Paroxysmal nocturnal hemoglobinuria clone in a case of myelodysplastic syndrome rapidly progressing to acute leukemia

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Abstract Myelodysplastic syndrome (MDS) comprises a group of stem cell disorders with considerable clinical and morphological heterogeneity. We report a case of MDS in a middle-aged male with clinical features of sepsis, dysplastic neutrophils and 6% blasts on bone marrow aspirate. A clone of neutrophils with deficient expression of CD16, CD55 and CD59 was found. A diagnosis of MDS with excess blasts with co-existent paroxysmal nocturnal hemoglobinuria (PNH) was made. Within a fortnight, the patient progressed to acute myeloid leukemia. We are reporting this unusual case of MDS displaying a sizeable clone of dysplastic neutrophils deficient in glycosyl phosphatidyl inositol anchored proteins, highlighting a common origin of PNH and leukemic clone.

Keywords MDS · PNH · Acute leukemia

Introduction

The myelodysplastic syndrome (MDS) represents a spectrum of stem cell malignancies that manifest dysplastic and ineffective hematopoiesis, and is associated with variable risk of transformation to acute leukemia [1]. Recent studies have shown presence of glycosyl phosphatidyl inositol (GPI) anchor deficient cells in MDS [2, 3]. Here, we report a case of MDS with a clone of GPI-anchor deficient dysplastic neutrophils with rapid progression to acute myeloid leukemia (AML).

Case report

A 39-year-old male presented in delirious state in emergency ward at our center with history of fever for one month. On examination, there was pallor and hepatosplenomegaly. Peripheral lymphadenopathy was absent. At the time of admission, his hemoglobin was 2.7 g/dL, total leukocyte count (TLC) was $47.7 \times 10^6/L$ and platelet count was $35 \times 10^6/L$. Widal test was negative and malarial parasite was absent. Cerebrospinal fluid examination was within normal limits. Peripheral blood smear showed 5% blasts, 36% myelocytes and 56% neutrophils, majority of which were dysplastic (Fig. 1A). Bone marrow aspirate showed a cellular marrow with myeloid hyperplasia (M: E ratio of 40:1), shift to left in myeloid series, 5% blasts and dysmyelopoiesis. Megakaryocytes were adequate. Patient was managed with antibiotics and transfused 6 units of blood and random donor platelets during his stay in hospital for 10 days. During this period his hemoglobin rose to 7.4 g/dL, TLC was $19.8 \times 10^6/L$ and platelet count was $13 \times 10^6/L$. He was discharged and advised to take oral antibiotics and vitamin supplements.

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Fig. 1A Peripheral blood smear showing dysplastic neutrophils

Fig. 1B Bone marrow aspirate showing a blast with auer rod

On his next visit in out patient department after 3 days, he was symptomatically better. Peripheral blood smear revealed an occasional blast and dysplastic neutrophils. Bone marrow aspirate showed predominantly myeloid series of cells, dysmyelopoiesis and 6% blasts. An occasional auer rod was also seen (Fig. 1B). Bone marrow biopsy was cellular, showed myeloid hyperplasia and an increase in blasts. Flow cytometric evaluation for GPI-anchored deficient clone which was done as part of an ongoing study on myelodysplastic syndromes at our center revealed 78.7% CD16 & CD55 deficient neutrophils and 73.8% CD59 deficient neutrophils in the peripheral blood (Fig. 2). Erythrocytes showed normal expression of CD55 and CD59. Ham's test and sucrose lysis test were negative. A diagnosis of myelodysplastic syndrome with excess of blasts (MDS-RAEB) and co-existent paroxysmal nocturnal hemoglobinuria (PNH) was made.

Within a fortnight, patient developed high grade fever. Peripheral blood smear at this time showed 14% blasts. Bone marrow aspirate revealed myeloid hyperplasia with myeloid to erythroid ratio of 50:1, dysmyelopoiesis and 30% blasts, which were positive for myeloperoxidase. A diagnosis of AML secondary to MDS was made. Due to financial constraints, patient declined further treatment and was discharged after 5 days in a stable state.

Discussion

Myelodysplastic syndrome is a group of clonal disorders of bone marrow manifested by refractory cytopenia and characteristic morphologic abnormalities of peripheral blood and bone marrow. Initial symptoms of MDS are weakness or pallor secondary to anemia, and less frequently, bleeding or infection. 25–40% of MDS patients develop acute leukemia, and MDS has thus been referred to a preleuke-

Fig. 2 Flow cytometric dot plots showing (A) neutrophils in R1 gate; (B & C) neutrophils with deficient (arrow) and normal (bold arrow) expression of CD16, CD55 & CD59

mic condition [4]. The International Prognostic Scoring System based on percentage of bone marrow myeloblasts, cytogenetic abnormalities and the number of cytopenia enables discrimination of patients into groups with varying expectations for survival and risk of and interval to AML progression. According to this model, the average time to AML transformation ranges from 9.4 years in 'Low risk' category to 0.2 years in 'High risk' category [5]. Cytogenetic correlative findings suggest that the genomic instability and biologically important genes present on chromosomes 5, 7 & 20 (most commonly) can alter survival and potential for leukemic evolution in MDS patients [5]. Our patient developed AML within a month of initial diagnosis. Cause for such rapid progression is not clear in our case because of lack of cytogenetic studies.

Deficiency of GPI-anchored proteins, a hallmark of PNH, is identified usually in the refractory anemia (RA) group of MDS. In two of the recent studies, a PNH clone was detectable in approximately 10% of patients with MDS, all of which belonged to RA group [2, 3]. The risk of AML in PNH is probably less than 2 % [6]. Long-term follow-up data of patients of MDS with PNH clone who progress to acute leukemia is not available. A key question regarding AML development in the PNH setting has been whether the abnormal environment of PNH marrow predisposes to leukemogenesis or whether AML blasts evolve directly from affected PNH cells. A review of literature presents conflicting views. Van Kamp et al documented presence of GPI anchored proteins on MDS cells whereas Nakahata et al and Longo et al demonstrated that the leukemic blasts arose from GPI anchored deficient cells [7–9]. The majority of neutrophils in our case were dysplastic which also lacked GPI anchored proteins, thus favoring a common pathogenetic origin of myelodysplastic and PNH clone.

To conclude, we have reported an interesting case of MDS-RAEB presenting with sepsis and sizeable clone of GPI-anchored deficient dysplastic neutrophils in which a rapid progression to AML was noted, the cause of which

remains unknown. This case demonstrating the GPI-anchored protein deficiency on dysplastic myeloid cells highlights a common origin of PNH and leukemic clone. In our view, evaluation for PNH clone and a longitudinal study relating the rate of progression to AML and cytogenetic abnormalities should be done in all cases of MDS.

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