Testicular Relapse of T-Cell Acute Lymphoblastic Leukemia in an Adult 11 years after Allogeneic Stem Cell Transplantation: A Case Report

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Introduction

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disease characterized by the proliferation of immature lymphoid cells—B-cells, T-cells, or Natural Killer-cells[1]. The utilization of genome-wide profiling has led to a better understanding of the structural genetic alterations and mutations that contribute to leukemogenesis in ALL and provides information for directing personalized medicine approaches with novel, targeted therapeutic agents. As a result of the incorporation of MRD testing, the improvement of risk-directed chemotherapeutic regimens, and refinement of allo-HSCT, the survival rates for ALL have dramatically improved. Despite these advances however, adult ALL still portends a poorer prognosis, with survival rates being 20% to 40%. Moreover, relapsed ALL remains a harbinger for dismal outcomes with median survival rates ranging from a mere 10% to approximately 25%.

Specifically, extramedullary relapse in leukemia, although not a frequent recurrence of leukemia, remains an intriguing and noteworthy cause of treatment failure in patients with ALL. The central nervous system and testes have been long regarded as immunological sanctuaries for cancer cells due to the physiologic blood-brain and blood-testes barrier, respectively. Advances in the therapeutic management of ALL have virtually eliminated the utilization of prophylactic craniospinal irradiation to the CNS or local irradiation versus orchiectomy to the testes. Guidance for the management of leukemic relapse involving the testicle is not standardized especially in the adult patient population, and even more specifically, in those who are status-post allo-HSCT, with case reports comprising much of the available literature. Therefore, given the rare occurrence and the paucity of definitive evidence for guiding treatment, extramedullary relapse of ALL, particularly of the testicle in adults in the post-allo-HSCT setting is a notable topic for discussion.

Case Presentation

Initial Treatment Course

A 43-year-old male was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) involving the mediastinum and with multi-compartmental adenopathy on both sides of the diaphragm without clinical evidence consistent with central nervous system nor overt testicular involvement. He received hyperCVAD plus nelarabine, alternating with intrathecal methotrexate and cytarabine, on protocol 2006-0328, achieving complete remission after 1 cycle. He went on to receive POMP maintenance and delayed intensification with nelarabine, during which he developed MRD positivity on flow cytometry. As a bridge to allo-HSCT, he received 2 cycles of MOAD, and then proceeded to a MUD allo-HSCT with a busulfan plus clofarabine conditioning regimen (on protocol 2009-0209) twenty-months after his initial diagnosis of T-cell ALL.

Presentation

Eleven years following his allo-HSCT, the patient, now 56-years-old, presented to his urologist with concerns over unilateral, non-painful testicular swelling. He was diagnosed with left-sided, acute epididymo-orchitis and was treated with a three-week course of ciprofloxacin. When his symptoms failed to resolve, he presented to his hematologist-oncologist. bilateral testicular ultrasound showed an enlarged left testicle with heterogenous echotexture as well as increased vascularity throughout the left testicle and epididymis (Fig. 2). Subsequent pathology from left-sided orchiectomy was consistent with relapse of his T-ALL (Table 1). Further work-up with a BMA revealed medullary relapse (Table 2).

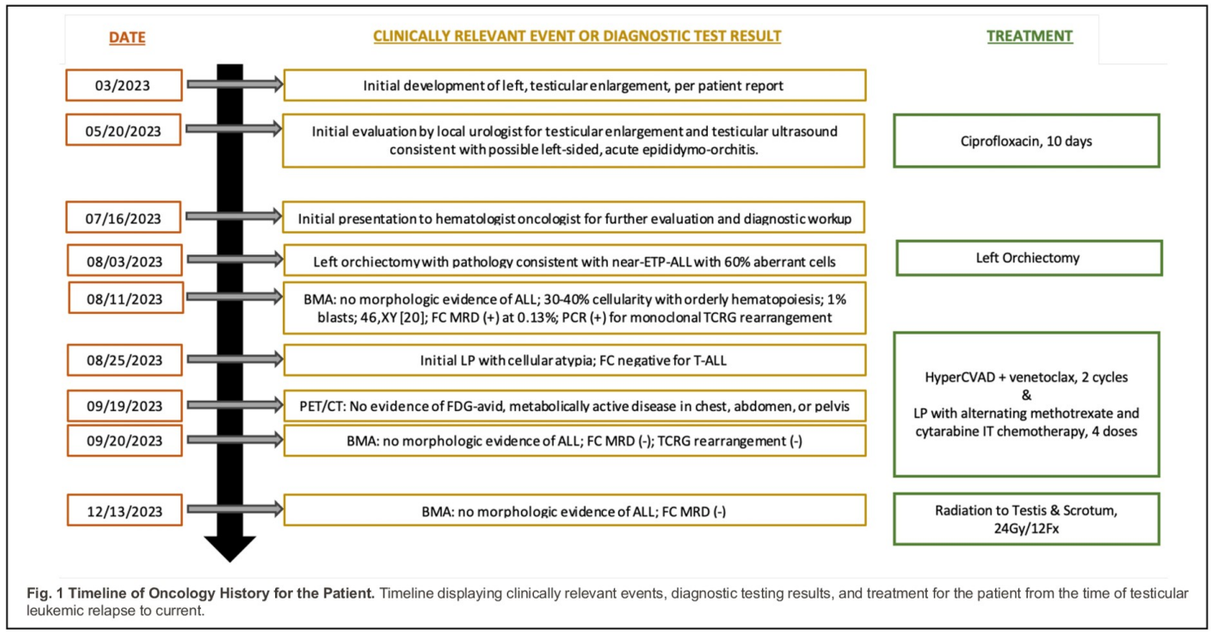

Fig. 1 Timeline of Oncology History for the Patient. Timeline displaying clinically relevant events, diagnostic testing results, and treatment for the patient from the time of testicular leukemic relapse to current.

Follow-Up & Outcome

The patient received 2 cycles of hyperCVAD with venetoclax and 4 lumbar punctures with alternating methotrexate and cytarabine IT chemotherapy. He achieved complete remission after his first cycle of therapy with flow cytometry negative for MRD; a PET scan showed no evidence of FDG avid uptake. The patient was reluctant to pursue additional cycles of intensive, salvage chemotherapy, additional IT chemotherapy prophylaxis, and a second allo-HSCT given the impact on his overall quality of life (QoL). However, he did go on to complete testicular radiation to the testis and scrotum (24Gy, 12 fractions), which he tolerated well. Until now, 6 weeks after completion of radiation therapy, the patient remains without evidence of disease relapse, systemically and in the remaining, right testicle. His most recent bone marrow aspiration and biopsy (performed just prior to the initiation of local radiation therapy and 6 weeks prior to the completion of this poster) revealed no morphologic or immunophenotypic evidence to support residual T-ALL, flow cytometry was negative for MRD, and PCR analysis was negative for monoclonal TCRG rearrangement.

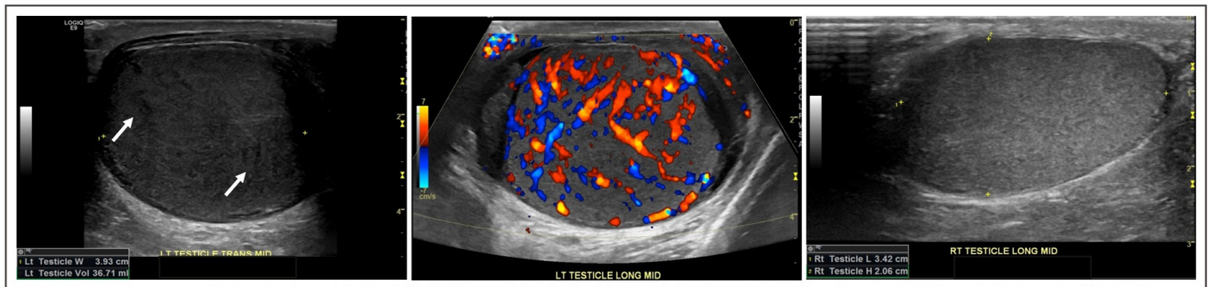

Fig. 2 Diagnostic sonographic imaging from July 19, 2023. A) Ultrasound (longitudinal, left testis) showing enlargement and heterogeneity (arrow) of left testicle, B) Color-flow doppler ultrasound (longitudinal, left testis) showing enlarged left testicle with hypervascularity, C) Ultrasound (longitudinal, right testis) normal echogenicity and size of right testicle.

Pathologist Interpretation	Next-Generation Sequencing Results
T-ALL, near-ETP phenotype involving the left testis, peritesticular soft tissue, and epididymis. *Aberrant T-Cell population positive for*: CD2 (dec); cytoplasmic CD3; CD5 (dec); CD7 (bright); CD10, CD13+33 (inc); CD34; CD38; CD45 (dim); HLA-DR, TdT	JAK3-A573V (VAF 85%, missense SNV) NOTCH1-Q2394 (VAF 42%, Nonsense SNV) FGFR3-S53R (VAF 36%, missense SNV) JAK3-L586V (VAF 82%, missense SNV) JAK3-C839Y (VAF 86%, missense SNV) MED12-E33* (VAF 83%. nonsense SNV) NOTCH1-V1721G (VAF 39%, missense SNV)

Table 1. Cytopathology data from orchiectomy specimen at time of leukemic relapse.

Pathologist Interpretation	Flow Cytometry	Molecular Diagnostics	Chromosomal Analysis
30-40% cellularity with orderly hematopoiesis	0.13% MRD	*TCRG Rearrangement*: Positive monoclonal T-cell rearrangement *TCRB Rearrangement*: Negative monoclonal T-cell rearrangement	46,XY [20]

Table 2. Pathology and molecular diagnostic data from bone marrow aspiration and biopsy at time of leukemic relapse.

Discussion

The clinical and diagnostic presentation of leukemic infiltration of the testis can mimic that of more common urogenital inflammatory processes, such as epididymo-orchitis, but a high index of suspicion for relapsed disease must be maintained in this patient population. Literature describes the occurrence of testicular relapse of T-ALL as occurring across all ages, but more uncommon amongst the adult populations; moreover, such an occurrence in a post-allo-HSCT setting is exceptionally rare. As such, the treatment for patients with testicular leukemia relapse post-allo-HSCT is still not well standardized. However, research has substantiated that systemic relapse occurs within months of testicular radiation or orchiectomy administered alone, and thus, treatment should be one of a systemic approach, with local testicular therapies being administered as an adjunct to intensive systemic chemotherapy such as hyperCVAD.

Some reports describe successful treatment of patients with only systemic chemotherapy and local therapy to the testes with irradiation with or without orchiectomy[3,4], whereas another case report described treatment with orchiectomy alone in a pediatric patient status-post allo-HSCT[5]. However, given the dismal post-relapse survival statistics for these patients, especially in T-ALL, consideration for aggressive management with a second allo-HSCT after re-induction to induce MRD negativity may portend the best durable remission, and has been recommended by others. The role and efficacy of more novel therapeutics such as venetoclax, navitoclax, and daratumumab, everolimus, CD5- or CD7- engineering CAR-T therapy are being investigated via early-phase clinical trials, and the results may provide better guidance on the guidance of such rare recurrences of T-ALL.

Conclusions

With the development of high-intensity chemotherapeutic regimens that incorporate chemotherapeutic agents which are known to penetrate the blood-testes barrier, the need for testicular-directed local therapies has been largely removed from the treatment algorithms for ALL. Leukemic relapse of the testes following allo-HSCT in the adult patient is an exceedingly rare clinical scenario, making it difficult to evaluate the literature for well-established management protocols to guide therapy. However, salvage treatments for testicular leukemic relapse, whether in a clinically isolated relapse or not, should mimic a systemic approach given the high likelihood of systemic relapse soon after extramedullary recurrence, despite localized treatment with testicular irradiation or orchiectomy[2].

Nonetheless, the rarity of T-ALL testicular relapse is a detriment for clinicians working to establish definitive, transformative therapeutic management regimens, especially in the relapse-refractory setting. Ultimately, the approach for management should integrate a multidisciplinary team approach to include hematology-oncology, urology, and radiation oncology.

References

1) Gaudichon J, Jakobczyk H, Debaize L, et al. Mechanisms of extramedullary relapse in acute lymphoblastic leukemia: Reconciling biological concepts and clinical issues. *Blood Rev.* 2019;36:40-56. doi:10.1016/j.blre.2019.04.003
2) Nguyen HTK, Terao MA, Green DM, Pui CH, Inaba H. Testicular involvement of acute lymphoblastic leukemia in children and adolescents: Diagnosis, biology, and management. *Cancer*. 2021;127(17):3067-3081.
3) Bhadri V, McGregor M, Venn N, et al. Isolated testicular relapse after allo-SCT in boys with ALL: outcome without second transplant. *Bone marrow transplantation*. 2010;45(2):397-399.
4) Conter V, Rabbone ML, Jankovic M, et al. Isolated testicular relapse in a boy with acute lymphoblastic leukemia following allogeneic bone marrow transplantation. Case Reports
Research Support, Non-U.S. Gov't. *Haematologica*. Sep-Oct 1989;74(5):507-9.
5) Kodama Y, Okamoto Y, Ijichi O, et al. Continued complete remission without systemic therapy for isolated testicular relapse after bone marrow transplantation in a boy with acute lymphoblastic leukemia. *Pediatr Transplant*. Sep 2009;13(6):769-72. doi:10.1111/j.1399-3046.2008.01023.x