CD20-Positive T-Cell Large Granular Lymphocytic Leukemia: A Case Report and Literature Review

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Abstract

T-cell large granular lymphocytic leukemia (T-cell LGLL) is a rare disorder characterized by the monoclonal expansion of CD3-positive cytotoxic T cells. Cell morphology and immunophenotyping are the main tools for diagnosis. Typical phenotypic findings include the expression of markers CD3+, CD5+dim, CD8+, CD16+, CD57+, and T-cell receptor (TCR) αβ (+). However, a few cases may present with the CD3+/CD4+ phenotype or the double expression of CD4 and CD8. Similarly, in 20% of cases, TCRγδ is positive. In this study, we aimed to describe a rare, unusual case of T-cell LGLL that exhibited expression of the B-cell antigen, CD20. Additionally, we performed a literature review to compare the clinical characteristics of our patient to those of other patients with CD20-positive T-cell LGLL and to seek new therapeutic possibilities.

Keywords: T-cell large granular lymphocytic leukemia; CD-20; Rituximab

Introduction

T-cell large granular lymphocytic leukemia (T-cell LGLL) represents a relatively rare, heterogeneous disorder of mature cytotoxic T lymphocytes. T-cell LGLL accounts for 2% to 5% of all chronic T-cell lymphoproliferative disorders. The median age at diagnosis is 60 years, with an equal male to female ratio [1].

The most common clinical features of T-cell LGLL are recurrent infections, oral ulcers, and fatigue. These symptoms are related to neutropenia and anemia. Common autoimmune findings include red cell pure aplasia and autoimmune hemolytic anemia. Therefore, T-cell LGLL is frequently associated with rheumatoid arthritis and other diseases of connective tissue [2]. However, 30% of T-cell LGLL cases may not present any symptoms, and the diagnosis arises incidentally [3].

The diagnosis is typically based on the morphology and immunophenotype of cells in peripheral blood. However, in rare cases with low numbers of large granular lymphocytes, a bone marrow examination is required. The World Health Organization criteria for diagnosing T-cell LGLL include persistent (>6 months) lymphocytosis; large granular lymphocytes in peripheral blood with a characteristic morphology and immunophenotype; and a clonal rearrangement of the T-cell receptor (TCR) gene [4]. Lymphomas associated with T-cell LGLL have a classical phenotype; they express cell surface markers CD3+, CD5+dim, CD8+, CD16+, CD57+, and TCR αβ (+) [2,5]. Less commonly, malignant cells may present a phenotype of CD3+ / CD4+CD8-; CD3+/CD4-/CD8+; or CD3+/CD4+/CD8+ [6]. The CD20 antigen is considered a B-cell marker, but it has been reported in rare cases of T-cell malignancies [4]. In T-cell LGLL, the aberrant expression of CD20 was previously described in only four cases [6-10].

The pathogenesis of T-cell LGLL is not entirely defined, but mutations in genes involved in the JAK/STAT pathway play a role in a subset of cases. Immunodeficiency is the cornerstone of initial treatment. Typically, T-cell LGLL is indolent and non-progressive. Previous studies showed that patients had a median survival of 13 years [5,11,12].

Here, we describe the fifth case of T-cell LGLL that was CD-20 positive, and we provide a literature review to highlight specific features associated with this presentation. We interrogated the data to explore different therapeutic approaches to treating cases of T-cell LGLL with CD20 antigen expression. The literature review was performed in PubMed with the search term large granular leukemia and CD20.

Case Report

A 57-year-old man was referred to the Dermatology Department of the Hospital das Clinicas in Sao Paulo University for an evaluation of infected leg ulcers. The medical history indicated that he first noted a spontaneous ulcer in the right leg 12 years ago. After that, the ulcer had grown with recurrent infections. After two years, the ulcer had healed. In the last 10 years, the patient presented with three other ulcers in the right leg, and three others in the left leg. All the ulcers exhibited the same characteristics and frequently needed antibiotic therapy. In December 2015, the two ulcers in the left leg increased in size and exhibited purulent exudation and necrotic areas. These ulcers were refractory to oral antibiotic therapy. After the initial examination, the patient had been followed by a general physician. That physician noted leucopenia and severe neutropenia (<500 × 109/L), but the cause was not defined.

A physical examination showed discrete hepatosplenomegaly and no peripheral lymphadenopathy. The ulcers in the left leg were deep, with a well-defined border; moreover, the edge of the ulcer exhibited granulated tissue and purulent exudation. The surrounding skin was erythematous and hardened.

The dermatology staff acquired a cutaneous biopsy that was examined histologically. They concluded that the lesion was pseudoepitheliomatous epidermal hyperplasia with neutrophils in the epidermis and superficial dermis; not being ruled out the hypothesis of gangrenous pyoderma.

Because the blood counts showed persistent neutropenia, a
A hematology specialist was called to evaluate the case. The blood count showed a hemoglobin level of 115 g/L, a platelet count of 374 × 10^9/L, and a white blood count of 1.79 × 10^9/L (neutrophils were 0.22 × 10^9/L and lymphocytes were 0.75 × 10^9/L). These counts were confirmed by comparing to results from previous exams and serial blood counts that had been conducted during the hospitalization.

An initial investigation revealed that the iron profile was suggestive of anemia, which is often observed in a chronic disease, but the serum vitamin B12 and folate levels were within normal ranges. The protein electrophoresis result was normal and the serologic tests were negative for HIV and for viral hepatitis C and B. Rheumatoid factor and antinuclear antibodies were present in high titers. Abdominal ultrasonography confirmed the hepatosplenomegaly, and a computed tomography scan excluded deep lymphadenopathy. Initially, we diagnosed a chronic severe autoimmune neutropenia, and our mean diagnostic hypothesis was that this neutropenia was secondary to T-cell LGLL.

The cytological and immunophenotyping analyses of peripheral blood samples did not indicate any increase in the number of large granular lymphocytes. A bone marrow aspirate revealed a shift in granulocyte maturation to myelocytes and promyelocytes, and about 5% of the total nucleated cells were large granular lymphocytes, based on morphology. The karyotype analysis showed normal results. Immunophenotyping by flow cytometry showed an expansion of cytotoxic T cells, which accounted for about 20% of the total number of cells. These cytotoxic T cells exhibited expression of CD3+dim, CD4-, CD5+dim, CD8+, CD16-, CD56-, CD57+, and an anomalous co-expression of CD20+ (Figure 1). Clonality was defined by detecting a clonal TCR-γ gene rearrangement by polymerase chain reaction (PCR) using specific primers sequences, followed by fragment analysis in sequencer Genetic Analyzer 3500 (Applied Biosystems, Foster City, CA). The resulting data were analyzed using the GeneMapper V 3.2 software (Applied Biosystems, Foster City, CA). A monoclonality spike was determined by visual examination of the electropherograms (Figures 2A and 2B). A bone marrow biopsy also showed interstitial infiltration of small cells that were CD3+, CD7+, and CD57+, based on immunohistochemistry (Figures 3 and 4).
Our final diagnosis was T-cell LGLL, which presented with neutropenia and recurrent infections. The therapeutic approach was immunosuppression based on cyclosporine. After four months, no response was achieved; therefore, we changed the therapy to methotrexate.

Discussion

In this study, we described a rare case of T-cell LGLL with aberrant expression of CD20. T-LGLL is a chronic lymphoproliferative disorder that typically presents with cytopenias, recurrent oral ulcers, and infection. Therefore, T-cell LGLL is commonly associated with an abnormal number of large granular lymphocytes in the peripheral blood. Autoimmune conditions occur in 40% of cases. A physical examination is typically poor, but in some cases, it shows hepatosplenomegaly and lymphadenopathy. Cutaneous involvement is not common in T-cell LGLL. In a clinical context, an examination of cell morphology and immunophenotyping cells in peripheral blood can strongly suggest the diagnosis; however, a determination of T-cell monoclonality is necessary to confirm the diagnosis [13].

We consider the present case unusual in several aspects. First, the clinical presentation was atypical, marked by clear cutaneous involvement. Despite the fact that the majority of reviews about T-cell LGLL have mentioned that cutaneous involvement is rare, there are a few descriptions of different skin presentations, including nodules, ulcers, telangiectasia, and cutaneous thrombotic and necrotizing mycroangiopathy. In 1992, Helm et al. described a pyoderma gangrenous-like ulcer, which was a cutaneous manifestation of LGLL [14-17]. Although we could not ascertain skin infiltration by large granular lymphocytes in our patient, the presentation of ulcers that mimicked pyoderma gangrenous in the histology suggested that this case might have represented a second atypical cutaneous presentation. Moreover, the pathologic presentation in our case was not typical, because we did not detect lymphocytosis or an increase in the number of large granular lymphocytes in peripheral blood. The diagnosis was suspected, based on the clinical features, and it was confirmed with the bone marrow examination.

The second unusual aspect of this case was the immunophenotyping results. We found that, in addition to expressing the classic markers of T-cell LGLL (CD3, CD5, CD8, and CD57), the leukemic cells also anomalously expressed the B-cell marker, CD20. There are two hypotheses for CD20 expression in T-cell LGLL. In one hypothesis, the leukemic clone may be derived from CD20+ mature T-cells, which naturally occur in normal individuals. In the other hypothesis, the leukemic clone may be related to a lineage infidelity, where the malignant cells express CD20 in an aberrant manner [10].

Among the four CD20+ cases described in the literature, all patients were men, with a median age of 70 years. Only one of these patients showed lymphocytosis. The other three patients, like our case, did not present significant lymphocytosis. Indeed, none was associated with autoimmune findings. These features might be a clinical characteristic of this particular variant of a CD20+ T-cell LGLL. However, different of our patient, the four patients previously described with CD20+ T-cell LGLL did not present skin involvement.

The management of T-cell LGLL is based on immunosuppression. The first-line options are methotrexate, cyclophosphamide, and cyclosporine, and all have an overall response rate of 50%. Other options include erythropoietin, granulocyte colony-stimulating factor, prednisone, alemtuzumab, pentostatin, and fludarabine. In a retrospective study, Costa et al. investigated the effects of fludarabine as a first-, second-, or third-line therapy in six patients. They demonstrated a high rate of complete hematologic and molecular response, with excellent compliance and tolerability rates [18]. However, in our case, the CD20 expression suggested the possibility of using monoclonal antibodies, like rituximab, which could potentially provide a better response [13,19].

Rituximab treatment was described in a few cases of T-LGLL, which were associated with rheumatoid arthritis, to control the autoimmune aspects of the disease [20-22]. In general, good responses were achieved with a monoclonal antibody against CD20. Cornec et al. described two cases; in one patient, complete T-LGLL remission was achieved, and it was sustained for 8 years after the first rituximab infusion. In the second patient, rituximab therapy was followed by immediate neutropenia recovery; then, one year later, the LGLL clone showed marked shrinkage [21]. Raposo et al. and Verhoeven et al. also described one and three cases, respectively, where rituximab therapy improved rheumatoid arthritis control and increased the neutrophil count, with sustained responses [20-22]. In the four cases of CD20+ LGLL described previously in the literature, rituximab was not used as a therapeutic option. However, theoretically, in those cases, rituximab could have improved the outcomes by directly inhibiting the leukemic cells, as reported for other CD20+ T-cell lymphomas [23,24].

In the near future, as new studies and case studies emerge, rituximab may be included as an option for management, because in T-cell LGLL, there is chronic autoantigen stimulation. Therefore, rituximab may play an important role in changing the microenvironment and promoting the cytokine balance by depleting B-cells. Rituximab might also be proposed as a second-line agent in refractory cases, even in cases where the T-cell LGLL variant is CD20-. [13].

Conclusion

In conclusion, this study showed that CD20+ T-cell LGLL may represent a distinct biologic and clinical disease entity, with therapeutic implications. These preliminary findings must be confirmed with additional case studies in future.

References


