IJHOSCR

Case Report

International Journal of Hematology-Oncology and Stem Cell Research

Report of Granular Blasts in Adult B-Cell ALL: A Rare Morphological Mimic of AML

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Received: 07, Mar, 2025
Accepted: 14, Sep, 2025

ABSTRACT

Granular ALL is one of the uncommon morphological variants of acute lymphoblastic leukemia (ALL), characterized by cytoplasmic granules in lymphoid blasts. This rare morphological presentation may lead to diagnostic misinterpretation. Case reports of such presentations enhance understanding of disease biology and therapeutic considerations.

Case presentation: A 22-year-old woman with Granular ALL has been discussed here. In the Peripheral blood smear (PBS) of this patient, cytoplasmic granules were identified in the cytoplasm of lymphoblasts. Further examinations were conducted on the bone marrow aspiration (BMA) sample of the patient, including karyotyping, flowcytometric and conventional molecular evaluations for ALL. The flow cytometric results were consistent with a diagnosis of B-ALL; the karyotyping analysis showed 47, XX, +17[4], and molecular findings revealed no detectable abnormalities.

Conclusion: Due to the misdiagnosis of Granular ALL as AML, the identification of distinguishing diagnostic features of Granular ALL is clinically significant. In this context, flow cytometric, cytogenetic, and molecular findings are invaluable to distinguish between these two types of acute leukemia.

Keywords: Acute lymphoblastic leukemia; Cytoplasmic granules; Flow cytometry; Cytogenetic; Bone marrow

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the second most prevalent form of acute leukemia, is characterized by the arrested differentiation and the clonal proliferation of lymphoid progenitor cells in the peripheral blood, bone marrow, and extramedullary sites[1]. Acute leukemia is defined by the presence of≥20% blasts in the blood and/or bone marrow[2]. The presence of granules in lymphoid blasts, unlike myeloid blasts, is rare.

Granular morphology in ALL is infrequently observed, reported in approximately 1.7–7% of all cases, with ~4–5% in children and even fewer in adults [3,4]. The clinical and pathological characteristics and optimal treatment of granular ALL remain unclear, especially in adult patients[5,6]; diagnostic confirmation requires the diagnosis of ALL versus AML by immunophenotyping and cytogenetic and molecular methods. Here, we present a case of adult granular B-ALL in a young woman, illustrating the diagnostic challenges and definitive diagnostic findings by immunophenotyping and molecular analysis.

Case presentation

The case, from northeastern Iran, was a 22-year-old woman with constitutional symptoms (B symptoms), including fever, generalized weakness and fatigue, loss of appetite, weight loss, night sweats, and bleeding signs such as superficial and subcutaneous bleeding.

Additionally, the patient had clinical signs of anemia. In the physical examination, only splenomegaly was observed. Laboratory results are summarized in Table 1. An expert pathologist examined the peripheral blood smear and reported a 70% blast count, with 10-15% of the blasts exhibiting azurophilic cytoplasmic granules (Table 1). These granules were readily apparent in the cytoplasm (Figure 1). Nevertheless, there were no *Auer* rods in the blast cells. For confirmation of granularity, at least three granules should be observed in the cell[4]. The peroxidase staining was performed, and was negative, supporting a lymphoid lineage of the blast cells. Molecular analysis was conducted, and the results were also negative for these translocations: t(4;11), t(1;19), t(12;21), t(9;22)(q34.1;q11.2)(BCR-ABL1 fusion in at breakpoints corresponding to p190 (minor BCR) and p210 (major BCR)).

Karyotyping was also performed on the patient (Figure 2). The metaphase preparation was suboptimal for structural chromosome analysis, and the cells exhibited inadequate mitotic activity during culture; therefore, we were unable to analyze all the metaphase cells. Only four analyzable metaphase spreads were obtained for numerical analysis; the available metaphases revealed 47, XX, +17[4].To further classify the blast population, flow cytometry analysis was performed, revealing positivity for CD19, CD10, CD34, and TdT, as well as partial CD20 expression; MPO was negative (Table 2). Taken together, morphology (granular blasts), cytochemistry (MPO−), immunophenotype, and cytogenetics were consistent with a diagnosis of B-cell acute lymphoblastic leukemia.

Table 1: Complete blood count results

RBC ×10^6/µL	**WBC ×10^3/µL**	**PLT ×10^3/µL**	**Hb (**g/dl), **HCT (%)**	**Blast (%)**
4.1×10*6	34,000	80,000	9, 27	70

Table 2: Immunophenotypic profile by flow cytometry

CD4	**CD7**	**CD8**	**CD10**	**CD19**	**CD20**	**CD33**	**CD34**	**CD117**
-	**-**	**-**	**+**	positive (80% of Blasts)	positive (51% of Blasts)	**+ (**aberrant expression)	**+**	**-**

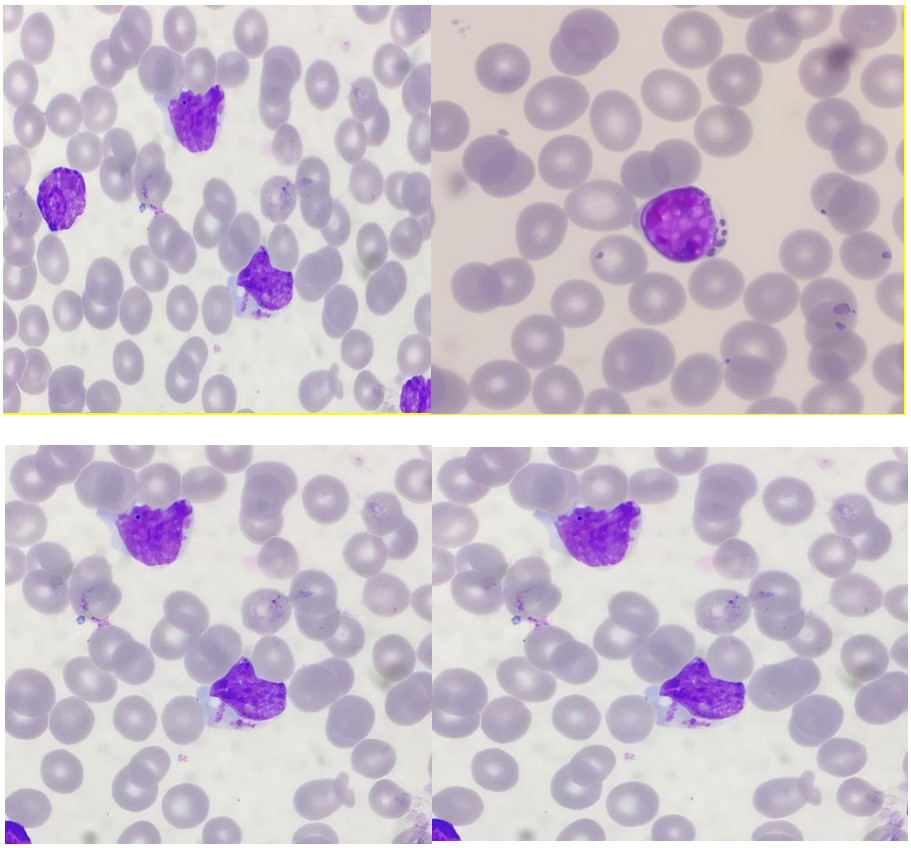

Figure 1. Peripheral blood smear showing blasts with prominent azurophilic cytoplasmic granules (Wright-Giemsa stain, ×1000). Granules may mimic AML morphology

Figure 2. Conventional karyotyping from bone marrow aspirate showing trisomy 17 (47,XX,+17) Only 4 metaphases available due to poor growth

DISCUSSION

In the morphological categorization of myeloid blasts, some types of cells contain azurophilic granules; this feature is typically absent in lymphoblasts. Therefore, the observation of these granules is rare in ALL[7]. Cytoplasmic granules in lymphoblasts have been variably described as lysosomal aggregates or abnormal vesicles, but their exact nature remains uncertain[8].

Additionally, a study that is likely one of the first reports on granular ALL cases revealed that electron microscopy findings showed these granules to be composed of small vesicles closely packed within a protein matrix, somewhat similar to those found in Chediak-Higashi syndrome lymphocytes, but distinct from them[9]. It is noteworthy that the blast phenotype, defined as granular, and our basis for categorizing it as such, was to have at least how many granules? According to the study by L. CRESO et al., granular ALL is characterized by the presence of more than 5% marrow blasts with at least three azurophilic cytoplasmic granules[4]. We also followed this principle in the present study.

The differentiation of granular ALL from AML remains diagnostically challenging. Although a few cases of this rare ALL have been reported to date, there is still little information about granular ALL, and reporting more cases will help to gain better insight into disease pathogenesis, therapeutic response, and clinical management of the disease.

Prognostic implications of Granular ALL remain a subject of debate: some studies suggest inferior outcomes, while others show no apparent difference. More systematic studies are required, particularly in adults[3,4]. Although some studies suggest that the granular type of ALL is not of high importance in prognosis[10,11], the features that indicate a poor prognosis underscore the biological complexity of this rare type of ALL. This importance is more pronounced in adult cases, as it is rarer in adults.

In this study, the patient was a recently diagnosed young adult female. The patient was considered a new case, and unfortunately, there is no clear information on the treatment process. In PBS of this patient, 10–15% of blasts had granules, meeting the diagnostic threshold (>5% blasts with ≥3 granules).

According to the study conducted by Sangyang Jia et al., in which they examined the laboratory findings of 19 adult patients with granular ALL (18 cases were reported before, in addition to the index case presented in the study), all adults belonged to the L2 subtype[12]; our case study was also L2. Also, in the cited study [12], most of the patients were B-cell type (90 %), which was compatible with the present study.

Another point that can be mentioned about the article of Sangyang Jia et al. is that only four out of the total 19 cases of examined adults were under 30, which shows the low prevalence of granular ALL in adult populations; but it is more rare in younger adults under the age of 30, like the case of the present study (she was 22 years old)[12]. Regarding age distribution, ALL follows a bimodal incidence pattern, with the first peak occurring in childhood and the second around the age of 50[13].

Studies conducted on children's population revealed that some genetic syndromes, such as Down syndrome, Fanconi anemia, etc, confer increased susceptibility to some types of ALL [14,15]. Also, in many cases of granular ALL, cytogenetic tests show cytogenetic abnormalities. For example, the case investigated in Wenpeng Ni et al.'s study had trisomy 6 and 7 and monosomy 17 [16], like the case studied by Juhye Roh et al., which had also monosomy 7[17]. Our studied case also had trisomy 17. It appears that genes related to the development of granular ALL are located on specific chromosomes, such as chromosomes 7 and 17. Focused investigation of these chromosomal loci in ongoing research and molecular studies, including next-generation sequencing (NGS), is crucial and likely helps researchers identify the responsible genes and enhance treatment methods. Our case presents the evidence that chromosome 17 aberrations may be recurrent in granular ALL. Philadelphia chromosome has also been documented in the granular ALL cases[18], but it was not found in our case.

The exact mechanisms underlying the phenotypic mimicry of AML remain unclear. Granular ALL mimics AML; however, some findings suggest that this event likely occur at a stage proximal to pluripotent hematopoietic precursors[1,2,19]. We were unable to report the treatment course and outcome, which

limits prognostic interpretation. Considering the different results and limitations of information sources, such as missing data and diversity in disease characteristics and treatment methods, as well as the novelty of this type of ALL, drawing definitive conclusions remains challenging due to data limitations and heterogeneity in clinical presentations.

CONCLUSION

An accurate diagnosis remains the cornerstone of effective treatment. Because Granular ALL is frequently misclassified as AML, clinicians should be aware of this uncommon morphological variant of ALL. To differentiate these two malignancies, flow cytometric profiling is essential. Additionally, according to recent advances in molecular diagnostics, including NGS, there is likely enhanced diagnostic precision that requires further research.

In terms of treatment response and overall survival, as mentioned, unfortunately, granular ALL individuals have a poorer prognosis than the non-granular B-ALL. These findings underscore the need for further research to improve clinical outcomes in this patient population.

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