A case of deep vein thrombosis after spinal cord injury diagnosed as JAK2-V617F-positive essential thrombocythemia.

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Abstract

***Background*: Deep vein thrombosis (DVT) is a severe early complication of spinal cord injury.**
***Case presentation:* A 67-year-old woman was injured falling down the stairs at home and was diagnosed with a spinal cord injury. She was admitted to our hospital for further medical treatment. The day after admission, she became dyspneic, which required tracheal intubation followed by respiratory management. We started an antiplatelet agent for DVT prophylaxis during treatment. However, contrast-enhanced computed tomography (CECT) of the bilateral legs revealed acute DVT of the femoral veins. We focused on the sustained platelet increase, consulted hematologists, and ultimately diagnosed ET.**
***Conclusion:* In emergency settings, the general condition of a patient rapidly changes. A precise consultation with a specialist for thrombosis and hemostasis may prevent complications such as DVT. Although we often assess laboratory data, such as complete blood counts, to follow up on the clinical course, in the case of rare diseases and conditions, abnormal findings may be overlooked. We always need to consider rare diseases and the timing of a consultation with a specialist.**

Key words: Deep vein thrombosis, Essential thrombocythemia, Spinal cord injury

Introduction

Deep vein thrombosis and pulmonary embolism (DVT/PE) are called venous thromboembolism (VTE) with the same pathological process. DVT is detected in approximately 9–100% of cases of spinal cord injury (SCI) by screening methods[1,2] and accounts for 9.7% of all deaths within 1 year after injury[3]. According to the American College of Chest Physicians guidelines, SCI patients with motor paralysis are a high-risk group for VTE[4]. The prevention of VTE decreases mortality and the length of hospitalization and improves quality of life. Retrospective studies on patients with symptomatic VTE identified severe paralysis, male sex, and a lumbar-level injury as risk factors for VTE after SCI[5, 6].

Thrombocytosis is a commonly encountered clinical scenario, with a large percentage of cases discovered incidentally. The differential diagnosis for thrombocytosis is broad and the diagnostic process may be challenging. Thrombocytosis may be spurious, attributed to a reactive process or clonal disorders. In reactive cases of thrombocytosis, platelet counts are ≤ 1 million/μL.

Received February 16, 2024; Accepted August 28, 2024
DOI: 10.15100/0002001861

Essential thrombocythemia (ET) is a chronic Philadelphia-negative myeloproliferative neoplasm (MPN) that is characterized by a survival curve that is only slightly worse than that of an age- and sex-adjusted healthy population. It is a rare hematological malignancy, with an incidence that varies between 0.2 and 2.5:100 000 people per year and a prevalence of 38 to 57 cases per 100 000 people. The main characteristics of ET are marked thrombocytosis and a high frequency of thrombosis. The Japanese Society of Hematology guidelines recommend antiplatelet therapy (low-dose aspirin) for high-risk patients with ET. The V617F mutation of the Janus activating kinase 2 (*JAK2*) gene was recently detected in approximately 50% of ET cases [7], and the risk of thrombosis increases with the presence of this mutation. A risk classification, called the International Thrombosis Prognostic Score for thrombosis in essential thrombocythemia (IPSET-thrombosis score), incorporating the *JAK2* gene mutation has also recently been proposed [8].

Case report

A 67-year-old woman was transported to our hospital with quadriplegia after falling down the stairs at home. On arrival, vital signs were as follows: respiratory rate, 15 breaths/min, heart rate, 54 bpm, and blood pressure, 103/85 mmHg. While a sensorimotor disorder was noted at C4 or lower (Frankel Classification Grade A: Complete neurological injury - No motor or sensory function detected below the level of the lesion), an obvious bleeding tendency, such as purpura and petechial bleeding, was absent. Magnetic resonance imaging (MRI) showed spinal cord compression findings at C2–C4 and an intramedullary high-signal area on a T2-weighted image (Figure 1). The patient was diagnosed with SCI, and a foot pump was attached to the lower limbs for intermittent pneumatic compression to prevent DVT/PE.

On hospital day 2, tracheal intubation was performed for the serious respiratory status caused by SCI. On hospital day 12, the patient underwent C2-C5 cervical laminoplasty and tracheotomy. The platelet count gradually increased after surgery. On hospital day 27, the platelet count rapidly increased to 638,000/μL. As the patient developed pneumonia, which suggested reactive thrombocytosis due to acute inflammation, the platelet count was carefully followed. On day 36 of hospitalization, the platelet count increased to 845,000/μL and antiplatelet

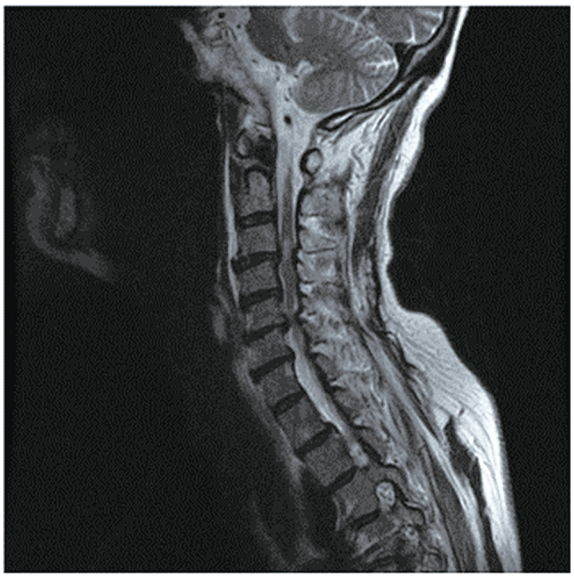

Figure 1. MRI of the spinal cord obtained on admission. legend: MRI showing spinal cord compression findings at C2–C4 and an intramedullary high-signal area on a T2-weighted image.

therapy with aspirin was initiated. Since this patient was considered to be at a high risk of VTE according to the Japanese Society of Thrombosis and Haemostasis guidelines, DVT prophylaxis using intermittent pneumatic compression was administered to prevent its development. The patient was not considered to be at a high risk of DVT. The platelet count temporarily decreased thereafter. However, since we observed another increase on hospital day 46, elevated doses of aspirin and clopidogrel sulfate were administered. On hospital day 72, swelling was noted in the bilateral lower legs. CECT revealed mild hematoma in both legs and DVT in the left leg (Figure 2). There was no pathophysiology of thrombosis in the left leg only. After a consultation with a cardiologist, an IVC filter was not implanted. Five thousand units of heparin was intravenously administered as a bolus infusion for the treatment of DVT, followed by the continuous administration of 500 units/h. The dosage was controlled using APTT as an indicator.

On hospital day 74, a large increase was observed in the platelet count (>1 million/μL) in addition to DVT and bleeding symptoms despite general prevention. We strongly suspected thrombosis and hemostasis disorders and consulted with hematologists in our hospital. The hematologist noted a continuous increase in the platelet count (450,000/μL or higher) and immature myeloid cells in the peripheral blood of the patient. After ruling

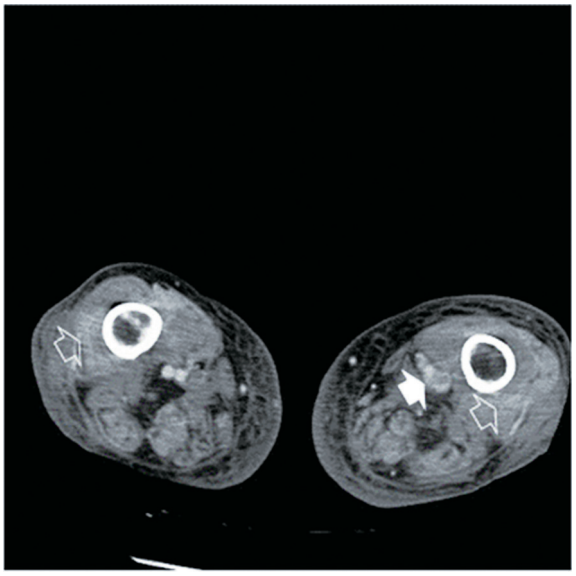

Figure 2. CECT of bilateral legs obtained 72 days after admission.
legend: Venous phase CECT showing a hematoma with DVT (➡) and bleeding (⇨).

out chronic myelogenous leukemia by fluorescence *in situ* hybridization (FISH) using the patient's neutrophils, bone marrow aspiration and biopsy were performed. In the patient's bone marrow, the megakaryocyte count and cellularity were both slightly reduced (ANC<1.0×10^9/L, the number of megakaryocytes per high-power field was 8/μL), and there were many mature megakaryocytes with large and irregular nuclei and platelet aggregation (Figure 3). Additionally, the *JAK2*^{V617F} mutation was detected in the peripheral blood of the patient (*JAK2* allele burden 14.8676%) and, thus, she was diagnosed with

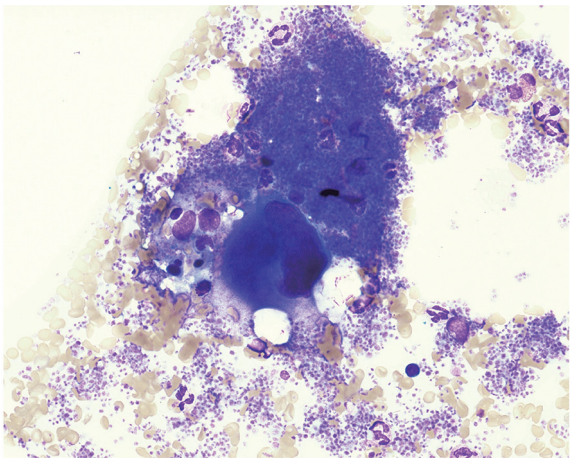

Figure 3. May-Grunwald Giemsa staining of a smear of a bone marrow aspirate.
legend: A megakaryocyte with large and irregular nuclei and platelet aggregation in the patient's bone marrow (×400).

ET in accordance with the criteria of the World Health Organization classification (2008 Version). Regarding the risk of thrombosis in patients with ET, the IPSET-thrombosis score was calculated, which confirmed that the risk was high (age ≥60 years and positive for the *JAK2*^{V617F} mutation). To prevent further thrombosis and control the platelet count, we intravenously administered ranimustine (MCNU) as cytoreductive therapy on hospital day 91. MCNU was administered 4 times by a drip infusion at the usual dose of 100 mg with intervals adjusted to the counts of peripheral blood cells. The patient's platelet count decreased to 331,000/μL, and there were no safety issues with the administration of MCNU. Therefore, the clinical course of SCI stabilized, and the patient was transferred to another hospital for recuperation on hospital day 145 (Figure 4).

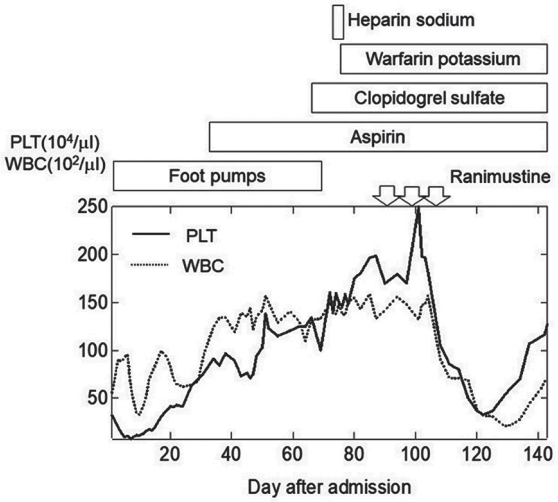

Figure 4. Clinical course of the patient after admission.

Discussion

We encountered a case of DVT after SCI that was diagnosed as JAK2-V617F-positive ET, even during the preventive use of a foot pump, in addition to a large increase in the platelet count (>1 million/μL).

DVT/PE are severe complications that are frequently encountered in patients who have sustained SCI. Several approaches for prophylaxis and treatment are currently available, including anticoagulation, pneumatic compression devices, and vena cava filters. In daily practice, we use the Japanese Guidelines for Prevention of Venous Thromboembolism released from The Japanese Society on Thrombosis and Hemostasis. The following are recommended:

- Short-term anticoagulation is contraindicated in the presence of a paraspinal hematoma.
- Due to the sensory disturbance in patients with SCI, the long-term use of intermittent pneumatic compression may cause ulcers and other skin complications and, thus, needs to be avoided.
- VTE prophylaxis needs to be continued as long as possible.

The present case was encountered approximately 10 years ago and sufficient evidence for the efficacy of low-molecular-weight heparin (LMWH) was limited; however, LMWH is now the preferred method for the prevention of DVT in high-risk patients. Depending on the involvement of spasms, Ca blockers also need to be considered.

The most common cause of thrombocytosis in general medical populations is a reactive, or secondary, process[9]. The degree of the elevation in the platelet count does not clearly differentiate clonal from reactive thrombocytosis. In a series of 732 medical and surgical patients with platelet counts of 500,000 per cubic millimeter or higher, 643 (88%) had secondary thrombocytosis; the most frequent underlying causes were tissue damage due to major surgery, infection, cancer, and chronic inflammation[10]. Similarly, in a series of 280 consecutive hospitalized patients with platelet counts of 1 million per cubic millimeter or higher, 231 (82%) had reactive thrombocytosis, 11 (4%) had thrombocytosis of an uncertain cause, and only 38 (14%) had MPN[11].

ET is a MPN characterized by an increased platelet count, megakaryocytic hyperplasia, and a hemorrhagic or microvascular vasospastic tendency. More than 10% of patients may develop the complication of thromboembolism in ET[12]. Risk factors for ET include age>60 years, a medical history of thromboembolism[11], and a platelet count >1.5 million/μL. Thromboembolism associated with ET accounts for 60%–70% of arterial thrombosis, such as cerebral infarction and myocardial infarction, while VTE, including pulmonary thromboembolism and DVT, accounts for the remainder.

Indications for the treatment of ET may be selected based on a patient's age, by clinical symptoms, such as thrombus or bleeding, and by a marked increase in the platelet count (≥1.5 million/μL). The main aims of treatment for ET are to control the platelet count and prevent thrombosis. The V617F mutation in the *JAK2* gene is found in approximately 50% of ET cases, and a high incidence of venous thrombosis was also recently detected in ET cases with this mutation[7]. In addition to the above-described findings, a correlation has been reported between *JAK2* mutations and the white blood cell count or thrombosis[13]. According to the Japanese Society of Hematology guidelines for hematopoietic tumors, even in a case with a low risk of ET, antiplatelet therapy needs to be initiated when there is a *JAK2* mutation, such as in patients with cardiovascular risk factors, including smoking, hypertension, hyperlipidemia, and diabetes.

An increase in the platelet count is occasionally detected in reactivity along with inflammation, such as trauma and infectious disease. Abnormalities in function or morphology are frequently absent when the platelet count increases due to reactivity, and this condition does not normally exhibit clinical symptoms, such as thrombosis and bleeding. Tefferi et al. proposed differential factors between ET and reactive thrombocytosis[14]. Based on this proposal, we suggest that when immature myeloid cells appear in a patient's peripheral blood, a differential diagnosis may be performed along with the suspicion of a particular blood disease and a consultation with a hematologist. Despite the development of various guidelines in the therapeutic area of emergency or intensive care, there are currently many opportunities to treat a diverse patient population through medical specialties, including rare diseases.

Disclosure

Approval of the research protocol: N/A.
Informed consent: Informed consent was provided by the patient's family to publish this case.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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