□ LETTERS TO THE EDITOR □

Differential Diagnoses of Macrocytic Anemia, Reticulocytosis and Low Serum Haptoglobin in Patients with Myelodysplastic Syndromes/Acute Leukemia: Comment on “Two Cases of Acute Erythroid Leukemia Presenting with Marked Macrocytic Anemia, Reticulocytosis and Hemolysis”

Key words: hemolytic anemia, reticulocytosis, pseudoreticulocytosis, ineffective erythrocytosis, acute myeloid leukemia

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To the Editor I read with particular interest the manuscript by Ota et al. (1). The authors stated that both patients presented with marked macrocytic anemia, reticulocytosis and hemolysis. However, they did not describe the detailed red blood cell (RBC) morphology. The published blood smear does not reveal the RBC morphology, and there are many overlapping RBCs (1). I would like to comment that there are many things to consider in both cases.

(A) Although rare, pseudoreticulocytosis is a well-recognized phenomenon in patients with myelodysplastic syndrome (MDS), a harbinger of acute myeloid leukemia (AML). In this situation, the reticulocytosis is a consequence of the delayed maturation of reticulocytes, as evidenced by *in vitro* reticulocyte survival studies (2). Do the patients have true reticulocytosis or pseudoreticulocytosis?

(B) A low serum haptoglobin level may be due to (i) intravascular hemolysis, (ii) extravascular hemolysis or (iii) ineffective erythropoiesis. MDS and AML are bone marrow failure syndromes and involve some degree of ineffective erythropoiesis; it is not rare to observe this phenomenon (3). In patient 1, the question arises, “Is the low serum haptoglobin level due to intravascular hemolysis, extravascular hemolysis or ineffective erythropoiesis?”

(C) While I agree that autoimmune hemolytic anemia (AIHA) may be a sequela of AML (4), direct antiglobulin tests (DATs) are not 100% sensitive in diagnosing AIHA. Approximately 1% of cases of autoimmune hemolytic anemia are DAT-negative for the following reasons: (i) RBCs

are coated with small numbers of IgG molecules below the level of detection of standard DATs, (ii) IgA and IgM autoantibodies are not detected by standard DATs, (iii) low-affinity IgG antibodies are eluted from RBCs during routine washing of the RBCs before the detection phase on standard DATs. In this situation, the more sensitive “superCoombs” test may be used to establish an AIHA diagnosis (5).

(D) A careful review of the peripheral blood smear almost always reaches the correct diagnosis of hemolytic anemia, which may be related to MDS/AML. For examples, the following conditions may be detected: (i) spherocytosis in patients with microangiopathic hemolytic anemia that may be due to AML-associated disseminated intravascular coagulation, (ii) microspherocytes in patients with warm autoimmune hemolytic anemia and, (iii) echinocytes in patients with acquired pyruvate kinase deficiency.

In conclusion, the authors could have done a better job of describing both patients in detail so that the readers would understand the exact pathological processes. Carefully reviewing the blood smears and performing appropriate investigations will make it possible to reach an accurate diagnosis. Clinicians should keep in mind that pseudoreticulocytosis is a recognized finding in MDS/AML patients.

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