CLINICAL VIGNETTE

Development of a Chronic T Cell Leukemia in a Patient with B Cell Hairy Leukemia: Does One Lymphoid Malignancy Predispose to Another?

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A 55-year-old male when he began experiencing exercise intolerance and was found to be pancytopenic with a white blood count (WBC) of 2.0 (x 10-3 / uL) and a hemoglobin of 8.0 (gm/ dL) and platelets of 50 (x 10-3 / uL). He presented for consultation and bone marrow biopsy (BM BX) demonstrated a hypercellular bone marrow with 40 % normal hematopoiesis and 50 % hairy cell leukemia (HCL). He was treated with a 7 day infusion of cladribine which he tolerated well. As anticipated, his pancytopenia resolved and serial complete blood counts (CBCs) for over 4 years had an absolute neutrophil count (ANC) > 2.0 (x 10-3/ uL) and hemoglobin > 13.0 (g/ dL) and platelets > 140 (x 10-3/ uL). His CBC pattern then showed a new and persistent neutropenia with an ANC 1.0. After 3 months he underwent a repeat BM BX. The clinical suspicion was for recurrent or progressive HCL. His BM BX however revealed normo-cellular hematopoiesis and no HCL and T cell large granular lymphocytic (T-LGL) population at 5.8 %. Additional molecular testing for clonality revealed T cell receptor beta gene (TRB) rearrangement was not clonal but the T cell receptor gamma gene (TRG) showed clonality (TRG alternative V + J1/2), confirming a clonal T-LGL leukemia, also known as T gamma disease. His serial CBCs since the 2nd BM BX showed somewhat variable neutropenia but with an ANC consistently 1.0 or higher and he had no evidence of recurrent infections requiring antibiotics. He continued on surveillance since he had not met criteria for treatment for his T-LGL leukemia.

Discussion

This case illustrates several issues relevant to patients with hematologic malignancies. Lymphoid malignancies arise in immune system cells and have both direct and indirect means of inducing immunodeficiency. Displacement of cells in the bone marrow by lymphoid malignancies can cause pancytopenia and hypogammaglobulinemia, by reducing normal lymphocytes. Lymphoid malignancies can be associated with autoimmune diseases and chronic antigenic stimulation of normal lymphocytes can predispose to lymphoid malignancies as with Helicobacter pylori infection and gastric lymphoma.

Hairy cell leukemia (HCL) is an indolent malignancy of small mature B lymphocytes which infiltrate the bone marrow, liver and spleen and gradually causing progressive pancytopenia. HCL represents 2% of all leukemias, or approximately 3 per million people per year. HCL occurs 4 times more commonly in men and more commonly in Caucasians with a median age at diagnosis of 50-55. While the etiology is unknown, risk factors may include exposure to pesticides, herbicides and gasoline or diesel fuel. Presenting symptoms and signs can include fatigue, recurrent infections, splenomegaly and pancytopenia, as was seen in this patient. HCL is incurable but is highly responsive to current treatments so that the median survival well over 10 years.[1] In the past, alpha interferon and splenectomy were fairly effective but have been supplanted by purine analog chemotherapy, specifically cladribine.[1] The overall response to cladribine is > 90% with substantial improvement to full normalization of blood counts which can last for years. While HCL is incurable, repeated administrations of cladribine, usually years apart, generally remain effective. Triggers for re-treatment include recurrence of the presenting symptoms above or asymptomatic progressive decline in CBC parameters. In this case the fall in ANC prompted a repeat BM BX to confirm relapsed HCL prior to re-treatment.

T cell LGL leukemia is a chronic, indolent malignancy of T lymphocytes characterized by accumulations of cytotoxic T cells in the blood and infiltration of bone marrow, liver and spleen. Even rarer than HCL, T LGL leukemia represents < 1 % of all leukemias with approximately 0.2 cases per million people per year. The median age of diagnosis of T-LGL leukemia is 66.5 years with a median survival of over 9 years. T-LGL can present as asymptomatic lymphocytosis detected on routine complete blood counts (CBCs) but 20-30% have recurrent infections or B symptoms of fevers, sweats and > 10% non-volitional weight loss.[2] The diagnosis of T-LGL leukemia is based on expansion of the LGL population in peripheral blood and demonstration of clonality, specifically T cell receptor (TCR) gene rearrangement as in this patient. The main CBC abnormality beyond lymphocytosis is auto-immune neutropenia and up to 40 % have associated conditions, most commonly rheumatoid arthritis (RA) or other lineage immune cytopenias. Daily oral prednisone and/ or weekly oral methotrexate (MTX) usually control LGL complications with salvage therapies including cyclosporine A and T cell targeting monoclonal antibodies. Triggers for treatment include the following: severe absolute neutropenia (ANC < 0.5), moderate absolute neutropenia (0.5 < ANC < 1.0) and recurrent infection, transfusion dependent anemia, severe thrombocytopenia (platelets < 50) or associated autoimmune conditions like RA requiring therapy.[2]

Given the natural complex interplay of B and T lymphocytes investigators have looked for evidence of one lymphoid malignancy increasing the risk of a second. Since the recognition of

HCL, there have been a number of reports of HCL associated with second hematological malignancies or lymphoproliferative disorders.[1-5] In the late 1980s case reports appeared linking LGL lymphocytosis, and in one case T LGL leukemia, and myeloproliferative disorders and myelodysplasia and HCL.[3] A series of 32 patients with HCL was found to have 10 patients with increased cytotoxic T cell LGL, all of which were found to be clonal.[4] In 2 patients, T-LGL was not present at HCL diagnosis but developed during follow up, as was seen in our patient. In 2011, a 63-year-old patient was described with simultaneous HCL, monoclonal B cell lymphocytosis and T-LG lymphocytosis.[5] The association of 2 mature post-germinal center type B cell malignancies and T-LGL CD4 & CD8 lymphocytosis suggested possible antigen driven proliferation with associated dysregulated homeostatic apoptosis leading to the clonal outgrowth of 2 separate lymphoid malignancies,[5] suggesting a possible mechanism for the repeated association of HCL and a 2nd B or T lymphoid malignancy.

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