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Discovery of G6PD deficiency in a patient with DUSP22-rearranged ALK-negative anaplastic large cell lymphoma in leukemic phase

Jessica Anderson

Eileen Putnam

Wei Liu

Madhu P. Menon

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CASE IMAGE

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Discovery of G6PD deficiency in a patient with *DUSP22*-rearranged ALK-negative anaplastic large cell lymphoma in leukemic phase

Jessica Anderson[1] | Eileen Putnam[2] | Wei Liu[2] | Madhu P. Menon[3]

[1]School of Medicine, Wayne State University, Detroit, MI, USA

[2]Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI, USA

[3]Department of Pathology, University of Utah and ARUP Laboratories, Salt Lake City, UT, USA

Correspondence: Madhu P. Menon, Department of Pathology, University of Utah and ARUP Laboratories, 500 Chipeta Way, Salt Lake City, UT 84108, USA.
Email: madhu.menon@aruplab.com

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An 88-year-old man with respiratory symptoms was found to have prominent lymphadenopathy in the chest, ill-defined low-density lesions in the liver (Figure 1A), and diffuse abdominal lymphadenopathy. A biopsy of the liver lesion revealed sheets of anaplastic cells with several cells demonstrating eosinophilic pseudo-nuclear inclusions ("doughnut cells") (Figure 1B, upper right inset), horseshoe-shaped nuclei ("hallmark cells") (Figure 1B, lower left inset), and occasional cells with multinucleation (Figure 1B, lower right inset). Immunohistochemistry demonstrated positivity for CD30, CD3, CD4, CD5, CD2, MUM1, and negativity for ALK1, CD7, CD8, TIA-1, granzyme B, CD20, and PAX5. This was consistent with a diagnosis of ALK-negative anaplastic large cell lymphoma (ALK-negative ALCL). Fluorescence in situ hybridization (FISH) studies detected positive *DUSP22* (*IRF4*) rearrangement and no *TP63* rearrangement. Subsequently, elevated serum uric acid (13 mg/dL) and lactate dehydrogenase (LDH) levels (1018 IU/L) were detected leading to suspicion of tumor lysis syndrome, which prompted allopurinol and rasburicase therapies. Following this, the patient's

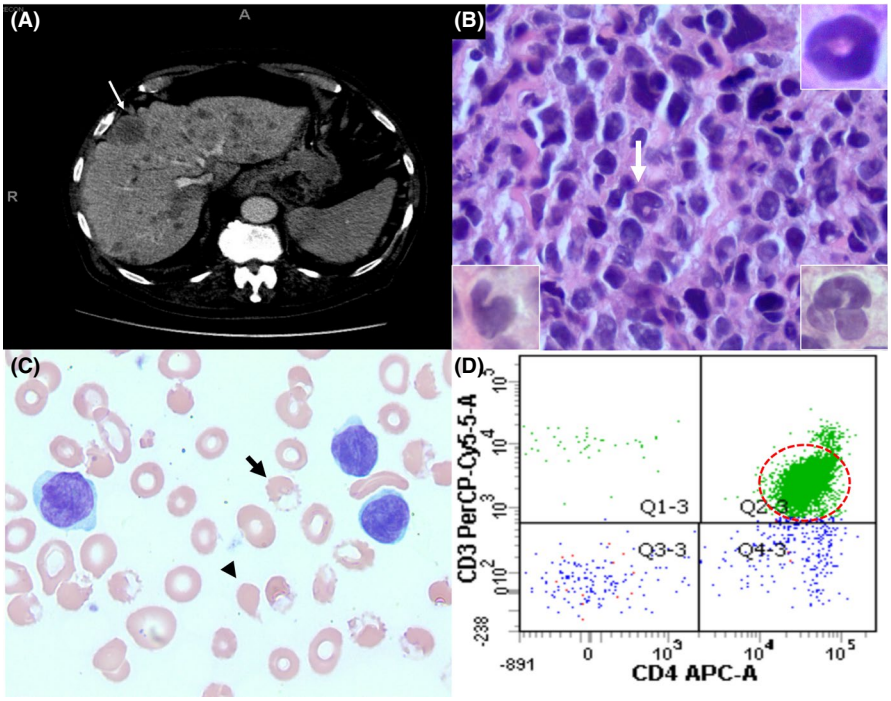

FIGURE 1 A, CT scan abdomen demonstrating multiple ill-defined low-density lesions with the largest measuring 3 cm (arrow). B, Hematoxylin and eosin (H&E ×500)-stained section from liver biopsy demonstrating sheets of anaplastic cells with occasional "doughnut" cell morphology (arrow and upper right inset), hallmark cells (lower left inset), and multinucleated cells (lower right inset). C, Post-rasburicase peripheral smear demonstrating blister cells (arrow), schistocytes (arrow-head), fragmented RBCs, and atypical ALCL lymphocytes. D, Flow cytometry of peripheral blood demonstrating CD3+ (dim), CD4+ ALCL lymphocytes (circled population)

hemoglobin dropped to 5.8 g/dL and laboratory workup showed low haptoglobin (<30.0 mg/dL), increased total bilirubin (3.2 mg/dL), and elevated D-dimer level (2.4 μg/mL FEU). Peripheral blood smear demonstrated blister cells, schistocytes, fragmented RBCs, and atypical lymphocytes (18%) with absolute lymphocyte count of 3 K/μL (Figure 1C). Peripheral blood flow cytometry revealed the presence of an atypical CD3+ (dim), CD4+ T-cell population (Figure 1D) (also positive for CD2, CD5, CD25 (dim, subset), T-cell receptor alpha/beta, and negative for CD8, CD7, CD26, CD56, CD16, CD57, and T-cell receptor gamma/delta) supportive of ALCL in leukemic phase. The presence of hemolysis raised the suspicion for glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD quantification confirmed low levels; 4.0 U/g Hgb (normal range, 7.0-20.5 U/g Hgb). Rasburicase was discontinued; patient was given blood transfusions and hemolysis resolved.

ALK-negative ALCL is an uncommon variant of mature T-cell lymphomas that comprises 40%-50% of systemic ALCL.[1] It affects the adult population and carries a worse prognosis as compared to ALK-positive ALCL, which occurs mostly in children/young adults and responds well to chemotherapy.[1] Peripheral blood involvement is rare, and most reported cases are ALK-positive ALCL in children. In a series of four adult patients with ALK-negative ALCL in leukemic phase, both survival and response to therapy were poor.[2] *DUSP22* rearrangement (30% of ALK-negative ALCLs) is associated with a good prognosis and "doughnut cell-" like morphology.[1] This patient was also discovered to have G6PD deficiency which is most commonly caused by mutations of the G6PD gene (x-linked).[3] In these patients, oxidative hemolysis can be triggered by ingestion of fava beans, infections, and a myriad of drugs (antibiotics, antimalarials, rasburicase, pegloticase, etc).[3] Peripheral smear generally demonstrates the presence of blister cells, bite cells, schistocytes, and polychromasia. RBCs can also exhibit Heinz bodies as exhibited by supravital stains. However, diagnosis is best established by a quantitative G6PD test.[3] A caveat is that false normal results can occur during or immediately after hemolysis (due to reticulocytosis) requiring a repeat analysis. In patients with tumor lysis syndrome, G6PD deficiency should be ruled out prior to rasburicase therapy.[3]

CONFLICT OF INTEREST

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

ORCID

Madhu P. Menon https://orcid.org/0000-0002-4075-4961

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