

Case Series: Malignant Flower Cells in Peripheral Blood

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ABSTRACT

The presence of lymphoid cells with flower-like nuclei in peripheral blood is an uncommon morphologic finding, classically associated with Human T-lymphotropic virus type 1 (HTLV-1) infection related Adult T-cell Leukemia/Lymphoma (ATLL). However, similar cytologic features may be observed in other hematolymphoid malignancies. To describe cases of hematologic neoplasms presenting with flower cells in the peripheral blood and to highlight their broader diagnostic spectrum. We report a series of patients with distinct hematologic malignancies who demonstrated flower cells on peripheral blood smear, thereby expanding the morphologic differential beyond ATLL. Recognition that flower-like nuclear morphology may occur outside the context of ATLL is important for accurate diagnosis and underscores the need to consider a boarder range of hematolymphoid neoplasms in the differential.

Keywords: Malignant, Flower cells, ATLL, ALL

INTRODUCTION

Peripheral blood smear review represents a cost-effective, minimally invasive diagnostic tool that provides significant clinical insight. In this case series, we describe three uncommon clinical presentations characterized by lymphocytes exhibiting flower-like nuclear morphology in the peripheral blood. Although these cells share certain morphologic features, they arise from distinct pathogenic mechanisms and exhibit divergent immunophenotypic and molecular profiles, prognoses and treatment implications. These observations highlight the critical importance of recognizing this morphologic pattern and pursuing a comprehensive diagnostic workup to ensure precise disease classification.

CASES DESCRIPTION

Case 1

A male patient in his mid-60s with an unremarkable medical history was hospitalized for progressive dyspnea and lower extremity edema and was admitted for acute congestive heart failure. Imaging during the admission demonstrated diffuse lymphadenopathy (up to 6 cm) involving the chest, abdomen, and pelvis, along with scattered hepatic hypodensities. Excisional lymph node biopsy revealed diffuse infiltration by pleomorphic neoplastic cells, positive for CD2, granzyme B, TIA-1, CD30, and CD43, negative

for ALK-1, with a high proliferation index, consistent with ALK-negative anaplastic large cell lymphoma (ALK-negative ALCL). Next-generation sequencing detected mutations in STAT3, RAD51, PLCG2, FANCI, FOXL2, MSH3, KMT2C. No rearrangement was detected. EBV serology was positive and HTLV1 antibodies were negative.

The hospitalization was complicated by hospital-acquired pneumonia, venous thromboembolism, elevated transaminases, and elevated creatinine necessitating dose reduction of chemotherapy (CHOP regimen). The patient was discharged with plans to initiate brentuximab-vedotin based chemotherapy as an outpatient. However, he was readmitted with acute hypoxic respiratory failure secondary to progressive pneumonia. Peripheral blood smear review revealed large cells with petal-like nuclear contours and abundant basophilic cytoplasm (Figure 1A,B). The patient passed away after one week from progressive respiratory failure.

Case 2

A male in his late 60s with multiple medical comorbidities initially presented with left lower quadrant abdominal pain and altered mental status. Laboratory evaluation revealed hypercalcemia (14.3 mg/dL), marked lymphocytosis (white blood cell counts increased to $50.3 \times 10^3/\mu\text{L}$ from a baseline

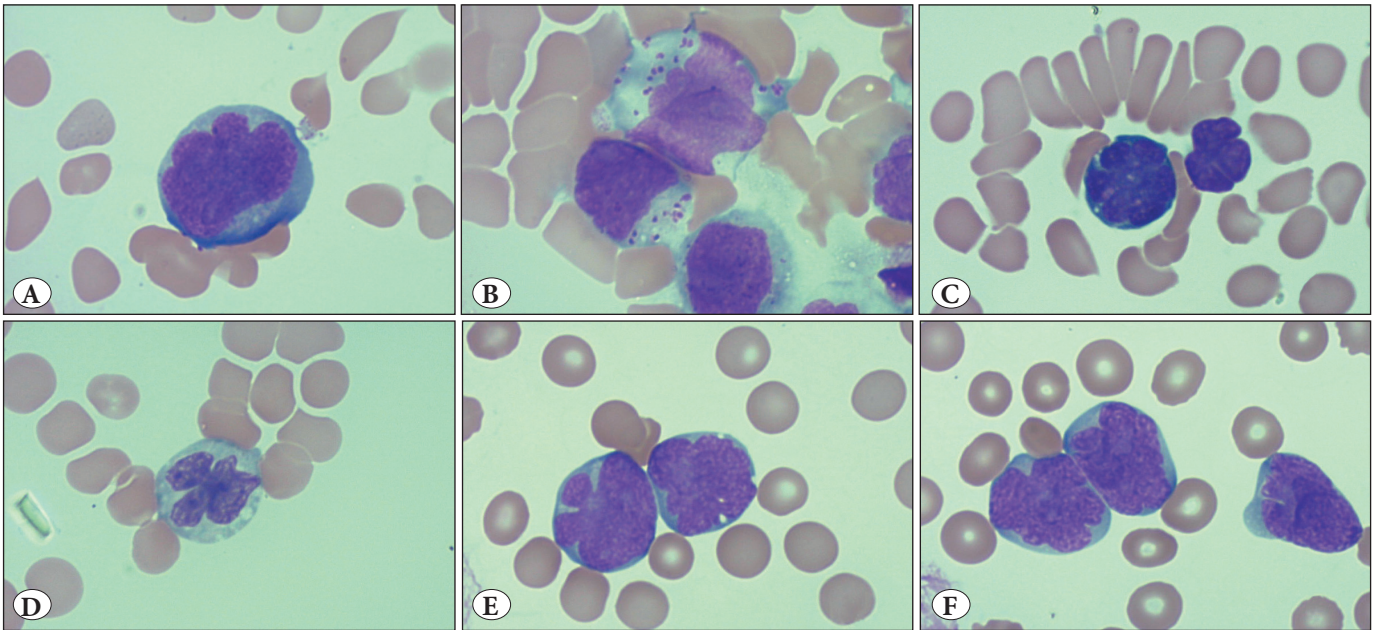


Figure 1: A, B) (100 x High Power field, hematoxylin eosin stain), the neoplastic cells are large in size, and demonstrate irregular nuclear contours, fine chromatin, occasionally with prominent nucleoli and scattered cytoplasmic granules. C, D) (100 x High Power field, hematoxylin eosin stain), the neoplastic cells are medium in size, with dense chromatin and irregular nuclear contours. E, F) (100 x High Power field, hematoxylin eosin stain), the neoplastic cells are large in size with disperse chromatin, irregular nuclear contours, and prominent nucleoli.

of $6 \times 10^3/\mu\text{L}$ within weeks) (Figure 1C,D), and thrombocytopenia ($69 \times 10^3/\mu\text{L}$). Imaging demonstrated mild lymphadenopathy involving jugular and bilateral axillary lymph nodes, splenomegaly, and a cirrhotic-appearing liver with evidence of portal hypertension.

Peripheral blood flow cytometry identified an abnormal T-cell population (70%) positive for CD2, cytoplasmic CD3, dim CD3, CD4, CD5, CD25, and CD45, with loss of CD7. The cells were negative for CD8, CD10, CD16, CD56, CD57, MPO, TdT, and CD79a. HTLV-I serology was positive and confirmed by Western blot. T-cell clonality testing demonstrated clonal T-cell receptor gene rearrangement. Peripheral blood smear revealed small to medium-sized mature lymphocytes with flower-like nuclear contours and abundant cytoplasm (Figure 1). Molecular studies detected mutations in NOTCH1 (p.P2514fs, p.S2423*, p.S2449fs, p.D1267N), KMT2D, APOB, ERCC5, SLC22A9, UGT1A8, PTPRD, NTRK1, GATA3, and SMARCB1. Review of the family history revealed that the patient was originally from West Indies, an HTLV-1 endemic region, and had a positive family history of HTLV-1 infection. The overall findings supported a diagnosis of adult T-cell leukemia (ATLL).

While awaiting initiation of zidovudine and pegylated interferon 2 alpha, the patient acutely decompensated, developing acute renal failure, tumor lysis syndrome, worsening

hypercalcemia, multifocal pneumonia, and acute hypoxic respiratory failure. He was transitioned to palliative measures and subsequently passed away.

Case 3

A young male in his early 20s presented with a 3-day history of well-demarcated, red violaceous, centrally ulcerated lesions on both lower extremities. He was initially treated for presumed Lyme disease but did not respond to doxycycline. His symptoms progressed, accompanied by malaise and weight loss. Physical examination revealed conjunctival pallor, cervical lymphadenopathy, splenomegaly, and rash.

Laboratory studies demonstrated severe normocytic hypochromic anemia (hemoglobin 5.1g/dl), thrombocytopenia (platelets $27 \times 10^3/\mu\text{L}$) and marked leukocytosis (WBC $> 450 \times 10^3/\mu\text{L}$) with 95% circulating blasts. Imaging revealed a large mediastinal mass. Peripheral blood flow cytometry showed CD34+ blast cells (91%) expressing subset CD2, subset cytoplasmic CD3, CD4, dim CD5, CD7, dim CD10, dim CD13, dim CD33, CD38, CD45 and negative for surface CD3, CD8, and TdT. CD1a immunostaining on bone marrow biopsy was negative. The findings supported a diagnosis of T-lymphoblastic leukemia favoring near-early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) (Figure 1E,F). HTLV1 antibodies were negative.

This case was previously reported by our group; however new molecular, therapeutic and prognostic data have since emerged. Next-generation sequencing detected a BCR::ABL1 fusion, along with mutations in NSD2, NRAS, DNMT2, NOTCH1, CTCF, NSD1, as well as copy number loss in CDKN2A, CDKN2B and MTAP. The patient received a pediatric inspired ALL protocol (CALGB 10403 followed by AALL0434) and achieved deep remission that is ongoing.

DISCUSSION

The lymphocytes in peripheral blood typically exhibit dense chromatin and scant cytoplasm. Occasionally large lymphocytes with abundant cytoplasm and cytoplasmic granules such as large granulocytic lymphocytes may appear in the circulation. Lymphocytes with irregular nuclear contours, immature nuclei or prominent nucleoli represent atypical findings that warrant further clinical investigation.

Traditionally, petal-like nuclei or “flower cells” are considered characteristic of T-cell neoplasm, most notably associated with HTLV-1-associated adult T-cell leukemia/lymphoma (ATLL) (1). Flower cells are most frequently observed in the acute form of ATLL but can also appear in smoldering or chronic ATLL subtype (2).

Although classically linked to T-cell malignancies, rare reports describe peripheral flower cells in other T-cell neoplasms. In T-lymphoblastic leukemia, these cells exhibit immature features, including a high nuclear-to-cytoplasmic ratio, dispersed chromatin, and prominent nucleoli. In contrast, cells from ALK-neg anaplastic large cell lymphoma (ALCL) are more pleomorphic and larger and occasionally with cytoplasmic granules (Figure 1B). A literature review also documents occasional flower-like morphology in B-cell neoplasms, including diffuse large B-cell lymphoma (3, 4), high-grade B-cell lymphoma (5), marginal zone lymphoma (6), Burkitt lymphoma (7), and plasma cell leukemia (8), as well as in non-malignant settings such as cytomegalovirus infection (9).

T cells neoplasms more commonly exhibit pleomorphic nuclear features, potentially reflecting lineage-specific mutational profiles. In our cohort, two of three patients carried NOTCH1 mutations, while the remaining patient harbored a STAT3 mutation, a key downstream effector of the NOTCH signaling pathway. The literature indicates that NOTCH signaling plays a critical role in transcriptional regulation and crosstalk activation of target genes via both canonical and non-canonical mechanisms (10). Notably, the non-canonical NOTCH signaling pathway influences

cellular architecture, including cytoskeletal dynamics and cell morphology. Activation of the JAK/STAT pathway via non-canonical NOTCH signaling suggests convergence of STAT3 and NOTCH1 mutations on shared oncogenic pathways (10). NOTCH1 mutations in mantle cell lymphoma are associated with blastoid and pleomorphic features (11), but one study by MD Anderson Cancer Center suggests enrichment in blastoid variants (12). Clinically, NOTCH activation in T-lymphoblastic leukemia correlates with improved early treatment response (10), consistent with our young Near-ETP-ALL patient; however this association was not observed in the patients with ATLL or ALK-negative ALCL.

Regardless of underlying mechanisms, the presence of flower cells combined with ancillary studies such as viral serology, immunophenotyping, and molecular profiling contributes to an accurate diagnosis and informs therapeutic strategies.

CONCLUSION

This case series highlights the broader spectrum of hematologic disorders in which flower cells may occur, emphasizing that their presence is neither pathognomonic for ATLL nor exclusive to HTLV-1 infection. While recognition of flower cells can serve as an important diagnostic clue, definitive diagnosis requires integration of HTLV-1 serologic status, clinical context, comprehensive immunophenotyping, and molecular studies. Their presence alone is insufficient for screening, and absence does not exclude disease.

Conflict of Interest

The authors declare no conflict of interest.

Authorship Contributions

Concept: DC, Design: DC, Data collection or processing: UMAM, DC, Analysis or Interpretation: UMAM, DC, Literature search: UMAM, DC, Writing: UMAM, DC, Approval: WYT, KM, YH, RV, VF, DC.

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