Granular ALL in an Elderly Woman Diagnosed by Flow Cytometric Immunophenotyping

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Sir,

Myeloblasts are classically described as cells with a moderate amount of granular pale basophilic cytoplasm and multiple prominent nucleoli while lymphoblasts typically are smaller with scanty agranular deep blue cytoplasm and inconspicuous nucleoli [1]. We would like to share a case where this classical morphological appearance proved to be a diagnostic red herring that was resolved only with the help of immunophenotyping.

A 78-year-old previously healthy lady presented with gradually worsening symptomatic anemia for the last 4 months requiring 6 units of packed red cell transfusion. Physical examination revealed only mild pallor with no organomegaly or lymphadenopathy. Her hemoglobin (immediately post-transfusion) was 12.5 g%, total leukocyte count $13.4 \times 10^9/l$ and platelets $35 \times 10^9/l$ with a reticulocyte count of 2.1 %. The peripheral smear revealed 59 % blasts that were 2–3 times the size of small lymphocytes with high NC ratio, clumped chromatin, regular nuclear contours and prominent nucleoli. Most showed coarse, variably-sized azurophilic cytoplasmic granules. No Auer rods or Phi bodies were seen. The blasts were cytochemically negative for myeloperoxidase (MPO) and periodic acid-Schiff stains. The provisional diagnosis was acute leukemia, morphologically undifferentiated to

myeloid (the latter in view of the cytoplasmic granularity and nucleoli). A subsequent bone marrow aspirate too revealed 85 % blasts of similar granular nature without any significant dysplasia in the few residual hematopoietic precursors present (Fig. 1).

Flow cytometric immunophenotyping revealed a single large cluster in the progenitor region (dim CD45, low to moderate side scatter) that co-expressed CD19 and CD10 along with CD34, HLA-DR, terminal deoxynucleotidyl transferase (TdT) and dim CD123 and CD79a along with CD13 (Fig. 2). The blasts were negative for CD20 as well

Fig. 1 Bone marrow smears showed 85 % blasts that were 2–3 times the size of mature lymphocytes with high N:C ratio, clumped chromatin and regular nuclear contours. A few showed nuclear indentations and prominent nucleoli. The cytoplasm was coarsely granular; however no Auer rods were seen. (May Grunwald Giemsa, 1000 $\times$). *Inset A* shows similar blasts in the peripheral smear. (May Grunwald Giemsa, 1000 $\times$). *Inset B* shows blasts negative for myeloperoxidase. A myelocyte serves as an internal control. (MPO, 1000 $\times$)

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Fig. 2 On flow cytometry, cells in the blast/progenitor region (side-scatter^{low}, CD45^{dim}) comprised 89 % of all acquired events (**a**). These cells co-expressed CD19 and CD10 (**b**), CD34 and HLA-DR (**c**) and showed heterogeneous expression (negative to dim positive) of CD13

(51 %, **d**). These cells were positive for TdT, CD79a (dim, **e**) and CD123 (dim, **f**). These cells were negative for CD3, CD38, CD14, CD41, CD61, CD64 and MPO (**g–i**)

as all T cell and other myeloid markers tested. Conventional cytogenetics did not yield any metaphases but fluorescence in situ hybridization was negative for deletions of chromosomes 5, 7 and 20. Reverse-transcriptase polymerase chain reaction was negative for the BCR-ABL1 fusion transcript. The final diagnosis was adult B-lineage acute lymphoblastic leukemia (ALL) with granular blast morphology and aberrant CD13 expression. After discussion

with her family, she declined intensive forms of therapy and chose to receive palliative and supportive care at a centre close to her residence.

Granular ALL is an uncommon morphological variant of ALL, accounting for ~2–8 % of all pediatric ALL [2]. To the best of our knowledge only a few unequivocal adult cases have been described in English language medical literature [3, 4]. Among these, our case at 78 years is likely

the oldest till date with this entity. Morphologically, it closely mimics AML and definitive diagnosis requires immunophenotyping. On flow cytometry, although the majority of prior cases are of the common or precursor B-type, a few cases of precursor T-ALL also occur [5]. Aberrant myeloid marker expression may be a clue to a blast crisis in a myeloproliferative neoplasm, although this possibility was excluded in our case by the negative BCR-ABL1 fusion transcript result. Mixed phenotype acute leukemia too was excluded as current criteria require demonstration of MPO or at least 2 monocytic lineage markers in the blasts [1].

Adult granular ALL patients previously described have shown a slight female preponderance with the oldest aged 58 years, to the best of our knowledge [3]. There is no consensus regarding the exact nature of these granules on electron microscopy (EM). A study on the peripheral blood showed >10 % of the blasts contained granules positive for EM-MPO activity although such cases would meet current criteria for AML with minimal differentiation (M0) [6].

Granular ALL may, apart from causing diagnostic confusion with AML, also be associated with a worse prognosis in pediatric patients [7]. The prognostic significance of this entity in adults is unknown. In conclusion therefore, despite the limitations in epidemiologic, clinical, laboratory and outcome data, granular ALL should be borne in mind while evaluating acute leukemias in adults. Supplementation of morphology by immunophenotypic approaches comprises the current standard-of-care for MPO-negative acute leukemias and should be considered an essential part of the diagnostic work-up of these neoplasms.

Ethics declaration This report is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest The authors have no competing interests to declare.

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