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Recurrent and Multiple Intracerebral Hemorrhages in Polycythemia Vera Secondary to Myelofibrosis: A Case Report and Literature Review

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Keywords
Polycythemia vera · Cerebral hemorrhage · *JAK2* V617F mutation

Abstract
Polycythemia vera (PV) is one of the myeloproliferative neoplasms and has higher frequency of the *JAK2* V617F mutation. Hemorrhagic stroke is rare in PV, and myelofibrosis is secondary to PV. A 76-year-old Japanese man was diagnosed as PV with the *JAK2* V617F mutation at the age of 63 years. He developed anemia together with secondary myelofibrosis, and then 40 mg ruxolitinib was started at 70 years. At 76 years, he presented with apathy and was diagnosed with intracerebral hemorrhage (ICH) in the right thalamus. Six months later, he developed multiple ICHs in bilateral cerebellar hemispheres. Leukocyte count was 57,600/μL, platelet count was 66,000/μL, and the level of hemoglobin was 8.7 g/dL. Bleeding time was 6 min. The agglutination ability when adding collagen was 41%. A patient with the *JAK2* V617F mutation developing hemorrhagic stroke due to late-stage PV and secondary myelofibrosis was reported, implying various mechanisms for recurrent and multiple ICH.

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Introduction

Polycythemia vera (PV) is affiliated with Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), such as essential thrombocythemia and primitive myelofibrosis [1]. The original diagnostic criteria of PV are (1) hemoglobin levels >16.5 g/dL in men and 16.0 g/dL in women or an increase in hematocrit >49% in men and >48% in women [1]; bone marrow trilineage proliferation with pleomorphic mature megakaryocytes; and presence of *JAK2* mutation [1]. About half of patients with PV have comorbid thrombotic events, whereas hemorrhagic events are more uncommon to range from 3% to 8.1% in PV [2]. Moreover, about 5% of PV cases transform into myelofibrosis [3].

Regarding cerebrovascular complications, only a few case series and single case reports on the association of ischemic stroke with PV have been reported; hemorrhagic stroke is rare in PV [4–7]. Furthermore, a few studies documented the scarcity of hemorrhagic stroke in myelofibrosis secondary to PV [8].

Diverse treatments such as phlebotomy, aspirin, and cytoreductive agents have been used for PV. Ruxolitinib, a selective inhibitor of JAK2, is effective in hematocrit control and in reducing the size of splenomegaly in patients with PV [9]. Herein, we report a patient with PV that transformed to myelofibrosis who was treated long term with ruxolitinib and who developed recurrent and multiple intracerebral hemorrhages (ICHs).

Case Presentation

The present patient was diagnosed with PV at the age of 63 years due to elevation of red blood cells and leukocytes. Hydroxyurea (500 mg) was started. Three years later, the *JAK2* V617F mutation was detected. When he was 70 years old, 100 mg aspirin was started, but he developed anemia together with secondary myelofibrosis, aspirin was discontinued, and then 40 mg ruxolitinib was started. The patient had no history of atherosclerotic vascular risk factors, including hypertension. At 76 years, he presented with apathy and was referred to our Neurology Department. On brain magnetic resonance imaging, diffusion-weighted and T2*-weighted conventional gradient-echo images showed a hypointense area in the right thalamus, and brain computed tomography showed iso- to high-density in this area (shown inFig. 1a–c). Six months later, he was admitted because of recurrent ICHs. On admission, his blood pressure was 110/80 mm Hg, and his heart rate was 80 beats per minute. On neurological examinations, his consciousness level was normal. He showed decomposition of the left upper and lower limbs in the finger-nose and heel-knee tests. No abnormal findings were obtained in other neurological examinations. The National Institutes of Health Stroke Scale score was 2. Brain computed tomography, diffusion-weighted images, and T2*-weighted gradient-echo showed multiple ICHs in the bilateral cerebellar hemispheres (shown in Fig. 1d–f). Laboratory data showed that the leukocyte count was 57,600/μL, and the platelet count was 66,000/μL. Levels of hemoglobin and hematocrit were 8.7 g/dL and 25.8%, respectively. Bleeding time was 6 min (normal range: 3 min). The agglutination ability when adding ADP was 48% of the normal value, and collagen was 41%, which were significantly lower than the values in normal subjects. The prothrombin time-international ratio, activated prothrombin time, and activated partial thromboplastin time were unremarkable.

After admission, the patient's blood pressure remained constant throughout the hospitalization period in the absence of any antihypertensive drugs. The treatment regimen consisting of oral carbazochrome sulfonate natrium hydrate and tranexamic acid was started. No expansions of cerebellar hemorrhages or new bleeding were observed, and the patient

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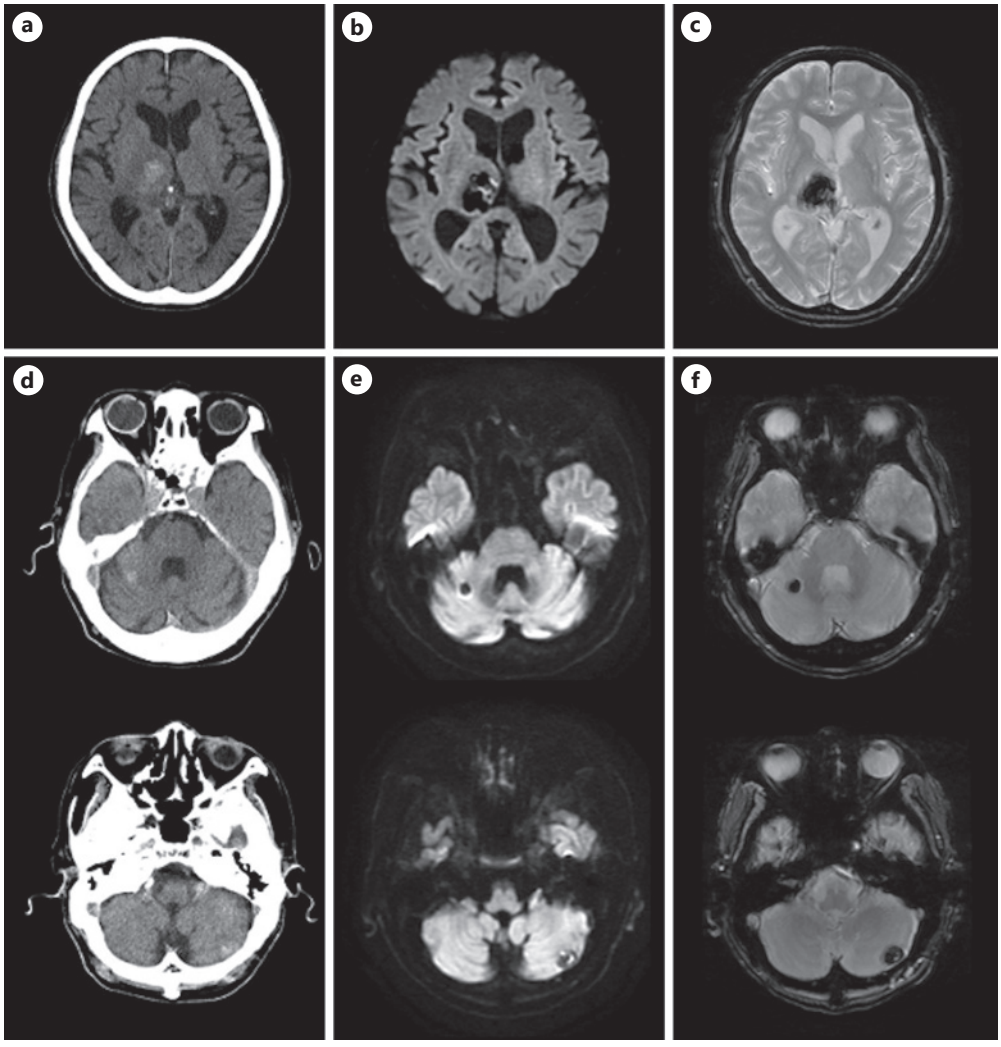

Fig. 1. Radiological imaging of current case. **a–c** Right thalamic hemorrhage as a patchy hyperdense lesion on unenhanced CT (**a**) and a hypodense lesion on DWI (**b**) and T2*-weighted conventional GRE imaging (**c**). **d–f** Hemorrhages in the bilateral hemispheres are seen as spotty lesions on unenhanced CT (**d**) and hypodense lesions on DWI (**e**) and T2*-weighted GRE images (**f**). GRE, gradient-echo; CT, computed tomography; DWI, diffusion-weighted imaging.

was discharged. After discharge, the treatment regimen for ICH was stopped, his daily blood pressure and monthly platelet counts were carefully monitored, and no further recurrence of ICH was observed. For the treatment of PV, ruxolitinib was continued because ruxolitinib was not considered a risk of ICH.

Discussion

PV is included among MPNs. MPN patients commonly carry mutations in genes such as *JAK2* [1]. Interestingly, 95% of PV patients have the *JAK2* V617F mutation, whereas about 60% of patients with other MPNs such as essential thrombocythemia and primary myelofibrosis have the *JAK2* V617F mutation. The remaining 2–5% of PV patients have a mutation in exon 12 of *JAK2* [1]. *JAK2*, which is a member of the nonreceptor tyrosine

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kinase family that is activated in a cytokine-dependent manner, propagates cell growth signals after phosphorylation of downstream STAT. The *JAK2* V617F mutation causes constitutive activation of this signal, which promotes cytokine hypersensitivity and induces erythrocytosis in PV [10].

We report a case of developing recurrent and multiple cerebral hemorrhages in late-stage PV that transformed to myelofibrosis, and who was treated with ruxolitinib for a long time. Since 1923 [4], only a few cases report with hemorrhagic stroke in a solitary occipital lesion [6], comorbid with multiple and large infarctions [7], or with cerebral venous thrombosis [5] have been reported in PV. Interestingly, hemorrhagic stroke was the initial presentation of PV in these cases (Table 1). In 351 patients with MPNs, 55 patients had 64 hemorrhagic events and had 2 times higher frequency of myelofibrotic transformation. Among these hemorrhagic events, 6 ICHs were included, of which the majority were due to other bleeding causes such as treatment with antithrombotic agents, cerebral amyloid angiopathy, and trauma [8]. Meanwhile, ICH is rare after ruxolitinib treatment in randomized controlled trials: none were reported for myelofibrosis, including post-PV myelofibrosis [11], and one case (0.9%) was reported in PV resulting from poorly controlled hypertension [9]. Thus, it is rare to comorbid with ICH in PV even after secondary myelofibrosis, and ruxolitinib could not be suitable for the cause of ICH.

The precise mechanisms leading to the development of ICH in PV are unclear. In our case, some possible explanations for ICH can be suggested. One possibility is a reduction in platelet count because of ineffective erythropoiesis due to the transition to myelofibrosis, which induced bleeding tendency. A second possibility is that a substantial increase in leukocytes could damage the vascular endothelium [12]; this possibility was shown to induce a breakdown of the blood-brain barrier in experimental ICH [13]. Moreover, leukocytosis is an independent predictor of hemorrhagic complications in MPNs [14]. A third possibility is that the *JAK2* V617F mutation itself decreased platelet aggregation when adding collagen and thrombin [15]. Collectively, despite long-term treatment with ruxolitinib, our case might have developed abnormal hemostasis and inhibition of platelet aggregation caused by these possible mechanisms, which led to prolonged bleeding time and subsequent recurrent and multiple ICHs.

Tranexamic acid which preserves the agglutination ability of platelets was used during admission for our case. After discharge, we carefully monitored daily blood pressure and monthly platelet counts under the treatment of ruxolitinib, and our case did not show any recurrences after treatment.

Conclusion

ICH comorbid with PV is rare, and the late period of PV that transformed to secondary myelofibrosis is also rare. Along with expanded life expectancy and progress of therapies, we may encounter more cases with a considerably late-phase MPN, as in our case. Further work is warranted to elucidate the mechanism as well as to define the treatment strategies.

Statement of Ethics

Ethical review and approval were not required for the study on human participants in accordance with the local regulation and institutional requirements. Written informed consent for publication of this case report and the accompanying images was obtained from the patient.

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Table 1. Previously reported cases and our case with hemorrhagic stroke secondary to PV

References	Age/sex	Atherosclerotic risk factors	Treatment for PV before stroke	Location of hemorrhage	Type of hemorrhagic stroke	RBC count, $\times 10^4/\mu L$	Leukocyte count, $\times 10^3/\mu L$	Platelet count, $\times 10^4/\mu L$	JAK2 V617F mutation	Neurological symptoms	Duration between diagnosis of PV and hemorrhagic stroke	Remark
Ryle [4]	48/M	None	None	NA	ICH	980	18.75	NE	NE	Headache, left-sided numbness	Simultaneous	None
Sirin et al. [5]	77/M	HT, DL	None	Right temporal lobe	ICH and SDH	NE	20.6	82.1	Positive	Headache, nausea, vomiting, paraparesis, back pain, urinary retention	Simultaneous	Concurrent with CVT and SDH
Chen et al. [6]	50/F	HT	None	Right occipital lobe	ICH	941	NA	Slightly increased	Positive	Headache, left homonymous anopia	Simultaneous	None
Wang et al. [7]	60/F	HT	None	Bilateral hemisphere	Hemorrhagic infarction	756	22.18	34	NE	Dysarthria and tetraplegia	Simultaneous	Hemorrhages secondary to multiple infarctions
Our Case	76/M	None	Ruxolitinib, HU	Right thalamus and bilateral cerebellar hemispheres	Recurrent ICH	269	57.6	6.6	Positive	Left-sided cerebellar ataxia	6 years	Secondary transformation to MF

PV, polycythemia vera; RBC, red blood cell; JAK2, Janus activating kinase 2; NA, not available; ICH, intracranial hemorrhage; NE, not examined; HT, hypertension; DL, dyslipidemia, SDH, subdural hematoma; CVT, cerebral venous thrombosis; HU, hydroxyurea; MF, myelofibrosis.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Author Contributions

Hidenari Hasui, Tatou Iseki, and Yuji Ueno designed the case report and wrote the manuscript. Daiki Kamiyama, Nobukazu Miyamoto, Chikage Kijima, Kenichiro Hira, and Norio Komatsu contributed to data collection and interpretation. Nobutaka Hattori supervised this case report and clinical practice.

Data Availability Statement

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

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