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Case Report

Adult T cell large granular lymphocytic leukemia

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Introduction

Large granular lymphocyte (LGL) leukemia is a rare chronic lymphoproliferative disorder manifesting as leukemia in absence of any lymphadenopathy. This entity was first described in 1985 as a clonal disorder involving tissue invasion of marrow, spleen, and liver.¹ Clinical presentation is dominated by recurrent infections associated with neutropenia, anemia, splenomegaly, and autoimmune diseases, particularly rheumatoid arthritis (RA).² We report a case of T cell LGL leukemia in an old woman patient suffering from chronic anemia who was diagnosed and treated at our hospital.

Case report

A 61 year old female patient was admitted in the intensive care unit with chief complaints of weakness, breathlessness, swelling of feet. The complaints were gradually increasing since last two months. She had a history of blood transfusions twice in the past year. On examination she had severe pallor, bilateral pitting pedal edema up to knees and mild splenomegaly. There was no hepatomegaly or lymphadenopathy. There was no history of any joint disease or recurrent clinical infections. No joint deformity was observed.

Complete blood count revealed a hemoglobin of 1.3 gm%, total leukocyte count of 8800/cmm and a differential leukocyte count of 92% lymphocytes and 08% polymorphs. The Absolute lymphocyte count (ALC) was 8196/cmm. The Absolute neutrophil count (ANC) was 472/cmm. The platelet count was normal. The corrected reticulocyte count was 0.5%. The Peripheral blood smear showed lymphocytosis, few smudge cells and normocytic RBCs with moderate anisocytosis. The lymphocytes were predominantly large lymphocytes, which were having moderate to abundant cytoplasm containing fine or coarse azurophilic granules. The nuclei showed clumped chromatin (Fig. 1). Rheumatoid factor and Indirect Coomb's test were positive. Her iron stores and serum ferritin levels were within normal range. Her biochemical examination was fairly normal. Serological examination revealed no evidence of HIV or CMV infection. The ultrasound of abdomen confirmed mild splenomegaly and no hepatomegaly.

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Bone marrow examination revealed marked hypercellularity for age (Fig. 2). The predominant series were mature appearing lymphocytes of morphology similar to that seen in peripheral smear, constituting upto 40% of the marrow cells (Fig. 3). The erythroid, myeloid and megakaryocytic series were suppressed. The myeloid series showed maturation arrest. Erythroid series constituted 22% of marrow cell population. Bone marrow iron stores were normal. In view of presence of significant amount of erythroid precursors in the marrow, Pure red cell aplasia was ruled out. A single etiology for such severe anemia could not be established. Therefore, multiple factors like leukemic infiltration of marrow and autoimmune hemolytic anemia were deduced as the cause of anemia in this patient.

Flowcytometric analysis of blood showed that 95% of cells were of lymphoid origin. These lymphoid cells expressed CD2, CD3, CD5 (weak), CD7 (weak), CD 8 (strong), CD 11c, CD 57, CD 16 + 56 (weak) and CD 38 (heterogenous). The cells were CD4 negative. HLA DR was positive. These findings were suggestive of Adult T cell Large granular lymphocytic leukemia. The clonality of the lymphoid cells was indirectly proven by 96% of the cells expressing CD 8 and only 02% expressing CD 4.

Patient recovered well after repeated transfusions. She has been put on low dose Oral Methotrexate and has been asked for monthly follow up. The patient has been on irregular follow up since one and a half years. The peripheral blood picture has shown minimal change till the last follow up. The patient still has to be admitted once in six months for severe anemia and has to undergo multiple blood transfusions.

Fig. 1 – Peripheral blood smear showing lymphocytosis with normal platelet counts (400x). Inset: Note that the lymphocytes have abundant cytoplasm containing fine and coarse azurophilic granules. Leishman stain (1000x).

Fig. 2 – Bone marrow showing marked hypercellularity for age (60 years). Leishman stain (100x).

Discussion

This was an interesting case since although the patient presented with a chronic lymphoproliferative disorder, lymphadenopathy was characteristically absent and the patient had severe anemia along with mild splenomegaly. The Peripheral Blood smear also revealed lymphocytes of a peculiar morphology. These findings were in contradiction to those seen in chronic lymphocytic leukemias (usually of B cell origin) which are more commonly associated with lymphadenopathy while severe anemia is rare entity in such cases.

Fig. 3 – Bone marrow showing large granular lymphocytes. Leishman stain (1000x).

Large granular lymphocytes (LGLs) are 15–18 μm in size, having round or kidney shaped nuclei and abundant cytoplasm that contains typical azurophilic granules. Normally, LGLs make up to 10%–15% of peripheral blood mononuclear cells (PBMCs).

B-cell lymphoid neoplasms account for 80% of all lymphoid neoplasms. In contrast, T/NK-cell lymphoid neoplasms account for only 6% of all lymphoid neoplasms.³ Adult T cell leukemias account for an incidence of 9.6% of all T cell and NK cell lymphomas.⁴ Hence, this is a rare type of leukemia and data is limited in literature.

T-cell large granular lymphocytic (T-LGL) leukemia represents 2%–3% of all mature lymphocytic leukemias and is defined by the current World Health Organization (WHO) classification as a persistent (>6 months) clonal expansion of peripheral blood T-LGL cells, usually between 2 and $20 \times 10^9/\text{L}$, without a clearly identified cause.⁵

The underlying pathologic mechanisms of the disease are not well understood. It is found to be frequently associated with autoimmune disorders. This suggests that it may arise from clonal expansion of cytotoxic T cells due to sustained immune stimulation.⁶ Studies have shown that long-term survival of LGL is promoted by constitutive activation of multiple survival signaling pathways, such as the JAK/STAT3, sphingolipid, and Ras/MEK/ERK pathways. This phenomenon leads to global deregulation of apoptosis and development of resistance to normal pathways of activation-induced cell death.⁷

T – Cell LGL leukemia affects men and women equally. The mean age of onset is 60 years. Approximately 30% of the patients are asymptomatic at diagnosis.⁷ Symptoms arise due to neutropenia, anemia or Rheumatoid Arthritis. 45% develop severe neutropenia (absolute neutrophil count [ANC] < 500/ μL).⁸ The anemia is caused due to Pure red cell aplasia or autoimmune hemolysis.⁵ Transfusion dependent anemia occurs in 5–35% of the patients.⁸ Thrombocytopenia is infrequent. In 20–50% of cases the main physical finding is moderate splenomegaly⁸ while lymphadenopathy is rarely seen.⁵

Phenotypically, T – cell LGL leukemia cells retain many phenotypic and functional properties of normal cytotoxic effector cells. 80%–90% of patients with T-LGL leukemia show a phenotype of $\text{CD3}^+\text{CD8}^+\text{CD57}^+\text{CD56}^-\text{CD28}^-$, $\text{TCR-}\alpha\beta^+$.⁷ It is essential to ascertain the clonality of this disease by assessing TCR rearrangements using techniques like PCR. Human leukocyte antigen HLA DR has often been found to be positive.⁹ Rarely uncommon variants are encountered which express CD4^+ with or without coexpression of CD8^+ .⁷

Histopathologically, T-LGL leukemia invariably affects the spleen. The major findings are leukemic cell infiltration of the red pulp cords and sinuses, plasma cell hyperplasia, and prominent germinal centers.¹⁰ The bone marrow biopsy may contain nodules of B lymphocytes and scattered LGL. However, the morphology of LGL is better appreciated in the aspirate. Pure red cell aplasia and granulocyte maturation arrest have been observed. Lymph nodes can have expanded paracortical areas containing plasma cells and LGL but usually are not involved.⁹

Treatment of leukemic LGL is based on immunosuppressive therapy, primarily using low doses of methotrexate or cyclophosphamide. No standard therapy has been

established because of the lack of large, prospective trials.⁷ Other drugs which have been tried are cyclosporine A, corticosteroids and pentastatin.⁵ Splenectomy has also been found to be an effective therapeutic option in certain cases.¹¹ However, other therapeutic options need to be explored since curative therapeutic modalities for this disease are yet to be found.⁷

T-LGL leukemia is generally a chronic disease with a 10-year survival of more than 80%, and approximately 30%–50% of patients do not require therapy.⁶ Spontaneous regression of the disease has been reported.¹² Mortality and morbidity usually occur as a consequence of neutropenia or anemia.¹⁰

An unusual aggressive variant of T-cell LGL leukemia has been reported in the United States and is characterized by fever, marked hepatosplenomegaly, mild lymphadenopathy with lymphocytosis, and bone marrow involvement.¹³

The diagnosis of T cell LGL should be considered in patients with chronic or cyclic neutropenia¹⁴ or in patients with pure red cell aplasia or rheumatoid arthritis who have increased concentrations of LGL cells. The differential diagnosis is Cytomegalovirus or HIV infection which can lead to a mildly increased concentration of LGL cells.¹⁰

Our patient was a classic case of T-cell LGL leukemia based on the WHO classification. Ironically, rather than the hematological malignancy itself, the patient was suffering from transfusion dependent anemia. She is presently under follow up but still has to undergo repeated blood transfusions. Search for other alternatives of therapy will remarkably improve quality of life in such patients.

Conflicts of interest

All authors have none to declare.

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