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Isolated Testicular Recurrence of AML in Patients With Chronic GVHD > 1 Year Following Allogeneic Stem Cell Transplant

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Background: Patients with chronic graft-versus-host disease (cGVHD) following allogeneic transplant for myeloid leukemias seem to experience a reduced risk of relapse than comparable patients without cGVHD. It is unclear to what extent extramedullary sites are impacted by a graft-versus-leukemia effect.

Design/Method: Case Series and review of the literature.

Results: We present 2 cases of pediatric patients with Acute Myelogenous Leukemia who developed isolated testicular relapse more than a year following hematopoietic stem cell transplantation despite having had extensive cGVHD. Both patients were off immunosuppression and cGVHD medications when testicular relapse occurred. At time of relapse, these patients were negative for minimal residual disease in the marrow and the marrow contained all donor cells by engraftment studies. No evidence was found for lymphocyte infiltration into the affected testicle in either patient.

Conclusions: Although a reduction of marrow relapse can be appreciated in patients with myeloid leukemias and chronic GVHD, this graft-versus-leukemia process may be less robust in extramedullary sites and careful surveillance should be maintained to allow early intervention before overt marrow involvement.

Key Words: acute myeloid leukemia, testicular relapse, pediatric, allogeneic stem cell transplant, chronic graft-versus-host disease

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Chronic graft-versus-host disease (cGVHD) is associated with reduced incidence of relapse in patients with myeloid leukemias.¹ Although this may provide some degree of protection from relapse systemically, areas with intact barriers from the blood remain especially susceptible. In other words, immunologically privileged sites, such as the testes, may be shielded from GVHD activity and are therefore at higher risk for extramedullary relapse. In fact, testicular relapse often presents as a therapeutic problem in boys with acute leukemias, although less likely in acute myelogenous leukemia (AML) than in acute lymphoblastic leukemia. Here, we present 2 pediatric patients diagnosed with cGVHD more than a year following transplant with subsequent isolated testicular relapse.

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The authors declare no conflict of interest.

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MATERIALS AND METHODS

Case #1

Patient 1 was diagnosed with CNS negative AML at 15 years of age and presented with isolated testicular relapse at age 18. At initial diagnosis, the cytogenetics demonstrated t(8q22;21q22) and FISH + for RUNX1T1-RUNX1. He was treated as per the AAML 0531 regimen. At the end of induction I, his minimal residual disease (MRD) was 3% and FISH was positive at 1.6%. At the end of induction II, MRD was undetectable and FISH was negative. Immediately after induction II, he received a 10 of 10 sibling donor marrow transplant with 1.87×10^8 total nucleated cells/kg. His conditioning regimen consisted of standard dose myeloablative Busulfan (Area Under the Curve [AUC] targeted to $5000 \text{ umol} \cdot \text{min/L}$)/Cytosin (200 mg/kg). Both the patient and donor were CMV negative and the patient received tacrolimus for immunosuppression.

He developed acute GVHD (aGVHD) with maximum stage III gut involvement that responded well to a steroid pulse. However, he subsequently developed extensive cGVHD of the GI tract and experienced diarrhea, loss of appetite, and weight loss. The patient responded well to tacrolimus and prednisone and he was consequently weaned to budesonide maintenance only, which was weaned off by 22 months posttransplant. At 32 months posttransplant, however, the patient developed right testicular nontender swelling. His biopsy revealed positive results for recurrent AML exhibiting the same markers as at diagnosis. There was no evidence of donor lymphocyte infiltration in the testicle. PET-CT, bone marrow biopsy (MRD negative), and examination of the CNS were all negative for relapse. Chimerism studies performed at day +100, 1 year, and time of relapse by restriction fragment length polymorphism were exclusively donor.

Case #2

Patient 2 was diagnosed with CNS positive AML at 5 years of age and presented with isolated testicular relapse at age 7. At initial diagnosis, the cytogenetics demonstrated t(9;11) and FISH was positive for MLL and negative for FLT3 ITD. He was treated as per AAML 0531 regimen. At the end of induction I, his MRD was 6.2% that declined to 1.2% at the end of induction II. His MRD was 0.5% after intensification I and 0.06% after recovery from intensification II and prior to transplant. The patient did not have a sibling donor and therefore received a 5/6 unrelated donor cord blood transplant with 9.7×10^7 total nucleated cells/kg and 7×10^5 CD34+ cells/kg. His conditioning regimen comprised of standard dose myeloablative Busulfan (AUC targeted to $5000 \text{ umol} \cdot \text{min/L}$)/Cytosin (200 mg/kg).

The patient received tacrolimus and prednisone for immunosuppression.

He developed aGVHD with maximum stage IV GI developing ileus. He responded to optimization of tacrolimus levels and a steroid pulse, but subsequently developed extensive cGVHD of the GI tract with dysmotility and was TPN dependent for several months before he was able to tolerate GI feeds. He was switched to sirolimus because of seizures associated with the tacrolimus and responded well, weaning prednisone and budesonide over the course of several months. At 14 months posttransplant, the patient developed right testicular nontender swelling and his biopsy was positive for recurrent AML exhibiting the same markers as at diagnosis. There was no evidence of donor lymphocyte infiltration in the testicle. PET-CT, bone marrow biopsy (MRD negative), and examination of the CNS were all negative for relapse. At day +100, 1 year, and time of relapse, restriction fragment length polymorphisms were exclusively donor.

DISCUSSION

Isolated testicular relapse of AML after allogeneic bone marrow transplantation and induced cGVHD is uncommon with only a couple of pediatric cases reported in the literature.²⁻⁴ In a retrospective study of extramedullary relapse in children with AML or acute lymphoblastic leukemia, none with an AML diagnosis presented with testicular relapse and the most common site of extramedullary recurrence occurred in the bone.^{5,6} In an analysis of 257 adult AML cases, 9% developed extramedullary relapse, with the skin and soft tissue as the most common sites and the lymph nodes, bone, and CNS as notable sites. Relapse in the testicle was rare, occurring in only 1 patient.⁷ While infrequent, testicular relapse is nonetheless a significant concern for patients with AML.

One strategy to reduce the risk of leukemic relapse is to induce cGVHD following hematopoietic stem cell transplant.^{1,8} Although there are well-documented protective effects of cGVHD with hazard ratios of 0.46 to 0.55,⁹ its therapeutic power is drastically reduced in immunoprotective sites—i.e. the CNS and testes.^{2,10,11} Chronic GVHD and acute GVHD (aGVHD) both occur when donor immune cells elicit an immunological response against the host's tissues, but cGVHD is associated with relapse reduction whereas aGVHD

often leads to toxicity and poorer prognosis.^{1,12} The 2 patients in this case series, despite having cGVHD and marrows that remained MRD negative, developed testicular relapse.

Currently, there are several methods to manage isolated testicular relapse in leukemias and lymphomas. One approach is to treat the patient with systemic therapy in conjunction with radiotherapy directed to the testicles.¹³ Other studies report that the optimal regimen for testicular involvement from AML include orchiectomy, because of the limitations of chemotherapy reaching the testicles, in addition to adjuvant chemotherapy.¹⁴ Both of our patients in this case series received orchiectomies immediately after testicular mass detection. In addition, the patient in case 1 received systemic reinduction therapy as well as a second transplant using peripheral blood stem cells from the same sibling donor as the first transplant and remains in remission. In case 2, the family declined both systemic reinduction therapy as well as a second transplant because of the significant past morbidity and the patient was treated with decitabine (100 mg/M²/cycle) alone for palliation.

The use of immunotherapy is emerging as a promising direction for control of numerous malignancies including AML relapse,¹⁵ although these methods are not without challenges since immunological privileged sites seem to be less susceptible to GVHD and graft-versus-leukemia effects, perhaps because of impaired T-cell infiltration in those sites, although the mechanism of such barrier is not understood.¹⁶⁻¹⁹ Nonetheless, a recent study highlights the importance of understanding the pathways that contribute to immune privilege and cancer immune evasion to better develop efficacious immunotherapies.²⁰ Presently, some immunotherapies utilize leukemia-associated antigens and allogeneic T cells to induce graft-versus-leukemia effects, perhaps allowing better T-cell infiltration and tracking of cancer cells in sanctuary sites.²¹⁻²³ Monoclonal antibodies, alloreactive NK cells, interleukin-2, peptides, and other effector molecules can also be used in active and passive immunotherapy strategies.²⁴ It is important to include significant number of patients with extramedullary relapse in these studies to ascertain the ability of these therapies to impact patients with overt or occult disease in these sites. Future patients would benefit greatly from therapies that demonstrate they can more directly target immune privileged sites and eradicate residual AML cells that commonly escape therapeutic agents.

TABLE 1. Patient Characteristics

Parameters	Case 1	Case 2
Age at diagnosis	15	5
Diagnosis	CNS negative AML	CNS positive AML
CNS status at diagnosis	Negative	Positive
CNS status at relapse	Negative	Negative
Testicular status	Isolated testicular relapse	Isolated testicular relapse
Cytogenetics	t(8q22;21q22)	t(9;11)
Molecular	FISH + for RUNX1T1-RUNX1	FISH + for MLL and – for FLT3 ITD
Induction I MRD	3%	6.2%
Induction II MRD	Undetectable	1.2%
Transplant type	10/10 sibling donor marrow	5/6 unrelated donor cord blood
Conditioning regimen	Myeloablative Busulfan (AUC targeted)/Cytosin	Myeloablative Busulfan (AUC targeted)/Cytosin
Immunosuppression	Tacrolimus	Tacrolimus and prednisone
Acute GVHD	Maximum stage III GI	Maximum stage IV GI with ileus
Chronic GVHD	GI tract	GI tract
Donor engraftment at day 100 and 1 y	All donor	All donor
Time of relapse post-HST transplantation	32 mo	14 mo
Treatment strategy	R orchiectomy/reinduction/2nd transplant	R orchiectomy and Decitabine

CONCLUSIONS

Chronic GVHD is associated with reduced systemic relapse rates, but ongoing disease surveillance should be maintained for immune privileged sites as well including a thorough physical examination with each visit. Current and future immune-based therapies should demonstrate their ability to provide treatment that penetrates into extramedullary sites, or be combined with therapy that does (Table 1).

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