Letter to the Editor
Diagnostic Hematology

Ann Lab Med 2023;43:303-306
https://doi.org/10.3343/alm.2023.43.3.303
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

A Rare Case of Extensive Erythrophagocytosis by Pathological Erythroblasts in a Patient With Myelodysplastic Syndrome

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Dear Editor,

Patients with AML of the bone marrow (BM), multiple myeloma, malignant lymphoma, solid tumor BM invasion, and chronic myeloid leukemia-related blast crisis may experience erythrophagocytosis [1-3]. We discuss a rare case of phagocytic proerythroblasts in the context of MDS. The Institutional Review Committee of Army Medical University Xinqiao Hospital, Chongqing, China, approved this study (XQYY-2022-069) and waived the need for informed consent.

A 65-year-old man presented at the hospital in March 2021 complaining primarily of growing exhaustion and died three months later due to a rapidly deteriorating clinic course. Laboratory tests revealed an elevated ferritin level of 2,130 ng/mL, elevated lactate dehydrogenase level of 621 IU/L, and pancytopenia (white blood cells: 0.9×10^9/L, platelets: 10×10^9/L, and Hb: 47 g/L, with 3% myeloblasts in the peripheral blood). Trilineage dysplasia was detected in a BM smear, with 56% of the cells being erythroblasts and 8% being myeloblasts. The aspirate also showed extensive erythrophagocytosis, which was mediated by immature erythroid precursors, as indicated by the large vacuoles and blebs in the cytoplasm (Fig. 1A and B). A quarter of all erythroid cells were phagocytic erythroblasts. Intense periodic acid-Schiff (PAS) stain positivity with a coarsely granular staining pattern was detected in the pathological erythroblasts (Fig. 1C). Approximately 35% of the cells were ring sideroblasts (Fig. 1D). Phagocytized erythrocytes did not exhibit myeloperoxidase staining (Fig. 1E). Transferrin- and glycophorin A-positive erythroid cells were identified by flow cytometric analysis of BM samples (Fig. 2).

All tests for fusion genes associated with AML were negative. A single-nucleotide polymorphism in *TET2* (NM_001127208.3: exon 3: c.86C>G: p.Pro29Arg rs12498609), with a 39% variant allele frequency, was discovered by next-generation sequencing. *SF3B1* mutations were not detected by next-generation sequencing. Chromosomal analysis revealed a complex karyotype of 43-52,XY,+1,+3,+4,del(5)(q22q35),+6,-7,-9,-10,-12,del(12)(p12),+16,+17,+18,-19,-20,+mar1,+mar2,+mar3,+mar4,+mar5[cp6]/73-89,XX,-Y,-Y,-3,-4,del(5)(q22q35)×2,-6,-7,-9,-12,-19,-19,-20,-20,+mar1×2,+mar2×2,+mar3×2,+mar4×2,+mar5[cp13]/46, XY[1].The ultimate diagnosis was MDS with excess blasts (MDS-EB; 2016 WHO classification), with a score of 7.5 according to the revised International Prognostic Scoring System (IPSS-R) [4], placing the patient in the very high-risk group.

Received: July 10, 2022
Revision received: September 10, 2022
Accepted: October 11, 2022

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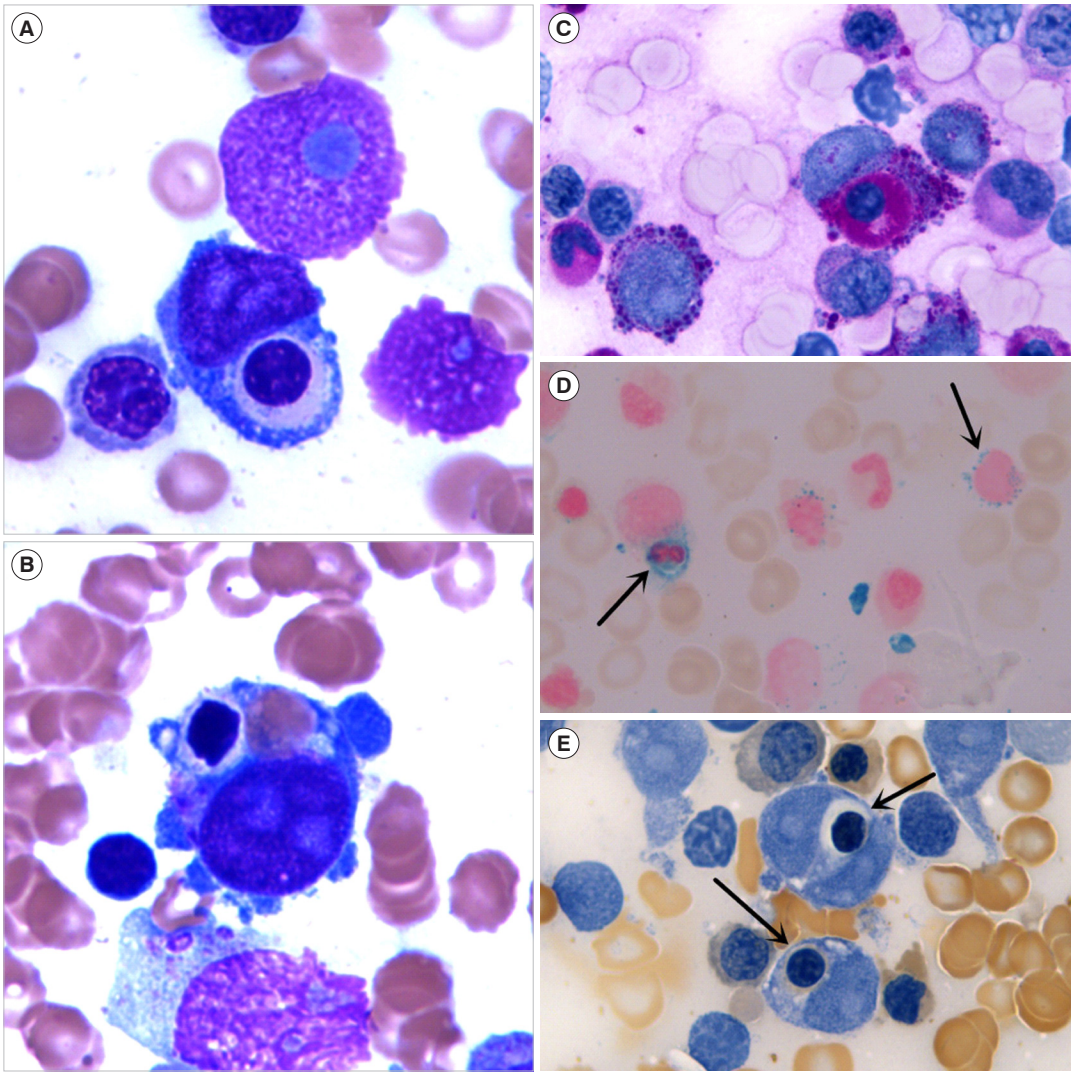

Fig. 1. Results of bone marrow aspirate analysis. (A, B) Bone marrow smears showing pathological erythroblasts with distinct cytoplasmic vacuoles that had phagocytized both an erythrocyte and a late erythroblast. (C) Pathological erythroblasts exhibiting strongly positive periodic acid-Schiff staining. (D) Ring sideroblasts were evident in iron staining(Indicated by black arrows). (E) Phagocytized erythrocytes were negatively stained for myeloperoxidase (Indicated by black arrows).

The patient passed away despite receiving three rounds of azacitidine chemotherapy.

When levels of immature erythroid precursors are elevated, MDS with substantial erythroid hyperplasia can be morphologically identical to high-grade lymphoma, pure erythroleukemia (PEL), AML with myelodysplasia-related changes (AML-MRC), plasmablastic myeloma, or acute megakaryoblastic leukemia [5]. The pronormoblast-like cells in the present case expressed CD71 and some CD235a but were negative for CD61 and strongly positive for PAS staining. They also had morphological features, such as cytoplasmic vacuolation, increased basophilia, peripheral bleb formation, negative staining for the BM megakaryocyte marker CD41, and 35% ring sideroblast positivity, all sufficient to show neoplastic hyperplasia of the erythroid lineage.

The 2008 WHO categorization criteria for erythroleukemia have been divisive because they have low reproducibility [6]. A modest increase in the number of myeloblasts can result in a change in the diagnosis from MDS to erythroleukemia, which will affect the chosen course of treatment because blast frequencies are calculated using nonerythroid cells as the denominator. Similar effects can be observed in diagnosis and treatment when the erythroid fraction is slightly different (50% vs. 50%). Because of these factors, only the PEL criteria were retained in 2016 WHO recommendations. Morphologic dysplasia is a frequent finding

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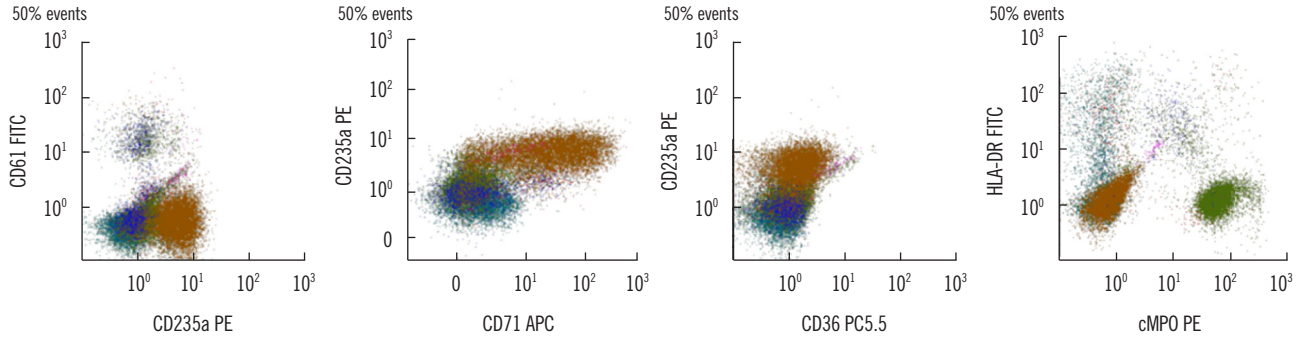

Fig. 2. Flow cytometry-based immunophenotyping results. Brown dots indicate an increased frequency of erythroid cells (up to 41.21%) that were positive for CD71 and CD235a and negative for CD36.

in both MDS and AML-MRC, which is consistent with AML-MRC developing from MDS. The 2016 diagnostic criteria could be used to diagnose MDS-EB in the current case. The patient may have been in the transitional stage of progression to AML-MRC at the time of examination because of his rapid advancement.

Huhn, *et al.* [7] showed that cytosolic acid phosphatase activity, which is frequently quite high in most immature cells, including erythroblasts, is directly related to the phagocytic potential of cells. Cell-in-cell (CIC) is another name for this phenomenon. CIC formations, i.e., one or more living cells contained within another nonphagocytic cell, have been identified in human cancers and have a significant impact on patient prognosis [8]. CIC formations can be classified as endocytic (cell cannibalism, phagocytosis, and enclysis) or invasive (entosis and emperipolesis), depending on how they develop [9]. Under unfavorable circumstances, cell cannibalism and entosis can promote tumor cell survival and growth by supplying nutrients to cells [10].

Our patient's rapid disease development and inadequate response to chemotherapy raise the likelihood of erythrophagocytosis being associated with a poor prognosis.

ACKNOWLEDGEMENTS

The authors would like to thank Xiangui Peng from the Department of Hematology at Xinqiao Hospital, Army Medical University, for his work in the revision of this article.

AUTHOR CONTRIBUTIONS

Qiang X, Chen X, and Chen S conceived and designed the study. Li J, Gou Y, and Wang P developed the methodology and analyzed and interpreted the data. Qiang X wrote the manuscript. Chen X reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

RESEARCH FUNDING

There are no funders for this work.

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