

Case Report

Large Granular Lymphocytes Leukemia: A Case Report with a Review of the Literature

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Abstract: Large granular lymphocytes (LGL) leukemias correspond to rare haemopathies secondary to clonal proliferation of large lymphocytes rich in azurophilic granules with phenotype T of CD3+ or CD3- (NK cell) profile. We report the case of a patient, 75 years old, who was admitted for pancytopenia associated with lymphocytosis at 8G / L all evolving in a febrile context. The clinical examination did not find tumoral syndrome. The blood smear founded very numerous granular lymphocytes representing 46% of all lymphocytes. The myelogram shows an aspect in favor of peripheral thrombocytopenia without other notable abnormalities. There is a cellular expansion of CD8+ NK T cells compatible with LGL-type proliferation. The bone marrow is infiltrated by these lymphocytes with a percentage of 28%. It is a pathology with an heterogeneous spectrum classified by the World Health Organization into three entities: LGL T leukemia and chronic NK cell expansions with chronic and indolent evolution and aggressive cell leukemia NK with usually a reserved prognosis. Recent advances in the knowledge of the pathophysiology of these haemopathies have made it possible to specify the mechanisms underlying the perpetuation of the LGL clone and to identify new therapeutic targets.

Keywords: Large Granular Lymphocytes Leukemias, Case Report, Three Entities, Literature Review

1. Introduction

Leukemias with large granular lymphocytes (LGL) correspond to rare haemopathies [1], secondary to clonal proliferation of large lymphocytes rich in azurophilic granules of phenotype T of CD3+ or CD3- (NK cell) profile. These lymphocytes constitute 10 to 15% of the total circulating lymphocytes.

It is a heterogeneous spectrum disorder that the World Organisation of Health classification distinguishes three entities: LGL T leukemia and chronic NK cell expansions that are chronically indolent and mainly characterized by the existence of associated cytopenia or autoimmune pathology, and aggressive NK-cell leukemia with low chemosensitivity, usually a reserved prognosis, and associated to a tumor

syndrome clinically. On the other hand, the characteristics that unite these three heterogeneous entities are based on the clonal expansion of an LGL population greater than 0.4 G/L in peripheral blood, with a characteristic T or NK phenotype over a period of less than six months [2]. These criteria make it possible to distinguish LGL leukemias from reactive LGL expansions. However, depending on the clinical and biological context, the diagnosis can sometimes be retained without waiting for six months. The latter is based on the demonstration of the clonal nature of Lymphocyte proliferation.

Recent progress in understanding the pathophysiology of these haemopathies has made it possible to specify the mechanisms behind the perpetuation of the LGL clone and thus to propose new therapeutic approaches.

2. Observation

We report the case of a 75-year-old patient with a pacemaker for cardiac arrhythmia, who was admitted for exploration of a bicytopenia associated with lymphocytosis at 8G / L, all evolving in a febrile context and a moderate alteration of the general state. The initial clinical examination found a conscious patient with a Glasgow score at 15/15, afebrile at 37.4 ° C, a blood pressure of 13/7 cmHg, a 100% oxygen saturation, a heart rate of 72 beats / min, a slightly discolored conjunctiva, a cutaneo-mucous pallor, no peripheral lymphadenopathy nor hepatosplenomegaly, the rest of the somatic examination is normal.

The biological assessment shows at the hemogram a non regenerative macrocytic normochromic anemia with Hb (hemoglobin) at 9 g/dl, a thrombocytopenia at 50 G/L, a white blood cells at 13 G/L whose neutrophils accounted for 1.1G/L and lymphocytes at 8G/L. The blood smear shows the presence of a large number of granular lymphocytes representing 46% of all the lymphocytes (Figures 1, 2). In the myelogram, the marrow is rich with many megakaryocytes without signs of dysgranulopoiesis or dyserythropoiesis evoking in the first place thrombocytopenia of peripheral origin. Note an excess of granular lymphocytes (28%).

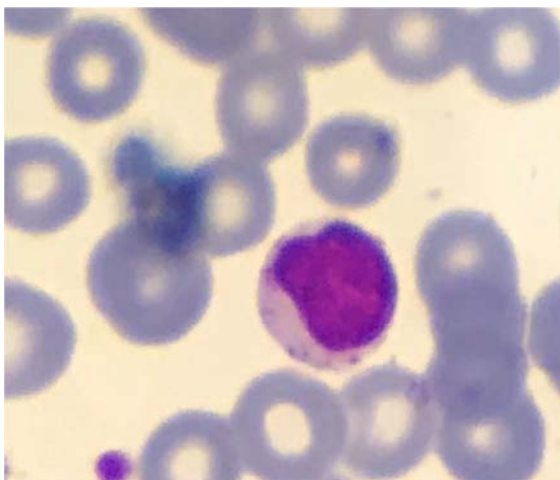


Figure 1. Cytological appearance of large granular lymphocytes. Core more or less regular, with rather abundant clear cytoplasm containing some large azurophilic granules (coloring May Grunwald Giemsa $\times 100$).

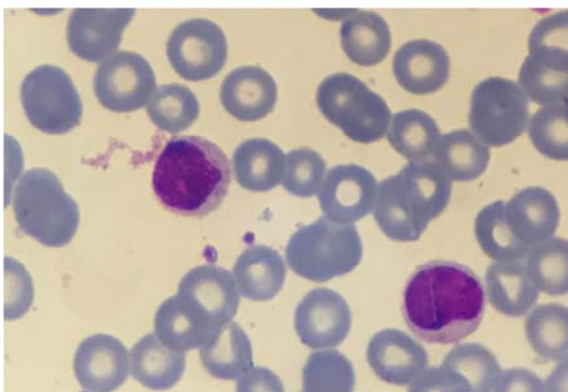


Figure 2. Cytological appearance of two large granular lymphocytes on blood froth (MGG $\times 100$ staining).

Peripheral blood immunophenotyping revealed no phenotypic abnormalities in the CD8+ T lymphoid population. It noted the presence of a CD3-/CD16+/ CD57+/ CD2+/ CD5-/CD7+ NK lymphocyte population with loss of CD56 expression and was estimated at approximately 38% of total lymphocytes. Immunophenotyping of lymphocyte subsets yields CD8+ T lymphocytosis and NK lymphocytosis. These results are identical at the level of the medullary blood. In the study of lymphoid clonality, we find the presence of a rearrangement of the TCR Gamma locus without disappearance of the polyclonal repertoire with the presence of the VDJ clonal rearrangement of the IgH locus with a high intensity without disappearance of the polyclonal repertoire. The karyotype study didn't shows a notable abnormality.

The remainder of the report shows IgG Lambda monoclonal gammopathy in the serum protein immunoelectrophoresis and signs of haemolysis, in particular a collapsed Haptoglobin at <0.08g / L and lactic dehydrogenase (LDH) at 355 IU / L, with no other notable anomaly. The direct Coombs test is negative. The serologies HIV, HCV, Toxoplasmosis, CMV and Parvovirus B19 are negative. HBV serology reports an old and cured hepatitis B profile. EBV serology is also in favor of an old infection. Immunoassay is negative for Antinuclear Acids. The radiological assessment, made of a thoraco-abdomino-pelvic CT scan, reports a discrete and homogeneous hepatosplenomegaly and a coelio-mesenteric ganglia of limited size especially at the level of the hepatic hile and the right iliac fossa.

In the absence of a therapeutic indication, the patient was not put on treatment with regular monitoring every three months by a blood test and a thoraco-abdominopelvic CT scan. The evolution is marked by the improvement of cytopenia with an increase in neutrophils around 1,2G/ L, an hemoglobin at 11.4 g/dL and platelets at 127 G/L. The scanner does not show any changes.

3. Discussion

LGL leukemias are rare, accounting for only 2-5% of lymphoproliferative syndromes in the West and up to 9% in Asia [1]. LGL T CD3+ leukemias account for 85% of LGL leukemias, whereas NK-cell chronic lymphoproliferative disorders account for only 5% [3]. They occur mainly in the West, affecting adults between 50 and 60 years old with a sex ratio of 1 [4]. They are classically associated with autoimmune diseases, including rheumatoid arthritis similar to Felty's syndrome [3]. Chronic lymphoproliferative NK-cell disorders occur in 5% of cases, 10% of which are aggressive and are mainly found in Asia in young adults and are closely related to EBV [5].

LGL leukemia and NK-cell chronic lymphoproliferative disorders have a similar clinical presentation [1]; general signs are rare, the splenomegaly syndrome is reported in 20 to 50% of cases, while hepatomegaly, more rare, is reported in only 20% of cases [4]. Adenopathies are also rarely present. Other associated clinical signs are related to the consequences of cytopenias including anemic syndrome and

repetitive infections that can be severe. Our patient presented a poor clinical picture with a discreet hepatosplenomegaly not obvious on clinical examination, cutaneo-mucous pallor and an infectious syndrome because of the febrile context.

Autoimmune diseases are found in more than one third of cases [6]. It is mainly, rheumatoid arthritis but other associations have been reported namely primary Gougerot-Sjogren's syndrome, systemic acute lupus erythematosus, thyroiditis and scleroderma [1]. One case reported by the University Hospital of Marrakech in 2019 is associated among others with autoimmune hepatitis [7].

Faced with poverty and the polymorphism of clinical presentations, the diagnosis remains essentially biological. Although, many reports point out that the absolute number of lymphocytes in the peripheral blood may be normal at the time of diagnosis, the median number of lymphocytes in a large series was 8 G/ L (approximately twice the upper limit of normal in adults), and most patients had absolute lymphocytosis in the peripheral blood. Neutropenia is also common and consist a major cause of morbidity in this disorder [8]. The mechanism of this neutropenia has not been

fully identified, since in the marrow the precursors show no abnormalities. Recent data suggest an increase in peripheral apoptosis of neutrophils, possibly related to an increase in circulating Fas-ligant in these patients [8]. The blood smear has a high level of LGL lymphocytes that can exceed 10 G / L and whose appearance is not always typical with a chronic and monoclonal expansion [1]. In aggressive NK cell leukemia, LGL is often elevated, with a moderate neutropenia, but anemia, thrombocytopenia, and haemostasis disorders are pronounced [9].

At the medullary level, lymphocyte infiltration rarely exceeds 50% of nucleated cells. Immunophenotyping is essential for the characterization of LGL leukemia. T LGLs have an activated mature post-thymic cell profile: CD3+ / TCRαβ+ / CD4- / CD8+ / CD16+ / CD28- / CD45RO- / CD57+. The expression of Fas (CD95) and Fas-ligant (CD178) is found in the majority of cases [10]. The expression of CD56 is generally associated with a more serious prognosis [11]. LGLs of the NK type are CD3- / CD2+ / CD4- / CD8+ / CD16+ / CD56+. This is how we differentiate between three pathological entities (Table 1).

Table 1. Immunophenotyping of LGL leukemias.

T LGL Leukemia	CD3+TCRαβ+CD8+CD16+CD57+
NK Chronic lymphoproliferative Disorders	CD3-CD8+CD16+CD56+
NK-cell aggressive Leukemia	CD3-CD8+CD16+CD56+

The search for clonality is essential in the diagnosis in order to eliminate the polyclonal character of an LGL reaction lymphocytoses, by studying the rearrangement of the gene coding for the TCR (T-cell receptor) by PCR, or indirectly by the analysis of KIR receptors (killer immunoglobulin-like receptor) by flow cytometry. However, the identification of this clonality is much more complex in NK expansions in the absence of TCR rearrangement; yet, in many cases, an imbalance in the expression of KIR at the level of the inhibitors / activators ration has been demonstrated in favor of activators that are overexpressed while certain inhibitors such as KIR3DL1 are absent [13]. At the cytogenetic level, the initial report of clonal cytogenetic abnormalities in T-LGL leukemia described two cases: one with clonal trisomy 8 and one with clonal trisomy 14 [8]. Since then, many cytogenetic abnormalities have been described in T-LGL leukemia, but none are considered pathognomonic. These abnormalities include, among others, structural abnormalities of chromosomes 7, 14, 3 and 5q. It should be noted that only 10% of karyotypes are abnormal [14].

Our patient had lymphocytosis at 8G/L, of which 46% were LGL associated with moderate neutropenia, an anemia and thrombocytopenia. The marrow was rich but infiltrated by these LGL representing 28% of the nucleated cells. Immunophenotyping found a lymphocyte NK CD3- CD16+ CD57+ CD2+ CD5- CD7+ population with loss of CD56 expression and was estimated to be about 38% of total lymphocytes. The karyotype did not detect any significant anomaly, and the clonality study noted the presence of a rearrangement of the TCRγ locus but without disappearance

of the polyclonal repertoire as well as the presence of a clonal rearrangement V (D) J of the IgH locus of high intensity without disappearance of the polyclonal repertoire. As a result, our patient is likely to have chronic NK-cell lymphoproliferative disorder with a generally good prognosis. Indeed, the monitoring of his health status notes a favorable evolution with an improvement in his blood count with a persistence of his discreet hepatosplenomegaly and coelio-mesenteric ganglia that remain of limited size.

LGL T leukemia and NK chronic lymphoproliferative disorders generally follow an indolent course, although studies indicate that 30-80% of patients become symptomatic and require treatment [15]. The heterogeneity of LGL leukemias and the absence of randomized trials on large numbers make it difficult to standardize treatment. In the first two entities, namely LGL T leukemias and chronic NK disorders, treatment is undertaken in cases of severe neutropenia <500 / μl, in case of symptomatic anemia or association with an autoimmune disease that justifies treatment [16]. Median survival is greater than 10 years and mortality is mainly infectious [6]. The prognosis of NK cell aggressive forms is reserved with a survival not exceeding two months in the absence of treatment [17]. Retrospective studies of immunosuppressive therapy protocols, such as Methotrexate, Cyclophosphamide, or Cyclosporine, have demonstrated a response rate of approximately 50% for each agent in both indolent forms of the disease [15]. Aggressive forms remain chemoresistant with a better response for Methotrexate, Etoposide and Ifosfamide [18].

4. Conclusion

In the mid-1970s, a distinct type of lymphoproliferative disorder characterized by leukemic proliferation of T lymphocytes containing important azurophil cytoplasmic granules and expressing Fc receptors for the immunoglobulin G heavy chain γ was identified [8]. Recent advances in the understanding of the pathophysiology of LGL leukemias have shown that clonal expansion was probably due to a viral stimulus and that long-term survival of the lymphocyte clone was due to strong cytokine secretion, particularly IL-15 and a resistance of the LGL lymphocyte to apoptosis. These data offer new therapeutic perspectives through the identification of new targets.

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