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Case Report

Therapy-related B-cell acute lymphoblastic leukemia after treatment for multiple myeloma

Smeeta Gajendra[1], Leena Gupta[1], Tanima Dwivedi[1], Gurvinder Kaur[1], Deepshi Thakral[1], Lata Rani[2], Lalit Kumar[3], Ritu Gupta[1]

[1]Department of Laboratory Oncology, Dr. B.R.A. IRCH, All India Institute of Medical Sciences, New Delhi 110029, India; [2]Genomics Facility, Centralized Core Research Facility, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi 110029, India; [3]Department of Medical Oncology, Dr. B.R.A. IRCH, All India Institute of Medical Sciences, New Delhi 110029, India

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Abstract: Changing landscape of treatment has significantly improved survival in multiple myeloma (MM) in last two decades by using proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, and autologous stem cell transplantation (ASCT). With the associated improvement of overall survival, cumulative exposure to these agents have led to an increased incidence of secondary malignancies. Therapy-related myeloid neoplasms are more frequent than therapy-related B-cell acute lymphoblastic leukemia (t-B-ALL). We describe four patients who developed t-B-ALL following treatment for MM. All had received novel agents, three had lenalidomide maintenance, and two had undergone ASCT. Latency from MM diagnosis to t-B-ALL ranged from 3 to 7 years. Age ranged from 57-63 years with pancytopenia being the presentation. Bone marrow aspirates revealed Myeloperoxidase negative blasts with B-lineage immunophenotype. Cytogenetic and molecular findings were variable. At B-ALL diagnosis, clonal plasma cells or monoclonal band were absent, supporting clonal independence. Patients were treated with vincristine, anthracycline, and steroid-based regimens and achieved measurable residual disease negativity in two patients, however, only one patient alive at 21 months of follow-up and the remaining three succumbing within seven months of diagnosis. Therapy-related B-ALL is a rare but aggressive secondary malignancy in MM, commonly detected when presented with cytopenias. Prognosis of this entity is poor, in comparision to de novo B-ALL, underscoring the need for vigilant clinical follow-up, an urgent need to identify factors that predict the development of therapy-related malignancies and exploration of tailored therapeutic strategies.

Keywords: Secondary hematologic malignancy, therapy-related B-ALL, multiple myeloma, immunomodulatory drugs, autologous stem cell transplantation

Introduction

Multiple myeloma (MM) is a multifocal neoplastic proliferation of clonal plasma cell accounts for approximately 10-15% of all hematologic malignancies and 1% of all malignant tumors [1]. Incidence of MM increases progressively with age with >90% of cases occurring in >50 years (median age: 70 years). Over the past two decades, the therapeutic landscape of MM has undergone a paradigm shift with the introduction of novel agents, including proteasome inhibitors (PIs) (bortezomib, carfilzomib), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide, pomalidomide), and monoclonal antibodies (daratumumab, isatuximab). Autologous stem cell transplantation (ASCT), remains standard in frontline consolidation therapy, and further improved these outcomes and was incorporated into standard treatment of MM for eligible patients. These therapies substantial increased survival, extending median overall survival from approximately three years to nearly 8-10 years [2, 3]. However, due to improved overall survival, there is increased incidence of subsequent second malignancy after MM. There is higher incidence of secondary malignancies raise concerns regarding the long-term genomic consequences of sustained therapeutic pressure and cumulative exposure to cytotoxic and immunomodulatory agents [4-7].

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The risk of therapy related malignancies is primarily associated with cumulative exposure to cytotoxic chemotherapy, especially alkylating agents such as melphalan, as well as topoisomerase II inhibitors in earlier treatment eras. High-dose therapy followed by ASCT, although highly effective, has also been implicated in increasing the risk of secondary hematologic malignancies. In addition, prolonged exposure to IMiDs, such as lenalidomide, particularly in combination with prior alkylator therapy, may contribute to clonal hematopoiesis expansion and leukemogenic evolution [8, 9]. Patient-related factors including advanced age, germline predisposition syndromes, and the presence of age-related clonal hematopoiesis of indeterminate potential (CHIP) further modify individual susceptibility. At the biological level, these agents induce DNA damage, genomic instability, and selective clonal pressure favoring expansion of pre-leukemic hematopoietic stem cell clones [8, 10, 11].

The cumulative incidence of therapy-related neoplasms in MM has been estimated to range from 5% to 7%, influenced by several factors including patient-related (increasing age, male, ethinicity, genetics and environment), disease-related (M-protein size and sub-type, myeloma genetics, immune dysregulations) and treatment-related (type of induction regimen, duration of therapy, and maintenance chemotherapy) [12]. The incidence of subsequent haematological malignancies in patients diagnosed with MM is much higher than non-haematological malignancies. Secondary solid malignancies include gastrointestinal, kidney, bladder, and skin cancers. Therapy-related myeloid neoplasms, comprising therapy-related myelodysplastic syndromes (t-MDS) and acute myeloid leukemia (t-AML), constitute the most common secondary hematologic cancers in MM patients [5, 12, 13]. These neoplasms are typically associated with high-risk cytogenetic abnormalities, relatively short latency periods, and dismal prognosis in comparison to de novo cases. However, therapy-related B lymphoid malignancies, including therapy-related B-acute lymphoblastic leukemia (t-B-ALL) and secondary aggressive lymphomas such as diffuse large B-cell lymphoma, are very uncommon. t-B-ALL is exceedingly rare, with only few case series and isolated case reports previously described in the literature. So that, this entity is likely underrecognized, due to its abrupt onset, aggressive clinical course, and frequent presentation with cytopenias that may be initially attributed to chemotherapy related or relapse of MM. t-B-ALL is characterized by adverse cytogenetic abnormalities, suboptimal responses to conventional ALL-directed therapy, and an overall dismal prognosis. These features underscore the need for clinical awareness, improved understanding of its pathogenesis, and the development of therapeutic strategies tailored specifically to t-B-ALL, distinct from de novo B-ALL and t-MDS/AML [14, 15].

Preventing therapy-related malignancies in MM remains challenging but may be improved through a more individualized, risk-adapted approach. Reducing cumulative exposure to alkylating agents, thoughtful selection and duration of maintenance therapy, and careful treatment planning are all important considerations. Emerging minimal residual disease (MRD)-guided therapeutic strategies may further help in de-escalating treatment intensity and potentially reducing long-term toxicity. Identifying patients at higher risk, such as those of advanced age or with evidence of clonal hematopoiesis may further aid in risk stratification. Long-term follow-up is essential and should include regular clinical assessment, complete blood counts, prompt evaluation of unexplained cytopenias and MRD assessment. Early recognition of secondary malignancies is critical, as it may enable more timely intervention and potentially improve outcomes.

Herein, we report four patients who developed t-B-ALL following treatment for MM. We aim to highlight the heterogeneous presentations, diagnostic challenges, therapeutic complexities, and outcomes through detailed clinicopathologic characterization, including immunophenotypic, cytogenetic, and molecular analyses. By reviewing the limited existing literature, we want to raise awareness among clinicians and pathologists involved in the long-term care of MM survivors and emphasize the importance of vigilant surveillance for secondary hematologic malignancies in this expanding patient population.

Case presentation

Case 1

A 62-year-old female presented with right hip pain, fatigue and weight loss for 3 months. Complete blood counts (CBC) showed haemoglobin (Hb) 10.2 g/dL, platelet count 257×10^9/L, and total leukocyte count (TLC) 6.3×10^9/L. MRI of hip revealed intra medullary expansile soft tissue lesion in diaphysis of right femur with endosteal scalloping of cortex and periosteal reaction, initially suggestive of fibrous dysplasia. Positron emission tomography/computed tomography (PET/CT) revealed a hypermetabolic lesion consistent with plasmacytoma of right femur. A biopsy from the lesion confirmed the diagnosis of plasmactoma. The peripheral blood smear (PBS) showed rouleaux formation. Bone marrow aspirate (BMA) showed ~16% plasma cells and bone marrow biopsy showed focal plasma cell aggregates. Serum LDH was 117 mg/dL and beta-2 microglobulin was elevated at 6.2 mg/L. Serum protein electrophoresis (SPEP) showed an M-protein spike of IgG kappa 4.2 g/dL, and markedly deranged serum free light chain (SFLC) ratio (κ/λ 39.5). She was diagnosed as plasma cell myeloma (PCM), International Staging System (ISS)-III. The patient underwent closed reduction and internal fixation with nailing followed by radiotherapy for the femoral lesion. She subsequently received six cycles of bortezomib, pomalidomide, and dexamethasone (VPD), along with zoledronic acid. Lenalidomide maintenance was initiated approximately five months after completion of induction.

After nearly four years of follow-up, she presented with pancytopenia (Hb 8.2 g/dL, platelet count 27×10^9/L, and TLC 0.8×10^9/L). BMA showed 25% blasts that were negative for Myeloperoxidase cytochemistry (MPO). Flow cytometric immunophenotyping (FCMI) showed 20% blasts, positive for CD45 (dim), CD19, cytoCD79a, CD10, CD20 (partial), CD22 (heterogenous), CD81, CD27 (heterogenous), CD38, and negative for CD34, CD13, CD33, cytoMPO, CD7, CD3 and other markers tested. A diagnosis of B-ALL was established. SPEP did not reveal any M-spike and SFLC was normal. Karyotyping revealed normal 46, XX and next-generation sequencing did not detect any pathogenic mutations. The patient received therapy consisting of Vincristine, Prednisolone and Duanorubicin. The end of induction (EOI) MRD was negative. She remained alive with MRD negativity for 21 months from the time of diagnosis.

Case 2

A 63-year-old male presented with shortness of breath and easy fatigability for 2 months. CBC showed anemia (5.3 g/dL) and thrombocytopenia (52×10^9/L) with a normal TLC (4.1×10^9/L). The PBS showed rouleaux formation and BMA demonstrated 90% plasma cells. Serum LDH was 148 mg/dL and beta-2 microglobulin was elevated at 4.9 mg/L. SPEP showed a monoclonal IgG kappa spike of 9.3 g/dL and SFLC assay showed deranged κ to λ ratio (587.4). Cytogenetics revealed t(14::16), gain of 1(q) with tetraploidy (extra chromosome 4, 14, 17 and 20). She was diagnosed with PCM, ISS-III. Treatment started with Bortezomib, Cyclophosphamide and dexamethasone (VCD) along with injection zolendronic acid, followed by initiation of lenalidomide maintenance.

After approximately six years of follow-up, he presented with gum bleeding. CBC revealed pancytopenia (Hb 7.4 g/dL, platelet count 5×10^9/L, and TLC 1.2×10^9/L). PBS showed pancytopenia with 12% blasts. BMA showed 70% MPO negative blasts. FCMI showed 20% blasts, positive for CD45 (dim), CD19, cytoCD79a, CD34, CD10, CD20, CD58, CD22, CD38 and negative for CD13, CD33, cytoMPO, CD7, CD3. A diagnosis of B-ALL was established. SPEP did not reveal any M-spike and SFLC was normal. NGS detected TP53 and TET-1 mutation. The patient received therapy consisting of Vincristine and prednisolone. The EOI bone marrow was in remission, and MRD was negative. Despite initial response, the patient had a rapidly progressive course and succumbed approximately five months after the diagnosis of B-ALL.

Case 3

A 60-year-old hypertensive male presented with a complaint of acute backache. PET/CT revealed a lytic lesion with soft tissue component in the body and pedicle of L2 vertebra with vertebral collapse, suggestive of plasmacytoma. CBC and PBS showed normal count

and BMA did not show an increase in plasma cells. SFLC assay was normal, κ to λ ratio (0.46). The biopsy from the vertebral lesion confirmed the diagnosis of solitary plasmacytoma. The patient received radical radiotherapy for the same. Approximately one year later, he developed progressive fatigue and recurrent low back pain. CBC (Hb 13.0 g/dL, platelet count 263×10^9/L, and TLC 6.3×10^9/L) was within normal limits, but PBS demonstrated rouleaux formation. BMA revealed approximately 50% plasma cells. Serum lactate dehydrogenase was elevated at 347 mg/dL, and beta-2 microglobulin was 3 mg/L. SPEP demonstrated a monoclonal IgG lambda spike of 2.5 g/dL, while the SFLC was mildly derange (κ to λ ratio (2.18)). Cytogenetics revealed loss of 1p21. A diagnosis of PCM, International Staging System stage I, was established. He first received four cycles of bortezomib, cyclophosphamide, and dexamethasone (VCD). Then He was started on lenalidomide maintenance therapy. This was further undergone ASCT, followed by two cycles of bortezomib, lenalidomide, and dexamethasone, which resulted in complete remission.

The patient presented with bleeding manifestations after approximately five years of sustained remission. CBC revealed anemia (hemoglobin 11.2 g/dL) and thrombocytopenia (28×10^9/L) with a normal leukocyte count (4.7×10^9/L). PBS showed lymphocyte predominance with 4% blasts and thrombocytopenia. BMA demonstrated approximately 80% blasts that were negative for MPO cytochemistry. FCMI revealed CD45 dim positive blasts expressing, CD19, cytoplasmic CD79a, CD34 (subset), CD10, CD20, CD58, CD304 (dim), CD73 (dim), CD22, and CD38 (partial), with absence of myeloid and T-cell markers. SPEP showed no monoclonal protein, and the SFLC ratio was normal. A diagnosis of B-ALL was established. Fluorescence in situ hybridization (FISH) revealed hypodiploidy with monosomy of chromosomes 5 and 9. The patient was started with vincristine, daunorubicin, and prednisolone. Post-induction BM examination showed persistent disease, and re-induction therapy was administered. Post-reduction chemotherapy, he achieved morphologic remission; with 0.04% MRD positive. The disease relapsed within two months, and the patient succumbed to progressive leukemia approximately one month after relapse.

Case 4

A 57-year-old man was diagnosed with IgG kappa PCM, ISS-II, while being evaluated for low back pain at an outside center. CBC showed normal counts (Hb 13.0 g/dL and platelets 268×10^9/L and TLC 8.5×10^9/L). The PBS showed rouleaux formation and BMA demonstrated 16% plasma cells. Serum LDH was 234 mg/dL and beta-2 microglobulin was elevated at 2.7 mg/L. SPEP showed a monoclonal IgG kappa spike of 1.62 g/dL and SFLC assay showed deranged κ to λ ratio (8.75). He initially received five cycles of bortezomib, lenalidomide, and dexamethasone (VRD), following which he was referred to our institution. He subsequently received one additional cycle of the same regimen and underwent autologous stem cell transplantation. Lenalidomide maintenance therapy was initiated thereafter, and he remained in remission with a progression-free survival of approximately four years.

During follow-up, approximately four years, the patient developed pancytopenia, with hemoglobin of 9.5 g/dL, platelet count of 60×10^9/L, and total leukocyte count of 2.1×10^9/L. Peripheral blood smear revealed 36% circulating blasts. Bone marrow aspirate showed near-total replacement by blasts (approximately 95%), which were negative for myeloperoxidase cytochemistry. FCMI demonstrated a precursor B-cell population expressing CD45 (dim), CD19, cytoplasmic CD79a, partial CD34, CD10, CD20, CD58, dim CD123, heterogeneous CD22, and CD38, with absence of myeloid markers, cytoplasmic MPO, and T-cell markers. A diagnosis of B-ALL was established. The patient was treated with vincristine, daunorubicin, and prednisolone. Despite initiation of therapy, his clinical course was rapidly progressive, and he succumbed approximately 30 days after starting induction treatment.

Table 1 summarized all four cases of therapy-related ALL of our cohort.

Discussion

Therapeutic landscape of MM has evolved substantially over the past two decades with the incorporation of IMiDs, proteasome inhibitors, monoclonal antibodies, and high-dose therapy supported by ASCT, resulting in doubled overall

Table 1. Summary of the therapy-related ALL cases in our cohort

Parameter	Case 1	Case 2	Case 3	Case 4
Age at PCM diagnosis	62 years	63 years	60 years	57 years
Sex	Female	Male	Male	Male
Initial diagnosis	PCM, ISS-III	PCM, ISS-III	PCM, ISS-I	PCM, ISS-II
BM plasma cells (%)	16%	90%	50%	16%
Serum LDH	117 mg/dL	148 mg/dL	347 mg/dL	234 mg/dL
Beta-2 microglobulin	6.2 mg/L	4.9 mg/L	3 mg/L	2.7 mg/L
Immunoglobulin type/level	IgG κ M spike: 4.2 g/dL, SFLC κ/λ: 39.5	IgG κ M spike: 9.3 g/dL, SFLC κ/λ: 587.4	IgG λ M spike: 2.5 g/dL, SFLC κ/λ: 2.18	IgG κ M spike: 1.62 g/dL, SFLC κ/λ: 8.75
Cytogenetics at MM diagnosis	Inadequate	Tetraploid, extra copies of 4, 14, 17 and 20, t(14::16), gain (1q)	Loss of 1p21	Negative for t(4::14) t(14::16), t(11::14), del 13q14, del 17p
Treatment (PCM)	VPD ×6 + Zoledronic acid → Lenalidomide maintenance	VCD ×5 → Lenalidomide maintenance	VCD ×4 → ASCT → VRD ×2 → Lenalidomide maintenance	VRD ×6 → ASCT → Lenalidomide maintenance
Duration of CR	~4 years	~6 years	~5 years	~4 years
Age at ALL diagnosis	66 years	70 years	65 years	62 years
BM blasts (%)	25%	70%	80%	95%
FCMI profile	CD19+, CD10+, cytoCD79a+, CD20 (partial), CD22 (heterogeneous), CD81+, CD27 (heterogeneous), CD38+, CD45dim	CD19+, CD10+, cytoCD79a+, CD34+, CD20+, CD22+, CD58+, CD38+	CD19+, CD10+, cytoCD79a+, CD34 (partial)+, CD20+, CD22+, CD58+, CD304dim, CD73dim	CD19+, CD10+, cytoCD79a+, CD34 (partial)+, CD20+, CD22 (heterogeneous), CD58+, CD123dim, CD38+
Cytogenetics and Molecular profile at B-ALL diagnosis	Karyotype normal; NGS no pathogenic mutations	TP53 and TET1 mutations	Hypodiploidy (monosomy 5 & 9)	NA
ALL treatment	Vincristine, Prednisolone, Daunorubicin	Vincristine, Prednisolone	Vincristine, Daunorubicin, Prednisolone; rituximab added during consolidation	Vincristine, Prednisolone, Daunorubicin,
EOI MRD Outcome	EOI MRD-negative	EOI MRD-negative	No remission at EOI	NA
Survival Status	Alive, 21 months	Died, 5 months	Died, 7 months	Died, Day 30

Abbreviations: ISS, International Staging System; NA, Not available; ALL, acute lymphoblastic leukemia; PCM, plasma cell myeloma; BM, bone marrow; ASCT, autologous stem cell transplantation; CR, complete remission; SFLC, Serum Free Light Chain assay; IMiD, immunomodulatory drug; PI, proteasome inhibitor; MRD, measurable residual disease; LDH, lactate dehydrogenase; EOI, end of induction; NGS, Next Generation Sequencing; FCMI, Flow Cytometric Immunophenotyping.

survival rate, with median OS exceeding 10 years in standard risk MM. However, these improved survival is accompanied by development of long term therapy-related toxicities, most notably secondary malignancies [16]. While therapy-related myeloid neoplasms (t-MDS/t-AML) remain the most frequently recognized secondary malignancies in MM, therapy-related acute lymphoblastic leukemia (t-ALL), particularly B-cell lineage disease remains distinctly uncommon, and has not been officially recognized by the World Health Organization hematologic malignancy classification. Few case reports and case series were previously reported in the literature [4, 7, 12-14, 17-33]. The true incidence of t-B-ALL in MM is likely underestimated due to its rarity, diagnostic overlap with treatment-related cytopenias, poor outcome and limited long-term surveillance data. Determining whether development of B-ALL in a known case of MM is therapy-related or de-novo second malignancy relies on a combined approach of clinical, cytogenetic, and molecular features, as no single criterion is definitive. A prior history of exposure to cytotoxic agents, with potential to develop therapy related leukemia, along with an appropriate latency period (typically 2-10 years), supports a therapy-related etiology. Cytogenetic abnormalities such as complex karyotype, hypodiploidy, or KMT2A rearrangements and the presence of mutations associated with genomic instability (e.g., TP53 alterations) further strengthen this association. Evidence of pre-existing clonal hematopoiesis or clonal evolution from prior disease, when available, may provide additional support. However, in many cases, distinguishing t-B-ALL from a second primary (de novo) B-ALL remains challenging, and the diagnosis is often based on an integrated clinicopathologic assessment rather than definitive proof. Key features supporting a therapy-related etiology in our patients include prior exposure to cytotoxic therapy, an appropriate latency period, and the presence of high-risk cytogenetic/molecular abnormalities. These observations underscore the importance of maintaining a high index of suspicion in MM patients presenting with new-onset cytopenias or circulating blasts.

The latency period between MM therapy and the development of t-B-ALL is variably reported in the literature (2-14 years). In our series, the latency is ranged from 4 to 6 years. This prolonged interval strongly supports a model of cumulative patient, disease or therapy-induced genomic injury. Notably, all four patients had been exposed to prolonged multi-agent treatment regimens, including alkylating agents, inhibitors, IMiDs, proteasome and, in two cases, ASCT was performed. The treatment was similar as suggested across previously published cases (**Table 2**). These contributing factors primarily include current combined chemotherapy regimens which increase risk (i.e. high-dose melphalan with autologous stem cell transplant and lenalidomide maintenance therapy) rather than any single drug exposure.

Pathogenesis of therapy-related B-ALL is multifactorial, that reflect a complex interplay between patient-related factors and genomic insults resulting from MM therapy. Patient-related factors as advanced age, male sex, and comorbidities may increase vulnerability to develop t-B-ALL [34-36]. Myeloma therapy including alkylating agents such as melphalan and cyclophosphamide further induce DNA damage and genomic instability resulting in therapy-related leukemias [8]. IMiDs, particularly lenalidomide have been associated with an increased incidence of secondary hematologic malignancies in MM, and thalidomide exposure has been linked to TP53 abnormalities that may lead to leukemigenesis [8]. Agents including anthracyclines, topoisomerase II inhibitors, and radiotherapy cause further genetic insult that promote chromosomal breaks, deletions, aneuploidy, and complex karyotypes, leading to therapy-related leukemias [19].

Emerging data suggest that inherited and acquired defects in DNA damage response (DDR) pathways may further modulate individual susceptibility. Germline mutations in DDR-related genes such as *TP53, BRCA1, BRCA2, ATM*, and *MSH6* are detected at higher-than-expected frequencies in MM patients and have been associated with therapy-related myeloid neoplasms in up to 20% of cases [10, 11]. In parallel, somatic driver alterations in genes commonly implicated in de novo B-ALL, including *IKZF1, PAX5, TP53,* and *NOTCH1*, have been identified in t-B-ALL, often accompanied by more complex and unstable karyotypes, suggestive of therapy-driven clonal evolution

Table 2. Reported cases of therapy-related B-ALL in multiple myeloma patients

Author/Year	No. of Cases	Patient Characteristics	Prior MM Therapy (key drugs/ASCT)	Latency (yrs)	Cytogenetics/Mutations	B-ALL Presentation	Treatment of B-ALL	Outcome
Lau LG et al., 2005 [17]	1	60F; IgG MM, stage IIIA	VAD → tandem ASCT (melphalan)	3	Ph-; distinct IgH clone; chr 7 abnormalities, trisomy 8, del(20q)	Pancytopenia	Steroids only	Transient response; relapse
Piszcz J et al., 2012 [19]	1	56F; IgG MM, lytic bone disease	VCMP ×7 → MPT ×9 → thalidomide maintenance; no ASCT	9	Normal karyotype; MLL-; BCR-ABL-	Cytopenias	Supportive care, steroids	Death within days
Gonzalez MM et al., 2013 [13]	1	73M	VAD	8	46XY/+55XY, +9mar	Pancytopenia	Hyper-CVAD + Ara-C/MTX; POMP maintenance	Relapsed
García-Munoz R, 2013 [27]	1	62M; IgG-λ MM, stage IIIB	Bortezomib-dex; HDT/ASCT; lenalidomide maintenance	1.5	Normal karyotype	Pancytopenia	Induction therapy	Induction death (septicemia)
Junxun L et al., 2016 [15]	3	Adults (33-66 y); IgG MM	VADM/PAD/DVD; thalidomide ± lenalidomide; 2 ASCT	2.5-6	BCR-ABL-; MLL-; distinct IgH rearrangements	Cytopenias	No ALL therapy (declined)	Poor; all died
Li J et al., 2016 [6]	1	66M	Bortezomib-dex; later VPDM; thalidomide maintenance	3.2	-	Leukopenia	CHOP	Died
Khan AM et al., 2018 [9]	2	53F & 69F	Bortezomib-dex; ASCT; lenalidomide maintenance	1.3-6	Trisomies 8, 10, 21; monosomy 20	Neutropenia, thrombocytopenia	POMP, hyper-CVAD	2 CR
Aldoss I et al., 2018 [10]	11	Older adults; female predominance	Alkylator ± IMiDs; ASCT ~18%	6.8 (0.8-50.7)	KMT2A rearrangements, Ph+, chr 5/7 abnormalities	Cytopenias, marrow blasts	Hyper-CVAD ± TKI; alloHCT frequent	Inferior OS vs de novo ALL
Mei J et al., 2019 [28]	2	68M & 65F; IgG-κ MM	Bortezomib-dex; thalidomide maintenance; VAD/TAD/BTD	0.25-2.2	Hypodiploid, complex karyotype	Leukopenia	Low-dose chemo/declined	Both died within months
Lee HY et al., 2019 [29]	2	54M (IgA κ) & 54F (IgG κ), plasmablastic	PAD → ASCT → thalidomide maintenance	8.2	Normal/hyperdiploid clone	Dyspnea, cytopenias	Induction + consolidation/Hyper-CAD	Remission
Sinit RB et al., 2019 [23]	1	82M; long-standing MM	VAD → melphalan/pred → thalidomide (36 mo) → lenalidomide (6 yrs); no ASCT	14	Trisomies 3, 7, 11, and trisomies/tetrasomies 9 and 15; TP53 del	Cytopenias	DVd; inotuzumab at relapse	Alive with disease
Tashakori M et al., 2020 [25]	1	65F; MM in remission	Double ASCT; lenalidomide + elotuzumab maintenance	5	Trisomy 8; TP53 mutations	Pancytopenia; plasmacytoid blasts	NR	NR
Germans SK et al., 2020 [26]	2	64M & 43M; biclonal MM/IgG-λ MM	Radiation, CyBorD, KRD, ASCT, len maintenance	2-6	del13q, del17p/TP53, FGFR3-IGH; TP53, CREBBP mutations	Cytopenias, marrow blasts	Hyper-CVAD; inotuzumab	1 long remission; 1 died
Barnea Slonim L et al., 2021 [36]	6	Older age; female predominance	Cytotoxic chemo ± radiation	1-7	TP53 loss, hypodiploidy, KMT2A, del(5q/7q), complex karyotype	Cytopenias	Standard ALL regimens ± alloHCT	Poor OS
Khan DSR et al., 2022 [4]	1	68F	Lenalidomide-dex-pamidronate; len maintenance	6	Normal (46XX)	Pallor, edema	Hyper-CVAD	Poor
Parrondo RD et al., 2022 [20]	14	Mean 63.9 y; IgG MM; ISS-I	Lenalidomide-based ± ASCT; len maintenance	6	Hypodiploid/neartriploid; BCR-ABL-	Leukopenia	Hyper-CVAD; allo-HCT	Poor overall
Kallen et al., 2022 [16]	8	Median 63 y; 4M/4F	Lenalidomide/bortezomib/dex; thalidomide, cyclophosphamide, carfilzomib; 5 ASCT; all len maintenance	2.5-7.3	Multiple: gain 1q, del17p, t(14;20), t(9;22), hyper/hypodiploidy, del7p, t(11;14)	Pancytopenia, blasts	Hyper-CVAD, blinatumomab, inotuzumab, allo-SCT	5 died; 2 CR; 1 residual
Barnell EK et al., 2023 [22]	17	Median ~60 y; long-term MM survivors	Len maintenance (all); ASCT majority	4-6	TP53 variants (14/17); Ph-; clonal independence	Cytopenias	Hyper-CVAD; some allo-HCT	Inferior outcomes
Conoley AJ et al., 2025 [24]	1	Adult MM, advanced	Alkylator chemo; ASCT	4-5	11q23/MLL rearrangement	Cytopenias	mini hyperCVAD	CR
Mamlekar H et al., 2025 [18]	1	62M; IgG-λ MM; renal dysfunction	Bortezomib + thalidomide + dex; len maintenance (≈2 yrs); no ASCT	3-4	TP53 del; BCR-ABL-; MLL-; IgH-; normal karyotype	Bicytopenia	DFCI ALL protocol	Death during induction

Ayoub J et al., 2025 [30]	1	69M; IgA lambda MM	bortezomib, lenalidomide, and dexamethasone, followed by ASCT and lenalidomide maintenance	3	FLT3-ITD mutation+, Ph-, MLL- (at B ALL diagnosis)	Isolated thrombocytopenia	NR	NR
Present series	4	57-63 y; 3M/1F	Novel agents; 2 ASCT; 3 len maintenance	3-7	Variable: normal, TP53, hypodiploidy; NGS mostly negative	Pancytopenia ± bleeding	Vincristine + anthracycline + steroid regimens	2 MRD- CR; 1 refractory; 1 ongoing

Abbreviations: ALL, acute lymphoblastic leukemia; allo-HCT, allogeneic hematopoietic cell transplantation; ASCT, autologous stem cell transplantation; B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system; CR, complete remission; CyBorD, cyclophosphamide-bortezomib-dexamethasone; DFCI, Dana-Farber Cancer Institute protocol; FISH, fluorescence in situ hybridization; Hyper-CVAD, cyclophosphamide-vincristine-doxorubicin-dexamethasone; IMiD, immunomodulatory drug; ISS, International Staging System; KRD, carfilzomib-lenalidomide-dexamethasone; MM, multiple myeloma; MRD, measurable residual disease; NGS, next-generation sequencing; NR, not reported; OS, overall survival; PAD, bortezomib-doxorubicin-dexamethasone; PI, proteasome inhibitor; POMP, prednisone-vincristine-methotrexate-mercaptopurine; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VAD, vincristine-doxorubicin-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone.

[37]. Pre-existing clonal hematopoiesis (CH), particularly involving *DNMT3A, TET2, ASXL1*, and *TP53*, is increasingly recognized in older MM patients and may provide a permissive substrate for leukemic transformation under therapeutic selection pressure [38-40]. This dual process of acquired genomic injury and clonal predisposition likely explains why only a small subset of heavily treated MM patients ultimately develop t-B-ALL.

Our four cases underscore the biological and clinical heterogeneity of this entity. At the time of B-ALL diagnosis, none of the patients showed evidence of active myeloma, supporting the concept that t-B-ALL arises independent of plasma cell clone, not through lineage transformation. Flow cytometric immunophenotyping demonstrated a precursor B-cell phenotype (CD19, cCD79a, CD10, CD22), with variable expression of CD20, CD34, and CD38. Cytogenetic and molecular findings were heterogeneous, ranging from normal karyotype to hypodiploidy, with pathogenic mutations (*TP53, TET1*) identified in only one case. These findings mirror previous reports, which emphasize clonal independence and marked genetic variability in MM-associated t-B-ALL [19].

Clinically, t-B-ALL is indistinguishable from de novo ALL and typically presents with cytopenia-related symptoms such as fatigue, infections, or bleeding [14]. In our cohort, all patients presented with pancytopenia, and bone pain at diagnosis creating diagnostic ambiguity due to overlap with MM-related skeletal disease. Importantly, the absence of residual monoclonal protein was a key clue supporting an independent leukemic process. These observations highlight the importance of maintaining a high index of suspicion for secondary leukemia in long-term MM survivors presenting with unexplained cytopenias, even years after disease free status.

Therapy-related B-ALL is generally associated with an adverse prognosis and poses significant therapeutic challenges. Management should be individualized, taking into account patient age, performance status, prior therapies, and disease biology. Treatment options include intensive chemotherapy regimens, targeted therapies such as blinatumomab or inotuzumab ozogamicin, and consideration of allogeneic hematopoietic stem cell transplantation in eligible patients. In our series, standard vincristine, anthracycline, and corticosteroid based induction regimens resulted in variable responses, with evidence of chemoresistance, consistent with prior reports [14, 19]. Although novel immunotherapeutic strategies such as blinatumomab and inotuzumab ozogamicin have demonstrated efficacy in relapsed or refractory ALL, their role in MM-associated t-B-ALL remains inadequately defined. Similarly, CD19-directed CAR T-cell therapy and allogeneic hematopoietic stem cell transplantation, while theoretically attractive, are frequently precluded by comorbidities, cumulative toxicity, and poor performance status [41, 42].

The outcomes observed in our cohort underscore the aggressive nature of this entity. At 21 months of follow-up, only one patient remained alive, while the other three died within seven months of diagnosis. This is in keeping with prior reports demonstrating significantly poorer survival in therapy-related ALL compared with de novo B-ALL, even among patients undergoing hematopoietic cell transplantation [24]. The rarity of t-B-ALL has limited the feasibility of prospective studies and, consequently, the development of robust evidence-based treatment strategies. In practice, management is often extrapolated from de novo ALL paradigms, which may not fully capture the distinct biological and clinical features of therapy-related disease [8, 14, 19, 24].

Conclusion

The development of t-B-ALL following contemporary, highly effective MM treatment remains uncommon, but relevant as patient survival continues to improve. It is not originated from residual myeloma clone, but from accumulation of genetic damage caused by a combination of patient-specific factors, disease biology, and prior therapies acting on a vulnerable hematopoietic system. Clinically, these cases show considerable genetic diversity, tend to behave aggressively and are associated with poor outcomes. This underscores the need for individualized risk assessment and therapeutic approaches. Importantly, clinicians should remain alert to the possibility of secondary leukemias in long-term survivors who develop otherwise unexplained cytopenias, as earlier detection may facilitate more effective and timely management.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Smeeta Gajendra, Department of Laboratory Oncology, Dr. B.R.A. IRCH, All India Institute of Medical Sciences, New Delhi 110029, India. Tel: 9013590875, 011295-75116; E-mail: drsmeeta@gmail.com

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