A 31-year-old male patient presented with fever and pancytopenia. He was diagnosed as a case of chronic anemia since early childhood. The etiology of the anemia was never found despite extensive testing. His anemia was clinically characterized as being hemolytic with high serum lactate dehydrogenase (LDH) and indirect bilirubin and with splenomegaly. Testing for osmotic fragility of RBCs, G6PD and direct antiglobulin test (DAT) was made, among other tests. Molecular testing for alpha and beta thalassemia was negative and his marrow was hypercellular. He was maintained on corticosteroids. For three years prior to admission, the patient had also been maintained on erythropoietin which, according to his hematologist, decreased transfusion requirements and dependency. One week prior to admission, the patient developed fever and respiratory tract-like illness for which a presumptive diagnosis of pulmonary infection was made. He was found to have pancytopenia with the following counts:

- WBC: $3.1 \times 10^{9}$/L
- RBC: $2.43 \times 10^{12}$/L
- Hemoglobin: 8.7 g/dL
- Hematocrit: 25.5%
- Platelets: $46 \times 10^{9}$/L

A bone marrow aspirate and trephine biopsy were performed.

The aspirate revealed hypercellular particles that were almost totally replaced by early proerythroblasts with megaloblastoid maturation and dyserythropoiesis including binuclear and trinuclear forms with cytoplasmic vacuolation (Figure 1). The periodic acid-Schiff (PAS) stain showed block positivity in proerythroblasts (Figure 2). Rare granulocytic precursors were present. Occasional histiocytes with erythrophagocytosis were identified. Stainable iron was markedly increased. No ringed sideroblasts were identified.

The biopsy was hypercellular for age with 100% cellularity. Erythroid precursors were quantitatively markedly increased with predominant proerythroblast stage (Figure 3). Granulocytic precursors were quantitatively decreased and megakaryocytes were slightly decreased. Minor marrow populations, lymphocytes and plasma cells were not increased. Reticulin stain showed grade II/IV reticulin fibrosis.

The findings were so impressive that in conjunction with the pancytopenia, the possibility of acute erythroid leukemia of the pure erythroid subtype was considered. However, according to the 2008 World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues, a history of erythropoietin therapy should exclude...
such a diagnosis. A recommendation was then made for a repeat bone marrow examination in one month. The repeat examination showed normalization of the components of the marrow with reversal of the M:E ratio (Figure 4).

**DISCUSSION**

Acute erythroid leukemia is amongst the rarest types of acute myeloid leukemia.² The last edition of the WHO classification of tumours of hematopoietic and lymphoid tissues recognizes two types of erythroid leukemia: erythroleukemia (erythroid/myeloid) and pure erythroid leukemia.² Erythroleukemia is defined by the presence of 50% or more erythroid precursors of the entire nucleated cell population and 20% or more myeloblasts of the non-erythroid cells. Pure erythroid leukemia is a neoplastic proliferation of immature cells committed exclusively to erythroid lineage representing 80% or more of the marrow cells with no significant myeloblasts. Common presentations are profound anemia and circulating erythroblasts. The erythroid neoplastic cells show dysplastic changes represented by bi- or multi-nucleation; megablastoid nuclei and the cytoplasm frequently contain poorly demarcated vacuoles that can coalesce. Ring sideroblasts and PAS positivity can be seen. Neutrophilic and megakaryocytic dysplasia are frequent. The marrow is usually hypercellular. Hemophagocytic lymphohistiocytosis (HLH) has been described in association with erythroid leukemia.³

The differential diagnosis of acute erythroid leukemia is broad, and includes both non-neoplastic and neoplastic conditions. Among the non-neoplastic causes of erythroid hyperplasia, vitamin B12/folate deficiency and previous erythropoietin treatment need to be considered. Other less common non-neoplastic causes of reactive erythroid hyperplasia include toxin exposure, especially benzene, congenital dyserythropoiesis and Parvovirus infection.³
The diagnosis of acute erythroid leukemia of the pure erythroid type has been problematic. Prior to the last edition of the WHO classification, which clearly identified erythropoietin as a cause of benign reactive erythropoiesis that mimics pure erythroid leukemia, many of the cases diagnosed as definite or suspicious of primary erythroid leukemia were retrospectively re-diagnosed as benign reactive erythroid hyperplasia. Zuo et al, for example, reviewed a number of cases which showed predominant population of erythroid precursors and were either diagnosed as acute erythroid leukemia or suggestive of acute erythroid leukemia at the University of Texas M.D. Anderson Cancer Center. The authors identified a group of cases with previous history of erythropoietin administration, questioning the diagnosis in such cases, and considering prior erythropoietin treatment as an exclusion criterion for the diagnosis. The current WHO blue book does not list erythropoietin treatment as an absolute exclusion criterion, though the book mentions erythropoietin treatment in the differential diagnosis of pure erythroid leukemia.

In their review article, Zuo et al. state that, in their experience, the most common cause of a marrow that contains 50% or more erythroid precursor is erythropoietin treatment. This highlights the importance of excluding a history of erythropoietin treatment in such case scenarios. Furthermore, erythropoietin therapy, by means of increasing the erythroid precursors in the bone marrow, makes the estimation of blast count much more difficult. One of the most important differentiating points between erythropoietin-induced erythroid hyperplasia and pure erythroid leukemia, in addition to history of erythropoietin treatment, is that pure erythroid leukemia presents as anemia or pancytopenia, while patients on erythropoietin treatment usually show improvement of their pre-existing anemia in response to the treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES