The Fluctuation of Red Blood Cell Indices in Beta Thalassemia Trait: A Case Report

Somchai Insiripong, M.D.*,
Watcharin Yingsitsiri, M.D.*,
Juree Boondumrongsagul, M.D.*

Abstract: One common characteristic of thalassemiatraitis microcytosis or the mean corpuscular volume (MCV) of red blood cells (RBC) is less than 80 fL. However when the CBCs have been repeatedly studied, the RBC indices including MCV are found fluctuated as in our case study. She is 45-year old Thai who was accidentally found to have mild microcytic anemia with profound thrombocytopenia. Her hemoglobin electrophoresis shows the higherpercentages of Hb A_2 (4.9%) and of Hb F (8.0%). She is later confirmed using the genotype study to harbor the beta thalassemia, IVS1#5, heterozygosity without alpha-thalassemia-1 or alpha-thalassemia-2 genes. She has no underlying disease and no physical abnormality on the examination. After CBCs have been repeatedly tested for 18 times for the thrombocytopenia surveillance, there are fluctuations of many blood parameters, viz., 10 of 18 Hb concentrations less than 12 g% (55.6%), 8 with MCV less than 80 fL (44.4%), 15 with MCH less than 27 pg (83.3%) and all of them with RDW more than 15% (100%). In clinical practice, the MCV less than 80 fL or MCH less than 27 pg from one cross-sectional test is usually used as one of the screenings for thalassemia trait and MCV will have more chance than MCH to leave some cases with thalassemia traits unrecognized. Or in case of morphologic approach of anemia, MCV of beta thalassemia trait may alternatively mislead to wrong category between microcytic and normocytic groups.

Key words: Fluctuation of Red Blood Cell Indices, Beta Thalassemia Trait

* Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

บทคัดย่อ: **ความผันผวนของค่าดัชนีเม็ดเลือดแดงในผู้ป่วยเบต้าธาลัสซีเมียแฝง: รายงานผู้ป่วย 1 ราย**

สมชาย อินทรศิริพงษ์, พ.บ.*, วัชรินทร์ ยิ่งสิทธิ์สิริ, พ.บ.*, จุรี บุญดำรงสกุล, พ.บ.*

*กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา จ.นครราชสีมา 30000

เวชสารโรงพยาบาลมหาราชนครราชสีมา 2560; 39: 39-43.

คุณสมบัติที่พบบ่อยประการหนึ่งของผู้ที่เป็นธาลัสซีเมียแฝง คือ การที่เม็ดเลือดแดงมีขนาดเล็ก หรือการที่ค่าเฉลี่ยปริมาตรเม็ดเลือดแดง (MCV) น้อยกว่า 80 fL อย่างไรก็ตามเมื่อมีการตรวจเลือด CBC ซ้ำหลาย ๆ ครั้ง กลับพบว่าค่าดัชนีเม็ดเลือดแดงรวมทั้งค่า MCV มีความผันผวนดังในรายงานนี้ซึ่งเป็นผู้ป่วยหญิงไทย อายุ 45 ปี ตรวจพบโดยบังเอิญว่ามีภาวะโลหิตจางแบบ microcytic เล็กน้อยร่วมกับภาวะเกล็ดเลือดต่ำชัดเจนเมื่อตรวจ hemoglobin electrophoresis ก็พบว่า มี Hb A_2 สูง (4.9%) และ มี Hb F สูงเช่นกัน (8.0%) และเมื่อตรวจยีนส์ก็พบว่าผู้ป่วยเป็นเบต้าธาลัสซีเมียแฝงชนิด IVS1#5 ไม่มียีนส์แอลฟ่าธาลัสซีเมีย-1 หรือ แอลฟ่าธาลัสซีเมีย-2 เลย ผู้ป่วยไม่เคยมีโรคใด ๆ มาก่อน ตรวจร่างกายก็ไม่พบสิ่งผิดปกติเช่นกันเมื่อทำการตรวจ CBC เพื่อติดตามภาวะเกล็ดเลือดต่ำ 18 ครั้ง ก็พบว่าค่าต่าง ๆ ของเลือดมีความผันผวนตลอดเวลา ได้แก่ค่าความเข้มข้นเลือด (Hb) ต่ำกว่า 12 g% ถึง 10 ครั้ง (55.6%), ค่า MCV น้อยกว่า 80 fL พบ 8 ครั้ง (44.4%), ค่า MCH น้อยกว่า 27 pg พบ 15 ครั้ง (83.3%) และค่า RDW มากกว่าร้อยละ 15 ทุกครั้งในทางเวชปฏิบัติการใช้ค่า MCV น้อยกว่า 80 fL หรือค่า MCH น้อยกว่า 27 pg จากการตรวจเลือดเพียงครั้งเดียว เพื่อการคัดกรองเบต้าธาลัสซีเมียแฝงนั้น ค่า MCV จะมีโอกาสปล่อยผู้ป่วยให้หลุดรอดได้มากกว่าค่า MCH หรือ ในแนวทางการวินิจฉัยภาวะโลหิตจางที่อาศัยค่า MCV นั้น ค่า MCV ในเบต้าธาลัสซีเมียแฝง อาจทำให้การจำแนกหมวดหมู่สลับกลุ่มกันได้ระหว่างกลุ่ม microcytic กับ normocytic

คำสำคัญ: ความผันผวนของค่าดัชนีเม็ดเลือดแดง, เบต้าธาลัสซีเมียแฝง

Introduction

In morphologic approach of anemia, the mean corpuscular volume (MCV) of the red blood cells (RBC) generated by the automated hematology analyzer is used to classify anemia into three groups, micocytic, normcytic and macocytic. If the MCV is less than 80 fL, it will be allocated into the microcytic group. The three most common causes of microcytic anemia in clinical practice are the iron deficiency anemia, alpha or beta thalassemia trait and less often the anemia of chronic diseases[1]. For beta thalassemia traits, the microcytosis can be found in only 75 % of cases whereas the low MCH and low MCHC are found in 86 % and 10 %, respectively. Besides abnormal RBC indices, beta thalassemia traits also have the high percentage of Hb A_2, range 3.5-8%, mean 5.37%, and Hb F < 1% in 36% of cases and ranging 1-14% in the remainder. Their Hb concentration ranges between 8 to 15.5 g% and only 46% of them are anemic[2].

As other thalassemias, beta thalassemia trait is a genetically transmitted, autosomal recessive, disease. Therefore the clinical phenotypes including the Hb concentration and the RBC indices are directly under the control of genes. However, the expressivity of each phenotype may individually vary, for instance, the MCV ranging from 46.8 to 84.5 fL[3] or mean of

MCV 66.6 fL (range 55-85)[4]. In this case report, we demonstrate the hematological parameters of one beta-thalassemia trait from the long term study.

Case Report

A 45-year-old Thai woman was referred to a hematologist because of mild anemia with profound thrombocytopenia seen during the routine check-up. She had no complaint/an underlying disease/drug use/physical abnormality on the examination. Many blood tests were extensively investigated and CBCs were repeatedly examined every 3 to 4 months for many years.

Direct and indirect Coombs' tests were both negative. Hb electrophoresis: Hb A_2 A, Hb A_2 4.9 %, Hb F 8.0 %, no alpha-thalassemia-1 (SEA, Thai deletion types), no alpha-thalassemia-2 (a-T2T type), positive PCR for beta thalassemia (IVS1#5), ESR 22 mm./hr, serum iron 145 ug/dL, TIBC 249 ug/dL, ferritin 118.5-855.0 ng/mL.

HBsAg, anti-HCV, anti-HIV, VDRL, anti-dsDNA, ANA were all negative, FBS 97 mg%, cholesterol 248 mg%, normal liver, thyroid and kidney function tests.

The bone marrow biopsy: slightly hypercellular marrow (cell 60-70%), M: E around 1: 3, increased erythroid series, reduced megakaryocytes and the presence of only young megakaryocytes, no mali-gnancy seen.

CBCs every three to four months were shown in the table

Hb	MCV	MCH	RDW	WBC	N	L	plt
9.7	77.3	25.3	19.7	5,000	50.0	42.0	29,000
11.6	77.2	24.7	19.0	4,400	53.0	46.0	51,000
12.4	76.0	25.1	21.1	5,400	67.0	31.0	34,000
10.0	79.1	25.8	20.6	9,800	63.8	32.8	22,000
10.5	80.1	26.0	20.2	8,300	67.0	30.0	22,000
12.0	83.3	27.1	20.1	4,800	53.8	37.8	30,000
13.1	80.2	26.9	18.5	6,100	54.0	37.0	54,000
13.0	81.2	26.4	21.5	6,800	66.0	27.9	47,000
13.8	77.8	24.8	18.7	5,300	61.0	32.0	84,000
13.3	81.7	26.2	21.9	6,700	47.4	45.1	28,000
11.9	78.1	25.6	22.3	3,800	67.6	28.7	17,000
11.7	79.9	25.5	20.0	3,700	83.0	13.0	20,000
11.2	79.8	26.7	20.6	3,700	63.0	34.0	27,000
13.4	82.9	27.4	24.0	4,200	55.5	25.4	25,000
11.3	81.6	25.9	18.9	6,300	68.0	23.0	33,000
12.0	83.2	27.6	23.2	6,900	48.0	52.0	42,000
11.7	80.2	24.5	20.5	4,600	52.0	44.0	29,000
11.3	81.4	26.2	20.7	4,000	53.1	37.4	60,000

Most peripheral blood smears showed positive basophilic stippling, few target cells, few anisocytosis, few hypochromia. From 18 samples, there were 10 samples showing Hb level less than 12 g% (55.6%), 8 with MCV less than 80 fL (44.4%), 15 with MCH less than 27 pg (83.3%) and all 18 samples with RDW more than 15% (100%). Thrombocytopenia (platelet <100,000/mm^3) was persistent but slightly fluctuated through the study period.

She was diagnosed as beta thalassemia trait (IVS1#5) and amegakaryocytic thrombocytopenia. She never had petechia or other bleeding disorder and her menstruation was unremarkable. No specific treatment was offered to her however she did not progress to overt aplastic anemia, myelodysplastic syndrome or full blown SLE.

Discussion

Our case is proved to be beta thalassemia trait based on the slightly high Hb A_2 and high Hb F fractions on Hb electrophoresis and confirmed by the genotype study to be IVS1#5. Her clinical and laboratory manifestations are typically consistent with classical beta thalassemia trait, viz., mild anemia (Hb concentration 10.04$\pm$0.9 g% for female), no hepato-splenomegaly, mild microcytosis (MCV 46.8-84.5 fL), mild hypochromia (MCH 15.9-28.8 pg) and slightly high Hb A_2 (3.7-6.7 %) percentage[3].

In the investigation of the microcytosis in 466 patients in Switzerland (MCV <82 fL), iron deficiency is the most common cause (35.2%), deletional alpha-thalassemia is the second common (31.1%), followed by the beta-thalassemia heterozygosity (18.9%), other hemoglobinopathies (HbC, Hb S/C, HbE) (1.3%). Three cases (0.6%) had other possible causes of microcytosis. Of the remaining 60 cases, 28 had an inflammatory state. Finally, 32 cases (6.9%) remain unexplained[5]. Our case is demonstrated to have occasional low MCV, low MCH in some tests due to beta thalassemia heterozygosity and also she is proved to be free from common alpha thalassemia-1, alpha-thalassemia-2 genes and iron deficiency anemia.

When our patient has been followed in the long term, the MCV, MCH, and Hb concentration are shown to fluctuate and MCV < 80 fL is more common than MCH <27 pg. Karimi et al found that MCH <27 pg and MCV < 80 fL had sensitivities of 98.5% and 97.6% for the diagnosis of beta-thalassemia trait, respectively. A false negative value of MCH was about 1% lower than that of MCV and they suggested that MCH was a more sensitive screening test for detecting beta-thalassemia minor[6]. So, if each of these para-meters just only from one cross-sectional study is used for screening beta-thalassemia trait, some cases may be missed. Or in the case of the mor-phologic approach of anemia, the fluctuation of MCV of the beta thalassemia trait as demonstrated in our case may mislead to the wrong category between the microcytic and normocytic groups.

The RDW (red blood cell distribution width) more than 15% is found in every test in our case therefore it is not appropriate to beused to distinguish the iron deficiency from beta thalassemia trait. It is not consistent with the findings of Flynn et al who show RDW rises in most cases of iron deficiency but in only half cases of beta thalassemia trait[7].

Conclusion

A 45-year old woman with beta-thalassemia (IVS1#5) traitandamegakaryocytic thrombocytopenia

are tested for CBC for 18 times. Many blood parameters fluctuate, Hb<12.0 g%, MCV <80 fL and MCH <27 pg found in 55.6%, 44.4%, and 83.3%, respectively. If MCV <80 fL or MCH <27 pg from the single test is used to screen beta thalassemia trait, MCV will have more chance than MCH to miss some cases. Or in the morphologic approach of anemia, the inconsistency of MCV of beta thalassemia trait may mislead to the wrong category.

References

1. Schrier SL. Approach to the adult patient with anemia. In: UpToDate, Basow DS (Ed), UpTo Date, Waltham MA, 2008.
2. Mazza U, Saglio G, Caligaris Cappio F, Camaschella G, Neretto G, Gallo E. Clinical and haematological data in 254 cases of beta-thalassaemia trait in Italy. Br J Haematol 1976; 33: 91-9.
3. Bhukhanvala D, Seliya V, Shah A, Gupte S. Study of parents of β-thalassemia major children to determine cutoff values of hematological parameters for diagnosis of β-thalassemia trait and assessment of anemia in them. Indian J Med Sci 2013; 67: 117-22.
4. Harrington AM, Ward PCJ, Kroft SH. Iron deficiency anemia, beta-thalassemia minor, and anemia of chronic disease. Am J Clin Pathol 2008; 129: 466-71.
5. Mach-Pascual S, Darbellay R, Pilotto PA, Beris P. Investigation of microcytosis: a comprehensive approach. Eur J Haematol 1996; 57: 54-61.
6. Karimi M, Rasekhi AR. Efficiency of premarital screening of beta-thalassemia trait using MCH rather than MCV in the population of Fars Province, Iran. Haematologia (Budap) 2002; 32: 129-33.
7. Flynn MM, Reppun TS, Bhagavan NV. Limitations of red blood cell distribution width (RDW) in evaluation of microcytosis. Am J ClinPathol 1986; 85: 445-9.