

Clonal Eosinophilic Transformation in IDH1-Mutated Acute Myeloid Leukemia with Emergent ETV6 Gain

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Case Report

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Abstract

Acute myeloid leukemia (AML) may demonstrate clonal evolution under therapeutic pressure. The emergence of hypereosinophilia outside established eosinophilia-associated rearrangements remains incompletely characterized. We report a 42-year-old man with AML (88% blasts; >95% cellularity), 7q deletion, and *IDH1* p.R132C and two *DNMT3A* mutations, each at a variant allele frequency (VAF) of ~45%. Following 7+3 induction and intermediate-dose cytarabine reinduction for persistent disease, salvage azacitidine, venetoclax, and ivosidenib achieved morphologic remission. Low-level disease without eosinophilia persisted (1.6% atypical blasts by flow cytometry, 7q deletion in 6% by FISH, *IDH1* VAF 2.4%, and *DNMT3A* VAFs 26%/2.3%). During cycle 2 of azacitidine/venetoclax with ongoing *IDH1* inhibition, marked peripheral eosinophilia ($81.52 \times 10^9/L$) developed. Bone marrow showed 64% eosinophils and 1% blasts. Molecular and cytogenetic studies demonstrated re-expansion of the original clone (*IDH1* 41%, *DNMT3A* 44%/41%, 7q deletion 89.5%) and new *ETV6* gain (35%). *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, and *FLT3* rearrangements were not detected. Two months later, marrow showed 86% eosinophils and 1% blasts with persistent *IDH1*/*DNMT3A* mutations and *ETV6* gain (46.5%). The patient developed myocarditis and encephalopathy and died within 6 months of diagnosis. This case highlights clonal persistence and evolution presenting as hypereosinophilia during AML treatment. To our knowledge, this is the first reported case of profound hypereosinophilia associated with molecular and cytogenetic re-expansion of an *IDH1*-mutated AML clone during *IDH1*-targeted therapy in the absence of a canonical eosinophilia-associated rearrangement.

Introduction

Acute myeloid leukemia (AML) is a genetically heterogeneous and evolutionarily dynamic myeloid neoplasm in which early (“founding”) lesions in epigenetic regulators can persist through therapy and provide a substrate for relapse or phenotypic change under selective pressure.^{1,2}

Mutations in *IDH1*, typically involving the R132 hotspot, contribute to leukemogenesis by generating the oncometabolite R-2-hydroxyglutarate, with downstream epigenetic and differentiation effects.³ The mutant *IDH1* inhibitor ivosidenib can produce complete remissions and is now incorporated into multiple treatment approaches, including combinations with azacitidine that improve event-free and overall survival.^{4–6}

However, responses to *IDH* inhibition may reflect differentiation rather than eradication of the abnormal clone, and resistance can emerge through clonal selection and/or acquisition or expansion of cooperating driver lesions.^{7,8}

Eosinophilia arising in the course of AML treatment presents a diagnostic challenge because eosinophilia may represent a reactive process, treatment-related inflammation/differentiation effects, or evolution toward a distinct clonal eosinophilic myeloid neoplasm.⁹ The World Health Organization category of myeloid/lymphoid neoplasms with eosinophilia is classically defined by fusion tyrosine

kinase rearrangements involving *PDGFRA*, *PDGFRB*, *FGFR1*, or *JAK2*, while *ETV6* can serve as a recurrent partner in eosinophilia-associated kinase fusions such as *ETV6::ABL1*.¹⁰ When these defining rearrangements are absent, marked eosinophilia with clonality may fall into diagnostic exclusion entities (e.g., chronic eosinophilic leukemia, NOS) and is increasingly understood to be driven by heterogeneous somatic alterations and clonal evolution.^{10,11}

Here, we report an adult with *IDH1*-mutated AML harboring two distinct *DNMT3A* mutations and 7q deletion who achieved morphologic remission with ivosidenib-containing therapy, followed by development of profound marrow and peripheral eosinophilia accompanied by persistence and subsequent expansion of the original AML-associated clone and emergence of *ETV6* copy-number gain in the absence of common eosinophilia-associated rearrangements.

This case highlights an uncommon pattern of clonal eosinophilic transformation during targeted therapy and emphasizes the importance of integrating morphology with serial cytogenetic and molecular monitoring to distinguish reactive eosinophilia from therapy-driven clonal evolution (Fig. 1).^{8,11}

Case report

A 42-year-old man was diagnosed at an outside hospital with acute myeloid leukemia (AML) with 88% blasts in a markedly hypercellular marrow (> 95% cellularity) (Fig. 2A-C) and extramedullary liver involvement confirmed by biopsy. Fluorescence in situ hybridization (FISH) was positive for del(7q31). Next-generation sequencing (NGS) identified *IDH1* p.R132C (variant allele frequency (VAF) 45%), *DNMT3A* p.E491* (VAF 46%), and *DNMT3A* p.W409* (VAF 46%).

He received standard “7 + 3” induction chemotherapy. Post-induction marrow examination demonstrated persistent AML in a hypercellular bone marrow (80%) with 53% blasts by morphology and 64% atypical myeloid blasts by flow cytometry. Conventional cytogenetics showed 46,XY,add(7)(q11.2)[16]/46,XY[4]. The patient subsequently underwent re-induction with intermediate-dose cytarabine (IDAC).

The patient then received salvage azacitidine, venetoclax, and ivosidenib. Following cycle 1, bone marrow examination demonstrated morphologic remission with approximately 1% blasts in a 50–70% cellular marrow. However, measurable residual disease persisted, including 1.6% atypical myeloid blasts by flow cytometry, del(7q) detected in 6% of nuclei by FISH, and low-level persistence of the original molecular abnormalities (*IDH1* p.R132C (VAF 2.4%), *DNMT3A* p.E491* (VAF 26.0%), and *DNMT3A* p.W409* (VAF 2.3%)). Although the *IDH1* p.R132C and *DNMT3A* p.W409* variants were detected below the laboratory’s standard reporting threshold, they were considered significant given concordance with the patient’s previously identified diagnostic clone. Given morphologic remission, transplant evaluation was initiated.

During cycle 2 azacitidine/venetoclax with ongoing *IDH1* inhibition, the patient developed progressive hypereosinophilia, reaching a peak absolute eosinophil count (AEC) of $81.52 \times 10^9/L$. Repeat bone marrow examination demonstrated marked eosinophilic expansion, with eosinophils comprising 64% of

marrow cellularity in a 60–70% cellular marrow, while blasts remained low (~ 1% by morphology with an atypical myeloid immunophenotype demonstrated by flow cytometry) (Fig. 2D-F). Flow cytometry additionally identified 4% atypical monocytes. Despite the low blast burden, molecular and cytogenetic studies demonstrated marked re-expansion of the original leukemic clone, including del(7q) in 89.5% of nuclei by FISH and return of the original molecular abnormalities to near-diagnostic levels (*IDH1* p.R132C VAF 41.0%; *DNMT3A* p.E491* VAF 44.0%; *DNMT3A* p.W409* VAF 41.0%). Concurrent *RUNX1/ETV6* FISH demonstrated emergence of an *ETV6* copy-number gain in 35% of nuclei. A targeted eosinophilia-associated rearrangement panel was negative for *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, and *FLT3* rearrangements.

Despite persistently low blast counts, the eosinophilic process continued to progress. Follow-up marrow examination demonstrated further eosinophilic predominance (86% eosinophils) with persistent *IDH1* and *DNMT3A* mutations and increasing *ETV6* copy-number gain (46.5% of nuclei by *RUNX1/ETV6* FISH). Conventional cytogenetics additionally demonstrated persistent abnormalities involving chromosome 7q with evolving structural changes involving chromosome 12p13. The patient subsequently developed chest pain, neurologic symptoms, and marked troponin elevation, with cardiac MRI findings compatible with eosinophilic myocarditis. He was treated with high-dose corticosteroids, hydroxyurea, mepolizumab, and transition from ivosidenib to olutasidenib; however, progressive multiorgan dysfunction with central nervous system involvement ensued, and he died within 6 months of diagnosis.

Discussion

This case illustrates an unusual and diagnostically challenging pattern of AML progression, in which biologic relapse became apparent not through increasing blasts, but through marked eosinophilic expansion occurring in parallel with re-expansion of AML-associated molecular and cytogenetic abnormalities. Following salvage therapy with azacitidine, venetoclax, and mutant-IDH1 inhibition, the patient achieved morphologic remission with low-level residual disease, but subsequently developed abrupt and profound hypereosinophilia with hyperleukocytosis, myocarditis, and neurologic involvement. This eosinophilic phase coincided with *IDH1* and *DNMT3A* variant allele frequencies returning to near-diagnostic levels and a marked increase in del(7q) by FISH despite persistently low blast counts. This discordance is biologically plausible in IDH-mutated AML, as IDH inhibitors can promote differentiation of mutant leukemic cells without necessarily eliminating the underlying clone.^{5,7}

In relapsed/refractory IDH1-mutated AML, ivosidenib has been shown to induce durable remissions without universal molecular clearance.⁵ Clonal studies of IDH-inhibitor therapy have demonstrated that genetically abnormal leukemic populations may persist and contribute to differentiated hematopoietic cells during response, with subsequent progression occurring through clonal selection or evolution.^{7,8}

Eosinophilic differentiation associated with mutant-IDH inhibition has been reported previously. Galeotti and Coombs described eosinophilic differentiation in a patient with IDH2-mutated AML treated with enasidenib.¹² More recently, marked bone marrow eosinophilia was reported following azacitidine and

ivosidenib therapy in IDH1-mutated AML, where the eosinophilia was interpreted as a transient reactive or regenerative phenomenon.¹³ In contrast, our patient developed profound and sustained peripheral and marrow eosinophilia coincident with re-expansion of AML-associated molecular and cytogenetic abnormalities and severe eosinophil-mediated end-organ injury. To our knowledge, this combination of findings has not previously been reported during ivosidenib-containing therapy.

Differentiation syndrome (DS) was an important competing consideration given ongoing IDH1 inhibitor therapy, leukocytosis, and partial steroid responsiveness. DS is a recognized complication of IDH inhibition, including in patients treated with ivosidenib plus azacitidine, in whom it was reported in 14% in the AGILE trial.⁶ FDA analyses have emphasized the heterogeneous clinical presentation of IDH inhibitor-associated DS and the importance of prompt corticosteroid therapy and management of associated leukocytosis when clinically suspected.¹⁴ However, several features in this case argue against DS as the sole explanation. The patient demonstrated sustained marrow and peripheral eosinophilic expansion, a peak absolute eosinophil count exceeding $80 \times 10^9/L$, progressive end-organ injury, and simultaneous re-emergence of the AML-associated molecular and cytogenetic findings. Together, these findings raised concern that the eosinophilia reflected disease evolution rather than an isolated treatment-related differentiation syndrome.

The eosinophilic phenotype required distinction from reactive and drug-associated eosinophilia as well as a separate myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase fusion.^{15,16} Reactive eosinophilia was considered in light of the patient's infectious complications and immunosuppression, but negative parasitic evaluation, normal IgE and tryptase levels, and the parallel expansion of AML-associated molecular abnormalities argued against a secondary process. Drug-associated eosinophilia likewise remained possible given exposure to multiple medications; however, a drug reaction alone would not readily explain the concurrent molecular and cytogenetic progression.¹⁷

FISH studies for *PDGFRA*, *PDGFRB*, *FGFR1*, and *JAK2* rearrangements were negative; additional testing also failed to identify *FLT3* rearrangements, reducing the likelihood of a myeloid/lymphoid neoplasm with eosinophilia and a defining tyrosine kinase fusion.^{10,16} Although *ETV6* copy-number gain emerged, copy-number gain alone does not establish an *ETV6*-associated tyrosine kinase fusion. In the absence of an identifiable fusion partner and given the simultaneous re-expansion of the original *IDH1/DNMT3A/del(7q)* abnormalities, this finding was interpreted as a marker of clonal evolution.

Phenotypically, the eosinophilic phase shares features with clonal eosinophilic disorders, including marked eosinophilia and eosinophil-mediated organ injury.¹¹ However, because the eosinophilic phase emerged during the evolution of established AML and coincided with renewed molecular and cytogenetic evidence of the original disease, the overall findings favor eosinophilic differentiation/evolution in association with the underlying AML rather than classification as a separate chronic eosinophilic leukemia. The low blast count alone did not reflect the molecular and cytogenetic evidence of disease progression. Contemporary AML assessment increasingly incorporates measurable residual disease and molecular information alongside conventional morphologic evaluation.¹⁸ In this

case, serial molecular and cytogenetic assessment was particularly informative in recognizing disease progression despite minimal morphologic blasts.

Ultimately, the fatal outcome underscores that AML progression may not always manifest as overt blast expansion. In this patient, hypereosinophilia with myocardial and neurologic injury accompanied molecular and cytogenetic evidence of disease progression. Early recognition of a similar pattern, particularly when new or worsening eosinophilia parallels re-expansion of established leukemic abnormalities, should prompt reassessment of disease status and consideration of both eosinophil-directed and AML-directed management.

Declarations

Funding

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Consent for Publication

Consent for publication was obtained.

Author Contributions

H.E. collected and reviewed the clinical and pathologic data and drafted the manuscript. M.W. and D.F. contributed to the interpretation of the findings and revised the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

The data supporting the findings of this report are available from the corresponding author upon reasonable request. Data are not publicly available due to patient privacy and confidentiality considerations.

References

1. Ding L, Ley TJ, Larson DE, et al. Clonal evolution in relapsed acute myeloid leukaemia. *Nature*. 2012;481(7382):506-510.

2. Shlush LI, Mitchell A, Heisler L, et al. Tracing the origins of relapse in acute myeloid leukaemia to stem cells. *Nature*. 2017;547(7661):104-108.
3. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting α -ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-234.
4. Medeiros BC, Fathi AT, DiNardo CD, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia*. 2017;31(2):272-281.
5. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
6. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519-1531.
7. Quek L, David MD, Kennedy A, et al. Clonal heterogeneity of acute myeloid leukemia treated with the IDH2 inhibitor enasidenib. *Nat Med*. 2018;24(8):1167-1177.
8. Choe S, Wang H, DiNardo CD, et al. Single-cell analysis reveals mechanisms of response and resistance to IDH inhibition in acute myeloid leukemia. *Blood Cancer Discov*. 2023;4(1):54-69.
9. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2017;92(11):1243-1259.
10. Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood*. 2017;129(6):704-714.
11. Pardanani A. Chronic eosinophilic leukemia not otherwise specified and hypereosinophilic syndrome: contemporary diagnosis and management. *Am J Hematol*. 2020;95(11):1361-1375.
12. Galeotti J, Coombs CC. Enasidenib-induced eosinophilic differentiation in a patient with acute myeloid leukaemia with IDH2 and U2AF1 mutations. *Br J Haematol*. 2019;184(4):496.
13. Liwski C, Marcoux C, Conrad DM. Marked bone marrow eosinophilia post-azacitidine + ivosidenib treatment for acute myeloid leukemia. *Int J Lab Hematol*. 2026:1-3. doi:10.1111/ijlh.70111.
14. Norsworthy KJ, Mulkey F, Scott EC, et al. Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: a U.S. Food and Drug Administration systematic analysis. *Clin Cancer Res*. 2020;26(16):4280-4288. doi:10.1158/1078-0432.CCR-20-0834.
15. Reiter A, Metzgeroth G, Cross NCP. How I diagnose and treat myeloid/lymphoid neoplasms with tyrosine kinase gene fusions. *Blood*. 2025;145(16):1758-1768. doi:10.1182/blood.2023022417.
16. Klion AD. Approach to the patient with suspected hypereosinophilic syndrome. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):47-54. doi:10.1182/hematology.2022000367.
17. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(6):697-712.
18. Cloos J, Valk PJM, Thiede C, et al. 2025 update on MRD in acute myeloid leukemia: a consensus document from the ELN-DAVID MRD Working Party. *Blood*. 2026;147(11):1147-1167. doi:10.1182/blood.2025031480.

Figures

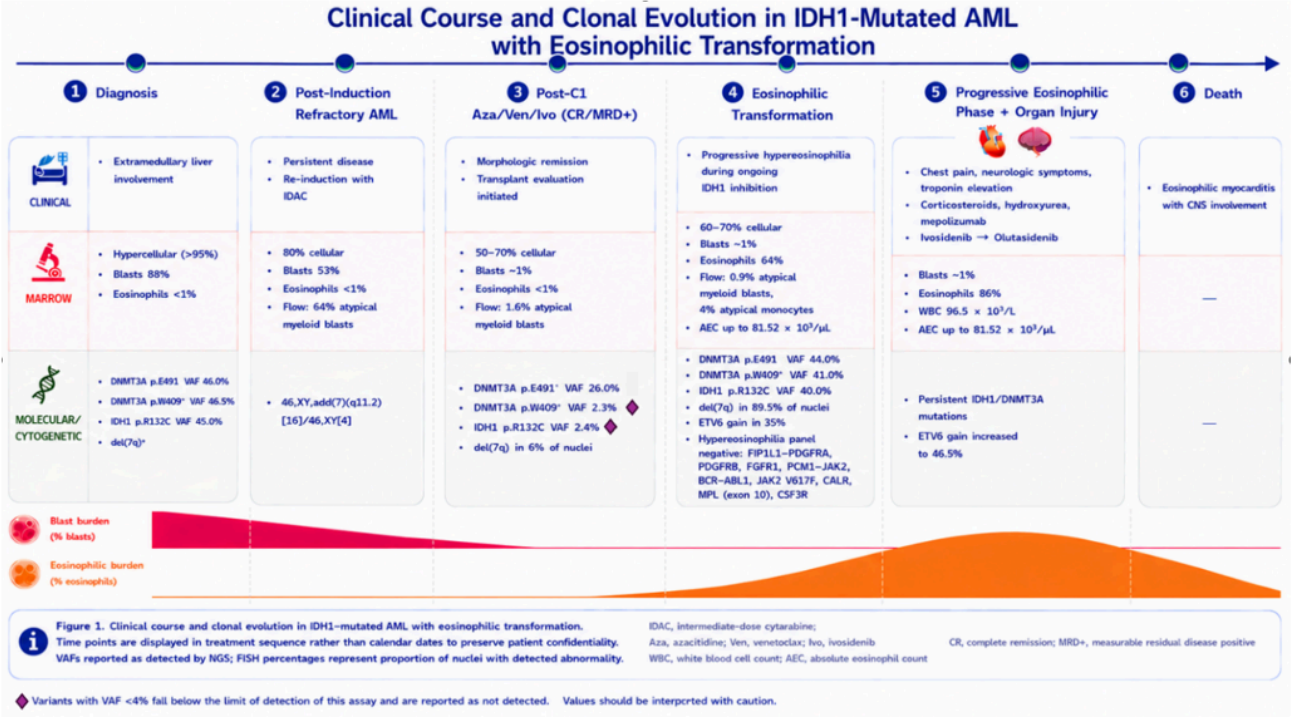


Figure 1

Clinical course and clonal evolution in IDH1-mutated acute myeloid leukemia with eosinophilic transformation.

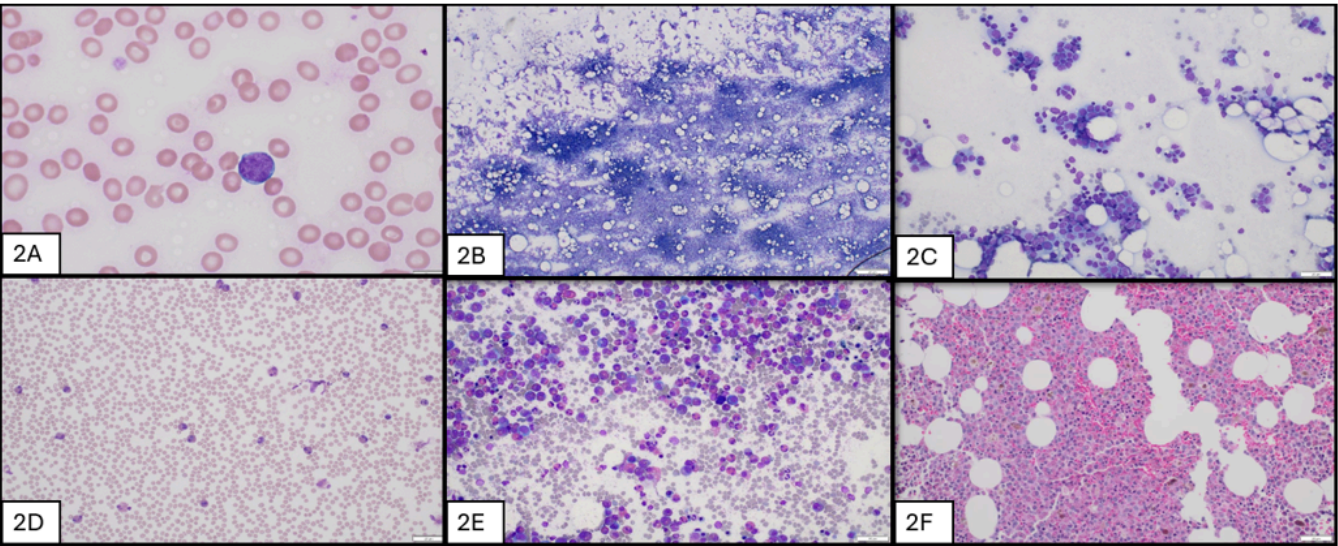


Figure 2

Morphologic findings during the course of AML and subsequent eosinophilic proliferation.

(A) Peripheral blood smear at initial AML diagnosis demonstrating a circulating myeloblast with high nuclear-to-cytoplasmic ratio and fine chromatin.

(B, C) Bone marrow aspirate smears at AML diagnosis showing a markedly hypercellular marrow extensively infiltrated by blasts.

(D) Peripheral blood smear obtained following remission induction therapy demonstrating marked eosinophilia.

(E) Bone marrow aspirate during evaluation of eosinophilia showing prominent eosinophilic proliferation with increased eosinophilic precursors.

(F) Bone marrow core biopsy demonstrating a hypercellular marrow with extensive eosinophilic infiltration and background trilineage hematopoiesis without morphologic evidence of recurrent acute myeloid leukemia.