Polycythemia in the Young

Insiripong S
Yingsitsiri W
Boondumrongsagul J
Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Mueang Nakhon Ratchasima, Nakhon Ratchasima, 30000

(E-mail : chaikorat@gmail.com)

บทคัดย่อ : ภาวะเม็ดเลือดแดงมากในผู้ป่วยอายุน้อย

สมชาย อินทรศิริพงษ์ พ.บ.
วัชรินทร์ ยิ่งสิทธิ์สิริ พ.บ.
จุรี บุญดำรงสกุล พ.บ.
หน่วยโลหิตวิทยา กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา
อำเภอเมือง จังหวัดนครราชสีมา 30000

ภาวะเม็ดเลือดแดงมาก เป็นภาวะที่มีมวลเม็ดเลือดแดงมากเกินในทางปฏิบัติใช้ความเข้มข้นฮีโมโกลบิน มากกว่า 18.5 กรัม% ในเพศชาย และมากกว่า 16.5 กรัม% ในเพศหญิงเป็นเกณฑ์ รายงานนี้เป็นการศึกษาย้อนหลังผู้ป่วยภาวะเม็ดเลือดแดงมาก ที่อายุน้อยกว่า 40 ปี กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา ในปี 2554-2558 ซึ่งมี 10 ราย เป็นชาย 9 ราย หญิง 1 ราย อายุ 24 ถึง 31 ปี เฉลี่ย 26.8±2.7 ปี มาพบแพทย์ด้วยอาการที่แตกต่างกัน ความเข้มข้นฮีโมโกลบินระหว่าง 17.3-21.3 กรัม% เฉลี่ย 18.3±1.3 กรัม% ไม่มีใครมีโรคหัวใจ หรือออกซิเจนในเลือดต่ำ ม้ามไม่โต ผู้ป่วย 6 ใน 10 ราย สูบบุหรี่ประจำ มีผู้ป่วยเพียง 2 รายเท่านั้นที่มี JAK2 V617F mutation เป็นชายและหญิงอย่างละ 1 ราย และเฉพาะสองรายนี้เท่านั้นที่ต่างก็มี Panmyelosis ในขณะที่รายอื่นๆ ปริมาณเซลล์ในไขกระดูกปกติ ระดับ Erythropoietin (EPO) ในกลุ่มที่ไม่มี JAK2 mutation เฉลี่ย 5.2±3.6 mIU/มล, พิสัย 1.0 ถึง 10.0 mIU/มล ไม่แตกต่างจากกลุ่มที่มี JAK2 V617F ที่ EPO มี 2.2±0.9 mIU/มล ผู้ป่วยทุกรายได้รับการเจาะเลือดออกบ่อยๆ เพื่อให้ค่า Hct ใกล้เคียง 45% ร่วมกับการรักษาโรคเดิม ติดตามการรักษา 2 เดือนต่อมา พบว่ากลุ่มที่ไม่มี JAK2 V617F ความเข้มข้นฮีโมโกลบินกลับเป็นปกติทุกราย เฉลี่ย 14.5 กรัม% ส่วนในผู้ป่วยที่มี JAK2 V617F mutation พบค่า ฮีโมโกลบิน 17.9 กรัม% ในเพศชาย และ 15.5 กรัม% ในเพศหญิง เนื่องจากไม่มีการตรวจมวลของเม็ดเลือดแดง จึงสรุปได้ไม่ชัดเจนว่าผู้ป่วยกลุ่มที่ไม่มี JAK2 V617F mutation ทั้ง 8 รายนั้น เป็นภาวะเม็ดเลือดแดงมากแบบปฐมภูมิหรือไม่

คำสำคัญ : ภาวะเม็ดเลือดแดงมาก ผู้ป่วยอายุน้อย ภาวะเม็ดเลือดแดงมากแบบปฐมภูมิ

Abstract

Polycythemia is the state of an increase of the red blood cell (RBC) mass and usually represented by the hemoglobin (Hb) concentration in practice that is more than 18.5 g% for males and 16.5 g% for females. This report was a retrospective study on the polycythemia patients of less than 40 years of age in the department of medicine, Maharat Nakhon Ratchasima Hospital between 2011 and 2015. Ten patients, nine males and one female were recruited. Ages ranged from 24 to 31, and mean age was 26.8±2.7 years. The manifestation of each patient was totally different. Their Hb ranged from 17.3 to 21.3 g%, mean 18.3±1.3 g%. No one had heart disease, hypoxemia and splenomegaly. Six patients were regular smokers. Only 2 patients, one man and one woman, had not only JAK2 V617F mutation but also

panmyelosis. The others had normocellularity. The mean EPO in JAK2 V617F-negative group was 5.2±3.6 mIU/ml, ranging from 1.0 to 10.0 mIU/ml and was not different from 2.2±0.9 mIU/ml of the JAK2 V617F-positive group. Phlebotomy was frequently performed for keeping Hct around 45% while the underlying diseases were also treated. At two-month follow-up, the Hb level among the JAK2 V617F-negative group became normal, mean 14.5 g%. For the JAK2 V617F-positive group, Hb level was 17.9 g% in male and 15.5 g% in female patient. Because the RBC mass was not studied, the 8 JAK2 V617F-negative patients could not be definitely diagnosed whether they had primary polycythemia.

Keywords : Polycythemia, The Young, Polycythemia Vera

Introduction

Polycythemia is the state of an increase of the RBC mass that is officially represented by the high hemoglobin (Hb) concentration or high hematocrit (Hct) in clinical practice. It can be classified as polycythemia vera (PV), the autonomous production of the erythroid precursors, and the secondary polycythemia which is the increased RBC production responding to the increased EPO level mainly due to the hypoxia from any cause. To distinguish PV from the secondary polycythemias, WHO proposed the criteria; 2 major : the presence of the JAK2 mutation and the high Hb, >18.5 g% for males and >16.5 g% for females, and 3 minor : the panmyelosis in the bone marrow, low serum EPO and the endogenous erythroid colony formation in vitro. To make the diagnosis of PV, it needs 2 major criteria or the presence of high Hb level and 2 minor criteria[1].

For PV, it is the disease predominantly of the 6th decade and more prominently in males[2] but for the secondary polycythemia, it can occur in the any group depending on the etiologies, congenital or acquired. If PV is found in the individuals with less than 40 years of age, it is considered unusual and called PV in the young[3-4]. So far, it has been occasionally reported[5]. Herein, we report case series of polycythemia in the young Thai patients and some of them fulfilled the criteria of PV.

Patients and Methods

This retrospective study was aimed to describe the patients who were referred to the hematology unit because of having polycythemia during routine investigation at the Department of Medicine, Maharat Nakhon Ratchasima Hospital between 2011 and 2015. Their chief complaints were individually different but the patients who had hypoxia, cyanotic heart disease, diabetes insipidus, high O_2 affinity hemoglobinopathy, chronic kidney or liver disease, or diuretic usage, would be excluded. All were investigated for JAK2 V617F mutation using the PCR method. The demographic and clinical data were expressed as percent, mean±standard deviation and analyzed with student-T test, p value <0.05 was considered statistically significant.

Results

Within the 5-year period, 10 cases, 9 males and 1 female were recruited. The chief complaints or underlying diseases were exclusively different in each patient including the cerebral venous sinus thrombosis, CVA, chronic headache, head injury, convulsion with subarachnoid hemorrhage, acute myocardial infarction with nephrotic syndrome, sudden left blindness, sudden dyspnea, abdominal pain and the last patient who was the only one lady, searching for the routine health check-up. Smoking was found in 6 of 10 (60%), frequent drinking in 7 of 10 (70%).

Their ages ranged from 24 to 31, mean 26.8±2.7 years. The initial hematologic parameters were shown in the table.

Table showed the initial hematologic parameters of 10 patients with polycythemia

	range	mean±SD
Age (years)	24-31	26.8±2.7
Hb (g%)	17.3-21.3	18.8±1.3
WBC (/mm^3)	5,700-25,400	12,630±7,162.6
Platelet (/mm^3)	156,000-701,000	267,800±160,898
Serum EPO (mIU/ml)	1.0-10.0	4.5±3.3
O_2 saturation (%)	95-100	98.9±1.7
MCV (fl)	70.7-109.6	90.0±10.2
Ferritin (ng/ml)	10.6-718.6	223.4±291.3

Note : Hb-hemoglobin, WBC-white blood cell, EPO-erythropoietin, O_2-oxygen, MCV-mean corpuscular volume

The JAK2 V617F mutation was found in 2 patients (20%) who had neither smoking nor drinking. And one of them was the only one female of our series.

The mean serum EPO was 4.5±3.3 mIU/ml (normal 3.7-29.5). If the patients were allocated into the JAK2 V617F-negative and positive, the EPO of the former was 5.2±3.6, range 1.0-10.0, compared to 2.2±0.9 mIU/ml of the latter, p 0.15.

Hb typing using the high performance liquid chromatography method, the Hb E trait was found in one man who had no JAK2 V617F mutation while the others had normal Hb constituents.

The bone marrow biopsy were allowed in 7 patients, only 2 patients who had JAK2 V617F mutation had panmyelosis while the rest without JAK2 V617F had normocellularity and normal trilineage.

During admission, phlebotomy was performed in every case every one to three days hopefully to bring the Hct to be around 45% before discharge. The main active diseases were appropriately treated in each patient. At the 2-month follow-up, Hb levels in all JAK2 V617F-negative patients became normal, ranging from 12.9 to 15.6, mean 14.5 g%. Among the patients with JAK2 V617F mutation, the Hb level was 17.9 g% in male and 15.5 g% in female.

Discussion

Only 2 from 10 patients had JAK2 V617F mutation along with the panmyelosis and the low EPO, so only these 2 patients completely fulfilled the criteria and could be definitely diagnosed as PV in the young while the rest had only polycythemia, no panmyelosis, no JAK2 V617F, normal or low EPO, the diagnosis of PV could not be concluded[6] even though JAK2 was actually found only in 3 from 11 PV patients with less than 20 years of age[7]. When the criteria for diagnosis of PV in JAK2-negative are considered, only 3 from our 8 patients had Hct>60% but no one had neutrophil >10,000/mm^3 or platelet >450,000/mm^3 or splenomegaly[8].

At the 2-month follow-up, the Hb level among all JAK2 V617F-negative men became normal. It seemed they had transient polycyhemia during some active diseases but the diagnosis of spurious polycythemia could not be made due to lack of the demonstration of the normal RBC mass[9]. Some authors claimed that high Hb level was not a good delegate of the increased RBC mass and could not be used to separate PV and apparent polycythemia because of its low sensitivity and low specificity[10].

Some authors showed that the minority of JAK2 V617F-negative PV patients may have other JAK2 mutations, eg., exon 12[11]. And all patients with this mutation always have only erythrocytosis, no leukocytosis, no thrombocytosis[12]. Moreover, they are always younger than the JAK2 V617F-positive group[13] but test for JAK2 exon 2 mutation is not available in our hospital.

Although the median survival of PV in the young is more than 23 years, the life expectancy is markedly lower than in the general population because PV may evolve into acute leukemia or myelofibrosis[4]. Moreover PV is more commonly found in the first degree relatives of the patients[14] probably due to the abnormal genes transmission[15], therefore when PV in the young is faced, the birth control should be strongly emphasized. And any study for making the definite diagnosis of PV should be attempted. And for treating PV in the young, hydroxyurea should be avoided because in the long term use, it may be associated with the occurrence of acute leukemia[16].

The EPO among JAK2 V617F-positive is not different from that of JAK2 V617F-negative groups. It is expected to increase in hypoxic polycythemia but it is metabolized by its target cells and its production is suppressed by erythrocytosis or an increased blood viscosity unless hypoxia is severe. Therefore many patients with hypoxic erythrocytosis may have normal EPO level[13].

Fujita et al found the microcytosis (MCV<79 fl) in 2 from 10 PV patients but no microcytosis in all 9 patients with secondary polycythemia at the initial presentation[2]. Similarly, our all 8 patients without JAK2 V617F had MCV>80 fl whereas only 1 of 2 definite PV patients had MCV<80 fl.

Conclusion

Ten cases of polycythemia in Thai young patients were studied. Their mean age was 26.8±2.7 years and the mean Hb was 18.8±1.3 g% and serum EPO was 4.5±3.3 mIU/ml. Only two of them had JAK2 V617F mutation and all 8 cases without JAK2 V617F had normal Hb concentration two months later.

References

1. *Tefferi A, Thiele J, Vardiman JW. The 2008 World Health Organization classification system for myeloproliferative neoplasms: order out of chaos. Cancer 2009; 115: 3842-7.*
2. *Fujita H, Kurosawa S, Nishimura S, Tomiyama J, Hamaki T, Ohwada A. Significance of microcytosis in the clinical course of erythrocytosis. Internet J Geriatr Gerontol 2009; 6: 1-6.*
3. *Najean Y, Mugnier P, Dresch C, Rain JD. Polycythaemia vera in young people: an analysis of 58 cases diagnosed before 40 years. Br J Haematol 1987; 67: 285-91.*
4. *Passamonti F, Malabarba L, Orlandi E, Baratè C, Canevari A, Brusamolino E, et al. Polycythemia vera in young patients: a study on the long-term risk of thrombosis, myelofibrosis and leukemia. Haematologica 2003; 88: 13-8.*
5. *Cario H, McMullin MF, Pahl HL. Clinical and hematological presentation of children and adolescents with polycythemia vera. Ann Hematol 2009; 88: 713-9.*
6. *Tefferi A, Thiele J, Orazi A, Kvasnicka HM, Barbui T, Hanson CA, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007; 110: 1092-7.*
7. *Giona F, Teofili L, Moleti ML, Martini M, Palumbo G, Amendola A, et al. Thrombocythemia and polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome. Blood 2012; 119: 2219-27.*
8. *McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008; 30: 447–59.*
9. *Watts EJ, Lewis SM. Spurious polycythemia-a study of 35 patients. Scand J Haematol 1983; 31: 241-7.*
10. *Johansson PL, Safai-Kutti S, Kutti J. An elevated venous haemoglobin concentration cannot be used as a surrogate marker for absolute erythrocytosis: a study of patients with polycythaemia vera and apparent polycythaemia. Br J Haematol 2005; 129: 701-5.*
11. *Williams DM, Kim AH, Rogers O, Spivak JL, Moliterno AR. Phenotypic variations and new mutations in JAK2 V617F-negative polycythemia vera, erythrocytosis, and idiopathic myelofibrosis. Exp Hematol 2007; 35: 1641–6.*
12. *Pietra D, Li S, Brisci A, Passamonti F, Rumi E, Theocharides A, et al. Somatic mutations of JAK2 exon 12 in patients with JAK2 (V617F)-negative myeloproliferative disorders. Blood 2008; 111: 1686–9.*
13. *Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood 2008; 112: 231-9.*
14. *Landgren O, Goldin LR, Kristinsson SY, Helgadottir EA, Samuelsson J, Björkholm M. Increased risks of polycythemia vera, essential thrombocythemia, and myelofibrosis among 24,577 first-degree relatives of 11,039 patients with myeloproliferative neoplasms in Sweden. Blood 2008; 112: 2199-204.*
15. *Ranjan A, Penninga E, Jelsig AM, Hasselbalch HC, Bjerrum OW. Inheritance of the chronic myeloproliferative neoplasms. A systematic review. Clin Genet 2013; 83: 99-107.*
16. *Weinfeld A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. Eur J Haematol 1994; 52: 134-9.*