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CASE REPORT **OPEN ACCESS**

HAEMORRHAGIC TRANSFORMATION IN ISCHEMIC STROKE INDUCED BY POLYCYTHEMIA VERA: A CASE REPORT

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ABSTRACT

Background: Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by the overproduction of red blood cells. This can lead to hyperviscosity, which significantly increases the risk of thrombosis, which in turn increases the risk of ischemic stroke. There is currently no reported case of haemorrhagic transformation of PV-induced acute ischemic stroke in Indonesia.
Case: A 62-year-old female was admitted to the emergency department after a sudden onset of left-sided weakness one hour before admission. She has a history of polycythemia vera, with prior hemoglobin levels reaching 22 g/dL, and had a previous ischemic stroke one year prior. On physical examination, the patient was alert, with a GCS of 15, blood pressure of 168/94 mmHg, left-sided hemiparesis, dysarthria, and facial drooping. Laboratory tests revealed elevated hemoglobin 16.8 g/dL, hematocrit 56%, platelets 466,000/µL, and leukocytes 20.4 x 10^3/µL. A non-contrast head CT showed a hypodense lesion in the right temporoparietal lobe with a hyperdense spot, consistent with hemorrhagic transformation of a thromboembolic infarction in the right middle cerebral artery (MCA) region, an infarct in the left thalamus, and cerebral atrophy.
Discussion: PV-induced ischemic strokes involve a confluence of hyperviscosity, endothelial activation, and platelet aggregation. The thickened blood compromises microcirculatory flow, particularly in the cerebral vascular, increasing embolic risks. HT occurs due to the reperfusion of ischemic tissues following the breakdown of the blood-brain barrier (BBB).
Conclusion: Hemorrhagic transformation can develop in PV-induced acute ischemic stroke. Effective management requires a multidisciplinary approach, integrating acute stroke care, rigorous hematologic control, antihypertensive therapy, lifestyle modifications, and antiplatelet treatment.

Keywords: hemorrhagic transformation, polycythemia vera, thromboembolic infarct

Introduction

Polycythemia vera (PV) is a type of myeloproliferative neoplasm defined by the abnormal overproduction of erythroid, myeloid, and megakaryocytic cell lines. Excessive production of red blood cells leads to hyperviscosity, which significantly increases the risk of thrombosis. Recent research has indicated that patients with PV have a risk of thrombotic events that is two to four times higher compared to the general population, affecting nearly 41% of patients with PV.[1-3] A previous history of thrombotic events is a strong predictor of future thrombotic events.

Genetic mutations such as JAK2V617F in PV patients also exacerbate this pro-thrombotic state.[4] Furthermore, ischemic events in PV patients are frequently underpinned by microvascular dysfunction and systemic inflammation, creating a cycle of vascular damage that predisposes to recurrent episodes.[5-6] This elevated risk is particularly concerning given that stroke is a major contributor to

mortality worldwide; thus, early diagnosis and management are crucial to mitigating stroke risk.

Hemorrhagic transformation (HT) is a potential complication that may develop after an ischemic stroke. HT is commonly used to describe hemorrhagic infarction that results from venous or arterial thrombosis and embolism.[7] Postmortem studies have revealed an HT rate of 18-42% in acute ischemic stroke due to arterial occlusion.[8] Generally, HT is associated with older age, obesity, hyperglycemia, hypertension, high degree of stroke severity, and large territorial artery occlusion. HT occurrence in acute stroke is a crucial factor to consider when determining whether to perform reperfusion therapy.[9] There is currently only one reported case of HT in acute ischemic stroke induced by PV, a rare manifestation, and none in Indonesia. We reported a 62-year-old female with recurrent ischemic stroke with hemorrhagic transformation, as well as a previous ischemic infarction in the left thalamus.

Case Report

A 62-year-old woman was taken to the emergency department after the sudden onset of left-sided weakness, tingling, and facial drooping, which had occurred one hour before admission. She has a history of polycythemia vera diagnosed in 2010, with prior hemoglobin levels reaching 22 g/dL, and had a previous ischemic stroke with right-sided weakness one year prior. Concerned about her symptoms signifying a new stroke episode, she sought medical attention.

Her medical history includes poorly controlled hypertension, heart disease with left ventricular hypertrophy and cardiomegaly, and polycythemia vera managed with phlebotomy until discontinued a year ago. On physical examination, the patient was alert, with a GCS of 15, but had elevated blood pressure (168/94 mmHg), left-sided hemiparesis (muscle strength, based on the MRC, was 4-/4-/4- on the left side), facial drooping, and dysarthria. The blood sugar level was 91 mg/dL. The NIHSS score was 9. Laboratory tests revealed elevated hemoglobin 16.8 g/dL, hematocrit 56%, platelets 466,000/µL, and leukocytes 20.4 x 10^3/µL. A lipid profile showed low HDL cholesterol, 28 mg/dL, and elevated uric acid, 8.0 mg/dL. Kidney and liver functions were normal.

A non-contrast head CT (Figure 1) showed a hypodense lesion in the right temporoparietal lobe with a hyperdense focus, consistent with hemorrhagic transformation of a thromboembolic infarction in the right middle cerebral artery (MCA) territory. A prior ischemic infarction was also seen in the left thalamus.

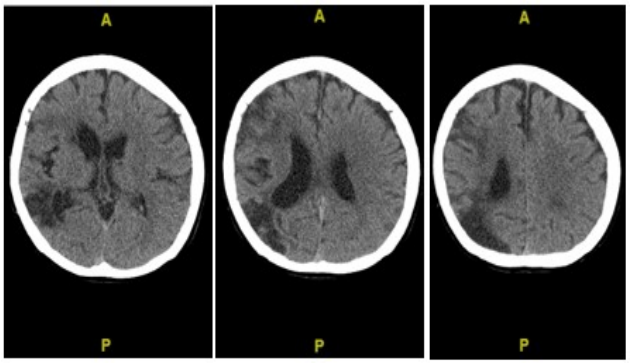

Figure 1. A non-contrast head CT scan on admission, one hour after onset: right temporoparietal lobe thromboembolic infarction with hemorrhagic transformation in the right MCA territory, and infarction in the left thalamus

Based on clinical findings and imaging, the patient was diagnosed with recurrent ischemic stroke with hemorrhagic transformation, as well as a prior ischemic infarction in the left thalamus. The treatment administered included 500 mg of intravenous citicoline, 80 mg of aspirin, and 75 mg of clopidogrel (Aspirin and clopidogrel were administered 24 hours after onset due to the presence of hemorrhagic transformation on the patient's CT scan). Blood pressure was controlled with 16 mg of candesartan and 2.5 mg of bisoprolol. Neurological rehabilitation was recommended, and the patient was referred for follow-up with the hematology department. The patient received hydroxyurea 500mg therapy from the hemato-oncologist. The NIHSS score upon discharge from the hospital two days after admission was 2.

Discussion

We presented a case of HT in acute ischemic stroke, which occurred in a patient with underlying PV and a history of stroke. The diagnosis of PV in our patient is reflected by elevated hemoglobin and hematocrit. The patient in this case is classified as high-risk polycythemia vera due to being over 60 years old and having a history of previous thrombosis. Our patient also presented with uncontrolled hypertension.

Previous studies have reported that ischemic strokes are intricately linked to PV, a myeloproliferative disorder marked by an elevated red blood cell mass and hyperviscosity. The elevated hematocrit levels >55% in many PV patients exacerbate blood viscosity, impairing laminar flow and increasing the likelihood of endothelial damage and thrombogenesis. Furthermore, JAK2V617F mutations, present in approximately 95% of PV cases, amplify pro-inflammatory cytokines and adhesion molecules, intensifying vascular inflammation and promoting thrombus formation. Studies have shown that PV patients have a 5-10% annual risk of thrombotic events, with cerebral ischemia being a common manifestation.[7,10,11]

Physiopathologically, PV-induced ischemic strokes involve a confluence of hyperviscosity, endothelial activation, and platelet aggregation. The thickened blood compromises microcirculatory flow, particularly in the cerebral vasculature, thereby increasing the risk of emboli. Elevated erythrocyte and leukocyte counts disrupt nitric oxide-mediated vasodilation and promote endothelial dysfunction. Simultaneously, upregulated tissue factor expression and activated platelets create a hypercoagulable state, which, in turn, predisposes to arterial or venous thrombosis.[12-14]

In this case, the hemorrhagic transformation (HT) of an ischemic stroke is evident from imaging findings, which reveal a thromboembolic infarction in the right MCA territory with hyperdense foci. HT occurs due to the reperfusion of ischemic tissues following the disruption of the blood-brain barrier (BBB). Elevated inflammatory cytokines, such as matrix metalloproteinases, weaken the BBB, allowing extravasation of blood components into the infarcted brain. PV is partly responsible for the mechanism of HT by increasing blood volume, which, in turn, leads to high pressure on the vessel wall, causing vessels to overfill and microaneurysm formation.[15] Once the vessels rupture, hemorrhage follows. The risk of HT is also amplified in patients with uncontrolled hypertension, such as ours, as it increases microvascular pressure and shear stress, and in hypercoagulable states like polycythemia vera, which exacerbate endothelial injury.[14,16,17] HT affects 15-43% of ischemic strokes treated conservatively, with symptomatic cases occurring in approximately 3-7%.[18-19]

The management of recurrent ischemic stroke in this patient involved a multifaceted approach. The patient received 500mg of citicoline as a neuroprotective agent. The patient also received aspirin and clopidogrel for the management of acute stroke. Still, these were administered 24 hours after onset due to the presence of hemorrhagic transformation on the CT scan. Cytoreductive therapy, Hydroxyurea 500mg, aiming to mitigate further thromboembolic events. Dual antiplatelet therapy, combining clopidogrel and aspirin, is gaining widespread use, with numerous studies evaluating its effectiveness and safety.

This combination therapy should be initiated within 12-24 hours of symptom onset and at least within 7 days of onset, and continued for 21 to 90 days, followed by single antiplatelet therapy to reduce the risk of recurrent stroke. Patients with large cerebral infarcts are at risk of hemorrhagic transformation and worse bleeding with early initiation of anticoagulation; thus, in that setting, it is reasonable to delay initiation of oral anticoagulation for 14 days after onset. A previous study has shown that this delay was not associated with the rate of recurrent stroke.[20] The national guideline also recommended the administration of aspirin and clopidogrel within 24 hours for 21 days to reduce the risk of secondary stroke in patients with minor stroke. In patients at risk of hemorrhagic transformation, which is supported by uncontrolled hypertension and CT scan results, it is advised to start anticoagulation after 14 days following onset, although it may be considered in specific clinical settings.[21]

The treatment of PV based on the national guideline is comprised of low-dose aspirin and phlebotomy with a hematocrit target of <45%. There is no particular difference between the treatment of stroke with and without a history of PV. This combination therapy offers the most significant benefits when started within 24 hours of a stroke and maintained for 4 to 12 weeks. Low-dose aspirin effectively reduces the occurrence of arterial and venous thrombosis and is recommended for primary thromboprophylaxis in patients diagnosed with PV. Research has shown that the use of antiplatelet drugs is not significantly associated with an increased risk of hematoma expansion.[22-23] Hence, it might be appropriate to begin antiplatelet therapy in ischemic stroke patients with hemorrhagic transformation within 2 to 7 days, depending on the severity and stability of the hemorrhage.[18] A large population-based cohort study involving older adults with PV found that phlebotomy and hydroxyurea were linked to enhanced overall survival and a reduced risk of thrombosis.[24]

Long-term management for this patient emphasizes integrating hematology expertise to tailor cytoreductive therapy, such as hydroxyurea, especially in high-risk PV patients like those with recurrent strokes.[25-27] Combined antiplatelet therapy of aspirin and clopidogrel may be continued, considering its efficacy in reducing ischemic recurrence by approximately 20% in complex cases of stroke with high thrombotic risk. Lifestyle modifications, including dietary sodium reduction and physical activity, are also critical in mitigating the patient's additional cardiovascular risks.[28,29,9] Focused rehabilitation interventions, such as physiotherapy and cognitive training, enhance neural plasticity, thereby facilitating functional recovery. Studies report that intensive rehabilitation in the first three months post-stroke can improve motor function by up to 65%, particularly in patients with moderate deficits.[30]

Conclusion

This case highlights the complex interplay between polycythemia vera (PV) and recurrent ischemic stroke with hemorrhagic transformation, exacerbated by poorly controlled hypertension and other vascular risk factors. The hyperviscosity and prothrombotic state associated with PV significantly increase the risk of

thromboembolic events, as seen in this patient. Hemorrhagic transformation can develop in acute ischemic stroke resulting from PV. Effective management requires a multidisciplinary approach, integrating acute stroke care, rigorous hematologic control, antihypertensive therapy, and secondary prevention strategies, including lifestyle modifications and antiplatelet treatment. This case highlights the importance of personalized, proactive care in reducing recurrence and improving outcomes for high-risk PV patients.

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