Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2189-23
Intern Med 63: 847-852, 2024
http://internmed.jp

【 CASE REPORT 】

Recurrent Stroke with Rapid Development of Intracranial Artery Stenosis and Subsequent Successful Mechanical Thrombectomy in Essential Thrombocythemia

Yuji Kato[1], Shohei Iijima[2], Shinya Kohyama[2], Tomoya Maeda[3], Tsugumi Sato[4], Shinichi Takahashi[1] and Satoshi Suda[1]

Abstract:
Essential thrombocythemia is a myeloproliferative neoplasm. Ischemic stroke is frequently the first manifestation of essential thrombocythemia. We herein report a patient with *JAK2*V617 mutation-positive essential thrombocythemia who developed recurrent ischemic stroke with rapid development of intracranial artery stenosis and subsequently underwent successful mechanical thrombectomy. The high *JAK2*V617F allele burden in our patient (58.4%) may have affected the patient's condition. We discuss similar reports in the literature and the possible pathophysiologic mechanism of large artery involvement in these patients.

Key words: essential thrombocythemia, early/prefibrotic primary myelofibrosis, *JAK2*V617 allele burden, histopathology

(Intern Med 63: 847-852, 2024)
(DOI: 10.2169/internalmedicine.2189-23)

Introduction

Essential thrombocythemia (ET) is a clonal stem cell disorder that shares several similarities with other myeloproliferative neoplasms (MPNs), particularly polycythemia vera (PV) and primary myelofibrosis (PMF) (1). In addition to mutations in the calreticulin and myeloproliferative leukemia protein genes, the hallmark of MPNs is the *JAK2*V617 mutation, which is positive in 95% of patients with PV and in 50% to 60% of patients with ET and PMF (2). The age, history of thrombosis, cardiovascular risk factors, leukocytosis, and *JAK2*V617F mutation positivity are risk factors for thromboembolic events in patients with MPNs (3).

Large-vessel thrombosis is unique to MPN-associated stroke because of the dynamic nature of the clinical and radiological features (4). A few cases of progressive stenosis in large vessels or retrieved thrombi have been reported (5-7), but no reports have described these complications occurring in the same patient.

We herein report a patient with *JAK2*V617 mutation-positive ET who developed recurrent ischemic stroke with rapid development of intracranial artery stenosis and subsequently underwent successful mechanical thrombectomy.

Case Report

A 77-year-old woman with no medical history was admitted because of ischemic stroke in the left hemispheric watershed territories (Fig. 1a-c). Magnetic resonance (MR) angiography showed mild stenosis of the left middle cerebral artery (MCA) (Fig. 1d). Routine blood tests were unremarkable except for a platelet count of 595×10^9/L. She was discharged home, and oral clopidogrel 75 mg was indicated for secondary stroke prevention.

Four months later, the patient was admitted to our hospital because of the sudden onset of total aphasia without hemiparesis. MR imaging revealed infarction of the left MCA territory, and MR angiography revealed occlusion of the distal M1 segment of the left MCA (Fig. 2). The patient

[1]Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, Japan, [2]Department of Endovascular Neurosurgery, Saitama Medical University International Medical Center, Japan, [3]Department of Hemato-Oncology, Saitama Medical University International Medical Center, Japan and [4]Department of Pathology, Saitama Medical University International Medical Center, Japan
Received: April 24, 2023; Accepted: June 12, 2023; Advance Publication by J-STAGE: July 26, 2023
Correspondence to Dr. Yuji Kato, yujik@saitama-med.ac.jp

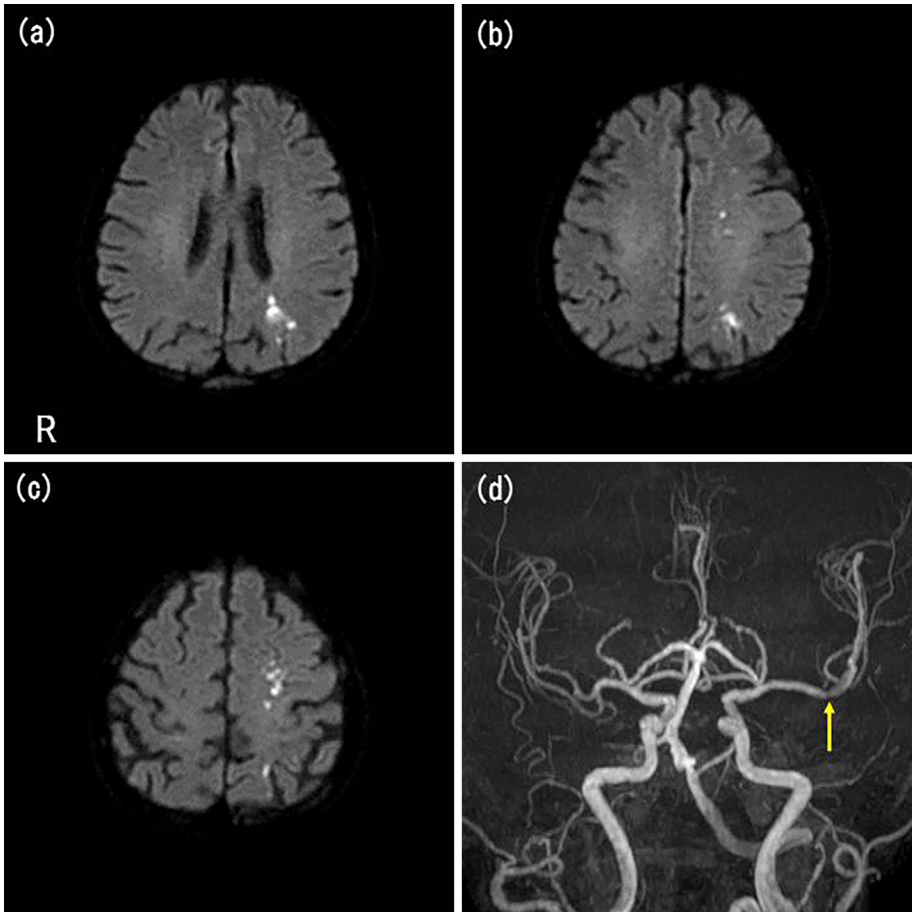

Figure 1. **(a-c) Diffusion-weighted magnetic resonance imaging shows fresh infarction in the left hemispheric watershed territories (the first stroke). (d) Magnetic resonance angiography shows mild stenosis of the left middle cerebral artery (arrow).**

was transferred into the angiosuite, where mechanical thrombectomy was performed. Alteplase was not administered because more than 4.5 hours had passed since the onset. A left internal carotid angiogram showed occlusion of the distal M1 segment of the left MCA (Fig. 3a). When a stent retriever was deployed at the occlusion site, recanalization of the blood flow occurred, and a small white thrombus was retrieved with the first pass.

Because the recanalized artery became reoccluded, probably due to preexisting atherosclerotic stenosis of the M1-M2 bifurcation, selective intra-arterial infusion of urokinase followed by oral prasugrel 20 mg and aspirin 200 mg was performed. The smaller-diameter stent was redeployed at the occlusion site to prevent iatrogenic dissection and maintain the blood flow of the stenotic lesion. Final angiography revealed partial recanalization of the blood flow (Fig. 3b).

The patient's aphasia gradually improved. The day after the procedure, MR imaging revealed slightly enlarged infarctions, and MR angiography revealed residual stenosis of the left MCA (Fig. 4). Initially, the patient was treated with prasugrel 3.75 mg from day 2. The retrieved thrombus was mainly composed of fibrin with erythrocytes and leukocytes (Fig. 5). Electrocardiographic monitoring and transthoracic echocardiography showed no evidence of embolic sources. Based on the clinical and histological evaluations, the patient's stroke etiology was determined to be large-artery atherosclerosis.

All blood test results were unremarkable, except for continued elevation of the platelet count (523-789×10^9/L) with a normal coagulation function. Genetic testing using allele-specific quantitative polymerase chain reaction revealed a *JAK2*V617F mutation (allele burden, 58.4%). Therefore, a bone marrow biopsy was performed after consultation with a hematologist. The subsequent bone marrow examination revealed numerous megakaryocytes, consistent with ET (Fig. 6). Although the dense clusters of megakaryocytes were atypical, the increased cellularity with expansion of granulopoiesis and reticulin fibrosis in the bone marrow indicated the possibility of prefibrotic PMF.

The patient was discharged home on the 59th hospital day with a modified Rankin scale score of 1. One month after discharge, additional treatment with 500 mg hydroxyurea was initiated.

Discussion

In the present case, the recurrence of ischemic stroke was probably due to not only progressive stenosis but also the

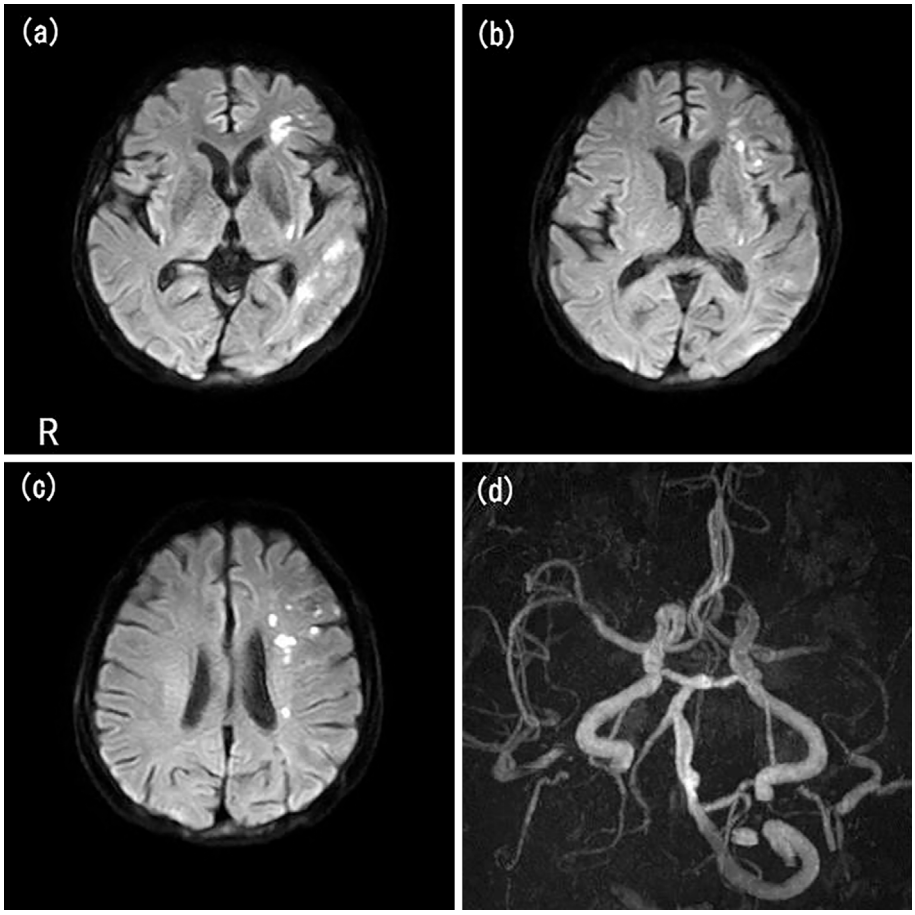

Figure 2. **(a-c) Diffusion-weighted magnetic resonance imaging shows fresh infarction in the territory of the left middle cerebral artery (the second stroke). (d) Magnetic resonance angiography shows occlusion of the distal left M1 segment of the left middle cerebral artery.**

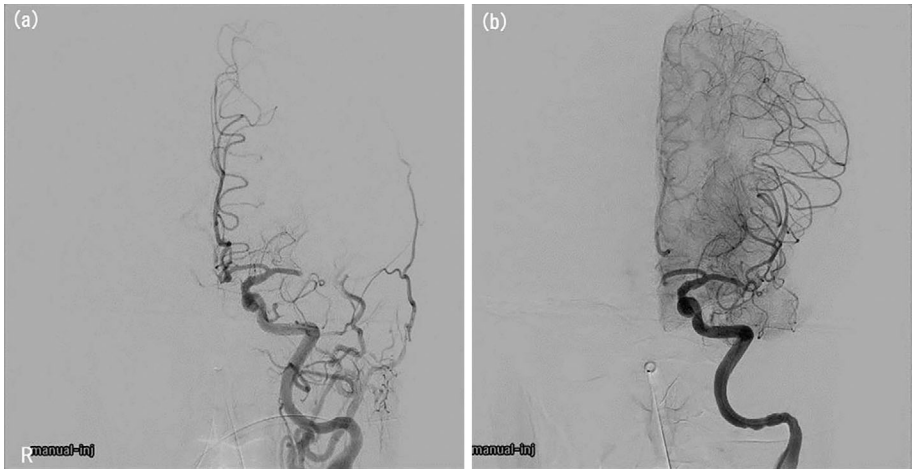

Figure 3. **(a) Left internal carotid angiography shows occlusion of the distal left M1 segment of the left middle cerebral artery. (b) After repeated thrombectomy, partial recanalization of the blood flow was obtained (thrombolysis in cerebral infarction 2a).**

prothrombotic state with ET. Although the exact mechanisms underlying the presence of only one lesion are unclear, the present case also showed atherosclerotic changes in the left VA. We need to follow this patient while considering the possibility of progressive arterial stenosis and newly developing lesions.

Half of patients with ET are asymptomatic, but 14% are diagnosed after arterial thrombosis (8). In fact, ischemic stroke is frequently reported to be the first manifestation of ET (9, 10). The present patient was asymptomatic and diag-

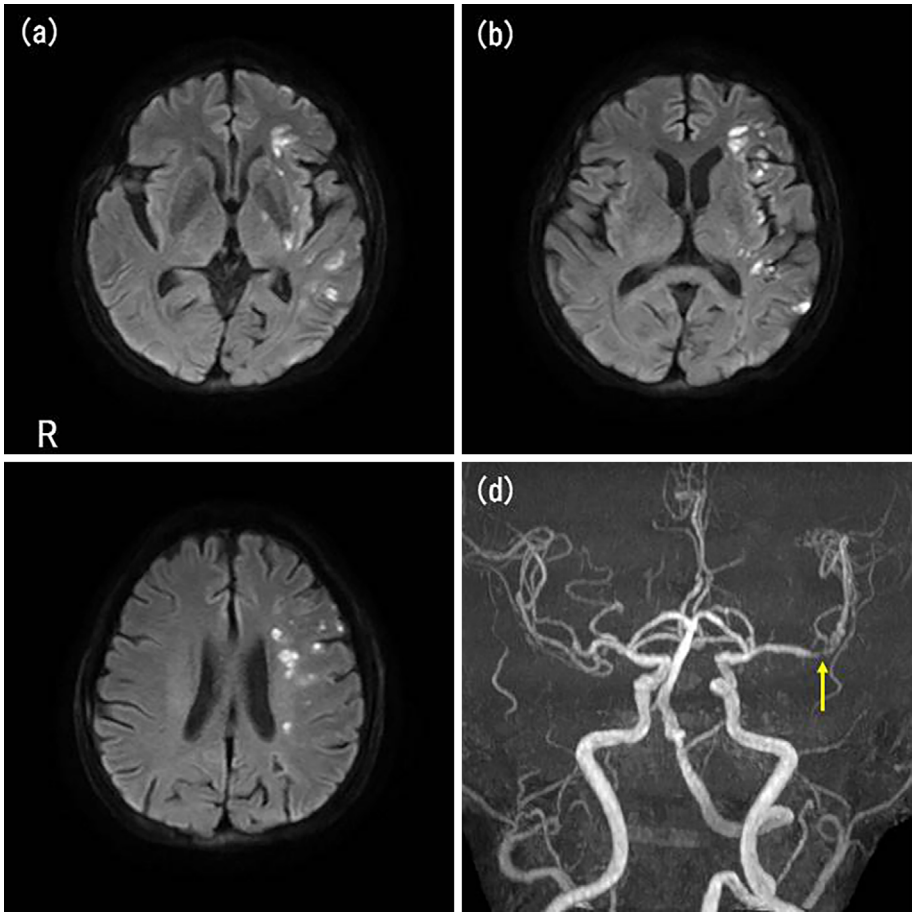

Figure 4. **(a-c) Diffusion-weighted magnetic resonance imaging shows slightly enlarged infarctions in the territory of the left middle cerebral artery (the second stroke). (d) Magnetic resonance angiography shows residual stenosis of the left middle cerebral artery (arrow).**

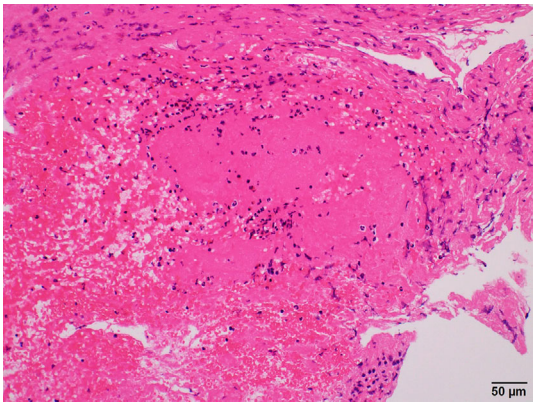

Figure 5. **A histological examination of the retrieved thrombus revealed that it was mainly composed of fibrin with erythrocytes and leukocytes (Hematoxylin and Eosin staining).**

nosed with ET after stroke recurrence, suggesting that ET is often underdiagnosed. Although ET-related acute ischemic stroke is relatively rare and accounts for approximately 0.25% to 0.50% of all ischemic strokes (9-11), suspected ET (persistently elevated platelet count above the threshold value of 450×10^9/L) should be confirmed in collaboration with a hematologist.

Only a few cases similar to the present case have been reported to date (5-7). Most of these patients with progressive stenosis of large vessels had *JAK2*V617 mutation-positive ET or PV (5-7). The retrieved thrombus in the present case was also a fibrin-rich thrombus, and there were no significant differences from the previously reported case (7). The further accumulation of cases involving the progressive stenosis of large vessels and retrieved thrombi is warranted.

The *JAK2*V617F mutation is a contributing factor to thrombosis in the international prognostic score for essential thrombocythemia (IPSET-thrombosis) (12). Wang et al. (13) reported that the expression of *JAK2*V617 promotes early lesion formation and increases complexity in advanced atherosclerosis. The mechanisms underlying the proatherogenic effect of *JAK2*V617 are multifaceted, involving different hematopoietic lineages and their interactions (13). Our patient showed a relatively high *JAK2*V617 allele burden (58.4%) for ET (median allele burden in Japanese cohort study: ET 30.7%, PV 77.6%, prefibrotic PMF 38.0%, post-ET MF 72.7%, overt PMF 48.2%) (14), which might have caused the rapid development of MCA stenosis and subsequent stroke. Further studies are needed and may be useful for clarifying the relationship between the *JAK2*V617 allele burden and arterial thrombosis (15, 16). In addition, of note, a

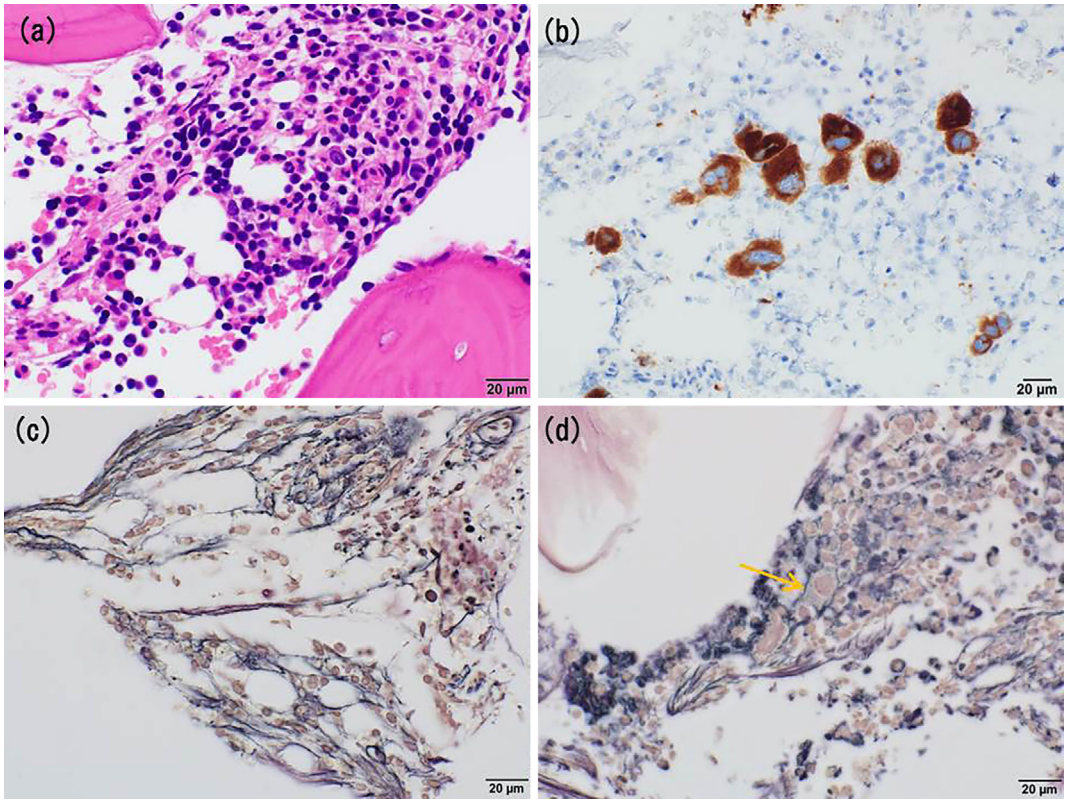

Figure 6. **(a) A bone marrow examination indicated slightly increased cellularity (Hematoxylin and Eosin staining). (b) CD61 immunostaining highlighted the loosely aggregated megakaryocytes (brown). (c, d) Silver staining demonstrated a loose network of reticulin fibers (marrow fibrosis grade 1). The reticulin fibers surrounded megakaryocytes (d, arrows).**

high *JAK2*V617F allele burden at the initial diagnosis is predictive of myelofibrotic transformation in ET (17).

One limitation of this study is that we were unable to definitively diagnose our patient with ET. The discrimination between ET and prefibrotic PMF is especially crucial, as it can influence the diagnostic strategy, outcome, and complications (18). Nonetheless, a previous study showed that both diseases have a high thrombotic risk (18). Compared with ET, prefibrotic PMF is associated with a higher white blood cell count, lower hemoglobin level, higher platelet count, higher lactate dehydrogenase concentration, higher *JAK2*V617 allele burden, and higher frequency of splenomegaly (19). Except for the higher *JAK2*V617 allele burden, none of these abnormalities corresponded to prefibrotic PMF in our case.

We reported a patient with *JAK2*V617 mutation-positive ET who developed recurrent ischemic stroke with rapid development of intracranial artery stenosis and subsequently underwent successful mechanical thrombectomy. The high *JAK2*V617F allele burden may have affected her condition. Further exploration of the underlying mechanisms may change the treatment strategy for such patients in the future.

Author's disclosure of potential Conflicts of Interest (COI).
Yuji Kato: Honoraria, Daiichi Sankyo. Shinya Kohyama: Honoraria, Daiichi Sankyo. Shinichi Takahashi: Honoraria, Otsuka Pharmaceutical and Novartis Pharma. Satoshi Suda: Honoraria, Daiichi Sankyo and Eisai.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood **127**: 2391-2405, 2016.
2. Baxter EJ, Scott LM, Campbell PJ, et al.; Cancer Genome Project. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet **365**: 1054-1061, 2005.
3. Casini A, Fontana P, Lecompte TP. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. J Thromb Haemost **11**: 1215-1227, 2013.
4. Ogata J, Yonemura K, Kimura K, et al. Cerebral infarction associated with essential thrombocythemia: an autopsy case study. Cerebrovasc Dis **19**: 201-205, 2005.
5. Nezu T, Aoki S, Ochi K, et al. A case of recurrent ischemic stroke involving subacute, progressive intracranial cerebral arterial sclerosis prior to diagnosis with *JAK2*-mutated polycythemia vera. J Stroke Cerebrovasc Dis **24**: e4-e6, 2015.
6. Crespo AM, Abraira L, Guanyabens N, et al. Recurrent stroke with rapid development of intracranial stenoses in polycythemia vera. J Stroke Cerebrovasc Dis **25**: e41-e43, 2016.
7. Nagai K, Shimoyama T, Yamaguchi H, et al. Clinical characteristics and brain MRI findings in myeloproliferative neoplasms. J Neurol Sci **416**: 116990, 2020.
8. Tefferi A, Pardanani A. Essential thrombocythemia. N Engl J Med **381**: 2135-2144, 2019.
9. Kato Y, Hayashi T, Sehara Y, et al. Ischemic stroke with essential thrombocythemia: a case series. J Stroke Cerebrovasc Dis **24**: 890-893, 2015.

10. Arboix A, Besses C, Acín P, et al. Ischemic stroke as first manifestation of essential thrombocythemia. Report of six cases. Stroke **26**: 1463-1466, 1995.
11. Richard S, Perrin J, Baillot PA, et al. Ischaemic stroke and essential thrombocythemia: a series of 14 cases. Eur J Neurol **18**: 995-998, 2011.
12. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an international prognostic score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood **120**: 5128-5133, 2012.
13. Wang W, Liu W, Fidler T, et al. Macrophage inflammation, erythrophagocytosis, and accelerated atherosclerosis in *Jak2*^{V617F} mice. Circ Res **123**: e35-e47, 2018.
14. Misawa K, Yasuda H, Araki M, et al. Mutational subtypes of JAK2 and CALR correlate with different clinical features in Japanese patients with myeloproliferative neoplasms. Int J Hematol **107**: 673-680, 2018.
15. Carobbio A, Finazzi G, Antonioli E, et al. JAK2V617F allele burden and thrombosis: a direct comparison in essential thrombocythemia and polycythemia vera. Exp Hematol **37**: 1016-1021, 2009.
16. Coucelo M, Caetano G, Sevivas T, et al. JAK2V617F allele burden is associated with thrombotic mechanisms activation in polycythemia vera and essential thrombocythemia patients. Int J Hematol **99**: 32-40, 2014.
17. Shirane S, Araki M, Morishita S, et al. Consequences of the JAK2V617F allele burden for the prediction of transformation into myelofibrosis from polycythemia vera and essential thrombocythemia. Int J Hematol **101**: 148-153, 2015.
18. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. J Clin Oncol **29**: 3179-3184, 2011.
19. Rumi E, Boveri E, Bellini M, et al.; Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. Clinical course and outcome of essential thrombocythemia and prefibrotic myelofibrosis according to the revised WHO 2016 diagnostic criteria. Oncotarget **8**: 101735-101744, 2017.