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CASE REPORT

A Rare Case Study of Granular Acute Lymphoblastic Leukemia Combined with Pleural Infiltration

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SUMMARY

Background: **Acute B-lymphoblastic leukemia (B-ALL) is a common hematologic malignancy characterized by blasts with a variable amount of cytoplasm, typically ranging from minimal to moderate, and containing few cytoplasmic granules. However, granular acute lymphoblastic leukemia, as a rare subtype, is distinguished by the presence of abundant coarse, purplish-red granules within the cytoplasm of the blasts, which can be confused with other diseases in clinical diagnosis.**
Methods: **The patient was examined using bone marrow morphological analysis, flow cytometry, genetic screening, and chromosome karyotype analysis.**
Results: **The case presented with a high number of coarse, purplish-red granules in the cytoplasm of the blasts, which morphologically resembles acute myeloid leukemia and basophilic granulocytic leukemia. Through cytochemical and immunophenotypic analyses, we ultimately diagnosed the case as granular acute lymphoblastic leukemia with pleural infiltration.**
Conclusions: **Granular acute lymphoblastic leukemia, as a rare subtype, requires particular attention in clinical diagnosis. Cases with similar morphological features should undergo comprehensive diagnostic workups, including cytochemical and immunophenotypic analyses, to avoid misdiagnosis. This case report provides an important reference for further understanding of granular acute lymphoblastic leukemia.**
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INTRODUCTION

Granular acute lymphoblastic leukemia (G-ALL) is a rare yet formidable hematologic malignancy often presenting diagnostic challenges, as its granular intracellular constituents, including granules and vesicles within lymphocytes, may mimic features of acute myeloid leukemia. Predominantly afflicting pediatric and young adult populations, G-ALL infrequently manifests in old-

er individuals. Clinical manifestations commonly encompass progressive malaise, anemia, pyrexia, and lymphadenopathy [1]. Therapeutic strategies primarily entail cytochemotherapy, though the exigency of bone marrow transplantation or adjunctive interventions may arise contingent upon disease severity and individual patient factors. Timely application of histochemical staining and immunophenotypic analysis is pivotal for accurate diagnosis and implementation of efficacious therapeutic modalities, thereby markedly enhancing patient prognosis and quality of life.

CASE PRESENTATION

A 47-year-old female patient was admitted to the hospital with a diagnosis of acute lymphocytosis. She reported symptoms of cough, dyspnea, and fatigue persisting over the past two weeks. Physical examination revealed the absence of detectable generalized and superficial lymph nodes, no presence of petechiae or ecchymosis on the skin or mucous membranes, absence of sternal tenderness, and non-palpable liver and spleen under the rib cage.

The patient had previously sought medical care at a local hospital due to fatigue, malaise, and cough following exposure to cold. Routine blood tests revealed elevated leukocyte levels, and a bone marrow smear indicated abnormal proliferation of primitive blood cells, constituting 89% of the absolute neutrophil count (ANC), consistent with a diagnosis of acute leukemia. Flow cytometry analysis demonstrated approximately 81.9% primitive/naive cells, indicating acute leukemia, with an immunophenotypic inclination towards acute B-lymphoblastic leukemia. Subsequently, the patient was transferred to our hospital for further management.

Upon admission, the patient's laboratory values showed: Alanine aminotransferase 10 U/L, Lactate dehydrogenase 262 U/L, Creatinine 89.9 μmol/L, Glucose 7.52 mmol/L, Potassium 3.98 mmol/L, Sodium 141.0 mmol/L, Calcium 2.26 mmol/L, Albumin 34.5 g/L. Routine analysis of pleural and abdominal fluid presented as yellow with clots, Levantha's test was positive, with a nucleated cell count of 3,462 x 10^6/L and a lymphocyte percentage of 94%. Additional biochemical tests of the pleural and abdominal fluid showed total protein 27.0 g/L, albumin 16.9 g/L, lactate dehydrogenase 268 U/L, and adenosine deaminase 16.1 U/L. A chest CT scan revealed a moderate volume of fluid in the right thoracic cavity and decreased air content in the surrounding lung tissue.

Bone marrow cytology revealed abnormal proliferation of the lymphocytic system, with primitive lymphocytes and naive lymphocytes constituting 75.0% of the absolute neutrophil count (ANC). Cellular morphology characteristics included uneven cytosol size, primarily composed of small, round or round-like cells with a small volume of light blue cytoplasm. The cytosolic nucleus appeared round-like or irregular in shape, accompanied by coarse granular nuclear chromatin and predominantly cryptic nucleoli. In addition, smear cells were easily observed, and some lymphocytes exhibited coarse purplish-red granules in the cytoplasm (Figure 1A). Cellular immunohistochemical staining demonstrated a negative peroxidase (POX) result (Figure 1B), while glycogen staining revealed the presence of coarse granules (Figure 1C). Further toluidine blue staining was performed to exclude basophilic leukemia, yielding a negative result (Figure 1D). These findings supported a bone marrow morphology consistent with acute lymphoblastic leukemia. Bone marrow flow cytometric analysis revealed an immunophenotype consistent with acute B-lymphoblastic leukemia (Figure 2A). Further investigation was conducted to determine whether the patient had a tumor infiltrating the pleural cavity. Cytometric Riesling staining of the punctured pleural fluid indicated a significant presence of primary naive lymphocytes, with observation of cytoplasmic purplish-red granules (refer to Figure 2B). Subsequent flow cytometric analysis of the pleural fluid identified 72.5% of abnormal immunophenotype B lymphoid primitive naive cells. The IKZF1 gene copy number variant (CNV) test revealed a deletion in the ETV6 gene (EXON 1, 2, 3, 5, 8). Screening for leukemia-associated fusion genes and bone marrow karyotype analysis showed no significant abnormalities. The patient's final diagnosis comprised acute B lymphoblastic leukemia with extramedullary lesions and tumor pleural infiltration. Upon admission, the patient received zoerythromycin, vincristine, and glucocorticoid chemotherapy, alongside gastric, liver, and renal protection, antiemetic therapy, hydration, alkalinization, and other required symptomatic treatments.

DISCUSSION

The bone marrow cell morphology in this case is notably distinctive. In addition to the typical cellular characteristics observed in acute lymphoblastic leukemia (including medium to abundant light blue cytoplasm, fine granular chromatin, small nucleoli, and crypts), a significant number of basophilic granules are evident within some cell cytoplasm. These granules are exceptionally rare in acute lymphoblastic leukemia and can be easily mistaken for those found in basophilic granulocytic leukemia and acute myeloid leukemia. Furthermore, the flow cytometric immunophenotyping in this case of granulocytic acute lymphoblastic leukemia revealed expression of CD19, partial expression of CD10, CD7, HLA-DR, cCD79a, CD13, CD33, and CD56, while it did not exhibit expression of CD2, CD34, CD20, CD117, MPO, and cCD3, consistent with an acute B lymphoblastic leukemia immunophenotype. Research has underlined the identification of IKZF1 gene deletion as a poor prognostic factor in pediatric acute B-lymphoblastic leukemia [2]. Notably, our patient's IKZF1 plus gene CNV test indicated ETV6 (EXON 1, 2, 3, 5, 8) gene deletion, which is present in 51% of

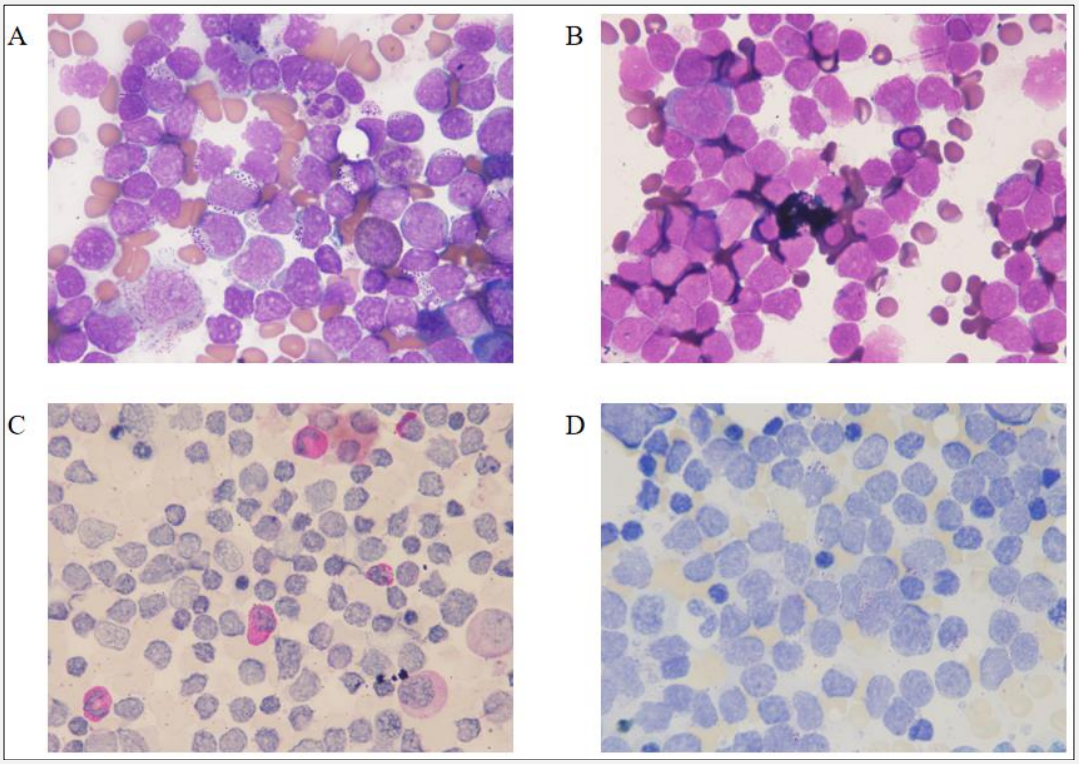

Figure 1: Bone marrow smear analysis.

A) Presence of numerous granular primitive naive lymphocytes observed in the cytoplasm (magnification x 1,000). B) Negative peroxidase staining result (magnification x 1,000). C) Positive identification of coarse granularity within the cytoplasm of primitive naive lymphocytes (magnification x 1,000). D) Absence of staining observed with Toluidine blue (magnification x 1,000).

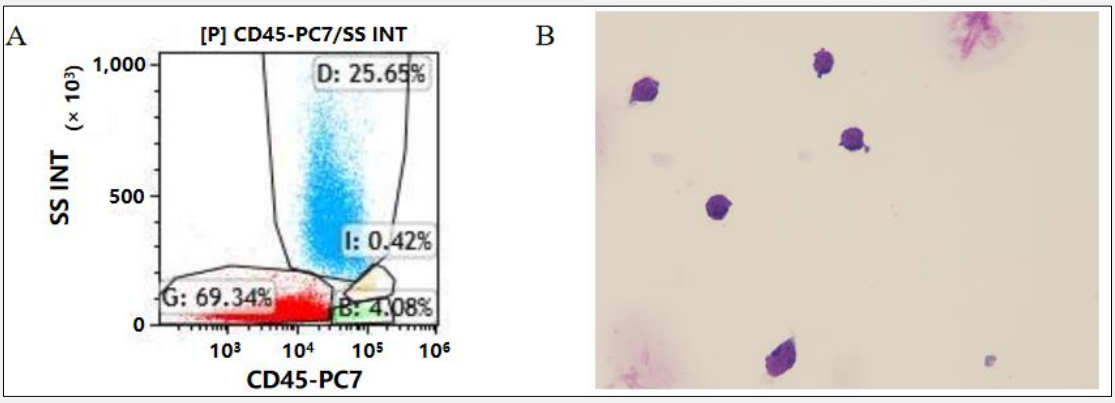

Figure 2. A) Bone marrow flow cytometric analysis reveals the presence of 69.34% abnormal immunophenotype B lymphoid primitive naive cells. B) A significant accumulation of granular primitive naive lymphocytes is observed in the pleural fluid (magnification x 1,000).

cases of B-ALL. Specifically, in ETV6-RUNX1 positive childhood ALL, the deletion of the ETV6 gene is associated with a more favorable prognosis [3].

G-ALL represents a rare subtype of acute lymphoblastic leukemia primarily detected in pediatric cases [4], notably associated with Down syndrome and sporadically reported in adults [5]. Differentiating this leukemia variant from acute myeloid leukemia poses diagnostic challenges, with pediatric cases exhibiting a less favorable prognosis as compared to their counterparts with different types of acute lymphoblastic leukemia. Cytoplasmic granules within lymphoblastoid cells in G-ALL present distinctive characteristics. Research indicates that these granules may stem from a swollen and fused endoplasmic reticulum possessing a low electron-density membrane-enveloped structure, distinct from organelles like lysosomes, mitochondria, and the Golgi apparatus [6,7]. Due to morphological similarities with progranules of myeloid precursor cells, immature basophils, and occasionally small Auer vesicles [8], immune phenotypic analysis becomes essential for determining cell lineage. Furthermore, the prognostic outlook for granulocytic acute lymphoblastic leukemia varies among pediatric and adult populations, with indications suggesting a potentially adverse prognostic impact of granular morphology in adults [9]. Nevertheless, research on G-ALL in adults faces limitations due to the small patient pool, warranting a detailed exploration of its specific clinical implications.

Apart from the rare G-ALL observed in this case, we noted a significant presence of prolymphocytes with purplish-red granules in the cytoplasm of pleural fluid cells, marking a distinctive finding. This observation may suggest an extensive extramedullary spread of leukemia cells, potentially linking to a poor disease prognosis. Notably, the escalation of primitive cells in the pleural fluid can influence treatment selection and efficacy evaluations. Systematic monitoring of pleural fluid cells enables healthcare practitioners to comprehend disease progression effectively and prompt adjustments to treatment strategies. The abundance of granular primitive lymphocytes in the pleural fluid not only signifies disease severity in this patient but also serves as a crucial clinical parameter guiding treatment decisions and monitoring practices.

CONCLUSION

In conclusion, establishing an early and precise diagnosis is pivotal for the management and prognosis of granular acute leukemia. Distinguishing acute lymphoblastic leukemia with basophilic granular inclusion bodies from acute myeloid leukemia and basophilic granulocytic leukemia poses challenges. Therefore, in the laboratory diagnostic assessment, reliance solely on cellular morphology manifestation should be avoided. It is imperative to analyze and diagnose the disease in conjunction with histochemical staining, flow cytometric analysis, and identification of leukemia-associated fusion genes, along with other multiple parameter cell analysis, to prevent misdiagnosis.

Declaration of Interest:
The authors have no conflicts of interest relevant to this article to disclose.

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