Int J Clin Exp Med 2016;9(6):9625-9627
www.ijcem.com /ISSN:1940-5901/IJCEM0019479

Case Report

Paroxysmal nocturnal hemoglobinuria with rise of blast cells in bone marrow: a case report and review of the literature

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Received November 9, 2015; Accepted January 23, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell clone disorder, and it is difficult to identify the difference between the untypical case of PNH and myelodysplastic syndrome (MDS). In current study, we described a case of PNH patient initially diagnosed as MDS and accepted treatment for 8 years, while lagging pathological symptoms of CD55/CD59 deficiency and soy urine was detected, the patient was eventually confirmed the diagnosis of PNH. After received treatment of blood transfusion, corticosteroid injection, as well as basification of urine, the disease progression of the patient was suppressed which manifested with soy urine turn to clear and white blood cell (WBC), hemoglobin (Hb) as well as platelet (Plt) recovered completely. This case shows that untypical PNH tend to be easily misdiagnosed as MDS. Furthermore, it points out the potential effective methods of differentiation and diagnosis of PNH and MDS.

Keywords: Paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, CD55/CD59 deficiency, soy urine

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired nonmalignant stem cell clone disorder that results in partial or complete deficiency of glycosylphosphatidylinositol (GPI)-anchored membrane proteins, such as CD55 and CD59 [1]. Chronic intravascular hemolysis, hematopoiesis failure and venous thrombosis are the clinical hallmarks of PNH [2]. It offers a challenge to differentiate PNH from other disorders, especially from myelodysplastic syndrome (MDS), for the correlative symptoms such as dyshematopoiesis and karyotypic abnormalities of bone marrow (BM) cells [3, 4]. Here, we first report a case of a patient initially diagnosed with MDS and was confirmed as PNH 8 years later, which owe to the lagging soy urine and deficiency of CD55/CD59, and we also present a review of literature.

Case report

A 45-year-old male patient was admitted to our hospital for 8-year MDS and 6-month hematuria in 2011. In September 2003, he began to feel fatigue, heart palpitations, no fever, and bleeding gums without incentive. His initial peripheral blood examination showed white blood cell (WBC), 2.3×10^9/L; hemoglobin (Hb), 81 g/L and platelet (Plt), 25×10^9/L. The bone marrow puncture revealed that hyperplasia was obviously active; the ratio of granulocyte to erythrocytic (G:E) was 0.38:1, 0.5% of the nucleated marrow cells were myeloblasts, and megaloblastic change appears in bone marrow. These results suggested abnormal hematopoiesis in granulocyte series, erythron series and megakaryocytic series in different extents. Meanwhile, the karyotypes of cells in BM were normal. The ratio of CD34+ cells to BM cells was 0.5% according to immunophenotyping classification, and no sign of vice infection were detected. Virological examination showed relatively normal levels of tumor markers CD55 and CD59. Thus, the patient was preliminarily diagnosed as MDS. In 2004, bone marrow puncture revealed marrow blast ratio 12%, tri-system dyshaematopoiesis, of peripheral blood cells,

Table 1. Values of CD55/CD59 of patient and normal individual in erythrocyte and neutrophil

Index	Patient	Control
CD55 (Erythrocyte)	80.50%	95%-100%
CD59 (Erythrocyte)	41.70%	95%-100%
CD55 (Neutrophil)	7.20%	< 5%
CD59 (Neutrophil)	34.20%	< 5%

Control: Normal individual.

as well as normal karyotypes, which performed in Institute of Hematology, Tianjin, China. Therefore, the patient was suspected as MDS with International Prognostic Scoring System (IPSS) score 2.0 and classified to intermediate-2 risk group. In April 2005, the marrow blast ratio in BM increased to 19% accompanied with pancytopenia and normal chromosome, which were detected in Shanghai Sixth People's Hospital. Thus, this patient was considered as MDS refractory cytopenia with multilineage dysplasia (MDS-RCMD) (IPSS2.0, intermediate-2 risk group). Because of the practical difficulties, he only received symptomatic treatments.

In March 2011, this patient was hospitalized for appearing typical paroxysmal soy urine, accompanied with jaundice in period and pallor anemia. Physical examination showed body temperature of 36.8°C, moderate anaemia in appearance, significant jaundice of the sclera, no skin hemorrhagic spot, as well as no abnormalities of heart, lung, liver or spleen. Blood examination revealed WBC count of 5.58×10^9/L, Hb count of 65 g/L and Plt count of 25×10^9/L. The bone marrow puncture showed that nucleated cell hyperplasia was active; the ratio of G: E was up to 0.6:1; granulocyte blood cell ratio decreased, along with dikaryon and giant leaf nuclei granulocytes; while red cell count was increased, with the appearances of megaloblastic erythroid-like change, double-nucleated red blood cells, nuclear budding, and other abnormal nuclear morphology as well as active megakaryocyte series hyperplasia; marrow iron-stain was positive; hemocoagulation was normal, accompanied by a negative Coomb's test. Biochemistry examination showed that total bilirubin, direct bilirubin and indirect bilirubin were slight increased. Lactic dehydrogenase (2072 U/L) was dramatically higher than normal value (15-220 U/L). Moreover, the result of positron emission tomography-computer tomography (PET-CT) scanning was normal. Flow cytometry analysis of peripheral blood cells indicated abnormal expression of CD55 and CD59 in erythrocyte and neutrophil: CD55 (80.5%) and CD59 (41.7%) in erythrocyte were significantly lower than normal value; CD55 (7.2%) and CD59 (34.2%) in neutrophil were obviously higher than normal value (**Table 1**).

Combined with above mentioned check, he was clinically diagnosed with PNH. The treatment regimen was including dexamethasone 15 mg, blood transfusion with washed red blood cells, Sodium bicarbonate for alkalinizing urine, plasmapheresis (plasma exchange) and so on. Two weeks later, the patient left hospital with the result of clear urine and normal value of blood consents (WBC, Hb, Plt). After more than one year (in June 2012), his WBC and Plt in peripheral blood were normal, while Hb was 85 g/L, lower than normal value. Moreover, this was accompanied with intermittent soy urine. His follow-up is still ongoing.

Discussion

It is obvious that the case was initially with dyshaematopoiesis, but without typical soy urine. That is why he was misdiagnosed or missed altogether.

One intriguing thing is the blast cells in BM. In the course of disease the blast cells ratio was from 0.5% to 19%, especially in the latter, the diagnosis of MDS must be differentiate. To our knowledge, the blast cells in PNH are still unclear now. Mannelli F et al. investigated systematically the phenotypic proliferation of BM cells from patients with PNH and MDS, and found the total amount of CD34+ cells on global cellularity were reduced, while antigenic proliferation of CD34+ cells did not show relevant abnormalities [5]. The data was parallel with the lack of significant differences of gene expression and proliferation between CD34+ cells from PNH patients and healthy individuals described by Chen G et al. [6]. It is important to note that not even an abnormal karyotype can rule out a diagnosis of PNH, since abnormalities have been reported in up to 24% of patients [7]. So cytogenetic analyses, Chromosomes and immune phenotype were performed from bone marrow in our case, no abnormalities were found along with the clinical feature that the blast cells dropped to normal with condition

improved, an assumption was presented firstly that the increased blast cells of bone marrow in PNH might be a compensatory reaction to reduce of cells in peripheral blood, which may be the key reason of this case had been in PNH for ten years. Further studies addressing this issue are warranted.

The other interesting finding is the expression of CD 55 and CD59 in PNH. Although determination of CD55 and CD59 in erythrocyte and neutrophil can be considered as a direct specific and reliable method for the diagnosis of PNH, PNH clones can be detected in the setting of MDS. PNH clone cells appeared in the high-risk group of MDS patients, such as RAEB, RAEB-t and CMML [8], While CD55/CD59 expression-lower cells were only in patients with MDS-refractory anemia (MDS-RA) [9]. These cells all can appear in patients with MDS, Aplastic anemia (AA) and PNH but with the degree of differences: the highest percentage of PNH was accounted for about 50% above, AA was about 5%-10%, MDS was between them [10, 11]. It is obviously difficult to make clear differentiation only by CD55 and CD59. Beyond GPI deficiency, some others immune antigen molecules, such as CD14, CD16 and CD45, may be helpful because of difference in the course of maturation in MDS and PNH [5]. It is a relatively reasonable approach that the analysis of CD55, CD59 gene expression was combining with detection of the immune antigen for the identification of PNH and MDS now.

Disclosure of conflict of interest

None.

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References

[1] Rosse WF and Ware RE. The molecular basis of paroxysmal nocturnal hemoglobinuria. Blood 1995; 86: 3277-3286.

[2] Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, Hillmen P, Luzzatto L, Young N, Kinoshita T, Rosse W, Socié G; International PNH Interest Group. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106: 3699-3709.

[3] Brodsky RA. Advances in the diagnosis and therapy of paroxysmal nocturnal hemoglobinuria. Blood Rev 2008; 22: 65-74.

[4] Araten DJ, Swirsky D, Karadimitris A, Notaro R, Nafa K, Bessler M, Thaler HT, Castro-Malaspina H, Childs BH, Boulad F, Weiss M, Anagnostopoulos N, Kutlar A, Savage DG, Maziarz RT, Jhanwar S and Luzzatto L. Cytogenetic and morphological abnormalities in paroxysmal nocturnal haemoglobinuria. Br J Haematol 2001; 115: 360-368.

[5] Mannelli F, Bencini S, Peruzzi B, Cutini I, Sanna A, Benelli M, Magi A, Gianfaldoni G, Rotunno G, Carrai V, Gelli AM, Valle V, Santini V, Notaro R, Luzzatto L and Bosi A. A systematic analysis of bone marrow cells by flow cytometry defines a specific phenotypic profile beyond GPI deficiency in paroxysmal nocturnal hemoglobinuria. Cytometry B Clin Cytom 2013; 84: 71-81.

[6] Chen G, Kirby M, Zeng W, Young NS and Maciejewski JP. Superior growth of glycophosphatidy linositol-anchored protein-deficient progenitor cells in vitro is due to the higher apoptotic rate of progenitors with normal phenotype in vivo. Exp Hematol 2002; 30: 774-782.

[7] Kawashima A, Sandler CM, Corl FM, West OC, Tamm EP, Fishman EK and Goldman SM. Imaging of renal trauma: a comprehensive review. Radiographics 2001; 21: 557-574.

[8] Kaiafa G, Papadopoulos A, Ntaios G, Saouli Z, Savopoulos C, Tsesmeli N, Kontoninas Z, Chatzinikolaou A, Tsavdaridou V, Klonizakis I and Hatzitolios A. Detection of CD55- and CD59-deficient granulocytic populations in patients with myelodysplastic syndrome. Ann Hematol 2008; 87: 257-262.

[9] Iwanaga M, Furukawa K, Amenomori T, Mori H, Nakamura H, Fuchigami K, Kamihira S, Nakakuma H and Tomonaga M. Paroxysmal nocturnal haemoglobinuria clones in patients with myelodysplastic syndromes. Br J Haematol 1998; 102: 465-474.

[10] Dong XY, Xu CG, Sun GR, Zhang T and Peng J. Expression of three kinds of GPI-anchor proteins in paroxysmal nocturnal hemoglobinuria, aplastic anemia and myelodysplastic syndromes patients and their clinical implications. Chin J Hematol 2004; 25: 198-201.

[11] Ishihara S, Nakakuma H, Kawaguchi T, Nagakura S, Horikawa K, Hidaka M, Asou N and Mitsuya H. Two cases showing clonal progression with full evolution from aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome to myelodysplastic syndromes and leukemia. Int J Hematol 2000; 72: 206-209.