Case Report-II

Large Granular Lymphocytic Leukemia

JAVID RASOOL, SAMOON JEELANI, SAJAD GEELANI, ABDUL RASHID LONE, MOHD. SHABAN

ABSTRACT

Large granular lymphocytic leukemia (LGL) affects adults and is rare in children, etiology being unknown. We describe a case of a fourteen year old boy who presented with symptomatic anemia with lymphocytosis and atypical lymphocytes. Bone marrow revealed hypocellularity with marked erythroid hypoplasia, lymphocytosis and increased eosinophils. Immunohistochemistry confirmed the diagnosis of LGL.

CASE: A 14 year old boy with recurrent history of chest infections presented in January 2002 with symptomatic anemia without any apparent source of blood loss. Examination revealed gross pallor and splenomegaly (6 cms below costal margin). Investigations: Hb 3.5 gms/dl, differential count showing 74% lymphocytes and absolute neutrophil count (ANC) of 200. Rest of blood count was within normal limits with a reticulocyte count of 1%. Peripheral smear showed normocytic normochromic anaemia with presence of atypical lymphocytes (fig 1). The lymphocytes were of medium size having an eccentric nucleus with mature chromatin without any visible nucleolus and abundant pale cytoplasm with azurophilic granulation. LDH, chest X-ray, liver and kidney function tests were normal. Rheumatoid factor and antinuclear antibody were negative. Ultrasonography showed mild hepatosplenomegaly. Immunohistochemistry

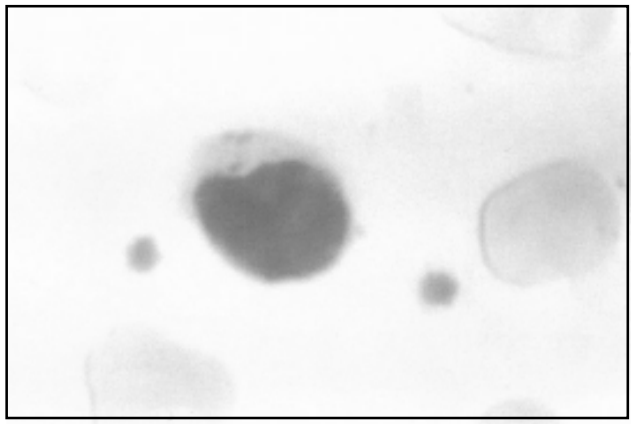

Fig 1. Peripheral blood smear showing atypical lymphocytes.

(IHC) showed majority of the lymphocytes to be positive for CD2(79.12%), CD3(88.07%), CD5(88.31%), CD8(70.14%), CD45(93.86%), CD57(89%) and weak positive or negative for CD4(11.60%), CD16(1.20%), CD25(0.46%), and CD34(0.12%). Bone marrow examination revealed marked erythroid hypoplasia (fig 2) with predominant normoblastic maturation, increase in eosinophils and adequate iron stores. Bone marrow trephine showed hypocellular marrow with marked erythroid hypoplasia, lymphocyto-

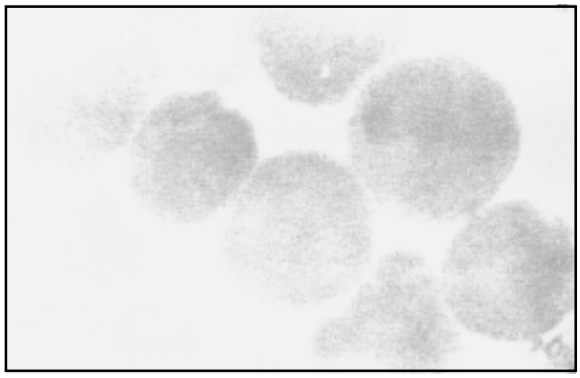

Fig 2. Bone marrow smear showing erythroid hypoplasia

Department of Clinical Hematology (Javid Rasool, Samoon Jeelani) and Medical Oncology (Sajad Geelani, Abdul Rashid Lone, Mohd. Shaban) Sheri-Kashmir institute of medical Sciences Soura Srinagar Kashmir190011
Correspondence to: **JAVID RASOOL**
E-mail: dr_javidrasool@yahoo.co.uk

sis and increase in eosinophils (10%). The diagnosis of pure red cell aplasia (PRCA) was made and he was treated with steroids and packed cell transfusions. He was transfusion dependent and underwent splenectomy in July 2003. Histopathology revealed congestion of red pulp with scattered foci of extramedullary hemopoiesis within sinusoids (fig 3). Post splenectomy patient received penicillin prophylaxis and was transfusion independent for four months. In August 2004, patient presented with respiratory tract infection and was managed with antibiotics. Chest X-ray was normal. The diagnosis of large granular lymphocytic leukemia was made in view of recurrent chest infections, PRCA, lymphocytosis, neutropenia and splenomegaly on presentation. Patient was put on 10mg of methotrexate weekly which was stopped after five months because of raised liver enzymes (bil 0.5; SGOT 225IU; SGPT 242IU; HBsAg, anti HCV and anti HEV- negative). Ultrasonography and computed tomography of abdomen were normal and patient was advised ursocol 150 mgs daily. During the treatment on methotrexate patient remained transfusion independent. In March 2006, patient was started on injection cyclophosphamide 300 mg/m^2 (3 weekly) for 3 months when LFT revealed bilirubin of 0.10, SGPT 584, TP 6.14, albumin 4.0, LDH 390 and there was no increase in Hb level. (Hb 3.7 g/dl, total leukocyte count 6110/mm^3, platelet 540 L/mm^3, differential count: polymorphs 21% lymphocyte 73%). However, he remained well and ambulatory with good exercise tolerance (performance score ECOG-1). Patient was noticed to have bronze colored skin and had received a total of 47 units of packed cell transfusion till June 2006. Ferrokinetics revealed serum ferritin of >800ng/ml (20-250ng/ml), serum iron 284 mg/dl (41-132), TIBC 346 µg/dl (259-388), saturation 82.2 %(16-31). Iron chelation was not possible due to financial constraints. Patient was advised to avoid transfusions as for as possible and injection cyclophosphamide was continued. In August 2006, patient developed severe symptoms with hemoglobin 1.4 gms/dl; and was given red packed cell transfusions. Patient was shifted from injection cyclophosphamide to oral cyclosporine (4 mg/Kg/day). Currently patient is again asymptomatic, off transfusions, has no bronze colour skin and the hemoglobin level has improved serially from 2.4 to 10.2 gms/dl. CBC in January 2007 revealed Hb- 10.2 gms/dl, TLC 6.74×10^9/L, DLC polymorphs- 16% lymphocytes- 84%, platelets 369×10^9/L. There in no evidence of cyclosporine toxicity. Cyclosporine levels, liver and kidney function tests are within normal limits.

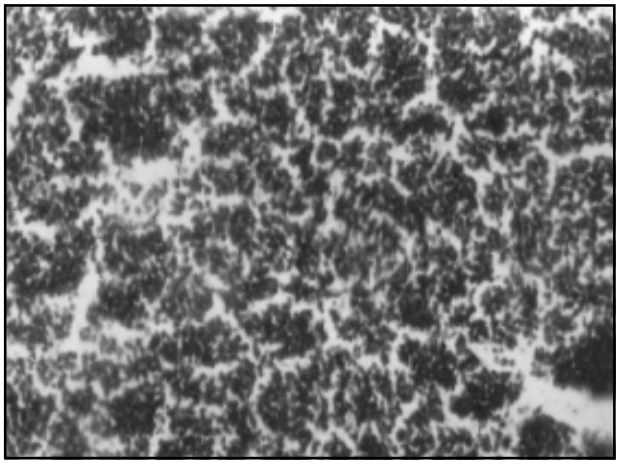

Fig 3. Splenic specimen showing scattered foci of extramedullary hemopoisis.

DISCUSSION

Large granular lymphocytes (LGL) are a heterogeneous group of thymus independent cells that are largely responsible for most NK-cell activity and have an important role in antibody dependent – cell mediated cytotoxicity. They constitute 10-15% of normal peripheral blood mononuclear cells. LGL can be classified into two major lineages: CD3+ LGL, representing in vivo activated cytotoxic T cells, and NK LGL, which lacks CD3 expression.[1, 2]. The term LGL leukemia is applied to two disorders distinguished by the phenotype of the clonally expanded cell population[3] In more than 90% of cases, there is a clonal expansion of CD3+, CD16+ T cells and the natural history is typically one of stability or slow progression. In the remaining patients, the LGL cells express a natural killer phenotype (CD3-,CD16+, CD57+), the disorder is more aggressive and severe thrombocytopenia caused by more marrow replacement and splenic infiltration may develop over months[3]. The etiology of T-cell LGL leukemia is unknown. T-cell LGL leukemia affects adults and is rare in children, it is slightly more frequent in females. Most pa-

tients with T-LGL present with recurrent infections secondary to neutropenia. Five to 20% develop thrombocytopenia which is generally mild and secondary to splenomegaly. An occasional patient presents with severe thrombocytopenia and the clinical picture of ITP[4]. On occasion the number of LGL cells is only slightly increased[3], making this condition hard to distinguish from severe ITP, in which an increase in CD56+, CD53- cells can also be observed[5]. Insufficient data have been reported to determine whether the response to treatment in T-LGL differs from that of primary ITP. Patients are asymptomatic or manifest with symptoms derived from cytopenias, especially recurrent infections, autoimmune disease or rarely present as pure red cell aplasia. Hepatomegaly is present in two-thirds of patients and splenomegaly in one half. Skin lesions may be present but lymphadenopathy is exceedingly rare. Most bone marrow specimens from the T-cell GLL (granular lymphocytic leukemia) patients contain interstitially distributed clusters of at least 8 CD8+ (83%) or TIA-1+ (75%) lymphocytes or clusters of at least 6 granzyme B+ (50%) lymphocytes, or granzyme B+. an additional T-cell GLL disease specific finding is the presence of linear arrays of intravascular CD8+, TIA-1+, or granzyme B+ lymphocytes, found in 67% of cases of T-cell GLL and in none of 25 control samples[6]. Cells from patients with LGL leukemia usually contain acid phosphatase and â-glucuronidase. T-LGL cells express the pan T-cell antigens CD2, CD3 and CD5 and the suppressor T-cell associated antigen CD8. They usually express NK-cell associated antigens such as CD16 (FC receptor for IgG), CD56 and CD57. Clonal rearrangement of the T-cell receptor has been reported [7, 8]. Few reports have been made of cytogenetic analysis in patients with this disorder. Chromosomal abnormalities are often not detected[9]; when detected there are no consistent abnormalities. Trisomies 8 and 14, $6q^-$, and inv (14) have been reported[10]. The most frequent structural abnormality appears to be deletion of 6q with two cases of del(6)(q^{21}) and 1 case of del(6)($q^{21}q^{25}$) reported as part of complex karyotypic aberrations, and 2 cases of del(6)($q^{21}q^{26}$) as the sole chromosomal abnormality[11]. Our patient is doing well on cyclosporine. Other treatment modalities include single agent alemtuzumab, alemtuzumab combined with pentostatin, fludarabine, and combination of fludarabine and cyclophosphamide. Significant responses have not been seen with any of these treatment regimens[12].

REFERENCES:

1. *Lanier LL, Phillips JH, Hackett J Jr, et al. Natural killer cells: definition of a cell type rather than a function. J immunol 1986;137:2735-2739.*
2. *MC Kenna RW, Parkin J, Kersey JH, et al: chronic lymphoproliferative disorder with unusual clinical morphologic, ultrastructural and membrane surface marker characteristics. Am J Med 1977;62;588-596.*
3. *Snowdon N, Bhavnani M, Swinson DR, et al: large granular T-lymphocytes, neutropenia and polyarthropathy: An underdiagnosed syndrome? Q J Med New series 1991;78:65-76.*
4. *Loughran TP Jr: clonal diseases of large granular lymphocytes. Blood 1993;82:1-14.*
5. *Garcia-Suarez J, Prieto A, Reyes E, et al: severe chronic autoimmune thrombocytopenic purpura associated with expansion of CD56+ CD3- natural killer cell subset. Blood 1993;82:1538-1545.*
6. *Morice WG, Kurtin PJ, Tefferi A and Hanson CA Blood 2002;99:268-274.*
7. *Waldmann TA, David MM, Bongiovanni KF et al. Rearrangement of gene for the antigen receptor on T-cells as markers of lineage and clonity in human lymphoid neoplasm. N Engl J Med 1985;313:776-83.*
8. *Aisenberg AC, Krontiris TG, Mak TW, et al. rearrangement of for the beta chain of the T-cell receptor in T-cell chronic lymphocytic leukemia and related disorders. N Engl J Med. 1985;313:529-533.*
9. *Dallapicolla B, Alimena G, Chessa L, et al. chromosome studies in patients with T-CLL chronic lymphocytic leukemia and expression of granular lymphocytes. Int.J cancer 1984;34:171-176.*
10. *Loughran TP, Kadin ME, Starkebaum Get al. Leukemia of large granular lymphocytes, association with clonal chromosomal abnormalities and autoimmune neutropenia, thrombocytopenia and hemolytic anemia. Ann. Intern. Med 1985;102:169-175.*
11. *Wong KF, Chan JC, Liu HS, Man C, K Wong YL. Chromosomal abnormalities in T-cell large granular lymphocytic leukemia: report of two cases and review of the literature. Br J Haematol. 2002;116:598-600.*
12. *A Ahmed, Huh Y, Keating M et al. T-cell large granular lymphocytic (T-LGL) leukemia: Experience in a single institution over 8 years. Leuk Res. 2007;31:939-45.*