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Sustained First Remission in an Adolescent With Hepatosplenic T-Cell Lymphoma Treated With T-Cell Leukemia Induction, Nucleoside Analog-Based Consolidation, and Early Hematopoietic Stem Cell Transplant

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Abstract

Hepatosplenic T-cell lymphoma (HTCL) is a rare malignancy. Prognosis is poor with only a few case reports of long-term survivors. While HTCL universally involves the bone marrow, the condition has been most often treated with multimodal lymphoma specific chemotherapy. We report a durable, sustained first remission in an adolescent treated for HTCL who received induction therapy according to a high risk T-cell leukemia regimen, a nucleoside analog-based consolidation, and allogeneic transplantation associated with GVHD.

Keywords

delta gamma lymphoma; GVHD; hepatosplenic T-cell lymphoma; nucleoside analog; transplant

INTRODUCTION

Hepatosplenic T-cell lymphoma (HTCL) (formerly hepatosplenic gamma-delta T-cell lymphoma) is a rare and aggressive malignancy which has been sparsely reported in the literature. The condition, which is most commonly seen in young men, usually has an indolent presentation with thrombocytopenia and splenomegaly being the most frequently reported signs [1]. Multiple treatment modalities have been attempted; most commonly CHOP-(cyclophosphamide, doxorubicin, vincristine, prednisone) and platinum-based lymphoma regimens, splenectomy and high-dose chemotherapy with autologous-or allogeneic-hematopoietic stem cell transplantation (HSCT) [2]. However, obtaining a complete remission is uncommon and prognosis remains poor with the median survival of HTCL being between 8 and 16 months [1,2]. There is therefore, no standard of care for this disease. We report a durable first remission in an adolescent treated for hepatosplenic T-cell lymphoma/leukemia who received induction therapy according to a high-risk T-cell leukemia regimen, a nucleoside analog-based consolidation, and allogeneic stem cell transplantation.

CASE REPORT

The patient presented as a formerly healthy 17-year-old female with chief complaints of acute pre-syncope and gross hematuria. Physical exam was notable for moderate splenomegaly with her spleen tip palpable 3 cm below the costal margin and pallor. She had no recent illnesses, fever, rash, or weight loss. Laboratory tests showed a peripheral white blood cell count of $29,000/\text{mm}^3$, a hemoglobin of 6.2 g/dl, and a platelet count of $145,000/\text{mm}^3$. Coombs test was negative. A reticulocyte count was 12.5% (reticulocyte index 2.6), a haptoglobin was $<6 \text{ mg/dl}$, an LDH was 1496 U/L, and a total bilirubin was 1.6 mg/dl. Bacterial and viral testing was negative. A peripheral blood smear showed microspherocytes and a population of atypical immature appearing lymphocytes (Fig. 1). Flow cytometric immunophenotyping on a bone marrow aspirate showed 45% of cells counted to be abnormal T cells positive for CD7, CD3, CD2, CD56, and CD45 and surface gamma-delta receptor. Cytogenetic studies, on bone marrow aspirate cells, showed 40% of cells with both isochromosome 7q and trisomy 8. PET CT showed hepatomegaly ($15 \text{ cm} \times 19 \text{ cm} \times 19 \text{ cm}$) and splenomegaly ($12 \text{ cm} \times 9.5 \text{ cm} \times 16 \text{ cm}$) with no specific focal radiotracer uptake. All findings were consistent with the diagnosis of gamma-delta T-cell leukemia/lymphoma (HTCL).

Induction chemotherapy was started following Children's Oncology Group (COG) protocol AALL0434 which included vincristine, daunorubicin, prednisone, PEG-asparaginase, and intrathecal cytarabine followed by intrathecal methotrexate. CSF showed no evidence of disease. Day 29 bone marrow aspiration showed a complete remission by flow cytometric, FISH, and cytogenetic analyses. She received consolidation therapy with a single course of FLAG chemotherapy including fludarabine at $30 \text{ mg/m}^2/\text{day}$ and ARAC (cytarabine arabinoside) at $2 \text{ g/m}^2/\text{day}$ on days 1–5 followed by GCSF. After bone marrow recovery, she began a HSCT preparative regimen that included cyclophosphamide and total body irradiation (1,200 cGy in four fractions). She subsequently received unprocessed bone marrow from her HLA identical brother. Graft-versus-host-disease (GVHD) prophylaxis included cyclosporine and a short course of methotrexate ($10 \text{ mg/m}^2/\text{dose IV}$ on days +1, +2, +3, and +4). The patient experienced complete engraftment by day 25 post-transplant. At 3.5 months post-transplant, the patient was admitted for fever and subsequently developed an acute change in mental status accompanied by encephalopathy. Neurological workup including LP, CT, MRI, and MRA showed no significant abnormalities. Her cyclosporine was stopped and replaced with mycophenolate mofetil (CellCept) and she was given 400 mg/kg of intravenous immunoglobulin for potential viral encephalitis. Her mental status returned to normal over the subsequent 3 weeks. After developing grade 3 gastro-intestinal toxicity from CellCept, her GVHD prophylaxis was changed to rapamycin. At the time of changing to rapamycin, which was 4.5 months post-transplant, she developed diffuse erythroderma consistent with acute GVHD (aGVHD) of the skin, which proved to be steroid responsive, but ultimately, steroid dependent. After a fourth prednisone pulse resulted in steroid psychosis and pseudoseizures, steroids were tapered and she was treated with narrow band ultraviolet B (UVB) light therapy. She received 4 months of UVB therapy and following its cessation, there was no recurrence of her skin only aGVHD. At 8 months post-transplant the patient developed a progressive normocytic, normochromic, and reticulocytopenic anemia in conjunction with elevated inflammatory markers. After an extensive work-up for both the anemia and inflammation revealed no acute condition, it was assumed the anemia was one of chronic illness, although ultimately it remained idiopathic. She received a single packed red blood cell transfusion and her anemia resolved over the next 1.5 months. She has since remained transfusion independent. At the time of her anemia she also experienced a 3-week period of thrombocytopenia with a nadir of $103,000/\text{mm}^3$ prior to spontaneous resolution. At 10 months post-transplant she began a 1-month taper of her rapamycin. A bone marrow aspiration at 1 year post-transplant showed no evidence of

disease by morphology, flow cytometric immunophenotyping, and cytogenetic analyses. At 21 months post-diagnosis and 18 months post-transplant, she has been re-immunized and remains off immunosuppressive therapy with no evidence of chronic GVHD. The patient has hypothyroidism, controlled on levothyroxine, and premature ovarian failure. She has returned to her pre-diagnosis activity level and functional status.

DISCUSSION

The majority of mature, post-thymic-T cells express the alpha beta heterodimer T-cell receptor (TCR) and further differentiate into CD4+ or CD8+ T lymphocytes. Gamma delta T cells, make up only 1–10% of all CD3+ cells [3] but have a broad range of functions in both innate and adaptive immunity [4,5]. Clinically, patients have been reported with nodal-, nasopharyngeal-, thyroid-, and intestinal-types of gamma delta T-cell lymphoma [6]. However, the 2008 WHO classification of mature B-cell, T-cell, and NK-cell neoplasms recognizes only two forms of this disorder [7]. The first is primary-cutaneous gamma delta T-cell lymphoma (CGD-TCL), which presents almost universally with involvement of the extremities with tumorous plaques and subcutaneous nodules; it is considered a disease that does not involve the bone marrow [7,8]. Like HTCL, the prognosis of CGD-TCL is poor with a 5 year overall survival (OS) of approximately 33% [8]. The second recognized type is hepatosplenic T-cell lymphoma. This entity was first reported in 1990 by Farcet et al. [9] who described two patients with disease that appeared phenotypically similar to GSD-TCL but lacked the usual tissue distribution; namely, it was not cutaneous and was found invading the spleen, liver, and bone marrow. Subsequently, published reports have demonstrated a consistent localization of the disease to the reticuloendothelial system as well as the bone marrow [1,10,11]. The median age of diagnosis is 34 years with a slight male predominance [1]. Splenomegaly, hepatomegaly and thrombocytopenia are the most common presenting features [1]. However, there have been several reports of Coombs-negative hemolytic anemia being a presenting symptom [12–14]. Malignant cells are CD3+, CD56+, CD5–, CD4–, CD8–, and positive for the expression of gamma delta TCR; in addition, isochromosome 7q [1] and/or chromosome 8 abnormalities are frequently observed [14].

Complete remission is rare in HTCL. However, in remission, thrombocytopenia is the usual first sign of relapse. In addition, while cytogenetic abnormalities at relapse are not known to change, there have been several patient samples of relapsed HTCL cells noted to have lost their gamma delta TCR expression [1]. While prognosis is usually poor, there have been case reports of long-term survivors who received intensive multimodal chemotherapy such as m-BACOP (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone) [2] and HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate) [15] as well as hematopoietic stem cell transplant using donor cells from cord blood [16] or bone marrow [17,18].

Our patient presented with Coombs-negative hemolytic anemia, thrombocytopenia, and a bone marrow containing malignant gamma delta cells showing cytogenetics containing the pathogenomic isochromosome 7q. With most case reports of long-term remission involving bone marrow transplantation [16–18], our treatment goal was to attempt remission and quickly consolidate with transplant from the best-matched allogeneic stem cell source. In light of the extensive bone marrow involvement with disease, we chose to induce a remission with treatment according to the COG T-cell leukemia protocol AALL0434. Based on the rare reports of HTCL treatment success using nucleoside analogs [11,12], we followed remission induction with a single course of consolidation therapy using the FLAG regimen. Finally, we performed bone marrow transplantation from her HLA identical brother. While we cannot prove whether or not the aGVHD in our patient contributed to her

prolonged remission there are two case reports of Graft versus lymphoma effect in HTCL [10,19]. In conclusion, we report a long-term remission with minimal adverse late effects in a patient treated with leukemia based induction, a nucleoside analog-based consolidation and early allogeneic transplantation associated with GVHD and possible Graft versus lymphoma effect with hope that this approach will be useful for other patients.

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Fig. 1. The patient's diagnostic peripheral blood smear showing blasts with a high nuclear to cytoplasmic ratio, multiple prominent nucleoli, irregular nuclear membranes, and irregular cytoplasmic projections; in addition, demonstrated in the erythrocyte population are multiple microspherocytes.