

CASE REPORT

Undiagnosed polycythemia, an uncommon cause of Wallenberg syndrome: A case report

Aadesh Rayamajhi¹  | Biraj Pokhrel¹  | Shambhu Khanal¹  | Anjan Shrestha²

¹Department of Internal Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

²Department of Hemato-oncology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Correspondence

Shambhu Khanal, Department of Internal Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal.

Email: shambhukhanal19@gmail.com

Abstract

A 26-year-old man presented with difficulty swallowing, dizziness, hiccups, and Horner's syndrome. Clinical and neuroimaging collaboration confirmed lateral medullary syndrome. Polycythemia was identified as the only attributable risk factor. However, the cause of polycythemia could not be assessed further. Polycythemia was managed with phlebotomy.

KEYWORDS

case report, ischemic stroke, lateral medullary syndrome, polycythemia

1 | INTRODUCTION

Wallenberg syndrome (WS), also known as lateral medullary syndrome (LMS) or posterior inferior cerebellar artery syndrome (PICA), was first described by Adolf Wallenberg in 1895.¹ It is a relatively uncommon stroke due to vascular event (ischemia) in the lateral part of the medulla oblongata in the brain stem with slightly male predominance.^{1,2} The blockade of the artery results in the ischemia, commonly occurring in the vertebral artery or posterior inferior cerebellar artery.

Wallenberg syndrome has a wide and varied neurological manifestations which occur according to the extent of the damage. WS or LMS can be clinically identified as the triad of Horner syndrome, ipsilateral ataxia, and contralateral hypoalgesia. Studies show that 75% of the patients have sudden onset of the symptoms. Sensory signs and symptoms are mostly the reported ones. Similarly, vertigo, nystagmus, headache, hoarseness, dysphagia, dysarthria, and facial paresis are the other clinical presentations of this syndrome.¹

The most common risk factor for developing LMS is vertebral artery dissection and atherosclerosis.^{3,4} Vertebral artery dissection is more common in younger adults⁵

whereas atherosclerosis in older patients having hypertension, diabetes, cigarette smoking, and/or coronary artery disease concomitantly.⁴ Computed tomography (CT) angiogram or magnetic resonance (MR) angiogram is very helpful in identifying the site of vascular occlusion and to rule out uncommon causes such as vertebral artery dissection.

Occasionally, an association of polycythemia has been drawn in the literature with focal cerebral ischemia,^{6,7} but none have yet described for WS. High blood viscosity, a consequence of polycythemia, causes reduced cerebral blood flow which can cause stroke. Herein, we report a 26-year-old otherwise healthy male who presented with left lateral medullary syndrome with complaints of dysphagia, ataxia, and hiccup in setting of polycythemia.

2 | CASE PRESENTATION

A 26-year-old man presented to the outpatient department with difficulty swallowing, dizziness, and unsteadiness along with hiccups for ten days. The difficulty in swallowing was sudden in onset, non-progressive, and was associated with speech disturbances which manifested

as decreased volume of voice and nasal intonations. He developed cough and nasal regurgitation with intake of both water and food. Similarly, the patient described sudden onset persistent spinning sensation and tendency to fall toward left side when he attempted to walk on the floor and sit upright on his bed. There was no associated tinnitus, fever, headache, loss of consciousness, weakness of limbs, and loss or altered sensation over his body. Likewise, the hiccups were frequent and persistent such that it interfered with his sleep and speech.

He was otherwise healthy, active, and had no significant chronic illnesses. His family and psychosocial history were unremarkable. Nevertheless, there was a three pack-years of smoking history. He did not consume alcohol.

On physical examination, the patient was 163 cm and weighed 52 kg with blood pressure 130/80 mm of Hg, pulse 88/min, and respiratory rate 16 breaths/min with an O₂ saturation (SpO₂) of 96% in room air. The general examination was unremarkable. The chest was clear to auscultation, cardiovascular, and abdominal examination were unremarkable.

On neurological examination, the higher mental function was intact. The signs of meningeal irritation were absent. Eye movements were normal. There was mild ptosis on left eye (Figure 1). Examination of cranial nerves was unremarkable except for the nerves seventh and ninth/tenth: Deviation of angle of mouth to the right side with non-prominent nasolabial fold; uvula was deviated to the right and absent gag reflex. Superficial and deep tendon reflexes were normal. Flexor plantar response was seen in



FIGURE 1 Deviation of angle of mouth to the right side with non-prominent nasolabial fold along with mild ptosis

either side. Tone and bulk of the muscles in the limbs were normal. In contrast to the motor examination, sensory examination, however, revealed decreased pin prick and temperature sensation on right half of the body as compared to the left. Deep sensation was preserved. Abnormal cerebellar signs were present on the left side including intention tremor, dysdiadochokinesia, finger-nose-finger, and heel shin test. The patient had ataxic gait with tendency to sway toward the left, and he could not perform tandem walking.

Investigations showed abnormal urine analysis and polycythemia (Table 1).

Urinalysis showed light reddish colored urine, which was slightly turbid with 3+ proteinuria and packed Red Blood Corpuscles (RBCs) in high power field.

The arterial blood gas revealed pH of 7.4, P_aCO₂ of 34.5 mmHg, P_aO₂ of 111 mmHg and HCO₃ of 22.1 mmol/L. 24-hour urine protein was 250 mg. Standard autoimmune markers including anti-nuclear antibodies were negative. Chest X-ray and electrocardiography did not show any remarkable findings. Subsequently, transthoracic echocardiography was done, which did not reveal any valvular heart disease, thrombus, and vegetations. The patient was managed conservatively along with occupational gait therapy. He was kept on aspirin 150 mg orally and 350 cc of blood was let down as per the hospital guideline.

On neuroimaging, there was approximately 12.2 × 8.5 mm sized, T1 low intensity (Figure 2), T2/fluid attenuated inversion recovery (FLAIR) sequence high signal intensity, area noted in left posterolateral aspect of medulla (Figure 3A,B). The corresponding area showed restriction of diffusion on DWI (Diffusion Weighted Imaging) which is suggestive of Left posterolateral medullary infarct (Figure 4). Moreover, loss of flow void was seen in the visualized part of the vertebral artery likely due to thrombus in FLAIR image (Figure 5). Neuroimaging ruled out acute demyelinating disease such as multiple sclerosis and space occupying lesions on the posterior fossa. Further investigations were done to find the possible etiology that could explain the cause for the symptoms. Subsequently, computed tomography (CT) angiography of head and neck was performed which showed normal internal and external carotid arteries bilaterally, and normal Circle of Willis. However, non-opacification of V1 to V4 segment of left vertebral artery with distal reformation of V5 segment was noted along with basilar artery fenestrations.

Bone marrow aspirated from left posterior superior iliac spine revealed normocellular marrow and was negative for malignancy. Eventually, biopsy sample of marrow was taken from the same site which showed mild hypercellular marrow for age with trilineage growth including erythroid, granulocytic, and megakaryocytic proliferation.

TABLE 1 Patient's abnormal laboratory values following admission, which demonstrated polycythemia

Parameters	Result	Normal reference
Hematological investigation		
CBC		
a. Hemoglobin (g/dl)	23.4	14.0–18.0
b. Total leukocyte count (cells/mm ³)	10,200	4000–11,000
c. Differential leukocyte count (%)		
Neutrophil	85	40–75
Lymphocyte	12	20–45
Monocyte	2	1–10
Eosinophil	1	0–6
Basophil	0	0–1
d. Total platelet count (cells/mm ³)	128,000	150,000–400,000
e. Total RBC count (cells/mm ³)	7.48 million	4.5–5.5 million
f. PCV (%)	70.9	40–54
g. MCV (fl)	94.9	82–92
h. MCH (pg)	31.3	26–34
i. MCHC (%)	33.0	32–36
Prothrombin time (PT) (s)	14.0	11–16
PT control (s)	12.0	
INR	1.28	
aPTT (s)	30.0	25.4–38.4
Liver function test		
Total bilirubin (mg/dl)	1.7	0.3–1.2
Direct bilirubin (mg/dl)	0.4	<0.2
Alkaline phosphatase (U/L)	57	30–120
ALT (U/L)	24	<50
AST (U/L)	42	<50
Total protein (g/dl)	6.0	6.3–8.3
Albumin (g/dl)	3.5	3.5–5.5
Lactate dehydrogenase (U/L)	315	0–246
Random blood sugar (mg/dl)	78	60–145

Abbreviations: ALT, alanine transferase; aPTT, activated partial thromboplastin time; AST, aspartate transferase; CBC, complete blood count; INR, International Normalized Ration; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; PCV, packed cell volume; RBC, red blood corpuscle.

Serum erythropoietin (EPO) was just above the upper reference limit with level of 30.40 mIU/ml (Reference range: 4.30–29.00). In addition, Janus Kinase (JAK) 2 Exon 14

**FIGURE 2** Low signal intensity area on T1-weighted image of brain on axial section

and Exon 12 mutations were not detected. With this, secondary polycythemia was considered as likely etiology.

3 | DISCUSSION

Polycythemia can have a primary or secondary and congenital or acquired cause. In primary polycythemia, there is increase in RBC mass due to intrinsic defect in the erythroid compartment in the bone marrow, whereas in the secondary polycythemia, EPO stimulates the bone marrow to produce red blood cells. Primary polycythemia involves the classical Polycythemia Vera which is identified by *JAK2V617F* exon 14 mutations in more than 90% patients, majority of those negative for exon 14 mutation possess mutations in exon 12.^{8–10} Secondary polycythemia differs from the former in that there is an increase of RBC mass caused by elevated serum EPO but that is not always the case as suggested by Mahe et al.¹¹ Most often, this is due to an appropriate physiologic response to tissue hypoxia, but secondary polycythemia can also result from autonomous EPO production (e.g., an EPO-secreting tumor). Secondary polycythemia develops in various cardiac, pulmonary or renal diseases, or from external hypoxia conditions.¹²

Blood viscosity has an exponential relation to hematocrit with aggregation of red cells increasing at high hematocrit levels. This generates a potential for vascular stasis provided red cell production is left unchecked.^{13,14} In this circumstance, thrombosis can occur

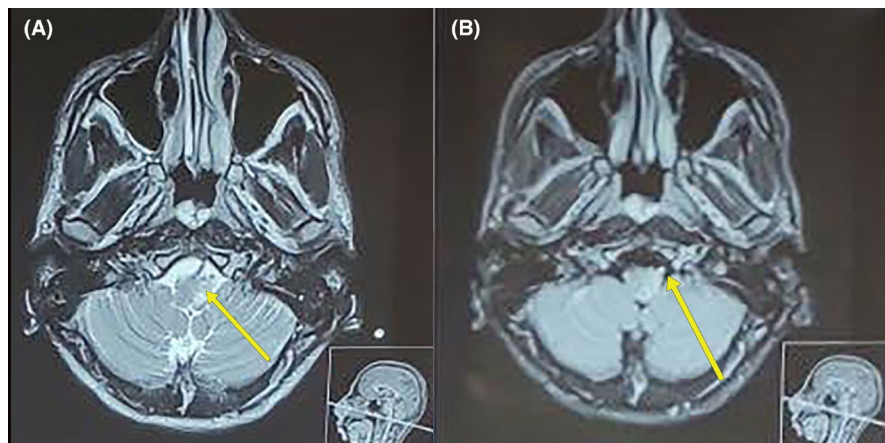


FIGURE 3 (A) High signal intensity area on T2-weighted image of brain on axial section. (B) High signal intensity area noted in left posterolateral aspect of medulla on axial FLAIR sequence. FLAIR, Fluid attenuated inversion recovery

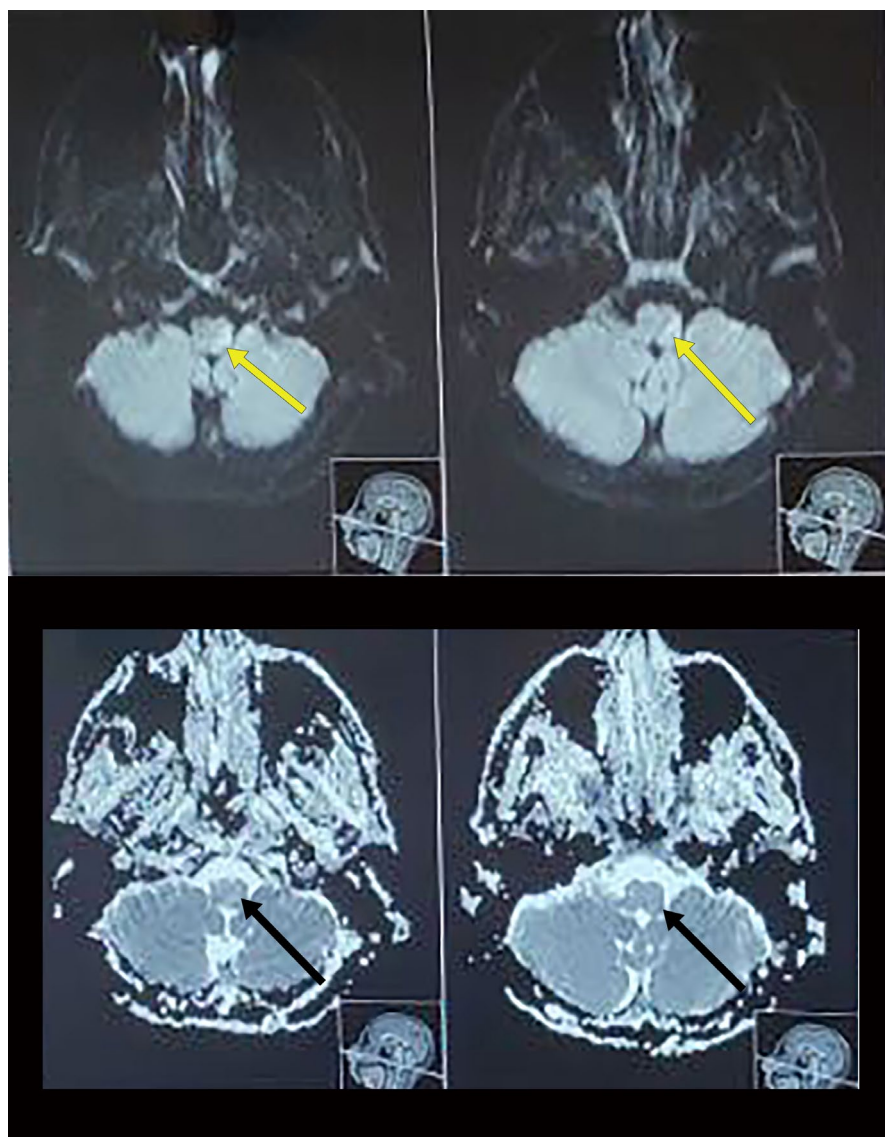


FIGURE 4 Left posterolateral area is bright on DWI (Diffusion Weighted Imaging) and dark on ADC (Apparent Diffusion Coefficient), suggesting the restricted diffusion

even in the absence of other mechanisms contributing to it. Accordingly, platelet-vessel wall interaction is enhanced at higher hematocrit levels irrespective of normal flow rates found in the arterial circulation. This mechanism could contribute to higher incidence of

arterial thromboses without requiring an elevation in platelet count.¹⁵ Marginalization of platelets, increased contact of platelets to vessel wall, and effect of high hematocrit on vessel walls satisfy all the three components of Virchow's triad. In line with this thought, strokes



FIGURE 5 Loss of flow void seen in the visualized part of the vertebral artery in FLAIR image on axial section. FLAIR, Fluid attenuated inversion recovery

manifesting in patients with polycythemia are due to propagation of a local thrombus.^{16,17}

Investigation for the cause starts with repeat and confirmation of the raised hemoglobin and measurement of an EPO level to indicate whether to pursue primary or secondary causes and then further investigations as appropriate.¹⁸ In our case, after evaluating for and ruling out all possible causes for polycythemia, we came to conclude renal disease might be the culprit for secondary polycythemia. However, CT scan of the abdomen did not show any renal pathology and we could not proceed further as patient denied for having renal biopsy despite indication. The management options for erythrocytosis include low dose aspirin and phlebotomy.¹⁸ However, there is no evidence suggesting routine use of phlebotomy for management secondary polycythemia.¹⁹ But as per our hospital guideline, we proceeded with phlebotomy for our patient.

Renal diseases are also closely associated with secondary polycythemia. Diseases including primitive neuroectodermal tumor (PNET), nephroblastoma, carcinoma, and neuroblastoma need to be ruled out.²⁰ In order to evaluate the presence of any renal etiology, urinalysis, renal function tests, renal ultrasound, and CT scan are required.²¹

Management of acute ischemic stroke in polycythemia is also unique; it is the only situation where the American Heart Association stroke guidelines suggest a possible value of haemodilution.²² Hence, we treated our patient

with hemodilution with venesection. We hope that this case report serves as a reminder of the association of LMS and secondary polycythemia.

At present, despite the limitations of the report, an unidentified renal disease was the most likely etiology for the present findings which is strengthened by the presence of hematuria and proteinuria on urinalysis; therefore, we would like to draw the attention to this unprecedented case in light of higher rates of adverse outcomes in undiagnosed cases.

4 | CONCLUSION

Although unusual, LMS may be an initial presentation of polycythemia. Ischemic stroke in a previously healthy individual who has polycythemia but minimal risk factors for stroke, requires further hematological workup in line of polycythemia. One might actually have grave consequences such as stroke if polycythemia is not diagnosed and addressed on time. All clinicians involved in the care of patients with stroke should be aware of the possible association of secondary polycythemia with ischemic stroke. Establishing etiology of polycythemia should be major goal in its workup till resources are available.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Surendra Rayamajhi, Department of Radiology, Tribhuvan University Teaching Hospital, for providing his inputs on the radiological images; the patient; and his family for their valuable support while preparing this manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

AR and BP involved in concept, collecting information, and manuscript writing. AR and BP participated in the literature review and edited the draft. SK and AS involved in patient care team and also independently reviewed the manuscript. AR, BP, SK, and AS: re-edited the draft and reshaped it into this manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

Need for ethical approval was waived. Consent from the patient deemed to be enough.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent will be available for review if asked by the editor-in-chief of this journal.

ORCID

Aadesh Rayamajhi  <https://orcid.org/0000-0003-1130-9006>

Biraj Pokhrel  <https://orcid.org/0000-0003-2059-5876>

Shambhu Khanal  <https://orcid.org/0000-0002-1247-7389>

REFERENCES

- Kim JS. Pure lateral medullary infarction: clinical-radiological correlation of 130 acute, consecutive patients. *Brain*. 2003;126(Pt 8):1864-1872. doi:10.1093/brain/awg169
- Sacco RL, Freddo L, Bello JA, Odel JG, Onesti ST, Mohr JP. Wallenberg's lateral medullary syndrome. Clinical-magnetic resonance imaging correlations. *Arch Neurol*. 1993;50(6):609-614. doi:10.1001/archneur.1993.00540060049016
- Caplan L. Posterior circulation ischemia: then, now, and tomorrow. The Thomas Willis Lecture-2000. *Stroke*. 2000;31(8):2011-2023. doi:10.1161/01.str.31.8.2011
- Lee MJ, Park YG, Kim SJ, Lee JJ, Bang OY, Kim JS. Characteristics of stroke mechanisms in patients with medullary infarction. *Eur J Neurol*. 2012;19(11):1433-1439. doi:10.1111/j.1468-1331.2012.03722.x
- Kratz SN, Butler KH. Vertebral artery dissection presenting as acute cerebrovascular accident. *J Emerg Med*. 2011;40(2):151-157. doi:10.1016/j.jemermed.2007.11.039
- Barabas AP, Offen DN, Meinhard EA. The arterial complications of polycythaemia vera. *Br J Surg*. 1973;60(3):183-187. doi:10.1002/bjs.1800600305
- Thakur KT, Westover MB. Cerebral infarction due to smoker's polycythemia. *BMJ Case Rep*. 2011;2011:bcr0820114714. doi:10.1136/bcr.08.2011.4714
- James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434(7037):1144-1148. doi:10.1038/nature03546
- Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356(5):459-468. doi:10.1056/NEJMoa065202
- Chen AT, Prchal JT. JAK2 kinase inhibitors and myeloproliferative disorders. *Curr Opin Hematol*. 2010;17(2):110-116. doi:10.1097/MOH.0b013e3283366b91
- Mahe K, Couturaud F, Kerspern H, Chauveau A, Ianotto JC. Evaluation of beta-2 microglobulin, erythropoietin and tobacco use in polycythemic cases. *Int J Hematol*. 2021;114(2):222-227. doi:10.1007/s12185-021-03164-0
- Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. *Leukemia*. 2009;23(5):834-844. doi:10.1038/leu.2009.54
- Chien S, Usami S, Taylor HM, Lundberg JL, Gregersen MI. Effects of hematocrit and plasma proteins on human blood rheology at low shear rates. *J Appl Physiol*. 1966;21(1):81-87. doi:10.1152/jappl.1966.21.1.81
- Wells RE Jr, Merrill EW. Influence of flow properties of blood upon viscosity-hematocrit relationships. *J Clin Invest*. 1962;41:1591-1598. doi:10.1172/JCI104617
- Turitto VT, Weiss HJ. Red blood cells: their dual role in thrombus formation. *Science*. 1980;207(4430):541-543. doi:10.1126/science.7352265
- Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol*. 2008;143(2):180-190. doi:10.1111/j.1365-2141.2008.07323.x
- Spivak JL. Polycythemia vera: myths, mechanisms, and management. *Blood*. 2002;100(13):4272-4290. doi:10.1182/blood-2001-12-0349
- McMullin MF. Investigation and management of erythrocytosis. *Curr Hematol Malig Rep*. 2016;11(5):342-347. doi:10.1007/s11899-016-0334-1
- Mao C, Olszewski AJ, Egan PC, Barth P, Reagan JL. Evaluating the incidence of cardiovascular and thrombotic events in secondary polycythemia. *Blood*. 2019;134(Supplement_1):3511. doi:10.1182/blood-2019-122943
- Jagtap SV, Kale PP, Huddedar A, Hulwan AB, Jagtap SS. Primary primitive neuroectodermal tumor of the kidney. *Indian J Pathol Microbiol*. 2018;61(2):252-254. doi:10.4103/IJPM.IJPM_277_16
- Hocking WG, Golde DW. Polycythemia: evaluation and management. *Blood Rev*. 1989;3(1):59-65. doi:10.1016/0268-960x(89)90026-x
- Adams HP Jr, delZoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-1711. doi:10.1161/STROKEAHA.107.181486

How to cite this article: Rayamajhi A, Pokhrel B, Khanal S, Shrestha A. Undiagnosed polycythemia, an uncommon cause of Wallenberg syndrome: A case report. *Clin Case Rep*. 2022;10:05752. doi:10.1002/ccr3.5752