Minimally Differentiated Erythroleukemia: Recognition of Erythroid Precursors and Progenitors

Key words: erythroid-specific markers, glycophorin A, differentiation markers, HLA-DR, CD36 antigen

The French-American-British group proposed the classification of erythroleukemia as acute myelocytic leukemia (AML) M6 (1). This definition is based on the association of an erythroblastosis comprising over 50% of the nucleated bone marrow cells and an excess of non-erythroid blast cells. However, this definition is restrictive because the content of erythroblastosis is heterogeneous according to the differentiation level of abnormal erythroblasts. Recently, minimally differentiated erythroleukemia (AML M6 'variant') was proposed as a rare subset of AML distinct from AML M6 by Garand et al (2). When immunophenotyping leukemic cells, they had a HLA-DR⁺⁺ CD36++ B⁻ T myeloid⁻ (CD33⁻) immunophenotype in addition to a proerythroblast-like or an undifferentiated morphology. The morphological features of the latter sometimes lead to an initial diagnosis of an undifferentiated acute leukemia or a minimally differentiated AML (AML M0) (3), before studying the erythroid markers on leukemic cells. Such cases as minimally differentiated erythroleukemia have been reported previously and designated as 'cryptic erythroleukemia' (4) or 'early erythroblastic leukemia' (5). Villeval et al (5) distinguished two main phenotypes that correspond to discrete stages of the normal erythroid differentiation: A) the phenotype is identical to that of an immature erythroblast which expresses glycophorin A (GPA) identified by monoclonal antibody. B) the phenotype is related to that of CFU-E which expresses carbonic anhydrase I (CAI) (6, 7), CD36 (8, 9) and A antigen, but not HLA-DR antigen. Clinically, it is interesting that minimally differentiated erythroleukemia may arise as de novo AML, in Down's syndrome, as myelodysplastic syndrome-related AML or as blast crisis in chronic myelogenous leukemia (2, 4, 5).

At present, there are many techniques which enable the recognition of erythroid precursors and progenitors: e.g., immunophenotyping with erythroid-specific monoclonal antibodies, ultrastructural detection of ferritin molecules (10, 11), in vitro colony assay and molecular techniques studying mRNA expression of α- or γ-globin, erythroid-specific δ-amino-levulinate synthetase and GATA-1 transcription factor genes (12-14). GPA, band 3, and spectrin are specific membrane components of mature erythrocytes. Loken et al (15) reported that GPA is present on CFU-E, but others have reported that GPA is first expressed on proerythroblasts (5, 16, 17) or basophilic-erythroblasts (18). Band 3 is first expressed on erythroblasts with weak or negligible expression (19). Spectrin is first expressed on proerythroblasts (5), but spectrin and spectrin-related proteins have been detected strictly in non-erythroid cells (20). In addition to these markers, hemoglobin and CAI are also specific for erythroid hematopoietic cells. Hemoglobin or CAI is first expressed on basophilic-erythroblasts (17) or erythroid progenitors (CFU-E and BFU-E) (5), respectively. Yokochi et al (21) developed two monoclonal antibodies, EP-1 and EP-2, detecting antigenic determinants with restricted expression on erythroid precursors and progenitors. There are many other markers, which are not erythroid-specific ones, but determinants of the differentiation level of erythroid cells: e.g., CD36 antigen (thrombospondin receptor or platelet glycoprotein IV), blood group antigens (ABH, M and N, P₁, Lewis, li and so on) (16, 22), CD71 (transferrin receptor), HLA-A, B, C and HLA-DR, CD41b, CD33, CD34, and GATA-1 transcription factor. As Muroi et al (23) pointed out in this issue of the Internal Medicine, sialyl-Tn antigen and neuron-specific enolase also appear to determine the differentiation level of erythroid cells as well as characteristics of minimally differentiated erythroleukemia blasts.

See also p 843.

In detail, they reported the relationship between Tn and sialosyl-Tn antigens and the differentiation of erythroid progenitors and precursors in another manuscript (24). In the future, erythroid-specific markers and differentiation markers of erythroid cells will likely be arranged according to their specificity and convenience and the differences between normal and leukemic erythroid precursors and progenitors would also be clarified.

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References