Erythroleukemia Presenting as Non-immune Haemolytic Anemia: A Rare Presentation

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Abstract Non-immune haemolysis is a rare manifestation of acute leukaemia and more so in acute myeloid leukemia. Here, we report a case of non-immune and non-fragmentation haemolysis as the initial presenting manifestation in a 55-year-old female with acute myeloid leukaemia (AML-M6). All other potential aetiologies of haemolysis were excluded, including drugs, paroxysmal nocturnal haemoglobinuria, immune and other known congenital and acquired causes of haemolytic anaemia. This case shows that malignant haematopoietic disorders should be considered in patients with newly diagnosed haemolysis.

Keywords Erythroleukemia · Non-immune haemolysis · Acute Myeloid Leukemia

Case Summary

A 55-year-old female presented with fatigue, jaundice and loss of appetite for last 1 month. She also complained of off and on fever with nausea and vomiting for 10–15 days. The patient had no significant history of illness, and her family history was negative for any haematological disorders. On examination, she was found to be afebrile with

pallor and icterus. Abdominal examination revealed soft abdomen with hepatosplenomegaly. The patient was admitted and investigated.

Her complete blood count (CBC) showed pancytopenia with haemoglobin (Hb) of 6.2 g%, white blood cell (WBC) count of $1.9 \times 10^9/L$ and platelet count of $92 \times 10^9/L$. Red cell indices showed haematocrit (HCT) of 18.4 %, red blood cell (RBC) count of $1.74 \times 10^{12}/L$; mean corpuscular volume (MCV) of 105.9 fL; mean corpuscular haemoglobin (MCH) of 35.8 pg; mean corpuscular haemoglobin concentration (MCHC) of 33.8 g/L and red cell distribution width (RDW) of 17.6 %; The reticulocyte count was raised 14.2 % with a corrected reticulocyte count of 6.5 %. Her LDH was mildly elevated, 374 U/L. Coomb's test (direct and indirect) was negative. Vitamin B12 and folic acid levels were within normal range that was 236 pg/mL and 15 ng/mL respectively. Bilirubin was 11 mg/dL, mostly indirect. Plasma-free hemoglobin was as high as 0.65 (normal range, <0.05 g/L). The patient's haptoglobin level was very low (<0.07 g/L). In view of jaundice, vomiting and mild hepatomegaly she was also investigated for hepatitis viral markers that were negative. Hence the patient was found to have pancytopenia with non-immune hemolysis. Other valuable investigation included flow cytometry for PNH that was negative for PNH clone.

The differential count on peripheral blood was showing polymorphonuclear cells, 18 %; lymphocytes, 69 %; blasts, 5 %; myelocytes, 1 %; metamyelocytes, 2 % and eosinophils, 5 %.

The peripheral smear stained with May-Grunwald-Giemsa showed predominantly macrocytic red cells with mild anisocytosis. There was no appreciable poikilocytosis with lack of spherocytes or red cell fragments. White blood cells showed leucopenia with absolute neutropenia and ~5 % circulating blast cells (Fig. 1). Platelets were reduced.

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Fig. 1 Peripheral blood shows normocytic normochromic red cells along with a blast containing an auer rod. (Wright–Giemsa X40)

Fig. 2 The myeloperoxidase stain on the bone marrow imprint smear showing positive blasts (*bright orange arrow*) along with an internal control (*thick black arrow*). Megaloblasts are seen (*thin black arrow*). (Wright–Giemsa X100). (Color figure online)

Bone marrow aspirate smears showed cellular marrow trails with erythroid hyperplasia comprising up to ~78 % of all nucleated cells. There was significant dyserythropoiesis including megaloblastoid changes in nuclei. These erythroid precursor cells were seen at all stages of maturation. The non-erythroid marrow elements showed significant dyshemopoietic changes and presence of ~60 % blast cells, medium in size with variable presence of few cytoplasmic granules. Few blast cells showed intra-cytoplasmic auer rod. The blast cells were positive for myeloperoxidase (Fig. 2). Myeloid cells showed dysmyelopoiesis with prominence of monocytoid cells. There was dysmegakaryopoiesis. Iron stain, showing an increase in iron storage (+3) with no ringed sideroblasts. Trephine biopsy revealed cellular marrow areas with

erythroid hyperplasia including several immature forms interspersed with sheets of blast cells. Normal hemopoietic elements were inconspicuous. The case was diagnosed according to WHO 2008 classification as acute erythroid/myeloid leukaemia (AML-M6a).

Discussion

Acute erythroleukemia (AEL) was first described by Copelli and DiGuglielmo in the early 20th century and was termed ‘erythroleukemia’ by Moeschlin. It is a rare entity comprising <5 % cases of all adult acute myeloid leukemia [1]. According to the WHO classification it is defined as having ≥ 50 % erythroid precursors in the entire population of nucleated bone marrow cells, and myeloblasts that account for at least 20 % of the nonerythroid cell population (acute erythroid/myeloid leukemia, formerly FAB M6a), or as having ≥ 80 % immature erythroid precursors with no significant myeloblastic component (pure erythroid leukemia, formerly FAB M6b) [2].

The causes of haemolytic anemia are manifold. However, depending upon the age, clinical and investigative features the differential diagnosis was narrowed down. Considering an elderly Indian female presenting with pancytopenia, vitamin B12/folate deficiency anemia with ineffective erythropoiesis was a strong possibility. However, significant reticulocytosis, normal vitamin B12/folate levels and lack of any history of vitamin supplements in the recent past excluded megaloblastic anemia. Even though there was megaloblastoid erythroid hyperplasia in bone marrow, but the presence of ~60 % blasts in the non erythroid cell count clinched the diagnosis of AML-M6a.

Pancytopenia with reticulocytosis in an elderly female warranted the exclusion of PNH. Immunophenotypic analysis was performed using forward scatter–side scatter (FSC–SSC), CD45–SSC and CD64–SSC gating for surface expression of the GPI-linked antibodies. CD55 and CD59, CD14 and CD66b expression on RBC, monocytes and neutrophils respectively, was analysed. The flow cytometric immunophenotyping was negative for the PNH clone studied (Fig. 3).

Autoimmune haemolytic anemia (AIHA) has been associated with malignant disorders like lymphoid neoplasms, myelodysplastic syndrome (MDS) as well as AML. However negative DAT along with absence of spherocytes excluded this possibility in our case. The inherited causes like glucose-6-phosphatase deficiency and hereditary spherocytosis were least likely. However, DAT negative AIHA is described in ~5 % of all cases of AIHA. The possible mechanism relates to RBC sensitization by a very small amount of IgG that is below the sensitivity of detection of the DAT reagent or sensitization by IgA and

Fig. 3 Flow cytometric immunophenotyping studying CD 59 in red cell (a), CD 55c and CD 66b in granulocytes (b) and CD 64 and CD 14 in monocytes (c) to be negative for PNH clones. (Color figure online).

IgM antibodies which are not detected using this reagent [3]. When compared to DAT positive AIHA, these cases tend to have lower reticulocyte counts, lower MCV and total proteins while Hb is higher. Hence, hemolysis in these patients tends to be milder than DAT positive AIHA [4].

A recent study demonstrated the acquired forms of alpha and beta thalassemia in conditions like MDS and AML [5, 6]. Hence in our case further genetic mutational analysis are required for the possibility, if any, of the underlying acquired alpha or beta thalassemia.

Hemolysis as a presenting feature is very rare in leukemia and is mostly immune. There are only a few case reports in the available literature [7, 8] of non-immune hemolysis as a presenting feature in patients of AML- M6. Ours is the first case in Indian subcontinent. This haemolysis found was not due to autoimmune, drug, or infective causes. Even though non-immune the exact cause of haemolysis remains unidentified.

As in the previous reports, our case study also demonstrates that AML should also be considered in patients with newly diagnosed haemolysis particularly when dysplastic

red cell precursors and/or concomitant cytopenias are present.

Allogeneic SCT seems to be beneficial for suitable transplant candidates with erythroleukaemia.

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