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Case Report

Therapy-Related Tp53-Mutated Precursor B-Cell Acute Lymphoblastic Leukemia Arising During Lenalidomide Maintenance Following Autologous Stem Cell Transplantation for Multiple Myeloma

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Abstract

Therapy-related acute lymphoblastic leukemia (t-ALL) is a rare but increasingly recognized complication of cytotoxic therapy. We report a case of TP53-mutated precursor B-cell acute lymphoblastic leukemia arising in a patient with multiple myeloma treated with CyBorD induction, autologous stem cell transplantation, and prolonged lenalidomide maintenance.

The patient presented with persistent cytopenias approximately six years after transplantation. Bone marrow evaluation demonstrated Philadelphia chromosome–negative B-ALL with a TP53 mutation at high variant allele frequency. The clinical course was complicated by infectious and treatment-related toxicities, necessitating de-escalation to maintenance therapy.

This case highlights the emerging recognition of therapy-related B-ALL in multiple myeloma, the role of lenalidomide exposure, and the challenges in management due to adverse disease biology and patient-related factors.

Introduction

Therapy-related acute leukemias are well-established complications of cytotoxic therapy, most commonly manifesting as myeloid neoplasms. Therapy-related acute lymphoblastic leukemia (t-ALL) is rarer and less well characterized, representing an increasing proportion of adult ALL diagnoses—up to roughly 6.9%–10% in contemporary series [1-3].

In multiple myeloma (MM), advances in treatment—including autologous stem cell transplantation (ASCT) and maintenance lenalidomide—have improved survival but increased the incidence of second primary malignancies (SPM), particularly hematologic malignancies [4-6]. Emerging evidence suggests that therapy-related B-ALL (t-B-ALL) arising in this context may represent a distinct clinical entity, frequently Philadelphia chromosome–negative, enriched for TP53 mutation and low hypodiploidy, and clonally independent from the antecedent plasma cell neoplasm [7-9].

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We describe a case of TP53-mutated therapy-related B-ALL developing during lenalidomide maintenance following ASCT.

Case presentation

The patient initially presented with IgG lambda multiple myeloma stage III according to the International Staging System (ISS)> He had multiple vertebral compression fractures and lytic lesions involving ribs, vertebrae, and left hemipelvis. He received seven cycles of CyBorD (cyclophosphamide, bortezomib, and dexamethasone) and achieved a very good partial response. Consolidative autologous stem cell transplantation was performed on November 16, 2018, and maintenance lenalidomide was initiated in early February 2019. The maintenance course was complicated due to hypokalemia requiring high-dose oral potassium replacement. Lenalidomide was discontinued in early 2025 owing to cytopenia, and the patient was taken off active myeloma-directed therapy. Disease control was maintained, and serum protein electrophoresis in February 2026 showed no visible monoclonal protein and a normal kappa/lambda free light-chain ratio of 0.97.

During lenalidomide maintenance, the patient developed persistent cytopenia and was diagnosed in July 2025 with precursor B-cell acute lymphoblastic leukemia (pre-B-ALL), Philadelphia chromosome negative, with 27% blasts on flow cytometry. Molecular studies showed TP53 mutation (50% variant allele fraction) and DNMT3A mutation (3% expressed fraction). Induction chemotherapy as per the GRAALL elderly protocol was initiated on August 15, 2025 [10,11]. The patient completed two cycles of induction and two of four planned cycles of consolidation, with the most recent cycle administered on November 1, 2025.

The leukemia treatment course had significant complications. The first induction cycle was complicated by methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia, a left arm deep vein thrombosis leading to discontinuation of therapy. In mid-October 2025, he developed a right forearm wound (query chemotherapy infiltration) that grew Staphylococcus and Enterococcus species, requiring ongoing wound care and surgical debridement, which subsequently improved. Recurrent olecranon bursitis emerged in late October and was managed symptomatically. Owing to the need for prolonged hospital stay and no outpatient support, the patient declined cycles three and four consolidation therapy and proceeded directly to the maintenance phase. He was discharged home in early January 2026 on maintenance therapy comprising methotrexate 37.5 mg weekly, folic acid 5 mg the day after methotrexate, and 6-mercaptopurine 25 mg daily, coupled with ongoing wound and PICC line care.

On March 24, 2026, the patient had mouth sores on the lower lip with associated swelling of the lips and cheeks. He reported ongoing drainage from the forearm wound. He disclosed that he had been taking his methotrexate incorrectly—approximately five tablets per day over three consecutive days rather than the full 37.5 mg (15 tablets) on a single day. This dosing error raised concern that his oral lesions represented methotrexate-related mucositis rather than herpes simplex reactivation, particularly as he remained on prophylactic acyclovir. Laboratory studies the preceding week showed hemoglobin 122 g/L, platelets 110 × 10^9/L, and neutrophils 3.4 × 10^9/L, with the hemoglobin and platelet counts modestly decreased from prior weeks; creatinine, electrolytes, and liver enzymes were normal, and LDH was mildly elevated at 287 U/L after having been normal through February.

At follow-up in March 2026, the patient remained clinically stable with mild cytopenias. Myeloma evaluation confirmed continued remission, with no detectable monoclonal protein and a normal free light chain ratio, supporting the diagnosis of a second primary malignancy.

Discussion

This case highlights several important aspects of therapy-related B-ALL arising in patients with MM.

Leukemogenesis and clonal evolution

The development of B-ALL in this patient likely reflects therapy-related leukemogenesis driven by prior exposure to melphalan and prolonged lenalidomide maintenance. Alkylating agents such as melphalan induce DNA damage and can select for TP53-mutant clonal hematopoiesis, which may survive myeloablative conditioning and expand after stem-cell reinfusion [12]. Lenalidomide has been implicated in the expansion of pre-existing clonal hematopoiesis, with data supporting lenalidomide-driven selection of TP53-mutant hematopoietic stem and progenitor cells [9]. The high variant allele frequency of TP53 in this case suggests clonal dominance and supports a model of therapy-driven selection [9,12].

The molecular profile at the time of B-ALL diagnosis comprised a TP53 mutation at 50% variant allele frequency (VAF) and a low-burden DNMT3A variant (reported as ~3%). DNMT3A is the single most commonly mutated gene in clonal hematopoiesis (CH), and a VAF in the 2%–3% range falls at the lower end of the conventional threshold defining clonal hematopoiesis of indeterminate potential (VAF ≥ 2%); such low-level DNMT3A clones are a common, largely age-related phenomenon that display among the slowest growth kinetics and the lowest progression risk of all CH drivers [16,17].

Two features support this variant most likely residing in a background CH compartment rather than driving the leukemic clone: its VAF is markedly discordant with both the blast fraction (27%) and the high-burden TP53 variant (50%), whereas a mutation central to the dominant population would be expected to approximate the clonal fraction. Also in cases of therapy-related neoplasia after autologous transplantation for myeloma, DNMT3A clones characteristically behave as quiescent bystanders while non-DNMT3A clones—particularly TP53—expand and drive transformation, a dynamic further favored by lenalidomide-associated selection of TP53-mutant clones [6,12,16]. This clonal-selection mechanism is also reflected in the recognition of lenalidomide-associated B-lymphoblastic leukemia as a distinct entity, in which TP53 aberrations are enriched [7,8].

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This interpretation is constrained by two limitations. In the absence of baseline sequencing at myeloma diagnosis or before cytotoxic therapy, it cannot be determined whether the DNMT3A variant represented pre-existing clonal hematopoiesis or a treatment-emergent clone. Also, without sequencing of non-hematopoietic tissue, a germline alteration cannot be formally excluded, although the low VAF is most consistent with a somatic, acquired clone [16]. Accordingly, the DNMT3A variant is best interpreted as a low-burden, clonal-hematopoiesis-associated lesion of uncertain but likely limited direct pathogenic contribution to the B-ALL, with the high-VAF TP53 mutation representing the dominant, disease-defining, and prognostically adverse driver [13,15].

Latency and clinical presentation

The latency of approximately six years from ASCT is consistent with prior reports; in the largest dedicated series, lenalidomide-associated B-ALL was diagnosed at a median of 54 months after first lenalidomide exposure, and t-ALL more broadly has a median latency of roughly 6–7 years from the primary diagnosis [1,7]. Presentation with isolated or subtle cytopenias is common and may delay diagnosis, as these findings are frequently attributed to treatment toxicity or may initially mimic a hematogone expansion on flow cytometry [8]. Early bone marrow evaluation is therefore critical in patients receiving long-term maintenance therapy.

Distinct biology of MM-associated t-B-ALL

Recent literature suggests that therapy-related B-ALL in MM patients represents a distinct biological entity characterized by high-risk molecular features. In a dual-institution cohort of 32 lenalidomide-associated ALL cases, disease was overwhelmingly B-lineage and BCR::ABL1-negative, with a high incidence of TP53 mutations (9/19 evaluable) and low hypodiploidy (8/26) [7]. This B-ALL is typically clonally independent from the underlying plasma cell neoplasm.[9] TP53 mutation is recognized as a poor-risk lesion in B-ALL and is independently associated with inferior survival in adults, particularly older patients with Ph-negative disease and high variant allele frequency [13-15]. The concurrent DNMT3A mutation further supports an underlying background of clonal hematopoiesis, one of the most common clonal hematopoiesis–associated lesions and a recognized substrate for therapy-related leukemogenesis [16,17].

Role of lenalidomide

Accumulating evidence links lenalidomide exposure to secondary hematologic malignancies. A patient-level meta-analysis of seven randomized trials found increased hematologic SPM incidence with lenalidomide (5-year cumulative incidence 3.1% vs 1.4%), with co-exposure to oral melphalan the principal driver [5]. A systematic review and meta-analysis found the significant SPM signal to be specific to the myeloma setting, and highlighted the recognized association of lenalidomide-associated B-ALL with TP53 mutation [9]. Although the most common hematologic SPMs remain therapy-related myeloid neoplasms, B-ALL is increasingly reported during lenalidomide maintenance in both MM and CLL [6,9]. Notably, regression of early B-ALL or B-ALL–immunophenotype populations has been described after lenalidomide discontinuation, suggesting an ongoing leukemia-promoting effect and a potential role for lenalidomide withdrawal in selected patients [7]. The NCCN and IMWG both acknowledge an increased risk of secondary cancers, especially with post-transplant lenalidomide maintenance, that must be balanced against its clear survival benefit [4,18].

Treatment challenges

Management of therapy-related B-ALL is complicated by both disease biology and patient-related factors. Although intensive chemotherapy and allogeneic transplantation remain standard approaches, many patients cannot tolerate such strategies due to age, comorbidities, or treatment-related toxicity, and t-ALL carries an adverse prognosis largely driven by high-risk features [1,2]. Importantly, outcomes of t-ALL appear comparable to de novo ALL among patients able to proceed to allogeneic transplantation [1,3]. In older, TP53-mutant, Ph-negative B-ALL, relapse risk remains high even with antibody-based approaches, though inotuzumab-, blinatumomab-, and venetoclax-containing regimens can improve remission rates [13,15]. In this case, cumulative complications necessitated de-escalation to maintenance therapy, reflecting real-world clinical practice. Optimal management strategies for this population remain undefined.

Conclusion

Therapy-related B-ALL is an emerging complication in patients with MM treated with ASCT and lenalidomide maintenance. Persistent cytopenia in this population should prompt early evaluation for secondary malignancies. Further studies are needed to better define the pathogenesis, risk factors, and optimal management of this rare but clinically significant condition.

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