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REVIEW

Acute myeloid leukaemia and myelodysplastic syndromes with 50% or greater erythroblasts: a diagnostic conundrum

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Summary

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) with ≥50% erythroblasts comprise up to 5% of all cases of AML and 15% of MDS. The classification of these entities is currently fraught with difficulty and requires integration of clinical, morphological and cytogenetic features. The current World Health Organization classification of haematopoietic tumours recognises the entities of pure erythroid leukaemia and acute erythroid leukaemia (erythroid/myeloid), however, some cases of AML with erythroid predominance may also fulfil criteria for AML with myelodysplasia-related changes or therapy-related myeloid neoplasms. Among these entities, pure erythroid leukaemia remains poorly characterised due to its rarity. In addition, there is significant clinicopathological overlap between acute erythroid leukaemia and cases of MDS with ≥50% erythroblasts. In this review, we discuss current areas of controversy regarding these disorders and present our approach to their diagnosis and classification.

Key words: Acute myeloid leukaemia, cytogenetics, erythroleukaemia, histopathology.

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INTRODUCTION

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) with erythroid predominance, defined as the presence of ≥50% erythroblasts, comprise up to 5% of AML and 15% of MDS.[1–3] The classification of these entities is currently fraught with difficulty and requires integration of clinical, morphological and cytogenetic features. The World Health Organization (WHO) 2008 Classification of Tumours of Hematopoietic Tissues[4] recognises the entities of acute erythroid leukaemia (erythroid/myeloid) (AEL) and pure erythroid leukaemia (PEL); however, cases of AML with ≥50% erythroblasts may also fulfil criteria for AML with myelodysplasia related changes (AML-MRC) or therapy related AML (t-AML). There is also lack of consensus regarding the most accurate means to categorise cases of MDS with ≥50% erythroblasts. In this review, we present our approach to the diagnosis and classification of AML and MDS with ≥50% erythroblasts through several case vignettes and highlight areas of controversy that require further investigation.

OVERVIEW OF CLASSIFICATION

The recognition of cases of AML and MDS featuring prominent erythroid hyperplasia in the bone marrow can be traced back to Di Guglielmo's first descriptions in the literature.[5] The historical course to the current WHO classification scheme has been detailed in several previous reviews.[6,7] In brief, the first French-American-British (FAB) classification of AML introduced 'erythroleukaemia (M6)' as a morphological subtype where erythroblasts exceeded 50% of all the nucleated cells in the bone marrow.[8] The revised FAB classification of AML recognised that in some cases of erythroleukaemia, the degree of erythroid hyperplasia was so great that the simultaneous requirement for >30% myeloblasts of total nucleated cells could not be fulfilled.[9] As a result, the authors introduced the concept of calculating myeloblasts as a percentage of non-erythroid cells. It was also later recognised that within the category of erythroleukaemia, there was a distinct subgroup of cases which featured immature blasts of erythroid lineage, minimal erythroid maturation and no excess of myeloblasts.[10] This entity was initially termed 'AML M6 variant' but was later renamed as pure erythroid leukaemia (PEL). In the current WHO 2008 classification, the classification of AML is based on a hierarchical approach, whereby the presence of specific cytogenetic or molecular features takes precedence. Cases of AML with recurrent cytogenetic abnormalities including t(15;17)(q22;q12), inv(16) (p13.1q22), t(8;21)(q22;q22), inv(3;3)(q21q26.2) or t(1;22)(p13;q13) are distinct entities each with unique molecular mechanisms that are classified separately regardless of the presence of erythroid hyperplasia. Acute myeloid leukaemia and MDS arising in the context of previous chemoradiotherapy are classified as therapy related myeloid neoplasms (t-MN). The WHO 2008 classification also introduced the entity of AML with myelodysplasia related changes, into which cases may be placed based on either a previous history of MDS, morphological multilineage dysplasia, or MDS-related cytogenetic abnormalities. As we shall discuss later, some cases previously recognised as erythroleukaemia may fall into this category and hence be 'reclassified' according to current criteria. Once AML with recurrent cytogenetic abnormalities, t-MN, and AML-MRC have been excluded, the remaining cases of AML with ≥50% erythroblasts may fulfil criteria for either AEL or PEL, both of which are subgroups of AML not otherwise specified. MDS is distinguished from AML in cases with ≥50% erythroblasts by the presence of <20% myeloblasts of non-erythroid cells.

CASE 1: PURE ERYTHROID LEUKAEMIA

Case presentation

A 55-year-old man was found to have moderate neutropenia and thrombocytopenia. His previous medical history was unremarkable. There were rare circulating blasts in the peripheral blood. A bone marrow aspirate and trephine biopsy was performed, which showed a markedly hypercellular marrow

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effaced with blasts (>80%) (Fig. 1). The cytoplasm of the blasts was deeply basophilic and there were occasional vacuoles. The blasts were myeloperoxidase (MPO) and CD34 negative but positive for glycophorin C on immunohistochemistry. Cytogenetics revealed a complex karyotype.

Discussion

Pure erythroid leukaemia is exceedingly rare and accounts for <1% of all cases of AML.[11] Due to its rarity, descriptions of PEL have been limited to small series and case reports.[11–14] It is morphologically unique and characterised by the selective proliferation of immature erythroblasts accounting for ≥80% of nucleated bone marrow cells and no increase in myeloblasts. Notably, there is an absence of erythroid maturation which is distinct from AEL. The immature erythroblasts typically feature a high nuclear:cytoplasmic ratio and deeply basophilic cytoplasm occasionally with vacuolation.[10]

The immature erythroblasts of PEL frequently demonstrate a MPO and CD34 negative immunophenotype with variable expression of CD117, CD13 and CD33.[11] Immunohistology can be used on trephine bone marrow specimens to confirm the erythroid lineage of the leukaemic blasts by targeting erythroid-specific antigens, most commonly either glycophorin A or C. It must be noted, however, that glycophorin A and C both identify erythroblasts at all stages of maturation as well as erythrocytes, and care must be taken not to overestimate the proportion of immature erythroblasts in cases of suspected PEL if these antibodies are used. E-cadherin (epithelial calcium-dependent adhesion protein) has the advantage of identifying proerythroblasts but not late erythroblasts or erythrocytes, hence is more specific for the immature erythroid fraction.[15] Immunohistology is particularly useful in quantifying the extent of bone marrow infiltration with immature erythroblasts in cases of suspected PEL. We have previously described the morphological features of cases of PEL diagnosed in three local institutions.[16] In 57% of PEL cases in our series, immunohistology revealed effacement (≥80%) of the marrow with abnormal glycophorin C and E-cadherin positive blasts despite erythroblasts accounting for <80% of total nucleated cells in the bone marrow aspirate, likely due to peripheral blood dilution of the aspirate sample. In this way, bone marrow trephine biopsy and immunohistology may lead to more accurate classification of cases as PEL.

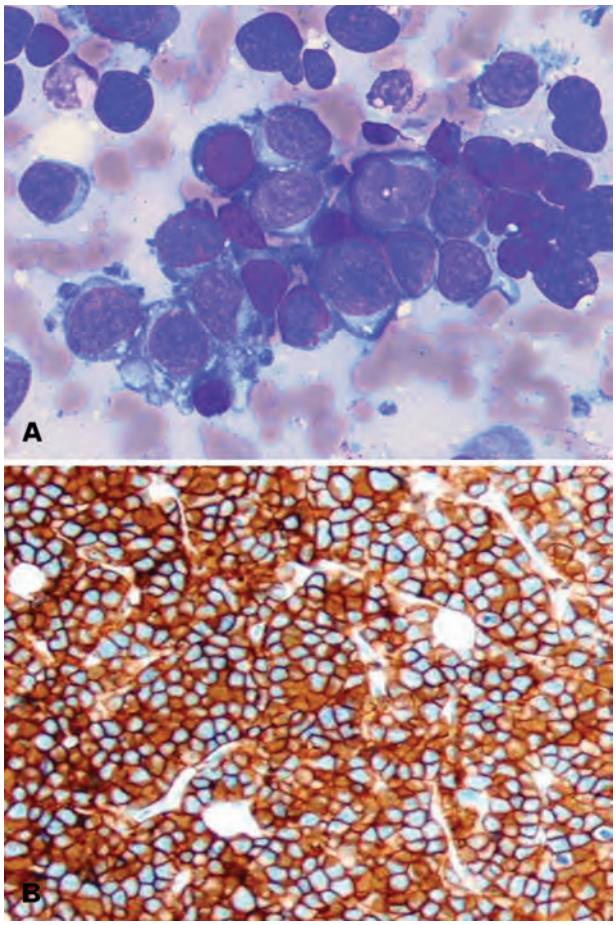

Fig. 1 (A) Pure erythroid leukaemia is characterised by a unique morphology on bone marrow aspirate (ICSH reference method stain) with a proliferation of immature blasts of erythroid lineage, minimal erythroid maturation and no increase in myeloblasts. (B) Glycophorin C immunohistochemistry on bone marrow trephine demonstrates marrow effacement by blasts of erythroid lineage.

Cases of PEL commonly feature complex chromosomal abnormalities.[14,17] In our pooled analysis of cases of PEL published in the literature from 1 January 2001 to 1 August 2014, 83% of cases had complex cytogenetics.[16] Although there are no recurrent cytogenetic abnormalities characteristic of PEL, structural abnormalities of chromosomes 5, 7 are common. Thus, it is not surprising that many cases of PEL are classified in the adverse cytogenetic risk group according to the revised MRC criteria for AML.[18] The molecular pathogenesis of PEL has not been well described. There appears to be a low incidence of FLT3-ITD or NPM1 mutations, although the number of cases analysed has been limited.[19] The prognosis of PEL is poor; the median overall survival OS of published cases is 3.5 months (range 0–9 months).[16]

At this point it is important to note that the WHO 2008 classification of AML recommends that where cases meet criteria for t-AML or AML-MRC, they should be classified as such in preference to subtypes of AML not otherwise specified, including PEL. Cases may fulfil criteria for AML-MRC on the basis of pre-existing MDS, mutilineage dysplasia (defined as ≥50% of cells in at least two myeloid lineages having morphologic dysplasia), or MDS-related cytogenetic abnormalities. On the basis of this, 41% of PEL cases are reclassified as t-AML and a further 42% as AML-MRC.[16] Despite their re-classification into these categories, the selective erythroid proliferation and maturation arrest seen in PEL suggest a unique pathogenesis that is not adequately reflected in classification with other cases of t-AML or AML-MRC. The molecular characterisation of PEL may be particularly useful to determine a distinct, or shared, pathogenesis to t-AML or AML-MRC. Currently, without this data, it may be prudent to recognise the distinct morphology of these cases with a note in parenthesis, i.e., t-AML or AML-MRC (with PEL morphology). Case 1 described above fulfils morphological criteria for PEL. However, the presence of a complex karyotype requires re-categorisation as AML-MRC (with PEL morphology).

CASE 2: ACUTE ERYTHROID LEUKAEMIA (ERYTHROID/MYELOID) VERSUS ACUTE MYELOID LEUKAEMIA WITH MYELODYSPLASIA-RELATED CHANGES

Case presentation

A 60-year-old man presented with fatigue and dyspnoea. There was no significant past medical history. A complete blood