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Acute Myeloid Leukemia with Cup-Like Nuclear Inclusions, and FLT3-ITD and NPM1 Mutations

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Case Report

A 69-year-old man presented to an outside hospital with fatigue, fevers, altered mental status, and dyspnea. Laboratory testing revealed a white blood cell count of 231 × 103/μL with 88% blasts, hemoglobin of 6.2 g/dL, and platelet count of 80 × 103/μL. Bone marrow biopsy confirmed a diagnosis of acute myeloid leukemia (AML) with flow cytometric analysis demonstrating two abnormal myeloblast populations, the first expressing CD11b (partial), CD13, CD33, CD45 (dim), CD64, CD117, and HLA-DR and the other CD10, CD11b, CD13 (subset), CD14, CD15, CD33, CD45 (moderate to bright), CD64, and HLA-DR. Both populations showed heterogeneous expression of myeloperoxidase and were negative for CD34 expression. Karyotype and FISH studies revealed no chromosomal abnormalities.

He received standard remission induction with cytarabine and idarubicin ("7&3"). His remission induction course was complicated by gastrointestinal bleeding, atrial fibrillation with rapid ventricular response, and ongoing neutropenic fever associated with pulmonary infiltrates and hypoxia despite broad antimicrobial treatment. No specific organism was ever identified and he became afebrile with normal oxygenation and pulmonary radiography shortly after bone marrow functional recovery. A repeat bone marrow biopsy on day 14 showed a hypocellular marrow without evidence of residual leukemia. No day 28 bone marrow biopsy was performed.

Roughly two months after the initiation of remission induction therapy he was referred to our center and a bone marrow biopsy showed slightly hypercellular marrow with multilineage hematopoiesis. Rare abnormal myeloblasts representing approximately 1% of marrow cellularity were present and expressed CD7 (subset, dim), CD13, CD15 (partial, dim), CD33, CD38, CD45 (dim), CD117, and HLA-DR. These myeloblasts were negative for CD34 expression. No mutations were identified by a 43-gene AML/MDS next-generation sequencing (NGS) panel or by single gene molecular assays for FLT3, NPM1, CEBPA, and CKIT. He was treated with intermediate-dose cytarabine with no complications. Allogeneic hematopoietic transplant was planned with his haploidentical daughter as the potential donor, but within three weeks he developed a new painless, non-pruritic rash on both his lower and upper extremities. Biopsy revealed leukemia cutis with concurrent bone marrow biopsy showing increased myoblasts representing 35% of marrow cellularity with an immunophenotype similar to what was noted in the preceding biopsy. The myeloblasts showed oval nuclei, fine chromatin, prominent nucleoli, "cup-like" nuclear invaginations, and scant cytoplasm rarely containing fine azurophilic granules (Figure 1). Karyotype and FISH studies remained normal, but mutational analysis demonstrated a 4 bp duplication in NPM1 exon 12 (W288fs) and a 21 bp in-frame internal tandem duplication in the juxtamembrane domain of FLT3 (FLT3-ITD). Additional point mutations were also detected in DNMT3A (R882H), FLT3 (F594L), IDH1 (R132C), and PTPN11 (A72D).

Re-induction therapy with cytarabine and clofarabine for five days provided no benefit as evidenced by the emergence of rapidly increasing peripheral leukemic cells on day 22 and beyond. Bone marrow biopsy confirmed refractory AML involving 80% of the marrow space. While no cytogenetic abnormalities were found, all the prior mutations continue to be detected. Concurrently, he developed disseminated varicella zoster, successfully treated with acyclovir. While his peripheral white blood cell count was virtually all myeloblasts requiring hydroxyurea to prevent leukostasis, he also had transfusion-dependent bone marrow failure. He was subsequently treated with decitabine since he was not interested in clinical trials. After the second cycle, his WBC count continued to increase, requiring increasing doses of hydroxyurea. He decided to initiate hospice care and died three days later.

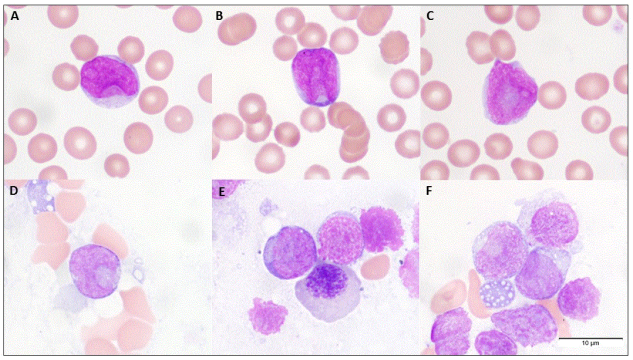

Figure 1: Blasts demonstrating cup-like nuclear invaginations in the peripheral blood (A-C), and bone marrow aspirate (D-F) with Wright-Giemsa staining at 1000x. Panels A and D show classic morphology with clear cup-shaped inclusions overlying the nucleus, while the remaining panels show morphologic variations. Images are taken with an Olympus BX51 microscope and Olympus DP27 camera.

Cup-like nuclear invaginations in blasts are thought to arise from in-folding of cytoplasmic material over the nucleus forming a distinct nuclear inclusion. These inclusions must span at least 25% of the nucleus in diameter, and when present in 10% or more of the blasts may be associated with distinct molecular findings [1]. While not specific, cup-like nuclear invaginations in AML were originally

described to be associated with either NPM1 mutations or FLT3-ITD mutations [1,2], but are in fact more strongly associated with concurrent NPM1 and FLT3-ITD mutations [3], a common occurrence [4]. Lack of CD34 and HLA-DR expression, and a normal karyotype are also features that have been seen with this distinctive morphology and mutational profile. As the presence of NPM1 and FLT3-ITD mutations carry prognostic significance, and given the emergence of FLT3-ITD specific tyrosine kinase inhibitors, the morphologic recognition of cup-like nuclear invaginations may be an early indicator of the presence of these mutations. Morphologic recognition of these cells can aid the diagnostic lab in triaging such cases for mutational analysis, and decrease turnaround time of these critical tests, which could improve treatment and outcomes in this subset of AML patients.

References

1. Chen W, Konoplev S, Medeiros LJ, Koeppen H, Leventaki V, et al. (2009) Cuplike nuclei (prominent nuclear invaginations) in acute myeloid leukemia are highly associated with FLT3 internal tandem duplication and NPM1 mutation. Cancer 115: 5481-5489.
2. Bennett JM, Pryor J, Laughlin TS, Rothberg PG, Burack WR, et al. (2010) Is the Association of "Cup-like" Nuclei WithMutation of the NPM1 Gene in Acute Myeloid Leukemia Clinically Useful? American journal of clinical pathology 134: 648-652.
3. Park BG, Chi HS, Jang S, Park CJ, Kim DY, et al. (2013) Association of cup-like nuclei in blasts with FLT3 and NPM1mutations in acute myeloid leukemia. Annals of hematology. 92: 451-457.
4. Cancer Genome Atlas Research Network (2013) Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 368: 2059-2074.