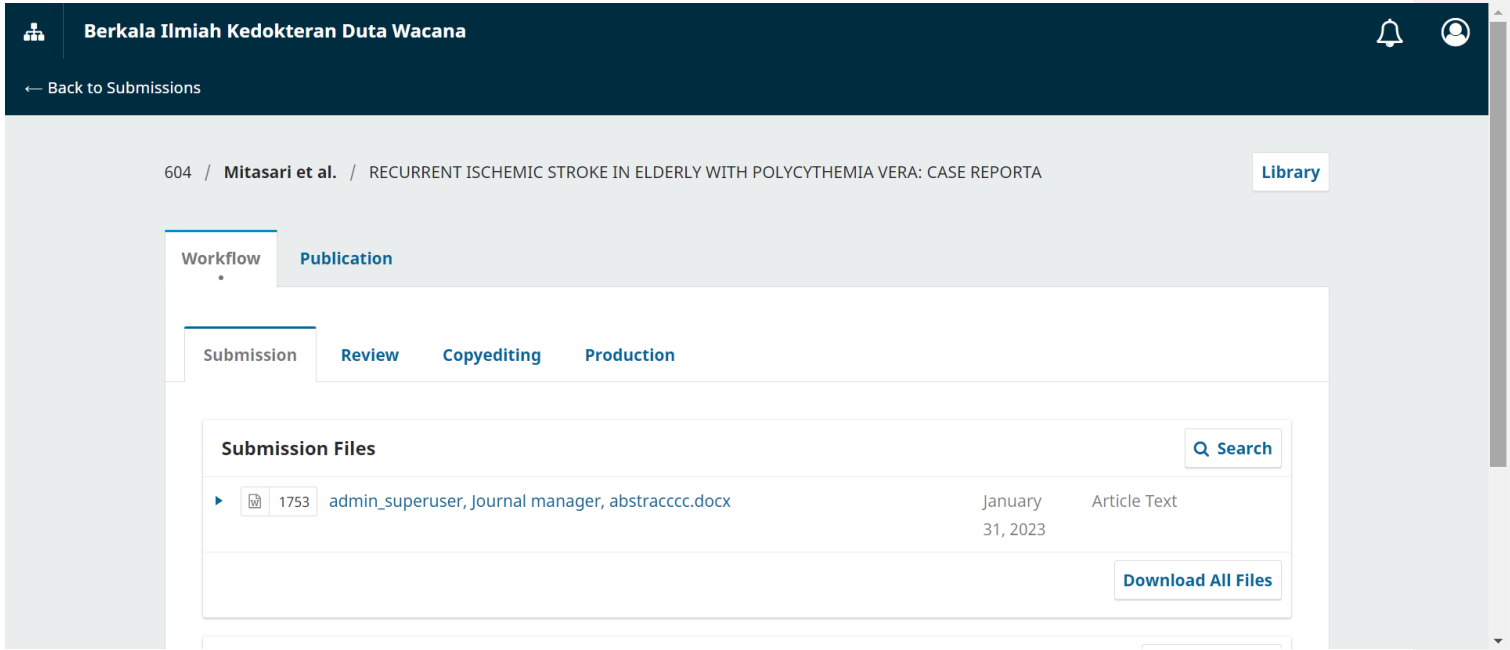
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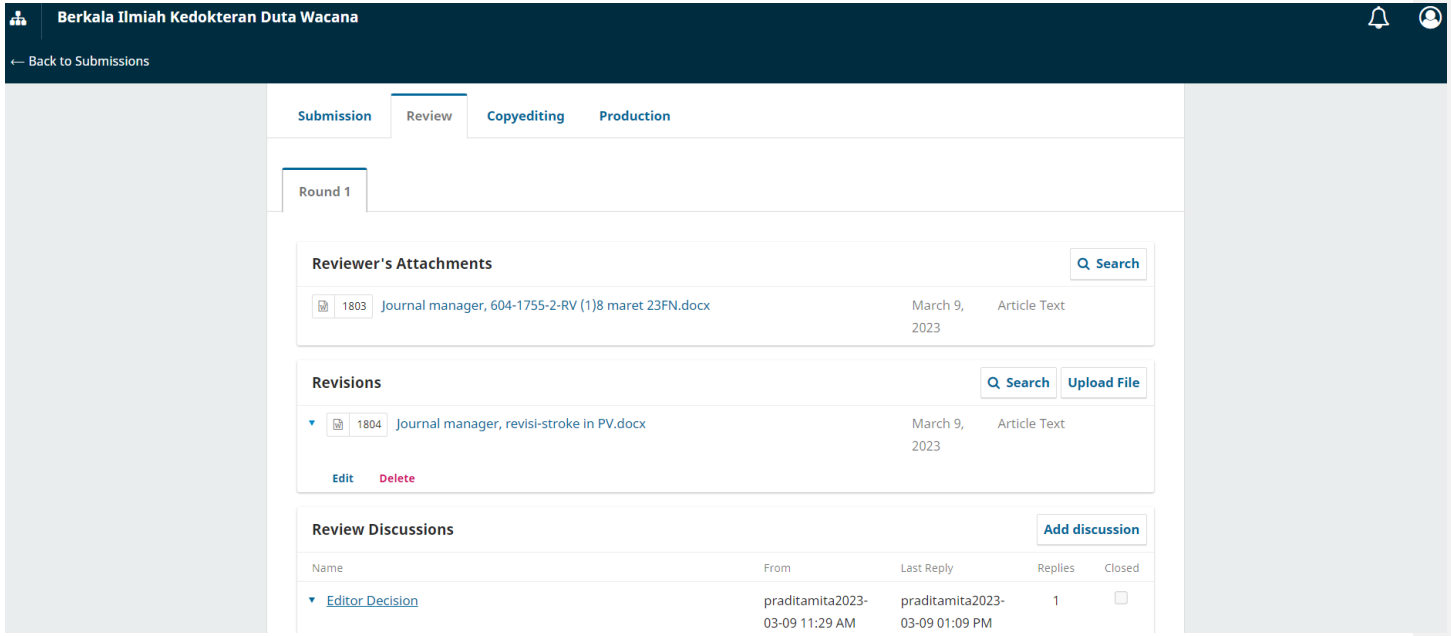
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Recurrent Ischemic Stroke In Elderly With Polycythemia Vera: Case Report

ABSTRACT

Background: Myeloproliferative disorders can rise a risk of thrombotic events. Ischemic stroke is one of presenting symptoms can be found in such patients. These coexisting conditions can burden patients with more severe complications.
Objectives: To discuss a case of polycythemia vera with multiple episodes of ischemic stroke.
Case description: The patient was a 70-year-old female with chief complaint of sudden rotatory dizziness with moderate to severe intensity. Nausea, vomiting, slurred speech, and facial muscle weakness were also reported. Onset of symptoms started 3 hours before hospital admission. Medical history including previous ischemic stroke in 2020 and 2015 with remaining right extremity weakness. Physical examination showed weakness, hypertension. Nystagmus horizontal bidirectional and upper motor neuron lesion of left CN VII and XII, weakness in right upper and lower extremities were observed. Physiological reflexes were increased, and pathological reflex was found. Head CT showed hypodense lesion led to her ischemic stroke diagnosis. Blood test showed increased hemoglobin count, leukocytosis but normal platelet count. Increased cell numbers and variations of size, morphology and distribution were found in peripheral smear. This finding was also supported with bone marrow examination which showed hypercellularity, panmyelosis with dysplasia of all hematopoietic lineage. Patient was diagnosed with polycythemia vera and treated accordingly.
Conclusion: Further examination of hematology, such as peripheral smear or bone marrow examination should be considered in patients with recurrent episodes of stroke to rule in underlying myeloproliferative disorders. Appropriate treatment and routine hematology follow up are in need to increase awareness of future thrombotic events or leukemic transformations.

Keyword: Polycythemia, Myeloproliferative Disorders, Thrombosis, Stroke

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INTRODUCTION

Myeloproliferative disorders are one of myeloid neoplasms according to World Health Organization (WHO) classification. Polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis, chronic myeloid leukemia (CML) are those included in this diagnosis group (Table 1).[1,2]

Thrombotic events can be frequently observed in PV patients, up to 49%.[3] Increased erythrocyte leads to increased blood viscosity which cause reduction in cerebral blood flow and eventually

ischemic stroke. Manifestations of thrombosis and cardiovascular events can reduce overall survival of patients with PV.[3,4] This report will discuss a case of patient who first presented as recurrent ischemic stroke with abnormal hematology tests suspected as myeloproliferative neoplasms.

Table 1. WHO classification of myeloid neoplasm and acute leukemia

WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), BCR-ABL1+
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
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MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2
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Acute myeloid leukemia (AML) and related neoplasms
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
B-lymphoblastic leukemia/lymphoma
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CASE DESCRIPTION

An elderly, 70-year-old, female was brought to emergency department with chief complaint of rotatory dizziness. Symptom was appeared in 3 hours onset before admission, with moderate to severe intensity and accompanied by nausea, vomiting. Slurred speech and facial weakness were also observed.

Previous stroke events were occurred in 6 years and 1 year prior of current episode which led to right side extremities weakness in patients. History of seizure, smoking, diabetes mellitus, cardiac disease or other metabolic diseases were denied.

Physical examination showed that patient was alert (GCS 15), hypertension (165/90 mmHg), normal pulse, respiration, and temperature. Head region examination showed isochor pupils with positive light reflexes, bidirectional nystagmus bidirectional. No neck rigidity or meningeal sign was found. Cranial nerve (CN) exam showed upper motor neuron lesion in left CN VII and CN XII. Limited movement and reduced motoric strength were observed in both upper and lower right extremities, but good results were found in the left side. Increased physiological reflex and pathological reflects were found only in right upper arm. Thorax and abdominal examination showed no abnormalities.

Patient was then brought up for head CT scan workup. Hypodense lesion was observed in right semioval center, left corona radiata, left internal capsule, and left lentiform nucleus suggesting an ischemic stroke.

Blood tests, however, showed significant elevation in erythrocyte count, hemoglobin, and hematocrit (Figure 1). Leukocytosis and neutrophilia were observed but platelet count was normal. Peripheral blood smear and bone marrow examinations were ordered to determine underlying hematological disorder in patient. Peripheral smear showed increased erythrocyte, normocytic with mild anisocytosis, normochromic, increased leukocyte, toxic granulation of neutrophil was found, and normal platelet morphology and distribution. This result led to suspicion of myeloproliferative neoplasm. Bone marrow examination was conducted for

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diagnosis and polycythemia vera was suggested.

Hypercellularity, panmyelosis or increased number of all three hematopoietic lineage, with distinguished dysplasia of all hematopoietic lineage were found in bone marrow examination. According to WHO 2016 criteria, presence of JAK2 or JAK2 exon mutation or serum erythropoietin level should be examined. Unfortunately, due to limitations of available testing, these tests were not carried out.

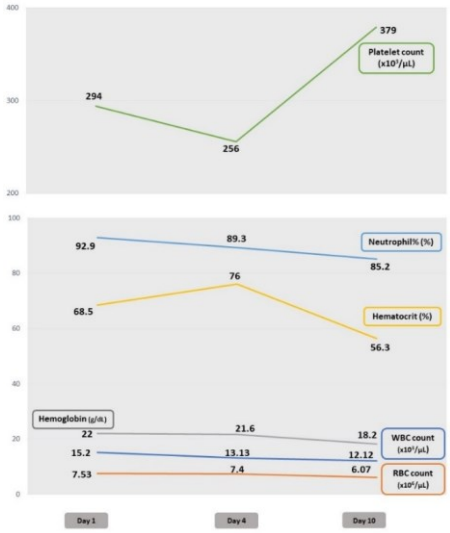

Figure 1. Serial hematology test result

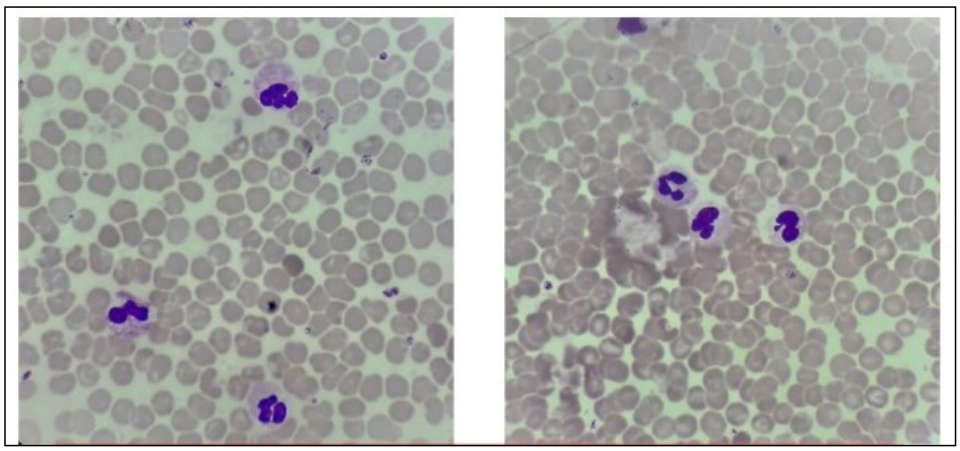

Figure 2. Peripheral blood smear examination showed increase of erythrocyte population with neutrophilia.

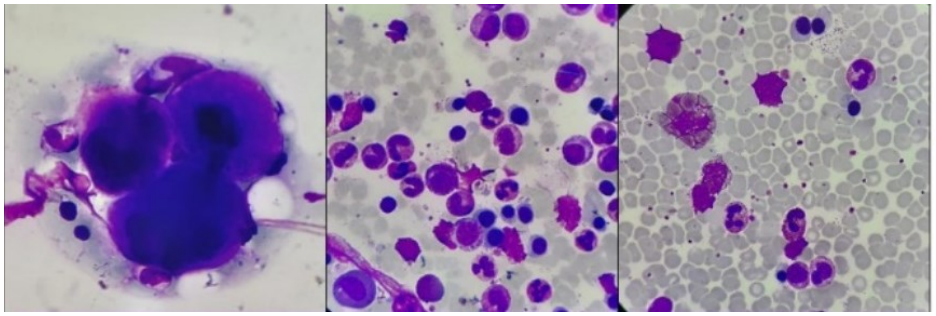

Figure 3. Bone marrow examination. Characteristics such as increased megakaryocytes (left picture), increased cellular number with significant number of erythroid precursors (middle) and granulocytes lineage predominant (middle and right picture)

Patient was then treated with phlebotomy and aspirin and were observed for a few days in intensive stroke care unit. Continuous monitoring was carried out during hospitalization period and no repeated event of thrombosis was observed. Later patient was discharged and advised for further monitoring by onco-hematologist and neurologist. Watchful observation and routine follow up should be scheduled for such patients to reduce the possibility of future thrombotic events or to detect leukemia transformation and initiate early treatment.

DISCUSSION

Myeloproliferative neoplasms refer to clonal hematopoietic disorders due to genetic mutations in hematopoietic stem cell. Polycythemia vera is the most frequent MPN diagnosis, with BCR-ABL1-negative or absence of Philadelphia chromosome.[5] A mutation JAK2 mutation, in exon 14 in almost all patients and in exon 12 (in a few) is usually found.[6] As a member of the Janus kinase family, this gene functions as a tyrosine kinase for receptors of erythropoietin and thrombopoietin. This mutation leads to autonomous response of stem cells to this regulatory protein causing independent increased of erythropoiesis, followed by thrombopoiesis and granulopoiesis.[7,8]

Manifestations of PV are usually panmyelosis in bone marrow with increases of all cell counts (erythrocytes, leukocytes and platelets), with or without splenomegaly.[7] Diagnosis criteria for PV can be seen in Table 2, with presence of all 3 major criteria or first 2 major criteria and the minor criterion is required for diagnosis.

Table 2. WHO criteria for PV diagnosis

Major criteria
1. Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women, or Hematocrit >49% in men, >48% in women, or Increased red cell mass
2. Bone marrow biopsy showin hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes
3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criteria
Subnormal serum erythropoietin level

Our patient met the first two major criteria, but due to limitations of testing

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availability, genetic mutation and erythropoietin levels were not tested. Hematocrit level even reached the critical value (>65%) and was still above targeted value or >45% after hospital care.

Increased of erythrocyte count or erythrocytosis leads to hyper viscosity due to increased red cell mass. This was believed as underlying mechanism causing reduced cerebral blood flow and arterial or venous thrombosis.[8] Leukocytosis was also reported in previous study as an independent risk factor for thrombosis.[3] Other manifestations such as ocular migraine, erythromelalgia, aquagenic pruritus, acquired von Willebrand disease and pseudohyperkalemia can be found in repercussion of thrombocytosis and basophilia.

However, due to low prevalence of PV, stroke episodes related to PV are still underdiagnosed.[9] This also happened to our patient who was not assessed or tested for hematological examination in her previous episodes of events.

Patients with PV are usually stratified for risk of complications such as thrombosis. Patients with age > 60 years or any history of thrombosis are categorized as high risk, meanwhile low risk are for those with none of these risk factors.[2] Risk factors for poor survival rate in patients with PV could be found in this patient, such as advanced age, leukocytosis, venous thrombosis. These factors are also risk factors of transformation to acute leukemia which lead to a further burden even fatality.[2,3]

Low-dose aspirin are recommended for low-risk PV patients. Meanwhile, platelet-lowering agents such as hydroxyurea can also be used in those who are not responding to aspirin administration.[2] In high risk patients, phlebotomy, hydration, antiplatelet and cytoreductive drugs are recommended to reduce risk of repeated strokes in the future.[3,10]

CONCLUSION

Further examination of hematology, such as peripheral smear or bone marrow examination should be considered in patients with recurrent episodes of stroke to rule in underlying myeloproliferative disorders. Appropriate treatment and routine hematology follow up are in need to increase awareness of and prevent future thrombotic events or leukemic transformations.

CONFLICT OF INTEREST AND FUNDING RESOURCES

None

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[BIKDW] Hasil Review Recurrent Ischemic Stroke In Elderly With Polycythemia Vera: Case Rep

1 message

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Reply-To: Yacobus Christian Prasetyo <yacobus.ch.p@staff.ukdw.ac.id>
To: Pradita Sri Mitasari <pradita.mita@staff.ukdw.ac.id>
Cc: Setyawati Setyawati <pradism23@gmail.com>

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Does this research match the BIKDW scope of the journal?:
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Are the research objectives or hypotheses clearly stated?:
Yes

Are they important to add current knowledge?:
Yes

Have the objectives been met?:
Yes

Is the study incomplete or too preliminary?:
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Study design and methodology
Is the study design correct for proposed research questions/hypotheses?:
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Are there any flaws or hidden information which should be addressed? And how serious are these?:

No/Unsure

Has the author chosen appropriate statistical (or qualitative) analyses, and been done correctly?:
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Soundness of results
Is the data valid and accountable?:
Yes

Has the author reported the power of the study?:
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Does the author use adequate sample size?:
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For the laboratory or animal research, are there enough repetitions of the experiments?:
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Interpretation
Have the data been analysed and interpreted correctly?:
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Is the work original? Please describe your reason in the comment if you think it is not original.:
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Have the author(s) mentioned the accessibility of all research materials for the public?:

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Describe how much the research add to current knowledge, and compare with existing literature

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Give an idea of the quality and completeness of the work; indicate its strengths.

State whether there are any major flaws or weaknesses.

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Major issues

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Reviewer C:

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Are they important to add current knowledge?:
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Study design and methodology
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Expansion of questions/comments made in the reviewing checklist:
Opinion:

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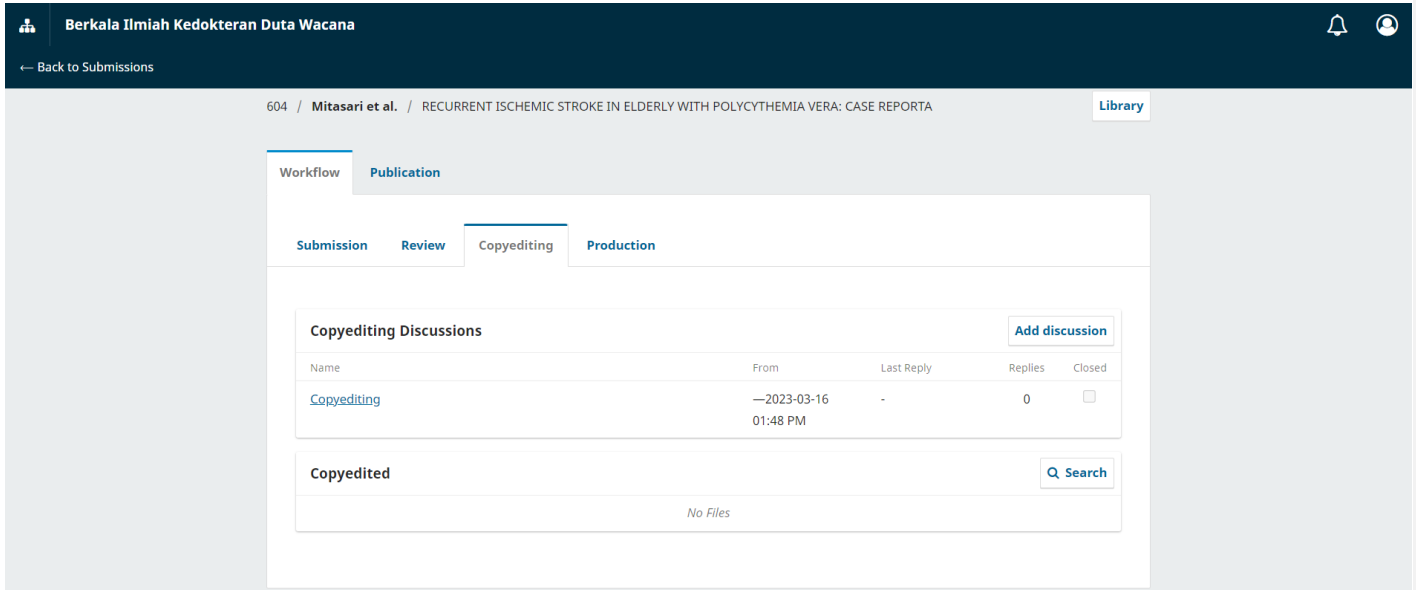
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myeloproliferative neoplasm. Bone marrow examination was conducted for diagnosis and polycythemia vera was suggested.

Hypercellularity, panmyelosis or increased number of all three hematopoietic lineage, with distinguished dysplasia of all hematopoietic lineage were found in bone marrow examination. According to WHO 2016 criteria, presence of JAK2 or JAK2 exon mutation or serum erythropoietin level should be examined. Unfortunately, due to limitations of available testing, these tests were not carried out.

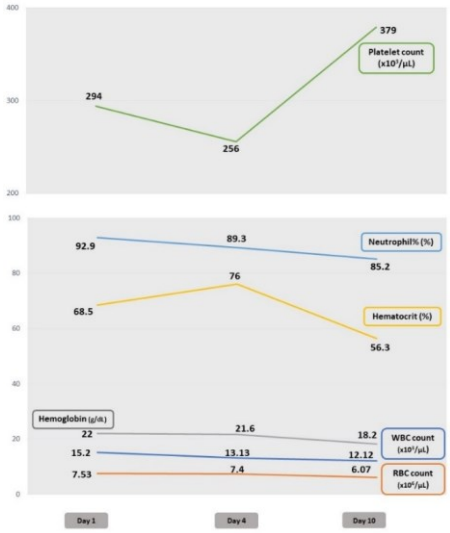

Figure 4. Serial hematology test result

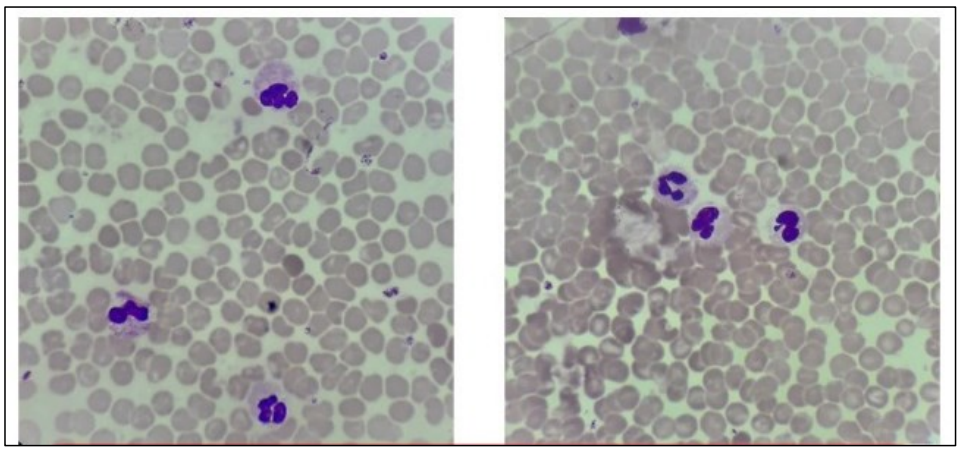

Figure 5. Peripheral blood smear examination showed increase of erythrocyte population with neutrophilia.

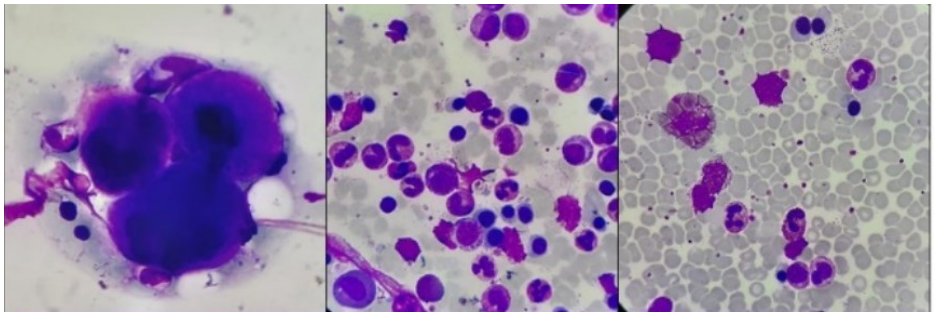

Figure 6. Bone marrow examination. Characteristics such as increased megakaryocytes (left picture), increased cellular number with significant number of erythroid precursors (middle) and granulocytes lineage predominant (middle and right picture)

Patient was then treated with phlebotomy and aspirin and were observed for a few days in intensive stroke care unit. Continuous monitoring was carried out during hospitalization period and no repeated event of thrombosis was observed. Later patient was discharged and advised for further monitoring by onco-hematologist and neurologist. Watchful observation and routine follow up should be scheduled for such patients to reduce the possibility of future thrombotic events or to detect leukemia transformation and initiate early treatment.

DISCUSSION

Myeloproliferative neoplasms refer to clonal hematopoietic disorders due to genetic mutations in hematopoietic stem cell. Polycythemia vera is the most frequent MPN diagnosis, with BCR-ABL1-negative or absence of Philadelphia chromosome.[5] A mutation JAK2 mutation, in exon 14 in almost all patients and in exon 12 (in a few) is usually found.[6] As a member of the Janus kinase family, this gene functions as a tyrosine kinase for receptors of erythropoietin and thrombopoietin. This mutation leads to autonomous response of stem cells to this regulatory protein causing independent increased of erythropoiesis, followed by thrombopoiesis and granulopoiesis.[7,8]

Manifestations of PV are usually panmyelosis in bone marrow with increases of all cell counts (erythrocytes, leukocytes and platelets), with or without splenomegaly.[7] Diagnosis criteria for PV can be seen in Table 2, with presence of all 3 major criteria or first 2 major criteria and the minor criterion is required for diagnosis.

Table 4. WHO criteria for PV diagnosis[1]

Major criteria
4. Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women, or Hematocrit >49% in men, >48% in women, or Increased red cell mass
5. Bone marrow biopsy showin hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes
6. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criteria
Subnormal serum erythropoietin level

Our patient met the first two major criteria, but due to limitations of testing

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availability, genetic mutation and erythropoietin levels were not tested. Hematocrit level even reached the critical value (>65%) and was still above targeted value or >45% after hospital care.

Increased of erythrocyte count or erythrocytosis leads to hyper viscosity due to increased red cell mass. This was believed as underlying mechanism causing reduced cerebral blood flow and arterial or venous thrombosis.[8] Leukocytosis was also reported in previous study as an independent risk factor for thrombosis.[3] Other manifestations such as ocular migraine, erythromelalgia, aquagenic pruritus, acquired von Willebrand disease and pseudohyperkalemia can be found in repercussion of thrombocytosis and basophilia.

However, due to low prevalence of PV, stroke episodes related to PV are still underdiagnosed.[9] This also happened to our patient who was not assessed or tested for hematological examination in her previous episodes of events.

Patients with PV are usually stratified for risk of complications such as thrombosis. Patients with age > 60 years or any history of thrombosis are categorized as high risk, meanwhile low risk are for those with none of these risk factors.[2] Risk factors for poor survival rate in patients with PV could be found in this patient, such as advanced age, leukocytosis, venous thrombosis. These factors are also risk factors of transformation to acute leukemia which lead to a further burden even fatality.[2,3]

Low-dose aspirin are recommended for low-risk PV patients. Meanwhile, platelet-lowering agents such as hydroxyurea can also be used in those who are not responding to aspirin administration.[2] In high risk patients, phlebotomy, hydration, antiplatelet and cytoreductive drugs are recommended to reduce risk of repeated strokes in the future.[3,10]

CONCLUSION

Further examination of hematology, such as peripheral smear or bone marrow examination should be considered in patients with recurrent episodes of stroke to rule in underlying myeloproliferative disorders. Appropriate treatment and routine hematology follow up are in need to increase awareness of and prevent future thrombotic events or leukemic transformations.

CONFLICT OF INTEREST AND FUNDING RESOURCES

None

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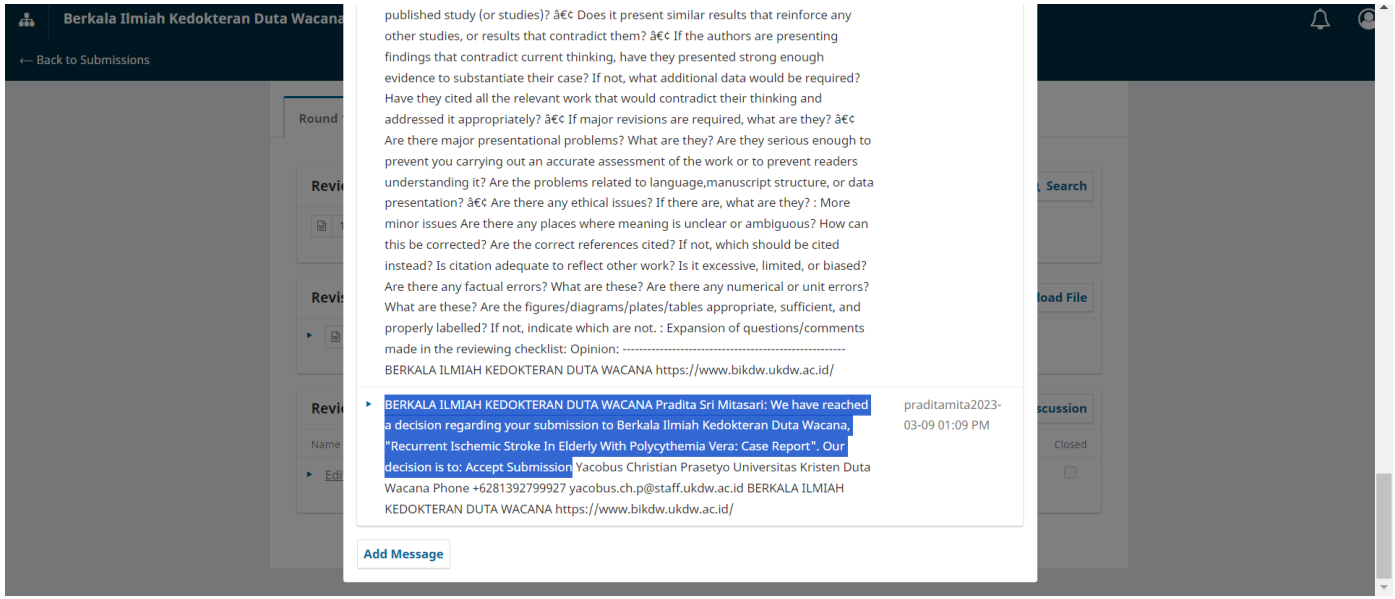
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published study (or studies)? â€¢ Does it present similar results that reinforce any other studies, or results that contradict them? â€¢ If the authors are presenting findings that contradict current thinking, have they presented strong enough evidence to substantiate their case? If not, what additional data would be required? Have they cited all the relevant work that would contradict their thinking and addressed it appropriately? â€¢ If major revisions are required, what are they? â€¢ Are there major presentational problems? What are they? Are they serious enough to prevent you carrying out an accurate assessment of the work or to prevent readers understanding it? Are the problems related to language,manuscript structure, or data presentation? â€¢ Are there any ethical issues? If there are, what are they? : More minor issues Are there any places where meaning is unclear or ambiguous? How can this be corrected? Are the correct references cited? If not, which should be cited instead? Is citation adequate to reflect other work? Is it excessive, limited, or biased? Are there any factual errors? What are these? Are there any numerical or unit errors? What are these? Are the figures/diagrams/plates/tables appropriate, sufficient, and properly labelled? If not, indicate which are not. : Expansion of questions/comments made in the reviewing checklist: Opinion: ---------- BERKALA ILMIAH KEDOKTERAN DUTA WACANA https://www.bikdw.ukdw.ac.id/
BERKALA ILMIAH KEDOKTERAN DUTA WACANA Pradita Sri Mitasari: We have reached a decision regarding your submission to Berkala Ilmiah Kedokteran Duta Wacana, "Recurrent Ischemic Stroke In Elderly With Polycythemia Vera: Case Report". Our decision is to: Accept Submission Yacobus Christian Prasetyo Universitas Kristen Duta Wacana Phone +6281392799927 yacobus.ch.p@staff.ukdw.ac.id BERKALA ILMIAH KEDOKTERAN DUTA WACANA https://www.bikdw.ukdw.ac.id/
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[BIKDW] Editor Decision

1 message

Tejo Jayadi <bikp9746@amuntai.iixcp.rumahweb.net> Thu, Mar 9, 2023 at 1:09 PM
Reply-To: Yacobus Christian Prasetyo <yacobus.ch.p@staff.ukdw.ac.id>
To: Pradita Sri Mitasari <pradita.mita@staff.ukdw.ac.id>
Cc: Setyawati Setyawati <pradism23@gmail.com>

BERKALA ILMIAH KEDOKTERAN DUTA WACANA
Pradita Sri Mitasari:

We have reached a decision regarding your submission to Berkala Ilmiah Kedokteran Duta Wacana, "Recurrent Ischemic Stroke In Elderly With Polycythemia Vera: Case Report".

Our decision is to: Accept Submission

Yacobus Christian Prasetyo
Universitas Kristen Duta Wacana
Phone +6281392799927
yacobus.ch.p@staff.ukdw.ac.id
BERKALA ILMIAH KEDOKTERAN DUTA WACANA
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