Case Report

Polycythemia Vera with Extremely High Serum Erythropoietin

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Abstract: *Serum erythropoietin (EPO) is often used to differentiate primary polycythemia or polycythemia vera (PV) from secondary polycythemia. The current major criteria for diagnosis of PV are high hemoglobin (Hb) level, > 18.5 g/dL for males, > 16.5 g/dL for females and the presence of JAK2 gene mutation while panmyelosis of the bone marrow, and low EPO level are minor criteria. Herein, I reported a 64-year-old Thai man who fulfilled both major criteria of PV; Hb level of 20.1 g/dL and presence of JAK2 V617F mutation but with high serum EPO level (> 200 mIU/mL). Despite the lack of history of smoking, the bronchiectatic change and mild splenomegaly, normal oxygen saturation, and mild renal impairment. A bone marrow biopsy showed panmyelosis with predominant erythroid precursors, consistent with PV, complicated by secondary polycythemia. The treatments consisted of the occasional phlebotomy, hydroxyurea, beta-2 agonists and topical corticosteroid aerosol. During 4 years and a half of follow-up, his Hb levels varied between 12.0 to 21.5 g/dL and he never developed any thrombotic complications. This case report reminds clinicians that serum EPO can be high in polycythemia vera and high level of EPO does not exclude PV.*

Keywords : ● *Polycythemia vera* ● *Secondary polycythemia*

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Introduction

Polycythemia is the state of an increase of the red blood cell (RBC) mass that is represented by the high hemoglobin (Hb) concentration or high hematocrit in practice. Primary polycythemia or polycythemia vera (PV) is one of the myeloproliferative neoplasms (MPN) in which autonomously increased proliferation and differentiation of the erythroid precursors are related to gene mutations, mainly *JAK2 V617F*.[1] In secondary polycythemia, the increase RBC production is associated with increased erythropoietin (EPO) level secondary to the hypoxic state from various causes, such as the high oxygen affinity hemoglobinopathy and chronic obstructive pulmonary diseases. To distinguish PV from secondary polycythemias, WHO proposed the criteria; 2 major: the presence of the *JAK2* mutation and the high Hb concentration, > 18.5 g/dL for males and > 16.5 g/dL for females, and 3 minor: the panmyelosis in the bone marrow, the low serum EPO level and the endogenous erythroid colony formation *in vitro*. To make a diagnosis of PV, it needs 2 major criteria and one minor criterion or the presence of the high Hb level and 2 minor criteria.[2,3] While increased serum EPO in cases of erythrocytosis is not suggestive of PV[4], I herein reported the man who completely fulfilled the major diagnostic criteria of PV with panmyelosis but his serum EPO level was extremely high.

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Case report

A 64-year-old Thai man presented to a community hospital with generalized pruritus with excoriation for a few weeks and was incidentally found to have a high Hb

level. When he was referred to a hematologist, a physical examination revealed only sparse excoriation over the trunk, hypertension (161/102 mmHg), and tachycardia (112/min). He has never smoked a cigarette. His underlying diseases included hypertension, hyperlipidemia and gout. He had been taking amlodipine 10 mg/day, allopurinol 300 mg/day, simvastatin 10 mg/day, and aspirin 81 mg/day.

A complete blood count (CBC) revealed a Hb level of 20.1 g/dL, a hematocrit of 60.2%, a RBC of $9.07x10^6$/uL, a white blood cell count of 25,500/uL, a platelet count of 724,000/uL, a mean corpuscular volume of 66.3 fL, a mean corpuscular Hb of 22.2 pg, a red cell distribution width of 22.8%, and a serum ferritin of 20.3 ng/mL. Serum erythropoietin was measured three times and all were > 200 (normal 2.60-34.0) mIU/mL. A hemoglobin electrophoresis revealed A_2A pattern with 2.4% Hb A_2, 1.1% HbF, the alpha-thalassemia-1 genotype was wild type for SEA and Thai allele by polymerase chain reaction assay (PCR) was negative. A pulmonary function test showed an O_2 saturation of 97-99% at room air, a forced expiratory volume (FEV1) of 1.96 L (84% of normal), a forced expiratory flow 25-75% of 1.54 L (57% of normal), an FEV1/forced vital capacity (FVC) ratio of 0.74, suggesting early obstructive small airway disease. His blood urea nitrogen was 20 mg/dL, creatinine was 1.62 mg/dL, estimated glomerular filtration rate (eGFR) was 46 mL/min/1.73 M^2. His serum total and direct bilirubin were 1.3 and 0.2 mg/dL, aspartate aminotransferase was 30 U/L, alanine aminotransferase was 48 U/L, alkaline phosphatase was 164 U/L, albumin was 3.9 g/dL, globulin was 3.1 g/dL. His fasting blood glucose was 89 mg/dL, uric acid was 11.4 mg/dL, cholesterol was 163 mg/dL, and triglyceride was 352 mg/dL. The bone marrow aspiration and biopsy showed marked hypercellularity in all series, with myeloid: erythroid ratio of 2:1, increased megakaryocytes, < 5% blasts, compatible with MPN suggesting polycythemia vera (PV). The bone marrow karyotype was normal male, 46, XY. A PCR test for *JAK2 V617F* mutation was positive.

A chest radiograph was unremarkable, but a computerized tomography of the chest showed a bronchiectatic change in the posterior segment of the right upper lobe, mild splenomegaly, and normal kidneys.

Taken together, the patient was diagnosed as PV co-existing with secondary polycythemia and treated with occasional phlebotomy, hydroxyurea 500-1,000 mg/day, theophylline, and aerosolized beta-2 agonist as well as corticosteroid.

During four and a half years of follow-up, CBCs were followed every two or three months and his Hb have fluctuated between 12.0 to 21.1 g/dL. However, he had neither arterial or venous thrombotic events nor episodes of dyspnea from chronic obstructive pulmonary disease.

Discussion

Our case was definite diagnosis of PV based on the two major WHO criteria: the elevated Hb level and the presence of *JAK2 V617F* mutation.[2] The *JAK2 V617F* mutation is highly sensitive and highly specific for PV[5,6] as 97% of PV patients are *JAK2 V617F* positive.[7]

High serum EPO level is unusual in PV. Mossuz et al, found that the EPO level in cases of PV ranged between 0.6 to 13.7 IU/L (normal 3.3-13.7) compared with 3.3 to 33.9 IU/L of secondary polycythemia patients.[8] Only 87% of PV patients had the EPO level below the normal range, and the low EPO level had 97% specificity and 97.8% positive predictive value for diagnosing PV. The significant overlap of serum EPO in PV versus control and versus secondary polycythemia can be noticed.[8] High serum EPO level has been reported in PV patients who had anemia from gastrointestinal bleeding[4] or were complicated by Budd-Chiari syndrome.[9,10] However, the very high serum EPO level seen in our case could be explained by secondary polycythemia on top of PV. Besides anemia, a common stimulation of EPO production is hypoxia. Our case had bronchiectasis with slightly abnormal lung function tests, but with normal O_2 saturation. Although impaired renal function as in our case, a borderline high serum creatinine (1.62 mg/

dL) and a low eGFR (< 60 mL/min/1.73 M^2 for men) is more likely associated with decreased EPO production[11], polycythemia and increased EPO have been reported in patients with hydronephrosis and chronic kidney diseases.[12-14] A combination of the polycythemia (Hb 22.0 g/dL), elevated EPO (27.4 U/L) is recognized in a case with impaired renal function (creatinine 2.27 mg/L) hydronephrosis of left kidney and non-functioning right kidney, with Hb and EPO normalized after right nephrectomy and the left kidney drainage.[12] In that case, elevated EPO was explained by a pressure on the renal tissue that slowly developed in hydronephrosis, leading to the local ischemia that stimulates EPO production. Similarly, elevated EPO and polycythemia has been reported with non-obstructive chronic kidney diseases.[13,14] Our case may have local renal ischemia associated with kidney impairment and hypertension. This case report serves to remind physicians that high EPO level cannot be used to exclude PV. The low level of serum EPO alone cannot be reliably used as an initial step to evaluate erythrocytosis despite its simplicity and relatively low cost. Some authors considered EPO to be a redundant test for diagnosis of PV[15] and it does not discriminate primary and secondary polycythemia.[16] The panmyelosis with predominant erythroid precursors in the bone marrow that was seen in our case can be used to distinguish PV from secondary polycythemia and other MPNs.[17] However, the marrow findings alone could not differentiate PV from secondary polycythemia or combination of the two conditions.

Conclusion

Serum EPO level may be elevated in PV, and therefore could not be used to exclude a diagnosis of PV.

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References

1. *Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management. Am J Hematol 2015;90:162-73.*
2. *Tefferi A, Thiele J, Orazi A, Kvasnicka HM, Barbui T, Hanson CA, et al. Proposals and rationale for revision of the WHO diagnostic criteria for PV, essential thrombocythemia and primary myelofibrosis: Recommendation from ad hoc international expert panel. Blood 2007;110:1092-7.*
3. *Tefferi A, Thiele J, Vardiman JW. The 2008 WHO classification system for myeloproliferative neoplasms: order out of chaos. Cancer 2009;115:3842-7.*
4. *Messinezy M, Westwood NB, El-Hemaidi I, Marsden JT, Sherwood RS, Pearson TC. Serum erythropoietin values in erythrocytoses and in primary thrombocythaemia. Br J Haematol 2002;117:47-53.*
5. *Tefferi A, Sirhan S, Lasho TL, Schwager SM, Li CY, Dingli D, et al. Concomitant neutrophil JAK2 mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol 2005;131:166-71.*
6. *James C, Delhommeau F, Marzac C, Teyssandier I, Couédic JP, Giraudier S, et al. Detection of JAK2 V 617F as a first intention diagnostic test for erythrocytosis. Leukemia 2006;20:350-3.*
7. *Michiels JJ, Bernema Z, Van Bockstaele D, De Raeve H, Schroyens W. Current diagnostic criteria for the chronic myeloproliferative disorders: essential thrombocythemia, polycythemia vera and chronic idiopathic myelofibrosis. Pathol Biol (Paris) 2007;55:92-104.*
8. *Mossuz P, Girodon F, Donnard M, Latger-Cannard V, Dobo I, Boiret N, et al. Diagnostic value of serum erythropoietin level in patients with absolute erythrocytosis. Haematologica 2004;89: 1194-8.*
9. *Jones C, Levy Y, Tong AW. Elevated serum erythropoietin in a patient with PV presenting with Budd-Chiari syndrome. BMJ Case Rep 2014 Dec 1; 2014. pii: bcr2014205663.*
10. *Thurmes PJ, Steensma DP. Elevated serum erythropoietin levels in patients with Budd-Chiari syndrome secondary to PV: clinical implications for the role of JAK2 mutation analysis. Eur J Haematol 2006;77:57-60.*
11. *Hsu CY, Bates DW, Kuperman GJ, Curhan GC. Relationship between hematocrit and renal function in men and women. Kidney Int 2001;59:725-31.*
12. *Stark S, Winkelmann B, Kluthe C, Roigas J, Querfeld U, Muller D. Polycythemia and increased erythropoietin in a patient with chronic kidney disease. Nat Clin Pract Nephrol 2007;3:222-6.*
13. *Sung CC, Lin SH. Nonobstructive hydronephrosis with secondary polycythemia. N Engl J Med 2011;365:e1.*

14. *Nistico A, Iliescu EA, Fitzpatrick M, White CA. Polycythemia due to obstructive sleep apnea in a patient on hemodialysis. Hemodial Int 2010;14:333-6.*
15. *Spivak JL, Siver RT. The revised WHO diagnostic criteria for PV, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood 2008;112:231-9.*
16. *Casadevall N. Determination of serum erythropoietin. Its value in the differential diagnosis of polycythemias. Nouv Rev Fr Hematol 1994;36:173-6.*
17. *Thiele J, Kvasnicka HM, Orazi A. Bone marrow histopathology in myeloproliferative disorders—current diagnostic approach. Semin Hematol 2005;42:184-95.*

รายงานผู้ป่วย

เลือดข้นปฐมภูมิ ที่มีฮอร์โมนอีริทโธรพอยอิตินในเลือดสูงมาก

สมชาย อินทรศิริพงษ์

หน่วยโลหิตวิทยา กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา

บทคัดย่อ *การตรวจระดับฮอร์โมนอีริทโธรพอยอิติน (EPO) มักใช้ในการวินิจฉัยแยกโรคเลือดข้นปฐมภูมิออกจากโรคเลือดข้นทุติยภูมิ ในปัจจุบันเกณฑ์หลักของการวินิจฉัยโรคเลือดข้นปฐมภูมิ หรือโพลีซัยธีเมียวีรา (PV) ประกอบด้วยระดับฮีโมโกลบินสูงผิดปกติ (> 18.5 กรัมต่อเดซิลิตรในเพศชาย และ > 16.5 กรัมต่อเดซิลิตรในเพศหญิง) ร่วมกับการตรวจพบการกลายพันธุ์ของแจ๊กทูยีน (JAK2) ส่วนการตรวจพบความผิดปกติในไขกระดูก และระดับฮอร์โมน EPO ในเลือดต่ำนั้นถือเป็นเกณฑ์รอง ในรายงานนี้ ผู้ป่วยชายไทย อายุ 64 ปี ที่มีผลการตรวจเลือดเข้าได้กับเกณฑ์หลักทั้งสองข้อของโรคเลือดข้นปฐมภูมิ ได้แก่ระดับฮีโมโกลบินสูงผิดปกติ 20.1 กรัมต่อเดซิลิตร และพบการกลายพันธุ์ของแจ๊กทูยีนแบบ V617F แต่พบระดับของ EPO สูงกว่า 200 มิลลิยูนิตสากลต่อมิลลิลิตร ทั้งๆ ที่ไม่มีประวัติสูบบุหรี่มาก่อน แต่เมื่อตรวจพบภาวะหลอดลมพอง มีม้ามโตเล็กน้อย ความอิ่มตัวของออกซิเจนในเลือดปกติ ตรวจชิ้นเนื้อไขกระดูกพบการสร้างเม็ดเลือดเพิ่มขึ้นโดยเฉพาะสายเม็ดเลือดแดง จึงให้การวินิจฉัยว่าเป็นโรคเลือดข้นปฐมภูมิ ที่อาจจะถูกแทรกซ้อนด้วยเลือดข้นทุติยภูมิ รักษาด้วยการเจาะเลือดออกเป็นครั้งคราว ให้ยาไฮดรอกซียูเรีย ยาพ่นขยายหลอดลมและสเตียรอยด์ ในระหว่างติดตามการรักษาเป็นเวลา 4 ปีครึ่ง ระดับฮีโมโกลบินอยู่ระหว่าง 12.0 และ 21.5 กรัมต่อเดซิลิตร ผู้ป่วยไม่เคยมีเกิดภาวะหลอดเลือดอุดตันแต่อย่างใด โดยสรุป ผู้ป่วยเลือดข้นมีระดับของ EPO สูงมาก ยังอาจเป็นโรคเลือดข้นปฐมภูมิ (PV) ได้*

Keywords : ● *Polycythemia vera* ● *Secondary polycythemia*

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