anticoagulation. She was therefore continued on ASA for secondary stroke prevention.

Case 2

A 75-year-old male was brought to hospital after he was found to have left-sided weakness and slurred speech that started an hour prior. He had been diagnosed with ITP a few years earlier with a remote history of life-threatening gastrointestinal hemorrhage and epistaxis a year ago. The cause of the bleeding was thought to be secondary to critical thrombocytopenia as gastroendoscopic evaluations were negative for malignancy and ulcer. Four months prior to this presentation, he experienced epistaxis with platelet count of 75×10^9/l. He was treated with corticosteroids and IVIG for ITP 6 months prior, and 2 months prior to presentation underwent splenectomy. His last platelet count was 349×10^9/l 2 days before stroke onset. His past medical history also included coronary artery disease, hypertension, and dyslipidemia. At the time of his stroke he was on ASA but not on any ITP-specific therapy. His blood pressure was 175/95 mmHg and heart rate was 90 bpm. His blood glucose level was 7 mmol/l (126 mg/dl). Neurological examination revealed left-sided neglect, right gaze forced deviation, left-sided weakness, decreased sensation, and dysarthria. NIHSS was 14. His CT of the head revealed a right distal MCA hyperdense sign in the sylvian fissure correlating with right M2 occlusion (Figure 2(A)). CTA of the head and neck demonstrated proximal occlusion of M2 segment of the right MCA (Figure 2(B) and (C)) with good collaterals and no significant atherosclerotic changes. Given the significant neurological deficits, the decision was made to proceed with thrombolysis using tPA. He then underwent a single pass successful EVT using combined approach with stent retriever and aspiration assisted by balloon guide catheter (Figure 2(D) and (E)). The door to successful recanalization time of TICI 3 was less than 60 min. He tolerated the procedure well with no immediate complications. Shortly after the procedure, his platelet count result became available, and it was 366×10^9/l, and his NIHSS improved to 9. His blood pressure remained stable ranging from 130/85 to 150/95 before and after intervention. He did not require acute antihypertensive therapy. After 2 h of thrombolysis/EVT, he developed hematemesis, drowsiness, and increasing left-sided weakness. Repeated CT head revealed a right frontoparietal, moderately large, intracerebral hemorrhage (ICH) with some subarachnoid hemorrhage (SAH) (Figure 2(F), (G), and (H)). His coagulation parameters were within normal range. INR was 1.1 units, PTT was 36 s, and fibrinogen was 3.2 g/l. In consultation with transfusion medicine, he was given 16 units of cryoprecipitate and one pooled unit of platelets. He was not started on corticosteroid or specific immunotherapy for ITP as it was felt that he was not in ITP relapse. He suffered from additional medical complications, including aspiration pneumonia, congestive heart failure, and AF. Upon discussion with family, goals of care were changed to palliative care and the patient ultimately died.

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Table 1: Clinical, imaging, and therapeutic characteristics in 27 patients reported in the literature with ITP and ischemic stroke

Patient #	Age	Platelet count $\times 10^9$/l	Clinical presentation	Mode of onset	Neuroimaging findings	Reperfusion or antithrombotic therapies	Hemorrhagic transformation	References
1	38	2	Hemiparesis	A week	Multiple cerebral infarctions in the left parietal and temporal regions.	No	No	[39]
2	31	80	Hemianopsia	NR	Right occipital lobe and hippocampal gyrus infarction. MRA: right PCA infarction	Antiplatelet	No	[40]
3	41	71	Vertigo, ataxia, diplopia	NR	Left midbrain infarction. MRA: left superior paramedian mesencephalic artery	Antiplatelet	No	[41]
4	31	132	Disoriented	1 day	Bifrontal infarctions. MRA: stenosis in bilateral distal ICAs and MCAs	Antiplatelet	No	[42]
5	63	2	Hemianopsia	NR	Right occipital infarction	No	No	[43]
6	79	22	Monoparesis, facial weakness, dysarthria	NR	Left periventricular lacunar stroke	Antiplatelet with platelet ≥ 50	No	[35]
7	43	55	Coma	Acute presentation	Diffuse supratentorial ischemia, left uncal herniation, bilateral carotid arteries occlusion, and thrombus within the basilar artery	No	No	[44]
8	33	84	Hemiparesis, dysarthria	Acute presentation	Right insular infarction. MRA: Distal right ICA occlusion	IA urokinase and IV heparin	No	[3]
9	64	17	Hemiparesis, aphasia	Acute presentation	Left MCA infarction and hemorrhagic transformation. MRA: Left ICA occlusion	Antiplatelet	Yes (Found at the baseline scan)	[45]
10	58	18	Vertigo, ataxia	1 day	Left cerebellar vermis infarction and hemorrhagic transformation	Antiplatelet	Yes (found at the baseline scan)	[46]
11	84	40	Aphasia, sensory disturbance, dysarthria	Acute presentation	left thalamic infarction	No	No	[47]
12	46	20	Hemiparesis, dysarthria, hemianopsia	10 h	Right MCA territory infarction. MRA: right MCA occlusion	Antiplatelet	No	[48]
13	60	20	Hemiparesis, dysarthria	A day	Left MCA border zone infarctions	Antiplatelet	No	[49]
14	51	270	NR	NR	Left frontal and parietal lobes infarction	Antiplatelet	No	[50]
15	33	51	NR	NR	Right SCA territory infarction	Antiplatelet	No	[50]
16	30	119	NR	NR	Right MCA territory infarction with cortical involvement	Antiplatelet	No	[50]
17	49	39	NR	NR	Left MCA subcortical infarction	Antiplatelet and anticoagulation	No	[50]
18	75	226	NR	NR	Bilateral hemispheric infarctions	Anticoagulation	No	[50]
19	72	182	NR	NR	Left centrum semiovale infarction. MRA: Left ICA occlusion	Antiplatelet and anticoagulation	No	[50]
20	49	43	NR	NR	Right MCA territory infarction. MRA: Distal right MCA occlusion	Anticoagulation	No	[50]
21	36	6	Vertigo	Paroxysmal transient episodes	Right cerebellar and vermis infarction. MRA: Right vertebral artery stenosis	No	No	[38]

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Table 1. *Continued*

Patient #	Age	Platelet count $\times 10^9$/l	Clinical presentation	Mode of onset	Neuroimaging findings	Reperfusion or antithrombotic therapies	Hemorrhagic transformation	References
22	68	119	Right upper limb weakness	A week	Left corona radiata infarction	Antiplatelet	Yes (incidental finding in repeated CT head after 3 months)	51
23	80	167	Tetraplegia	Acute presentation	Multiple bilateral cerebral and cerebellar infarctions	IV heparin	Yes (found on days 3 and 22)	52
24	37	43 → 568	Bilateral visual loss, right-sided weakness	Acute presentation	Bilateral basal ganglia, right occipitoparietal, and left occipital infarction	Antiplatelet	No	53
25	32	49	Vertigo, ataxia	Acute presentation	Left cerebellar infarction. MRA: Left vertebral artery occlusion	No	No	54
26	55	40	Right-sided weakness, aphasia	Acute presentation	Left MCA territory infarction. MRA: Left MCA occlusion	Antiplatelet with platelet ≥ 50	No	55
27	57	15	Left-sided weakness, dysartgeria	Acute presentation	Left MCA territory infarction	Antiplatelet and then discontinued	No	56

IA = intraarterial; ICA = internal carotid artery; IV = intravenous; MCA = middle cerebral artery; MRA = magnetic resonance arteriography; MRI = magnetic resonance imaging; NR = not reported; PCA = posterior cerebral artery; SCA = superior cerebellar artery.

Discussion

Summary of Reported Cases

The incidence of ITP in the general population is estimated to be 2 to 5 per 100,000 people.[2] A literature review reveals 27 case reports relating to ischemic stroke in patients with ITP (Table 1). Most of those patients had at least one vascular risk factor in addition to their ITP disorder. The mode of onset in all cases varied between acute and subacute presentations. None of the patients received thrombolysis or an endovascular procedure except a single report of intraarterial urokinase given to a patient with ischemic stroke with platelet count of 84×10^9/l.[3] More than half of the patients were started on antiplatelet for acute management and/or secondary prevention. Hemorrhagic transformation (HT) occurred in four patients, three of them were on antiplatelets and one was on anticoagulation. Two of the patients who developed HT had significant thrombocytopenia and the other two had a platelet count $>100 \times 10^9$/l.

Mechanism of Thrombosis

The general pathophysiology of ITP is that of an acquired autoimmune disorder, which can be primary or secondary, causing platelet destruction and impaired production.[2] Multiple hypotheses have been proposed to explain the mechanism of thrombosis in patients with ITP. The current leading hypothesis revolves around platelet microparticles (PMPs). PMPs are secreted by both activated and destroyed platelets as they are the natural elements that promote thrombosis for hemostatic control, but they also may, in part, be responsible for pathological thrombosis in patients with ITP. Compared to healthy controls, elevated levels of PMPs are detected in patients with ITP and concurrent ischemic events.[4] Elevated levels of PMPs have also been found in patients with ITP and vascular dementia due to ischemic small vessel disease – these patients also had higher platelet counts as well as more often had splenectomy.[5] PMPs are not alone to blame for thrombosis in ITP; it is thought that during immune-related platelet destruction there is a large proportion of immature activated platelets released from bone marrow, as well as large platelet–leukocyte–monocyte aggregates circulating and endothelium activating antibodies which all contribute to an increased risk of thrombosis.[1,3,5,6] Physiological nitric oxide (NO) in vessel endothelium in healthy individuals prevents platelet adhesion to vessel walls, and it is possible that in ITP, NO is depleted as a consequence of immune activation and also contributes to the prothrombotic state in ITP.[1,7] Neither of the patients presented in our case series were actively receiving intravenous immunoglobulin (IVIG) to treat their ITP, but IVIG is a known prothrombotic medication. Both of our patients had undergone splenectomy, which has consistently been shown to cause 2 times the risk of venous thromboembolism than the general population, and an insignificant increased risk of arterial thrombosis.[8] In our cases, we cannot be certain about the exact mechanism of ischemic stroke as both of them had AF and conventional vascular risk factors in addition to their ITP condition.

Clinical Decision-Making

We faced a management dilemma for our two patients given the insufficient data that represent the outcome of patients with ITP and ischemic stroke. Patients with significant thrombocytopenia ($<100 \times 10^9$/l) are already at increased risk of major

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bleeding and have been uniformly excluded from all major acute ischemic stroke clinical trials. The paucity of data surrounding the outcomes of these patients makes it difficult to weigh the risks and benefits of potentially lifesaving and disability-preventing therapies. Specific data related to the risk of bleeding after thrombolysis in patients with ischemic stroke and ITP are lacking. In general, the 5-year cumulative rate of spontaneous ICH in adult ITP patients is 1.4% which is 3 times higher than patients without ITP; however, all patients with reported spontaneous ICH had platelets of equal to or greater than 30×10^9/l.[9,10] There are other factors than ITP that increase the risk of intracerebral bleeding postreperfusion. AF, elevated blood pressure, taking an antiplatelet agent prior to EVT and thrombolysis, and statin use have all been associated with higher risks of symptomatic HT.[11] We cannot establish that the cause of postreperfusion ICH in our second patient was due to ITP. He had multiple additional factors other than his ITP including the fact he was on an antiplatelet agent at presentation, had a new diagnosis of AF, and a history of past severe bleeding events. ITP may have contributed to his risk for bleeding despite having normal platelet count.

Acute Stroke Therapy in Patient with ITP

The use of thrombolysis in patients with ITP

The American Heart Association/American Stroke Association (AHA/ASA) guideline recommended that tPA for patients with acute stroke and a clinical history of potential bleeding diathesis may be considered on a case-by-case basis because the safety and efficacy of tPA in this situation is unknown.[12,13] Significant thrombocytopenia regardless of the cause is considered a relative contraindication for tPA for acute ischemic stroke per AHA/ASA and the Canadian Stroke Best Practice Recommendations guidelines.[12,14] The relationship between platelet count and hemorrhage risk is unknown. There have been no randomized trials or prospective studies to evaluate the risk of hemorrhage in patients with acute ischemic stroke and significant thrombocytopenia. The threshold of $<100 \times 10^9$/l for platelets being a contraindication for thrombolysis was derived from an expert panel consensus. In a study that looked at patients in the Thrombolysis in Stroke Patients (TRISP) registry, among 7,533 tPA-treated stroke patients, 44 had significant thrombocytopenia ($< 100 \times 10^9$/l).[15] Three patients (6.8%) developed symptomatic ICH (sICH) using the Second European Cooperative Acute Stroke Study (ECASS II) criteria.[16] In the same study, the overall risks of sICH, poor functional outcome, and mortality did not differ significantly from those patients with a platelet count $>100 \times 10^9$/l. It was found that every decrease in platelet count by 10,000/l increased the risk of sICH by 2–5%, yet this was not associated with poor outcome or mortality. In addition, there are 27 patients in multiple studies and case reports who received tPA with significant thrombocytopenia.[17–22] The detailed information about the cause of thrombocytopenia was not available in most cases. Two of these patients (7.7%) developed sICH. By compiling patients from all the studies, the risk sICH in significant thrombocytopenia post-tPA is 7%. Although the sample size is very small, the rate is not significantly different than sICH in patients with normal platelet counts treated with tPA. In *in vitro* studies, tPA has shown to inhibit platelet aggregation, but does not affect platelet activation, and perhaps the reports of bleeding post-tPA in individuals with ITP are not as high as expected.[23] This further challenges the justification of withholding thrombolysis for platelet counts $<100 \times 10^9$/l. However, in ITP platelets may be dysfunctional for other reasons as discussed previously.

Performing EVT for patients with ITP

Similar to tPA, a specific data related to the safety of EVT in patients with ischemic stroke and ITP is lacking. Although EVT without thrombolysis in patients with ITP who present with the acute ischemic stroke and large vessel occlusion may be a safer option, the experience with EVT alone in these patients is also limited. Lower thresholds for thrombocytopenia regardless of the cause were used in the EVT studies, such as (Multi – MERCI: $<30 \times 10^9$/l, MR-CLEAN: $<40 \times 10^9$/l, SWIFT PRIME and EXTEND IA: $<100 \times 10^9$/l, DAWN and DEFUSE-3: $<50 \times 10^9$/l).[24–29] In the MERCI/Multi MERCI cohort, EVT was used in six patients with significant thrombocytopenia.[30] Symptomatic ICH was noted in one patient (platelet count was 16×10^9/l), mild SAH in another patient (platelet count was 64×10^9/l), and four patients did not develop any hemorrhagic complications (platelets counts were $37 - 94 \times 10^9$/l). A recently published retrospective observational analysis from a single center has assessed the EVT in patients with thrombocytopenia.[31] Fifteen patients with significant thrombocytopenia underwent EVT. The information for the cause of thrombocytopenia in each individual was not available. Symptomatic ICH occurred in one patient with no groin bleeding complication in any patients.

There are many factors that need to be considered when deciding to proceed with thrombolysis and EVT in patients with acute stroke. This includes premorbid functional status, presence of other medical comorbidities, severity of stroke, goals of care, and timely access to different therapeutic options. If patients are known to have ITP, consideration to the stability of the disease, last known platelet count and time of last seen well should be taken into account prior to initiating acute stroke therapy. It is reasonable to wait prior to initiating any therapy for the platelet count to return in patients who have active disease, have clinical stigmata of thrombocytopenia, or their most recent platelet count prior to presentation was $<100 \times 10^9$/l. In patients who present within the thrombolysis window but who are felt not to be eligible for thrombolysis, or who are outside the window, they should be considered for EVT. If a patient is known to have ITP or who has recent unexplained low platelet count, urgent consultation with hematology is recommended prior to proceeding with any therapies, and decisions should be made in collaboration with stroke clinicians, hematologists, the patients and their families where possible.

The use of antiplatelet and anticoagulation agents in patients with ITP

Data on the use of antiplatelet and anticoagulation in ITP for ischemic stroke are lacking; thus, the strategy for stroke prevention should be individualized according to the stroke mechanism, comorbidities, and risk of hemorrhagic complications. No direct

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evidence exists to recommend a platelet threshold for safe antiplatelet or anticoagulant use, but a survey of International ITP experts reported a threshold of platelets $>50 \times 10^9$/l for the use of both antiplatelets and anticoagulants in acute and long-term situations.[32] This value is also accepted in the cardiology literature as they suggest using dual antiplatelet therapy with clopidogrel and aspirin after stenting provided platelets are at least $>50 \times 10^9$/l.[33] If antithrombotic agents are indicated for acute or long term, a platelet count of $>50 \times 10^9$/l is recommended, and to hold them if platelet counts drop below this.[33–35] *In vitro* studies have shown that both aspirin and $P2Y_{12}$ inhibitors are able to block the prothrombotic effects of PMP, and thus either could be used in primary and secondary prevention. The stroke guidelines currently suggest aspirin as first line for secondary prevention.[36] The decision for long-term antiplatelet and anticoagulation treatment should be individualized and take into account the presence or absence of other stroke risk factors.

A therapeutic algorithm for patients with ITP and thrombotic complications has been proposed.[34] Anticoagulation is not recommended if there is a life-threatening hemorrhage or hemorrhage that requires transfusion (WHO grade III/IV). Corticosteroid and IVIG may be administered to increase the platelet count to a safe level $\geq 50 \times 10^9$/l before starting anticoagulation or antiplatelet agents. Case reports of patients with ITP and acute stroke have demonstrated that if a stroke is deemed to be caused by ITP, and a decision for acute stroke therapy has been proposed, immunosuppressing agents such as IVIg and corticosteroids can safely be initiated in the acute phase of stroke, the thrombopoietin receptor agonists (TPO-RAs) can also be considered in place of immunosuppressants to increase platelet counts.[35,37,38] Furthermore, thrombopoietin receptor agonists can be given to maintain the level of platelets. The therapeutic dose of anticoagulation can be considered for ITP patients with no hemorrhage, stable hemoglobin = WHO grade 0/I/II and platelet count $\geq 50 \times 10^9$/l. There is no specific data for direct oral anticoagulation (DOAC) in this context.

Conclusion

We presented two patients with ITP and acute ischemic strokes who were treated with thrombolysis and EVT. In the literature, there are 27 patients with ITP who presented with acute ischemic stroke, and only one of them was treated with acute reperfusion therapy. In addition, there are 92 patients with significant thrombocytopenia with no available data regarding the cause of thrombocytopenia, who were acutely treated (tPA = 71, EVT = 21). Seven patients developed sICH (tPA = 5, EVT = 2), and one patient underwent EVT developed mild SAH. A conclusion cannot be drawn based on these limited number of published cases and with the lack of detailed information about the etiology of the thrombocytopenia. Treatment of acute ischemic stroke in patients with ITP requires close collaboration between hematology and vascular neurology experts to find a balance between the benefit and risk of hemorrhagic complications. Guidelines are lacking for acute stroke and stroke prevention management in ITP patients. Given the pathology of ITP thrombocytopenia is unique, patients with ITP cannot simply be included in groups of patients with thrombocytopenia due to other causes. Future stroke studies, such as multicenter prospective cohort study, that include ITP patients and patients with thrombocytopenia are needed to provide evidence-based treatment plans.

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Statement of Authorship

AA conceived of the idea, acquired the data, contributed to the medical management of the patients, and drafted the initial manuscript. KP, MA, GA, CW, and HLS made critical revisions of the manuscript. GB, KB, and JR contributed to the medical management of the patients and made critical revisions of the manuscript. KK conceived of the idea and made critical revisions of the manuscript.

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