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Recurrent Cerebral Infarctions and Multi-Vessel Thrombosis in a Male Patient with Refractory Idiopathic Thrombocytopenic Purpura: a Case Report

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HIGHLIGHTS

- Idiopathic thrombocytopenic purpura (ITP) patients require special rehabilitation treatments.
- ITP presents mostly with bleeding tendencies, but thrombotic complications cannot be overlooked.
- There are few studies investigating male ITP patients with major vessel thrombosis.

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Idiopathic thrombocytopenic purpura (ITP) mostly presents with bleeding tendencies, and thrombotic events are very uncommon. Our case report presents a male patient with ITP refractory to standardized therapies who continuously showed thrombocytopenia and hematuria. With no evidence of autoimmune diseases or other secondary causes of ITP, he developed recurrent cerebral infarctions and deep venous thrombosis. Our report calls for attention to possible thrombotic events, as well as more common bleeding tendencies in patients with ITP and outlines rehabilitation treatment specially designed for ITP patients with rare thrombotic complications.

Keywords: Idiopathic Thrombocytopenic Purpura; Ischemic Stroke; Cerebral Infarction; Deep Venous Thrombosis; Rehabilitation

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an acquired disorder that causes an immune-mediated destruction of platelets [1]. ITP patients usually present with bleeding complications, such as petechiae, gingival bleeding, epistaxis, and intracranial hemorrhage. Rarely, thrombotic complications, including ischemic stroke and deep venous thrombosis (DVT), are caused by ITP [2,3]. Moreover, ITP is more common in females and patients with accompanying autoimmune diseases [4-6]. In this case report, we present a male patient with ITP and accompanying thrombotic complications. Previously, few cases of male ITP patients with cerebral infarctions were reported. Since only a handful of ITP patients with major vessel thrombosis are reported, there have been only a few rehabilitation plans aimed at simultaneously managing both bleeding and thrombotic complications. Thus, we suggest a rehabilitation treatment schedule specially designed for ITP patients with rare thrombotic complications.

CASE REPORT

A 50-year-old male patient first visited the hematology outpatient clinic on September 23, 2019 due to bruising and easy fatigability that had been continuous for a year. At the time of the visit, a complete blood count level showed thrombocytopenia of 18,000 platelets per microliter of blood, leukocytosis of 16,780 white blood cells per microliter of blood, and normal range of red blood cells (4.24×10^6/μL) and hemoglobin (13.8 g/dL). With impression of ITP, he was started on dexamethasone. A week later, intravenous immunoglobulin therapy was initiated, in addition to danazol. A bone marrow biopsy did not show any abnormalities and he was treated with azathioprine and rituximab. Still refractory with a platelet level of 10,000/μL, the patient was given one week of eltrombopag, which is an agonist of the thrombopoietin receptor, and underwent a laparoscopic splenectomy on November 28, 2019.

Throughout the patient's hospital stay, petechial rashes on both lower extremities (Fig. 1), thrombocytopenia, and hematuria continued. In order to diagnose underlying medical conditions for ITP, autoimmune antibodies were screened. However, lupus coagulants, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, anti-beta 2 glycoprotein I antibodies, and antinuclear antibodies all came back negative. Thrombotic thrombocytopenic purpura (TTP) was ruled out due to a normal range of ADAMTS 13 protein activity (63%) and a normal peripheral blood smear.

On postoperative day 5 on December 2, 2019, the patient suddenly complained of a speech problem that lasted about 20 minutes. Clinical examination did not show any other neurologic deficits, however, brain magnetic resonance imaging (MRI) revealed a left middle cerebral artery infarction (Fig. 2A) and left temporal lobe infarction with hemorrhagic transformation (Fig. 2B). To prevent recurrent ischemic stroke according to the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial [7], dual antiplatelet therapy of aspirin and clopidogrel was needed but could not be administered due to a low platelet level of 63,000/μL. After consultation from the neurology, neurosurgery, and hematology departments, he was discharged with aspirin monotherapy.

Two months later, the patient visited the emergency room with a severe headache (visual analogue scale of 8) and a week-long hematuria. The patient was mentally alert, rated 15

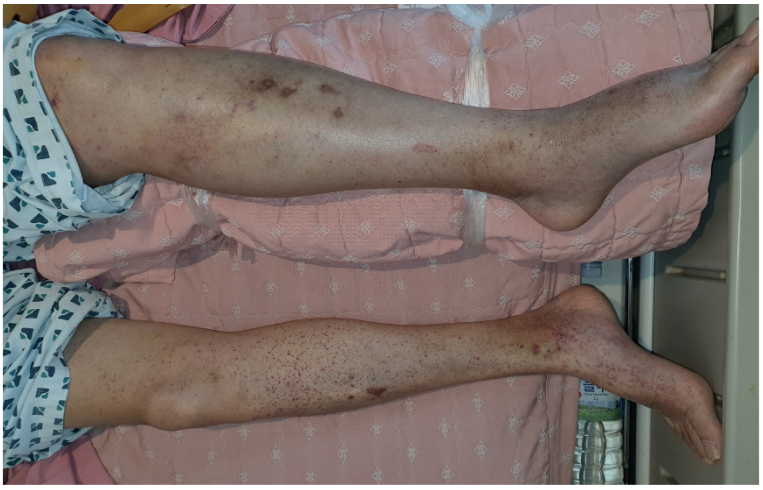

Fig. 1. Petechial rashes on both lower extremities and left lower extremity swelling due to deep vein thrombosis.

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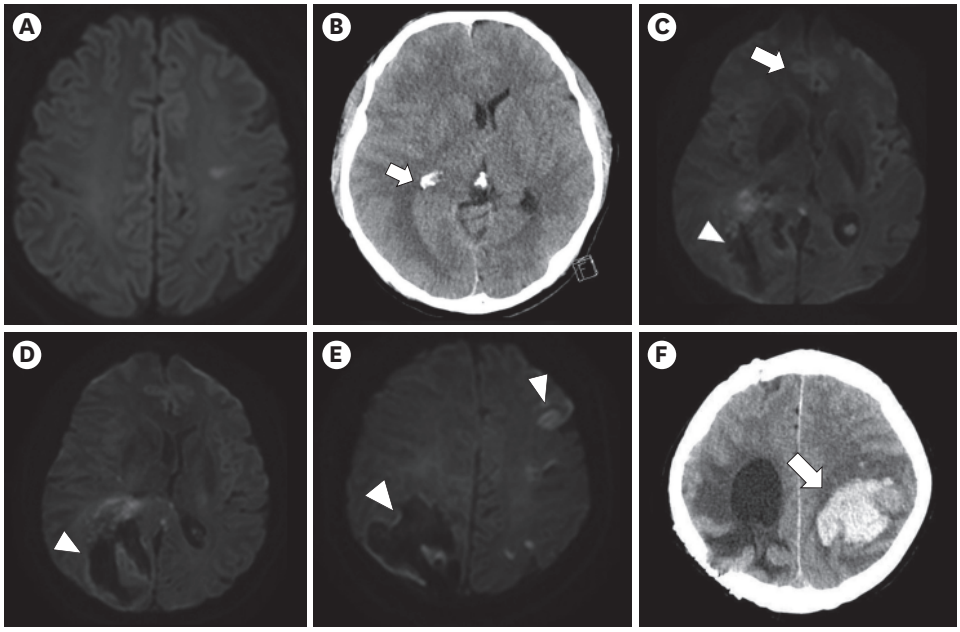

Fig. 2. A magnetic resonance imaging diffusion weighted image shows initial (December 2019) left middle cerebral artery infarction (A) and left temporal lobe infarction with hemorrhagic transformation (B). Brain MRI taken on February 2020 shows superior sagittal sinus thrombosis with associated venous infarction (arrow in C), hemorrhage in the right parietal lobe (wide arrowhead in C, D and E), and acute infarctions in the left cerebral border zone (narrow arrowhead in E). Brain computed tomography of August 2020 shows intracerebral hemorrhage in left temporoparietal lobe (arrow in F).

on the Glasgow Coma Scale (Eye 4 Motor 6 Verbal 5), and did not show any signs of motor weakness. A brain computed tomography (CT) revealed a dense artery sign, which is a radiologic sign of an early ischemic stroke, of the right posterior cerebral artery. Additionally, a brain MRI taken a day later showed superior sagittal sinus thrombosis with associated venous infarctions and hemorrhagic transformation in the left cerebral border zone (Fig. 2C). Thus, the patient underwent a decompressive craniectomy on February 27, 2020.

After the surgery, the patient's mental status was alert as before; rated 15 on the Glasgow Coma Scale. However, he showed left side muscle weakness of both upper and lower extremities, as evidenced by the Medical Research Council (MRC) muscle grade of 1. Functional Ambulatory Categories (FAC) score showed 0 and he immediately fell to the left side in a sitting position without help from others (Trunk Impairment Scale of 0). His Modified Barthel Index (MBI) was 28, showing a severe dependency level.

Moreover, the patient's platelet level was continuously lower than 10,000/μL. Therefore, anticoagulation could not be administered, and the patient's platelet level was maintained by transfusion. At postoperative day 2, the patient complained of right leg pain, but a lower extremity CT venography did not show signs of DVT at the time. At postoperative day 17, a left leg edema was observed and extensive thromboses at the left iliac, femoral, and popliteal veins were noted in a lower extremity CT venography (Fig. 3). Since anticoagulation could not be used due to ITP history, an inferior vena cava filter was inserted. On a DVT CT taken after one month, small thromboses were newly detected in the right common iliac and external iliac veins, and the inferior vena cava filter was maintained.

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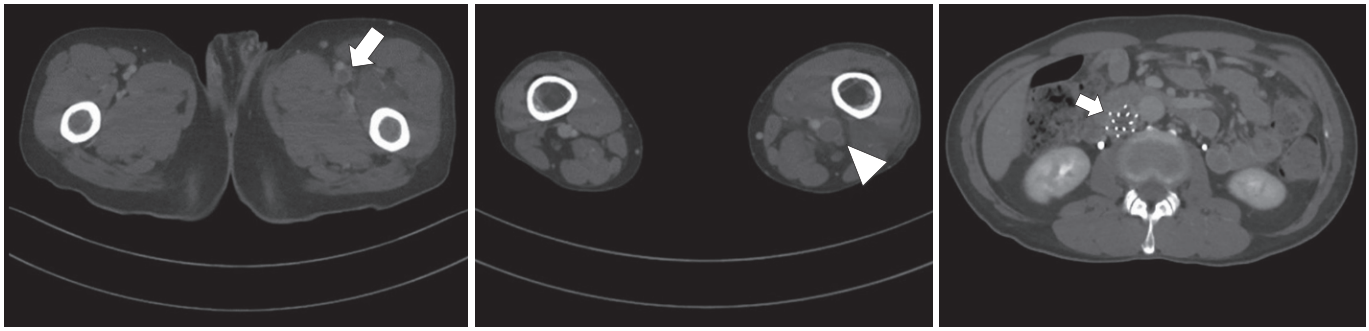

Fig. 3. Lower extremity computed tomography venography showing extensive thromboses at the left iliac, femoral (arrow on the left), popliteal veins (arrowhead), and inferior vena cava filter inserted (arrow on the right).

In this case, we devised a rehabilitation schedule specifically for the ITP patient with ischemic stroke. For the first 3 weeks after craniectomy, only careful bedside flexibility and strengthening exercises were provided due to pain in both lower extremities and potential bleeding risks. Moreover, initial neurologic examination, Mini-Mental State Examination (MMSE) score (23), thigh circumference (about 3–4 cm larger circumference for the left thigh), and thorough physical examinations were carried out during this period to serve as foundation for detecting future improvements or complications. Pain subsided 4 weeks after the operation and active mobilization and physical therapies were then carried out. Muscle strength of the left upper and lower extremities showed no improvement on the manual muscle test (MRC grade 1) until this point. He also showed continued impairment of trunk control, as evidenced by Trunk Impairment Scale of 0.

During 8 weeks of hospital stay in our department, intensive rehabilitation focused on standing and gait training with the help of therapists and the use of ankle-foot orthosis [8]. Left shoulder subluxation was caused by left upper extremity weakness. Thus, intra-articular injection and functional electrical stimulation on the left shoulder was carried out to relieve pain and regain muscle strength. Since his initial MMSE score was 23, cognitive examination and therapies were conducted. With oral motor facilitation, he was able to build up his diet from a special liquid diet to a general diet. He also displayed left side neglect, thus prompting treatment of visual scanning, environmental cues, and other visuospatial rehabilitations. Neurologic examinations and MMSE were performed every 4 weeks, while joint swelling and thigh circumference were measured every week.

Six months after intensive rehabilitation at several hospitals, left upper extremity muscle strength was improved to MRC grade 3, while left lower extremity raised to MRC grade 2. More importantly, he was able to walk independently on indoor even level ground with the supervision of others (FAC score of 3). Furthermore, he was alert and scored 30 on MMSE. MBI score mildly increased to 37 and he scored 18 on the Berg Balance Scale, 9 out of 20 in letter cancellation, and 43% on the line bisection tests. Left thigh circumference was continuously about 4 cm larger than the right side.

On August 25, 2020, however, he complained of left side visual disturbance and visited the emergency department. On brain CT, left temporoparietal intracerebral hemorrhage (Fig. 2F) was noted and his functional level deteriorated to bed ridden status (FAC score of 0). After the intracerebral catheter was inserted on August 27, 2020, he showed confused mentality and rated 13 on the Glasgow Coma Scale (Eye 4 Motor 5 Verbal 4). Left side motor weakness reoccurred, as evidenced by MRC grade of 1.

DISCUSSION

Previously reported cases of ITP combined with thrombosis were present more in females and patients with accompanying autoimmune diseases [4-6]. On the contrary, cases of male patients with both ITP and thrombosis were found in few reports [1,9-12]. Rhee et al. [1] reported a 33-year-old male patient with recurrent ischemic strokes resulting from ITP. Additionally, Mahawish et al. [9] demonstrated a case of a 79-year-old male patient with right-side weakness due to cerebral infarction caused by ITP, and Theeler and Ney [10] reported a right occipital lobe infarction in a 63-year-old male patient with ITP. However, none of the previous reports outlined rehabilitation plans in detail. The patient in our case report presents a significant dilemma for simultaneously managing both bleeding and thrombotic complications. We thereby suggest a strict rehabilitation protocol for ITP patients.

Thrombotic complications could arise from ITP by the natural course of the disease itself, the side effects of ITP therapies, and associated immunological diseases, such as antiphospholipid syndrome or TTP [2]. During the platelet destruction, humoral factors and platelet microparticles are released [13]. Platelet microparticles are procoagulant and induce thrombin activation and other coagulation factors to protect against bleeding in thrombocytopenic states. However, this cascade can paradoxically induce thrombosis.

In this case report, recurrent cerebral infarctions and DVT developed in a male patient with ITP refractory to steroid, intravenous immunoglobulin therapies, and a splenectomy. Mohren et al. [14] described that thromboembolic complications could occur in up to 10% of patients with hematologic disorders after a splenectomy. Complications included DVT, pulmonary embolism, and portal vein thrombosis. Moreover, Alvarado et al. [15] suggested that danazol may cause arterial thrombosis, and Emerson et al. [16] showed that intravenous injection of immunoglobulin led to thrombotic complications by increasing blood viscosity and vasospasm. Thus, previous comprehensive efforts to treat thrombocytopenia in this patient may have actually led to thrombotic complications.

TTP should be differentiated due to its clinical similarities with ITP, such as thrombocytopenia and bruising. The mechanism of TTP involves an acquired defect in the ADAMTS 13 protein, which serves a crucial role in cleaving large multimers of von Willebrand factor [17]. When von Willebrand factor multimers are increased in circulation due to a defect in ADAMTS 13 proteins, platelet adhesion increases and thus causes thrombus. Furthermore, overall circulating platelets decrease, and red blood cells are ruptured (schistocytes) due to the shear stress caused by clots within the blood vessels. In this patient, however, TTP could be ruled out by a normal range of ADAMTS 13 protein and a normal peripheral blood smear, which is a characteristic of ITP.

Since up to 17% of ITP patients are found to have antiphospholipid syndrome, this patient was screened for autoimmune antibodies. However, antiphospholipid syndrome antibodies, including anti-cardiolipin, anti-beta 2 glycoprotein I, and lupus anticoagulant, all came back negative, further complicating the diagnosis and the treatment methods. Since male ITP patients have lacked evidence of autoimmune antibodies, we suggest that thrombotic complications in these patients are more likely to be caused by primary idiopathic endothelial cell injury and not by autoimmune destruction of platelets. In future studies, endothelial cell biopsy is needed in order to detect endothelial cell injury in male ITP patients.

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The treatment of ischemic stroke in ITP patients remains a significant dilemma due to the possibility of additional hemorrhages. Acute ischemic stroke should be immediately treated with reperfusion therapy and anti-platelet therapy initiated to prevent secondary attacks [18]. In ITP patients, however, thrombolysis and anti-platelet therapies are contraindicated due to continued thrombocytopenia. Furthermore, intensive rehabilitation and early mobilization therapies may be limited due to high bleeding risks associated with ITP.

Ongoing bleeding risks of ITP patients were typically shown in our patient. He continuously presented with hematuria and petechial rashes on both lower extremities. Rhee et al. [1] insisted that antiplatelet therapy does not reduce the activity of platelet microparticles and may not be effective in reducing thrombotic complications in ITP after all. Therefore, the management of ischemic stroke in ITP patients must be planned individually, according to the presumed pathophysiologic mechanisms of stroke, co-morbidities, and the estimated risk of hemorrhagic complications.

Rehabilitative therapies in ITP patients with thrombotic complications should be initiated at an early stage but carried out with a strict time schedule due to the risk of re-bleeding [19-21]. For the first few days after the initial bleeding event, patients should undergo Rest, Ice, Compression, and Elevation (RICE) therapies and transcutaneous electrical nerve stimulation to reduce pain. Until pain subsides, gentle range of motion exercises, flexibility and strengthening exercises are recommended. In order to reduce recurrent bleeding complications, stretching exercises at this stage should be carried out actively by the patient, not passively. Moreover, joint swelling or warmth should be carefully monitored for the possibility of hemarthrosis and lower extremities circumference must be measured regularly to check for DVT.

Only after three or more weeks of gentle rehabilitation without complications, isotonic strengthening exercises and active therapies are started. Supervised exercise therapies are recommended over self-directed programs to better control intensity of therapy and to encourage morale of the patient. Calf muscle strengthening is helpful for enhancing venous return, which can prevent DVT or venous ulcers. Nevertheless, it is utmost important to remember the time schedule of rehabilitation therapies in these patients and not to rush active therapies at the initial stages which can aggravate bleeding and thrombotic complications.

In conclusion, our case report shows that ischemic stroke and DVT can occur as uncommon complications of ITP. The possibility of thrombotic complications should not be ruled out in ITP patients, and continuous neurologic examination should be planned in order to diagnose cerebral infarctions at an early stage. Moreover, post-stroke rehabilitative therapies must be carried out at an early stage, but with a strict time schedule of escalation to gain maximal functional level improvement and to avoid complications at the same time. Thus, both bleeding tendencies and thrombotic complications presents a great challenge, and the rehabilitative treatment should be individualized on a case-by-case basis.

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