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Successful integration of venetoclax into AYA (CALGB 10403) directed therapy for T/myeloid mixed-phenotype acute leukemia with extramedullary disease: A case report and literature review

Fatima Al Ali[1]*; Mansour Alfayez[2]; Tarek Owaidah[2]; Ayman Saad[2]; Amr Hanbali[2]

[1]Hematology and Oncology Fellowship Program, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

[2]Adult hematology consultant, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

***Corresponding Author(s): Fatima Al-Ali**

Hematology and Oncology Fellow, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Email: fsm.alali94@gmail.com

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Introduction

Mixed-Phenotype Acute Leukemia (MPAL) is a rare and heterogeneous disorder characterized by the co-expression of lineage-defining antigens from more than one hematopoietic lineage, typically myeloid with B- or T-lymphoid markers. It accounts for fewer than 5% of all acute leukemias and carries an unfavorable prognosis due to its complex biology, high rates of chemoresistance, and lack of standardized treatment guidelines [1]. Within this category, the T/myeloid subtype represents one of the rarest forms, often presenting with aggressive clinical features and a propensity for extramedullary disease [2]. T-lineage MPAL carries a significantly worse prognosis than T-ALL and is prone to misclassification with ETP-ALL, underscoring the need for expanded diagnostic panels [3]. BCR::ABL1-positive MPAL often presents at a younger age and shows better outcomes with TKI use [4]. Single-cell transcriptome studies identified a stemness-high subtype responsive to venetoclax [5].

The optimal therapeutic approach for MPAL remains controversial. Recent multicenter and molecular studies further emphasize the heterogeneity of MPAL, with Acute Lymphoblastic Leukemia (ALL)-based regimens achieving superior remission rates compared to Acute Myeloid Leukemia (AML) regimens, although long-term survival remains poor, and allogeniec Stem Cell Transplant (allo-SCT) remains critical [6]. Allo-SCT in first remission is frequently advocated, particularly in younger patients, though achieving deep remission before transplant re-

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mains a significant challenge.

The emergence of targeted therapies has provided new opportunities to address the therapeutic gaps in MPAL. Venetoclax, an oral selective inhibitor of the anti-apoptotic protein BCL-2, has demonstrated substantial activity in both AML and relapsed/refractory ALL, particularly in the setting of Minimal Residual Disease (MRD) persistence. Early incorporation of venetoclax into induction or consolidation regimens has been associated with enhanced cytotoxicity and improved clearance of leukemic clones, including in cases with extramedullary involvement [7,8].

Here we describe the case of a young adult with T/myeloid MPAL and concurrent extramedullary disease, in whom venetoclax was integrated early alongside an ALL-adapted regimen. This approach not only facilitated MRD clearance but also addressed extramedullary disease, allowing the patient to proceed successfully to haplo-identical stem cell transplantation. This report highlights the potential role of venetoclax as an adjunct to frontline therapy in this challenging leukemia subtype.

Case report

A 20-year-old female with no significant comorbidities, presented in May 2025 with progressive fatigue, cervical lymphadenopathy, and cytopenia. Laboratory evaluation revealed a White cell Count (WBC) of 9.4 × 10^9/L, and peripheral smear showed 4–5% circulating blasts. Flow cytometry of peripheral blood demonstrated 4–5% blasts co-expressing CD7, CD5 (subset), CD13 (partial), CD15, CD33, CD34, CD117, CD38, CD200 (partial), CD305, and MPO, findings consistent with T/myeloid Mixed-Phenotype Acute Leukemia (MPAL). Bone marrow biopsy performed the following day was markedly hypercellular (80–90%) with 58% blasts displaying an identical immunophenotype (Figure 1). Her karyotype revealed clonal del(6) and t(3;16) in 17/20 cells, while FISH was negative for common myeloid and lymphoid rearrangements. CNS evaluation with lumbar puncture and MRI was negative.

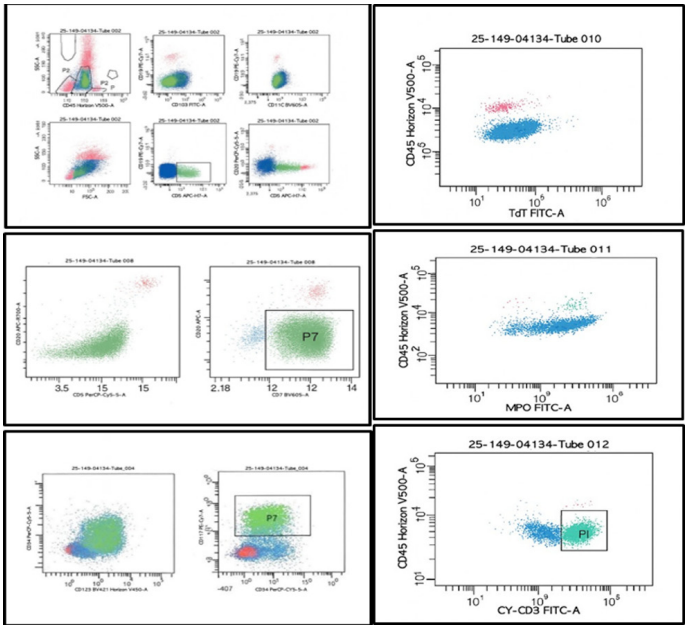

Figure 1: This immunophenotypic profile establishes both T-lineage commitment (cyCD3, CD7, TdT) and myeloid differen6a-6on (MPO posi6vity). By WHO/ICC 2022 criteria, the presence of cytoplasmic CD3 defines T-lineage, while MPO expression defines myeloid lineage.

Imaging with PET-CT showed multiple FDG-avid supra- and infra-diaphragmatic lymph nodes (SUVmax 14.4) and mild splenomegaly (Figure 2). Biopsy of a right cervical lymph node confirmed T/myeloid sarcoma, with blasts positive for MPO, CD3, CD7, BCL2, and CD99, variably expressing CD5, CD117, and CD34, with focal TdT positivity and a Ki-67 index exceeding 90%. Given the high disease burden, debulking with flat-dose cytarabine (1 gram) was administered, followed by induction therapy using CALGB 10403, a pediatric-inspired ALL protocol (vincristine, daunorubicin, PEG-asparaginase, prednisone, intrathecal methotrexate and cytarabine) (9) combined with venetoclax escalated to 400 mg/day (Table 1).

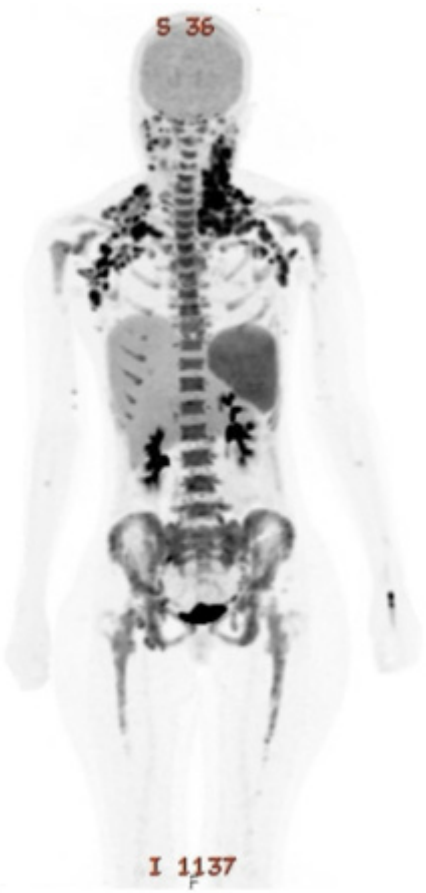

Figure 2: PET-CT showed multiple FDG-avid supra- and infra-diaphragmatic lymph nodes (SUVmax 14.4) and mild splenomegaly.

Table 1: Remission Induction.

Drug	Dose & Schedule
IT-Ara-C	Ara-C 70 mg IT on D7
Prednisone	60 mg/m²/day PO or IV in two divided doses on D1–28
Vincristine	1.5 mg/m² IV on D1, 8, 15, 22 (max dose 2 mg)
Daunorubicin	25 mg/m² IV on D1, 8, 15, 22
PEG-Asparaginase	2500 IU/m² IM or IV on D4
IT-MTX	15 mg IT on D14, D28
Venetoclax	200 mg/day D1–7, escalated to 400 mg D8– 14

At day 28 evaluation, the bone marrow was hypocellular (10–20%) with 2% blasts. Minimal Residual Disease (MRD) analysis detected 0.7% residual myeloid population (CD117+, CD13+, CD33+, CD34^dim, HLA-DR+, CD15+, CD38+), while no T-lymphoblasts were identified. PET-CT demonstrated an excellent metabolic response with residual low-level uptake in bilateral cervical lymph nodes. Owing to persistent MRD and extramedullary activity, consolidation with Hyper-CVAD Part B

(High-dose Methotrexate and Cytarabine (Ara-C)) was administered in July 2025, together with continuation of venetoclax (Table 2). Repeat marrow examination demonstrated normocellularity (70–80%) with trilineage hematopoiesis and no morphologic or immunophenotypic evidence of disease; MRD was negative at the 0.01% threshold. Repeat PET scan showed complete metabolic resolution of prior (Figure 3).

The patient subsequently underwent mismatched related allogeneic peripheral blood stem cell transplantation from a cousin donor, conditioned with Total Body Irradiation (TBI) 10 Gy, fludarabine, with GVHD prophylaxis regimen as post-transplant cyclophosphamide/tactrolimus and mycophenolate.

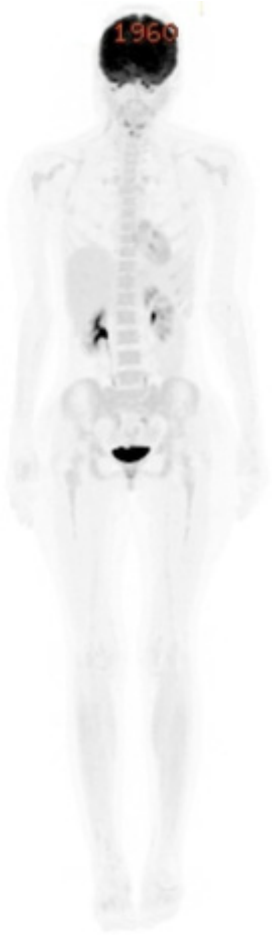

Figure 3: PET-CT post HYPER-CVAD B + venetocloax demonstrated an excellent metabolic response with residual low-level uptake in bilateral cervical lymph nodes.

Table 2: Hyper-CVAD Block B with Venetoclax.

Drug	Dose & Schedule
Methotrexate	200 mg/m² IV over 2 h on D1, then 800 mg/m² IV over 22 h
Leucovorin	15 mg PO/IV q6h, starting 12–24 h after MTX until MTX <0.1 µM
Cytarabine	3 g/m² IV q12h × 4 doses on D2–3 (adjust for age/renal function)
Methylprednisolone	50 mg IV q12h on D1–3
IT therapy	MTX or Ara-C per CNS prophylaxis/therapy schedule
Venetoclax	200 mg/day ramp-up, escalated to 400 mg/day, D1–14

D+45 post-transplant assessment showed complete molecular remission on PET scan and Minimal Residual Disease (MRD) negativity by bone marrow biopsy (Figure 4).

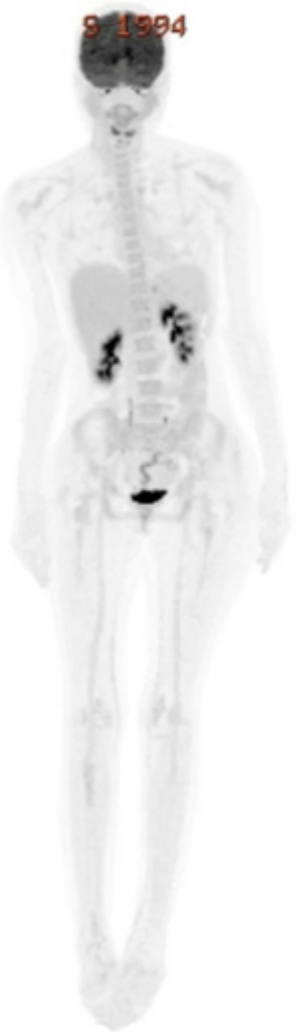

Figure 4: PET CT post allogenic stem cell transplantation suggestive of a complete metabolic response.

Discussion

Mixed-Phenotype Acute Leukemia (MPAL) represents one of the most challenging acute leukemias to diagnose and treat, owing to its biological heterogeneity, diagnostic overlap with other high-risk entities, and lack of standardized therapeutic algorithms. Large retrospective analyses confirm ALL-directed therapy improves remission, but allo-SCT remains essential [6]. Further comparative pathology work has underscored the unique challenges of T-lineage MPAL. In an analysis of 41 adult cases, T-lineage MPAL was associated with significantly poorer prognosis relative to conventional T-ALL, whereas Early T-Precursor (ETP) ALL demonstrated outcomes closer to T-ALL. Many T-lineage MPAL cases shared overlapping immunophenotypic features with ETP-ALL, highlighting the risk of misclassification. The authors recommended inclusion of CD19 and MPO in diagnostic panels to improve accuracy, thereby enabling more rational therapeutic decision-making [3]. Molecular heterogeneity further complicates the MPAL landscape. A prospective series of 75 patients identified BCR::ABL1 rearrangements in approximately 13% of cases. Although the presence of this fusion did not predict treatment response, allo-SCT significantly improved survival, underscoring the curative potential of transplantation across molecular subsets [4]. Beyond standard therapy, the integration of novel targeted agents has begun to redefine therapeutic options in MPAL. A single-cell transcriptomic analysis presented at Blood 2024 revealed that T/myeloid MPAL can be stratified into three malignant subpopulations: AML-like, ALL-

like, and a unique HOPX-expressing, stemness-high, quiescent subtype associated with the poorest outcomes [5]. Venetoclax, a selective BCL-2 inhibitor, was highlighted as a rational therapy for this stemness-enriched population. Clinical reports have already suggested benefit. Kankaria et al. described a case of acute undifferentiated leukemia achieving complete remission with FLAG-IDA plus venetoclax [10], while Liu et al. reported successful disease control in a B/T MPAL patient using a chemo-free regimen combining venetoclax, azacitidine, and blinatumomab [11]. Similarly, Yamamoto et al. documented the first case of therapy-related trilineage MPAL treated with venetoclax and azacitidine, resulting in complete remission [12]. Another case reports by Mekni et al. showed achieving of complete remissions in refractory MPAL using venetoclax plus azacitidine [13]. In a case report and literature review, Klocke et al. described the use of venetoclax in combination with decitabine for a patient with MPAL who had failed prior therapy, which resulted in a complete remission with incomplete hematologic recovery (CRi) [14]. A 2023 ASH report of six MPAL patients treated with venetoclax and blinatumomab (± azacitidine) achieved universal remission [15]. Studies are summarized in Table 3.

Table 3: Venetoclax-based (and related) regimens in MPAL / AUL: Case Reports & Series

Study (Year) / Journal	Design	Disease / Subtype	N	Setting	Regimen	Key Outcomes	Notes	Citation
Kanka ria et al., 2025	Letter / case	Acute Undifferen tiated Leukemia (AUL)	1	Newly diagno sed	FLAG- IDA + Venetocla x	CR achieved	AUL (ALAL) context; extrapolata ble to ambiguous lineage	10
Liu et al., 2024	Case report	B/T MPAL (complex karyotype)	1	Frontli ne, chemo- free strateg y	Venetocla x + Azacitidi ne + Blinatum omab	Hemato logic & molecul ar CR; maintai ned MRD– 1 year post- alloSCT		11
Yama moto et al., 2025	Case report	Therapy-related MPAL (B/T/Myeloid)	1	t-MPAL evolvin g from MN-pC T	Venetocla x + Azacitidi ne	CR; bridged to cord blood allo-SCT		12
Mekni et al., 2023	Letter / case	B/T MPAL (relapse after 2× ASCT)	1	Post- 2nd ASCT relapse	Venetocla x + Azacitidi ne	Morpho logic CR after 1 cycle; MRD later nega- tive; continued therapy	Infectious AEs managed; VEN dose adjusted with azole	13
Klocke et al., 2020	Case report	T/Myeloid MPAL NOS (relapse post- post- Decitabin alloSCT; NOTCH1 alloSCT) alloSCT e >1 year mutations	1	Relaps ed	Venetocla x +	CR; bridged to 2nd remis- sion	DNMT3A, IDH1, CBL,	14
Wu etal., 2023	Prospective case series (abstract)	CD19+ MPAL (B/My predominantly)	6	Frontline induc- tion	Blinatumomab + Venetoclax (± Azacitidine)	100% CR; 5/6 MRD <0.1%; 3 MRD <0.01%	One BCR::ABL1 received blina + TKI (olverembatinib)	15

Abbreviations: MPAL: Mixed phenotype acute leukemia; AUL: Acute undifferentiated leukemia; HMA: hypomethylating agent; CR: Complete remission; MRD: Measurable residual disease; allo-SCT: Allogeneic stem cell transplant; ASCT: Autologous stem cell transplant; t-MPAL: Therapy-related MPAL.

In our patient, the therapeutic approach deliberately combined ALL-directed chemotherapy with venetoclax to address both lymphoid and myeloid disease components and overcome early MRD persistence. Initial debulking with flat-dose cytarabine was employed to reduce leukemic burden before initiation of an AYA-adapted CALGB regimen with concomitant venetoclax escalation. CNS prophylaxis was administered with alternating intrathecal cytarabine and methotrexate. Despite an initial partial response with residual myeloid MRD and low-level extramedullary activity, consolidation with Hyper-CVAD Part B and continuation of venetoclax achieved complete MRD negativity. This paved the way for a haplo-identical stem cell transplant with TBI/fludarabine/post-cyclophosphamide conditioning, offering the prospect of long-term disease control.

This case highlights several important considerations. First, accurate diagnosis with broad immunophenotyping and molecular testing remains essential to differentiate T/myeloid MPAL from phenotypically similar entities such as ETP-ALL. Second, early integration of venetoclax into frontline therapy may augment remission depth, particularly in cases with high-risk biology or extramedullary disease. Finally, allo-SCT continues to represent the most effective consolidative option, and optimizing pre-transplant disease clearance with novel agents may be critical to improving survival in this rare and aggressive leukemia subtype.

Despite the encouraging outcome in this case, several limitations must be acknowledged. Evidence supporting the use of venetoclax in MPAL remains limited to case reports and small series, and its role in frontline therapy is not yet established through prospective trials. Furthermore, the heterogeneity of MPAL complicates treatment generalizability, as responses may vary by lineage predominance, molecular subtype, and extramedullary involvement. Future research should focus on multicenter collaborative studies that integrate immunophenotypic and genomic profiling to guide personalized therapy. Incorporation of targeted agents such as venetoclax, alone or in combination with immunotherapies and conventional chemotherapy, warrants systematic evaluation to define their optimal timing, safety, and long-term efficacy in MPAL.

Conclusion

T/myeloid MPAL represents a rare and biologically complex subtype of acute leukemia with limited evidence to guide treatment. This case illustrates the feasibility and potential benefit of integrating venetoclax early with ALL-directed chemotherapy to achieve deep remission and overcome both MRD persistence and extramedullary disease. The successful transition to haploidentical stem cell transplantation underscores the importance of combining novel targeted therapies with curative-intent strategies. While individual experiences such as this provide

valuable insights, prospective studies are urgently needed to define the role of venetoclax and other targeted agents in the frontline management of MPAL.

Author declarations

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

Informed consent was obtained from the patient for publication of this case report.

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