Title

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Journal

Proceedings of UCLA Health, 22(1)

Authors

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Publication Date

2018-11-09

CLINICAL VIGNETTE

Outpatient Evaluation of Neutropenia: A Case of Large Granular Lymphocyte Leukemia

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Leukopenia is one of the most common reasons for outpatient referral to hematology. We present a case of chronic neutropenia that was eventually diagnosed to be large granular lymphocyte (LGL) leukemia. We then briefly discuss our general approach to neutropenia.

Case Presentation

A 69-year-old otherwise healthy male with no significant past medical history was referred for the evaluation of chronic leukopenia. His leukopenia was initially noted 5 years ago (ranging 1.5-2.9 x 10^9/L) and was managed with close surveillance. Recently, his leukopenia worsened with an absolute neutrophil count (ANC) dropping below 200 cells/mm^3, accompanied by anemia and thrombocytopenia. In addition, he was found to have monoclonal protein (1.2 g/dL) on SPEP. Bone marrow biopsy showed a hypercellular marrow with 5-10% plasma cells with mixed kappa and lambda light chain expression. Karyotype and FISH were normal. Peripheral smear review showed scattered large granular lymphocytes that was later confirmed with peripheral blood flow cytometry and T-cell receptor (TCR) gene rearrangement analysis showing evidence of clonality. The diagnosis of LGL leukemia was made and trial of methotrexate was initiated.

Brief Overview of LGL Leukemia

LGL leukemia belongs to the rare chronic mature lymphoproliferative disorders of the T/natural killer (NK) cell lineage.[1] According to the WHO classification of tumors of the hematopoietic and lymphoid tissues, clonal LGL expansions are divided into three disorders: T-cell LGL leukemia (the most common), chronic lymphoproliferative disorders of NK cells, and aggressive NK-cell leukemia.[2] Pathogenesis of the disease involves a clonal expansion of LGL resistant to activation-induced cell death due to constitutive survival signaling.[3] LGL leukemic cells represent an expanded population of effector memory cytotoxic T cells, suggesting chronic antigen stimulation.[4] While about one third of patients are asymptomatic, patients can present with neutropenia-related fevers and recurrent bacterial infections. Cytopenias are common and most patients present with chronic neutropenia. Neutropenia, anemia, thrombocytopenia are found in approximately 80%, 48%, and 20% of patients, respectively.[5] Neutropenia in LGL leukemia results from impaired production in the bone marrow through cell-mediated mechanisms and increased neutrophil destruction mediated by humoral mechanisms.[6] Fatigue and B symptoms are present in 20-30% of cases and splenomegaly is found in 20-50% of cases. Lymphadenopathy is rare.[5] Approximately 40% of patients have an associated condition, most commonly rheumatoid arthritis in about 25% of cases. Other autoimmune conditions or hematologic malignancies can also coexist.[5] T-LGL leukemia can be associated with B-cell dyscrasias, and monoclonal gammopathy of undetermined significance (MGUS) is one of the most common concomitant B-cell dyscrasias.[7] A definite diagnosis of LGL leukemia requires finding evidence of an expanded clonal T- or NK-cell LGL population. The clonality of T-LGL can be proven by detecting clonal TCR rearrangement using TCR polymerase chain reaction analyses.[2,3,6] Since NK-LGL cells do not express TCR, restricted expression of activating isoforms of killer immunoglobulin-like receptor (KIR) has been used as a surrogate marker for monoclonal expansion.[3,8] Initially, an LGL count > 2 x 10^9/L was mandatory, but the diagnosis can be made with lower counts if these cells are clonal and the patient displays other clinical or hematologic features such as rheumatoid arthritis or cytopenias.[2,3,9] Because the clinical course of most patients with T-LGL leukemia is indolent, not all patients require treatment at the time of diagnosis.[2] Indications for treatment include severe neutropenia (ANC < 0.5 x 10^9/L), moderate neutropenia (ANC > 0.5 x 10^9/L) associated with recurrent infections, symptomatic or transfusion-dependent anemia, and associated autoimmune conditions requiring therapy.[10] Although there is no consensus on standard treatment, immunosuppressive therapy is considered the cornerstone of initial treatment, based on small retrospective studies and the fact that leukemic LGL represent constitutively activated cytotoxic lymphocytes. The most clinical experience has been reported using low-dose methotrexate, cyclophosphamide, and cyclosporine A as monotherapy or in combination with prednisone.[2,3,11] A minimum of 4 months of therapy is required prior to assessing a response.[3] Response rates may be 50-65% with the commonly used immunomodulators mentioned above.[12] The prognosis is favorable with median overall survival exceeding 10 years.[3,5] In contrast, the prognosis of aggressive NK-LGL leukemia is very poor because it is usually refractory to treatment.[3,13]

Our General Approach to Neutropenia

The diagnosis of an underlying malignancy is rare in patients presenting with chronic neutropenia; most cases are "reactive" and of benign nature. Neutropenia is not an uncommon finding on a routine CBC. Neutropenia is defined as ANC <1500 cells/mm^3 and can be graded as mild (1000-1500 cells/mm^3), moderate (500-1000 cells/mm^3), or severe (<500 cells/mm^3).[14] The normal range of neutrophil count must be stratified for age and ethnicity. Individuals of African descent and some Middle-Eastern ethnic groups may have constitutionally lower neutrophil counts, which is referred to as benign ethnic neutropenia or constitutional neutropenia. These individuals are not at increased risk for infection and do not require treatment.[6,15] Because the neutrophil count physiologically fluctuates over time, neutropenia should ideally be confirmed on at least 3 samples obtained over several weeks.[16] We often see improvement or normalization of neutropenia on repeat CBC, obviating the need for work-up. Neutropenia may be associated with various conditions ranging from nutritional deficiencies (e.g. iron, folate, vitamin B12, copper) to disorders of hematologic (e.g. MDS and leukemias), infectious (e.g. bacterial including mycobacterial and rickettsial, viral, fungal, parasitic), rheumatologic (e.g. SLE, RA, Sjogren syndrome), and iatrogenic (e.g. medication-induced, radiation) etiologies.[6,14,17] Our initial evaluation of neutropenia includes CBC with differential and a blood smear along with focused history and physical examination. Laboratory evaluation may extend to serum level of essential nutrients, liver function tests, serologic screening tests for infections (e.g. viral hepatitis, EBV, HIV), or sepsis workup (e.g. blood cultures, PT, PTT, D-dimer, LDH), based upon clinical suspicion. Screening labs for rheumatologic disorders (e.g. ANA, anti-DNA antibody, complement levels) may be informative in patients with suggestive signs and symptoms. Flow cytometry on peripheral blood is prompted by clinical suspicion for an underlying leukemia. A bone marrow biopsy is the most definitive evaluation, which would be considered in any patient with multiple lines of cytopenias. Hematologic consultation should be considered for all patients except those with stable mild neutropenia or those with an obvious offending drug.[17] Asymptomatic patients with mild to moderate neutropenia and no worrisome findings on these evaluations can be monitored with a serial CBC in an outpatient setting. The risk of infectious complications may increase as the ANC drops below 500 cells/mm^3.[6,14] Neutropenia that is drug-induced or due to acute viral infection should improve within days to weeks after cessation of the inciting event in most cases.[17] Neutropenia would be anticipated in the setting of chemotherapy or radiation where supportive management with granulocyte (or granulocyte-macrophage) colony-stimulating factor such as filgrastim is commonly used.[17] More aggressive interventions such as stem cell transplantation may be employed in patients with diseases of the bone marrow such as aplastic anemia, myelodysplastic syndromes and in several malignant hematopoietic diseases.[18]

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Submitted August 29, 2018