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Azacitidine-induced remission enables allogeneic transplantation in *TET2*/*BCOR*-mutant relapsed extranodal natural killer/T-cell lymphoma: a case report

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Running heads: Azacitidine response in extranodal T-cell lymphoma

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Disclosures

No conflicts of interest to disclose.

Contributions

CRO contributed to patient care and manuscript preparation. HAZ, CDB, AD, GM, SM, and TM contributed to patient care. DS, OH, and DMW were consulted on therapeutic decisions. KE contributed to patient care and manuscript preparation. JT contributed to patient care, supervised the study, and wrote the manuscript.

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Extranodal NK/T-cell lymphoma (ENKTL) remains one of the most lethal lymphomas in the relapsed/refractory setting. Asparaginase-based chemotherapy and, more recently, immune checkpoint inhibitors have improved outcomes, but there is no established standard of care for patients who are refractory to both asparaginase-based regimens and PD-1/PD-L1 blockade.

Recent genomic studies have underscored the high prevalence of alterations affecting epigenetic regulators including *TET2*, *BCOR*, *KMT2D*, and *ARID1A*, highlighting epigenetic deregulation as a central feature of ENKTL pathogenesis and a potential therapeutic vulnerability. Although preclinical work has shown that hypomethylating agents (HMA) can restore silenced differentiation programs and induce tumor regression in ENKTL models[1], clinical evidence supporting their use remains sparse. We report what appears to be the first case of relapsed ENKTL with co-occurring *TET2* and *BCOR* mutations achieving a complete remission with azacitidine (AZA) monotherapy, enabling subsequent allogeneic hematopoietic stem cell transplantation (allo-HSCT).

A 47-year-old woman of Middle Eastern origin presented to Geneva University Hospitals (Geneva, Switzerland) with progressive, painless swelling of the upper eyelid and ptosis. Orbital MRI revealed left-sided enhancing extraconal masses. A biopsy confirmed EBV-positive ENKTL (CD56+, cytoplasmic CD3ε+, CD5–, granzyme B+, TIA1+) (**Figure 1A**). Baseline [18F]-FDG PET/CT showed disease confined to the orbits. Plasma EBV DNA was 9.4×10^3 IU/mL, and both bone marrow and cerebrospinal fluid (CSF) analyses were negative. Her PINK-E score was 2, indicating intermediate-risk disease.[2] The patient provided written general research consent. Ethics approval was not required for this anonymized single case report under the Swiss Human Research Act (HRA).

The patient received four cycles of SMILE chemotherapy followed by radiotherapy, achieving a complete metabolic response with EBV clearance (**Figure 1B**). Fourteen months later, she relapsed with an orbital recurrence. Salvage therapy with pembrolizumab combined with two cycles of GELOX was administered, followed by radiotherapy with concurrent pembrolizumab and cisplatin.

Despite these treatments, the disease progressed with leptomeningeal dissemination and bone marrow involvement. High-dose cytarabine with pembrolizumab, additional radiotherapy, and intrathecal cytarabine plus methotrexate produced only transient normalization of CSF parameters without neurological improvement (**Figure 1B**).

Targeted next-generation sequencing of diagnostic biopsies using a limited 27-gene panel identified pathogenic mutations in epigenetic regulators, including a clonal *TET2* missense variant (c.5704T>A, p.Tyr1902Asn) affecting the dioxygenase catalytic domain and a splice-site *BCOR* mutation (c.4071+1G>A). Subsequent analysis of the relapse sample using a broader 400-gene panel confirmed the persistence of the *TET2* variant and identified a truncating *BCOR* mutation (c.1570dup; p.Ser524LysfsTer33), whereas the initial splice-site *BCOR* variant was no longer detected, consistent with clonal heterogeneity during disease progression (**Table 1**). Together, these alterations are expected to impair 5-methylcytosine oxidation and disrupt PRC1.1-mediated repression, respectively, leading to marked epigenetic dysregulation.[3]

Given the co-occurrence of *TET2* and *BCOR* mutations and reports of AZA responsiveness in *TET2*-mutant T-cell lymphomas[4], off-label AZA was initiated at 75 mg/m² subcutaneously on days 1–7 of a 28-day cycle, together with weekly intrathecal cytarabine. Treatment was well tolerated, with grade 2 fatigue, mild injection-site erythema, and one episode of transient grade 3 neutropenia. Following a single cycle, plasma EBV DNA became undetectable, neurological symptoms resolved, CSF cleared, and PET/CT at day 28 showed a complete metabolic remission (**Figure 1C**). This therapeutic response was confirmed by the absence of detectable NK/T cells in the bone marrow. Notably, no somatic variants were detected in this sample, arguing against the presence of a dominant ancestral clonal hematopoiesis of indeterminate potential (CHIP) clone in this patient within the analytical sensitivity of the assay. A second AZA cycle was given as bridging therapy before myeloablative conditioning (fludarabine 120 mg/m² and total body irradiation 10 Gy) and allo-HSCT from an HLA-matched sibling.

The post-transplant course was complicated by grade 2 acute GVHD of the skin and gastrointestinal tract, controlled with prednisone and later ruxolitinib. EBV viremia reappeared on day +70, followed by systemic relapse on day +133. Reintroduction of AZA was ineffective in the context of massive marrow infiltration and secondary hemophagocytic lymphohistiocytosis, and the patient died on day +160. Notably, we observed the persistence of *TET2* and *BCOR* mutations at lower allele frequencies (~4%) in the post-transplant relapse biopsy, together with the emergence of additional low-frequency mutations in *CSF3R* and *DNMT3A*, consistent with post-transplant clonal evolution that may have contributed to the lack of response to AZA re-exposure. Nonetheless, AZA produced a deep and rapid remission that created a window for potentially curative allo-HSCT.

Therapeutic options for relapsed or refractory ENKTL remain limited. Allo-HSCT offers the only possibility of durable remission but relies on achieving disease control beforehand. PD-1 blockade yields responses in approximately 40% of patients, aided by frequent *CD274* (PD-L1) 3'UTR alterations, yet durable control is rare.[5] In contrast, clinical experience with HMA in ENKTL is extremely limited. To our knowledge, only one complete remission has been reported, in a patient treated with oral azacitidine and romidepsin in a phase I study.[6] In this setting, the complete remission achieved with AZA monotherapy after multiple prior lines of therapy in our patient is notable.

Co-occurring *TET2* and *BCOR* mutations in our case may have contributed to a permissive epigenetic context for HMA activity, consistent with observations in other T-cell and myeloid malignancies harboring epigenetic lesions.[4] Yet epigenetic vulnerability in ENKTL likely extends beyond these specific alterations. Genomic studies show that ENKTL cases frequently carry mutations in chromatin modifiers or DNA methylation regulators. Xiong et al. reported that two-thirds of *TET2*-mutant tumors harbor additional epigenetic hits, including *BCOR* and *KMT2D*[7], findings echoed by Oishi et al.[8] and by recent profiling studies highlighting recurrent epigenetic drivers on the X chromosome.[9] Notably, this concept has been further supported by a recent clinical

study showing that DNMT inhibitors can overcome PD-1 resistance in relapsed/refractory ENKTL through epigenetic reprogramming and immune pathway restoration.[10] However, the phase 3 ORACLE trial comparing oral AZA with investigator's-choice standard therapy in relapsed/refractory TFH lymphoma did not meet its primary endpoint of improved progression-free survival and did not show a preferential benefit in patients harboring *TET2* or other epigenetic mutations, indicating that HMA activity is not restricted to specific epigenetic genotypes.[11] In addition, clinical reports have described responses to HMA in the absence of *TET2* mutations in angioimmunoblastic T-cell lymphoma, and functional screens in T-cell lymphoma models have not identified loss of *TET2* or *BCOR* as necessary for HMA sensitivity.[12,13] AZA can therefore be considered in selected relapsed/refractory ENKTL patients irrespective of *TET2*/*BCOR* status, particularly when standard options are exhausted.

Several biological features may account for the pronounced AZA sensitivity. Although co-occurring loss-of-function mutations in *TET2* and *BCOR* may have contributed to HMA sensitivity, our observation does not prove a purely tumor-intrinsic, AZA-only effect. AZA can enhance tumor immunogenicity through viral mimicry and interferon pathway activation[14,15], and persistent PD-1 receptor occupancy following prior pembrolizumab exposure may have further amplified this immune response, even if the delay between the last dose of pembrolizumab and the first administration of AZA was 3.8 months. This anti-tumor immune response may also have contributed to the neurological improvement despite limited CSF penetration of AZA. The combination of these mechanisms provides a coherent explanation for the rapid and profound remission observed after a single treatment cycle.

This case illustrates that azacitidine monotherapy can induce complete remission in relapsed ENKTL with epigenetic alterations, enabling subsequent allo-HSCT. These observations support further evaluation of HMA-based strategies in relapsed ENKTL, with integrated molecular profiling to better define the biological contexts associated with response.

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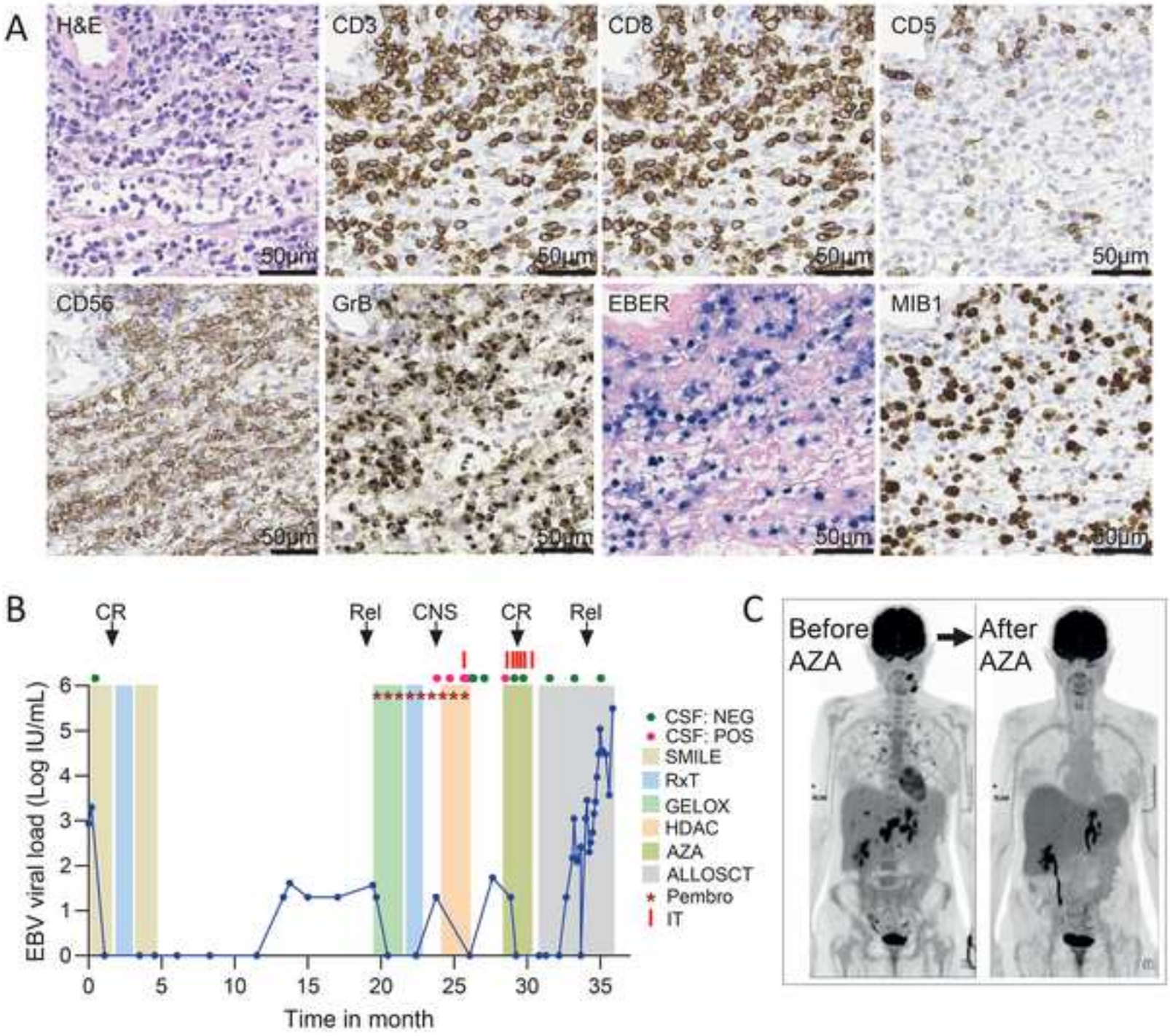
Table 1. Somatic variant summary across disease course. NGS analyses were performed using two different targeted sequencing panels. At diagnosis, a custom 27-gene T-cell lymphoma panel (Illumina MiSeq, IDT xGen Lockdown) was used, covering the following genes: *ARID1A*, *ATM*, *BCOR*, *CARD11*, *CCR4*, *CD28*, *CTNNB1*, *DDX3X*, *DNMT3A*, *FYN*, *IDH2*, *IRF4*, *JAK1*, *JAK3*, *KMT2D*, *PIK3CD*, *PLCG1*, *PRKCB*, *RHOA*, *SETD2*, *SOCS1*, *STAT3*, *STAT5B*, *TET2*, *TNFRSF1B*, *TP53*, and *VAV1*. At relapse, a 400-gene hybrid-capture panel (NGS400v5, Illumina NextSeq, Agilent SureSelect XT HS) was applied; the same 400-gene panel was repeated at post-transplant relapse. Matched germline DNA was sequenced with the 400-gene panel to exclude constitutional variants. VAFs: variant allele frequencies. D: diagnosis. R: relapse. PTR: post-transplant relapse. VUS: variant of uncertain significance.

Gene	**Variant (HGVS)**	**VAF**	**Timepoints**	**Pathogenicity**
TET2	c.5704T>A; p.Tyr1902Asn	42	D	Pathogenic
BCOR	c.4071+1G>A (splice site)	29	D	Pathogenic
EPHA3	c.815-1G>A	18	R	Likely pathogenic
TET2	c.5704T>A; p.Tyr1902Asn	38	R	Pathogenic
PLAG1	c.1217C>T; p.Ser406Phe	16	R	VUS
KRAS	c.38G>A; p.Gly13Asp	15	R	Pathogenic
TRRAP	c.10588G>C; p.Val3530Leu	17	R	VUS
BCOR	c.1570dup; p.Ser524LysfsTer33	24	R	Pathogenic
CSF3R	c.2486C>T; p.Thr829Ile	2	PTR	Likely pathogenic
DNMT3A	c.1227G>A; p.Trp409Ter	3	PTR	Pathogenic
TET2	c.5704T>A; p.Tyr1902Asn	4	PTR	Pathogenic
BCOR	c.1570dup; p.Ser524LysfsTer33	4	PTR	Pathogenic

Figure 1. Azacitidine induces complete remission in relapsed *TET2*- and *BCOR*-mutant NK/T-cell lymphoma. (**A**) Histopathological examination of the orbital biopsy showing dense infiltrates of atypical lymphoid cells with angiocentric growth and necrosis (Hematoxylin–Eosin, H&E). Tumor cells expressed CD3, CD8, CD56, and granzyme B (GrB), lacked CD5, and showed a high proliferative index by MIB1 staining. Epstein–Barr virus–encoded RNA (EBER) in situ hybridization confirmed EBV positivity. Scale bars, 50 μm. (**B**) Clinical course showing treatment timeline, plasma EBV DNA (blue line), and corresponding therapeutic interventions. SMILE: methotrexate (2 g/m² IV on day 1), ifosfamide (1.5 g/m²/day IV on days 2–4), etoposide (100 mg/m²/day IV on days 2–4), dexamethasone (40 mg/day on days 2–4), and L-asparaginase (6,000 IU/m²/day IV on days 8–17) (SMILE). RxT: radiotherapy, GELOX: gemcitabine (1,000 mg/m² IV on days 1 and 8), oxaliplatin (130 mg/m² IV on day 1), and L-asparaginase (6,000 IU/m²/day IV on days 1–7). Pembro: Pembrolizumab. HDAC: high-dose cytarabine (6g/m2 on days 1, 3 and 5). AZA: azacitidine (75mg/m^2 subcutaneously on days 1 to 7). HSCT: allogeneic hematopoietic stem cell transplantation. IT: intrathecal chemotherapy (methotrexate 15mg, cytarabine 40mg and methylprednisolone 15mg). CSF: cerebrospinal fluid. CR: complete remission. Rel: relapse. CNS: central nervous system. (**C**) Maximum intensity projection (MIP) [^{18}F]-FDG PET/CT images: Baseline pre- AZA PET/CT demonstrated intensely FDG-avid infiltration of the left premaxillary fat, accompanied by multiple FDG-avid lymphadenopathies involving the cervical, mediastino-hilar, mesenteric, and cardiophrenic regions as well as bilateral pulmonary FDG-avid foci, consistent with disease recurrence and progression. Following a single cycle of AZA therapy, the subsequent PET/CT demonstrated complete metabolic remission of all peri-orbital and systemic lesions.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