

# Rheumatoid arthritis and associated large granular lymphocytic leukemia – successful treatment with rituximab

Raposo A<sup>1</sup>, Cerqueira M<sup>1</sup>, Costa J<sup>1</sup>, Sousa Neves J<sup>1</sup>, Teixeira F<sup>1</sup>, Afonso C<sup>1</sup>

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## ABSTRACT

Large granular lymphocytic (LGL) leukemia is an uncommon, usually indolent, lymphoproliferative disorder strongly associated with various autoimmune diseases. The authors report a case of a 67-year-old woman with a long-standing rheumatoid arthritis, who developed neutropenia and associated recurrent infections, diagnosed with LGL leukemia. We describe the treatment approach and the response to an anti-TNF and afterwards to rituximab.

**Keywords:** Rheumatoid arthritis; Large granular lymphocytic leukemia.

## INTRODUCTION

Large granular lymphocytic (LGL) leukemia is an uncommon clonal lymphoproliferative disorder, which has usually an indolent clinical course and can be associated, at diagnosis or during evolution, with a variety of autoimmune disorders including autoimmune cytopenias, endocrinopathies, autoimmune arthropathies and vasculitides<sup>1,2</sup>.

The clinical presentation is similar to Felty Syndrome, with increased infectious complications associated with neutropenia, anemia and variable degrees of splenomegaly.

## CLINICAL CASE

A 67-year-old retired woman was diagnosed, since 2001, with rheumatoid arthritis (RA) (rheumatoid factor and anti-cyclic citrullinated peptides (CCP) posi-

tive), but without any strict follow-up or immunomodulatory treatment. She had also a past history of Hashimoto's thyroiditis; blepharospasm and oromandibular dystonia (Meige Syndrome) treated with thyroid hormone replacement, benzodiazepines and botulinum toxin injections in facial musculature.

Neutropenia was first detected in March of 2012, during a febrile condition requiring hospitalization. After an intensive investigation, only a sinusitis was identified and treated apparently with resolution of neutropenia. Afterward the patient progressively presented asthenia, anorexia and weight loss. She was referred to a hematologist, in order to complement the investigation and a bone marrow aspirate and culture were performed. A clonal proliferation of T-cells (TCR  $\gamma\delta$ ) was identified both in the peripheral blood and bone marrow studies.

The patient maintained recurrent infections and, in September of 2012, she was again admitted to the hospital, to treat an urinary tract infection by *Candida albicans* in a febrile neutropenic episode. Laboratory tests evidenced persistent neutropenia, reaching 0 neutrophils/mm<sup>3</sup>, and treatment with granulocyte colony-stimulating factor (G-CSF) was initiated. With this treatment the patient referred severe complaints of myalgia, arthralgia and swelling of multiple articulations and for this reason refused new G-CSF injections.

She was again admitted, in November of 2012, to our Rheumatology department with polyarthritis involving small joints of the hands and feet (metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints), shoulders and knees. Erosive damage was identified on X-ray. Laboratory tests showed anemia (Hb- 10.5g/dL, normocytic, normochromic), leucopenia with neutropenia (3120 leucocytes with 130 neutrophils /mm<sup>3</sup>), high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with no other significant findings. She maintained high levels of rheumatoid factor and anti-CCP, with negative

1. Serviço de Reumatologia, Hospital Conde de Bertiandos/ULSAM, Ponte de Lima

antinuclear antibodies and also a polyclonal hypergammaglobulinemia. No lymphadenopathy or organomegaly was found on physical examination or computed tomography. The previous medical evaluation was reviewed and a new peripheral blood smear revealed increased large granular lymphocyte cells. The immunophenotyping of a peripheral blood sample showed an increased number of T cells  $\gamma\delta$  (50%) with the following phenotype: CD3+, CD8+, CD45Ra+, CD11a+ and CD7, CD57 of variable expression +, TCR  $\gamma\delta$  +, with negative CD4, CD5, CD25, CD28, CCR7, CD RO and CD56. These results were consistent with T-large granular lymphocyte leukemia (T-LGL).

An infection was ruled out and prednisone (1mg/Kg/day) was started with gradual normalization of blood count and improvement of polyarthritis and general state. Methotrexate was introduced, with escalation in dose to 20mg, stopped due to oral intolerance and then changed to leflunomide 20mg. Leflunomide was also stopped after the appearance of a distal axonal sensorimotor polyneuropathy, improved with the suspension of this treatment.

In the presence of intolerance to previous immunomodulators and due to high disease activity (DAS28-6.02), treatment with etanercept 50mg subcutaneously, every week, was started. The polyarthritis was controlled within a few weeks, but etanercept was frequently interrupted due to superior respiratory tract infections with subsequent flare of the articular disease. On the other hand the neutropenia persisted as well as the clonal LGL. These facts lead to the decision of treating the patient with rituximab (two 1000mg infusions, two weeks apart). During the initial follow-up period we could find a progressive reduction of disease activity (DAS28 week 16: 2.05; delta DAS28: 4.73) and improvement of neutrophils (week 0: 690/mm<sup>3</sup>; week 16: 1060/mm<sup>3</sup>; week 24: 1530/mm<sup>3</sup>), without infectious interurrences. Treatment with steroids could be reduced to a lower dose of prednisone of 5mg/day. Between week 16 and 24 the patient developed a new articular flare (DAS28 week 24: 5.26) and new treatment with rituximab was programmed.

## DISCUSSION

One of the unique features of LGL leukemia is its common association with other clinical conditions, including autoimmune diseases, hematologic disorders and other malignancies. Up to one-third of patients

with LGL leukemia has RA, but other autoimmune diseases have been reported frequently<sup>3</sup>. Hashimoto's thyroiditis appears to be the most common associated immune endocrinopathy, as found in our patient<sup>2</sup>.

It affects predominantly adults aged 55 to 60 with an equal sex distribution<sup>2</sup>. The dysregulation of apoptosis might play a pivotal role in this clonal disorder, but the pathogenesis of this disease has not been yet completely elucidated. Normally, the T-LGL lymphocytes are eliminated via a Fas/Fas ligand pathway, that results in the formation of death inducing signaling complex and the activation of many apoptotic effectors, however, the clonal LGL leukemia cells fail to respond to this death pathway, accumulating in the peripheral blood and reticuloendothelial system<sup>3</sup>. A chronic activation of T-cells by a viral or an autoreactive antigen is among possible explanation behind this process. An immune mediated response may represent the trigger point for this process and could explain the association with autoimmune conditions seen in LGL leukemia<sup>2</sup>.

In most cases, it follows an indolent clinical course, but approximately 85% of patients present with neutropenia, or the associated infectious complications<sup>4</sup>. Anemia occurs in nearly 50% of patients, being the LGL leukemia the most common cause of pure red cell aplasia. Thrombocytopenia is observed less commonly than neutropenia. Other clinical features include fatigue, B symptoms and liver and spleen enlargement<sup>4,5</sup>.

Diagnosis is based on finding a sustained expansion of LGLs in peripheral blood with typical morphology on the peripheral smear; an expanded T-LGL population with a characteristic immunophenotype by flow cytometry; and evidence of T cell clonality by PCR, Southern blot, or flow cytometry. Typically, in T-LGL, the expanded clonal population is CD3+, CD4-, CD8+, CD16+, CD28-, CD57+, and the TCR of the expanded T-LGL clone is of the  $\alpha\beta$  type<sup>4</sup>. Less than 10% of patients express TCR- $\gamma\delta$  instead of TCR $\alpha\beta$  and were associated, in some studies, with a favorable prognosis (85% survival at 3 years) with similar clinical findings, recurrent infection and association with auto-immune diseases especially RA<sup>6,7</sup>.

Polyclonal expansions of LGLs may occur in patients with RA, most frequently associated with Felty syndrome (FS). LGL leukemia and FS share similar clinical presentations, are associated with longstanding RA, severe joint damage, increased incidence of extra-articular manifestations and a common haplotype (HLA- DR4). T-LGL leukemia has also been called

“pseudo-Felty” and the two conditions might be part of a single spectrum<sup>2,8</sup>.

The indications to treat T-LGL leukemia include severe neutropenia (< 500 neutrophils/mm<sup>3</sup>), moderate neutropenia (> 500 neutrophils/mm<sup>3</sup>) with symptoms from recurrent infections, symptomatic or transfusion-dependent anemia, and associated autoimmune conditions such as RA<sup>9</sup>.

Methotrexate and cyclosporine A inhibit Fas-ligand secretion by LGLs, reducing the amount of apoptosis, and both drugs have proved effective for controlling LGL leukemia and its associated neutropenia<sup>10</sup>. Cyclophosphamide has been successfully used, particularly in patients with pure red cell aplasia. Prednisone may be better served as an adjunct therapy with first-line immunosuppressive agents, providing only a temporary improvement in neutropenia, and is associated with relapses and frequent secondary effects<sup>9</sup>. Refractory patients or with very aggressive presentation have been treated with a CHOP-like treatment regimen (cyclophosphamide, vincristine, doxorubicin and prednisone). Other treatments that have been tested are purine analogues, alemtuzumab, bortezomib, splenectomy and allogeneic bone marrow transplantation, with variable results<sup>11</sup>.

The therapeutic approach to infectious complications involves continuing the basic therapy and adding a growth factor, specifically G-CSF, to achieve prompt recovery of the circulating neutrophil count and better control of infection<sup>12</sup>. Nevertheless, the larger supply of circulating activated leukocytes raises the risk of arthritic flare-ups and/or leukocytoclastic vasculitis in these patients<sup>13</sup>. A very clinically relevant flare of the disease was observed in our patient leading to the interruption of G-CSF treatment.

The treatment of T-LGL in the setting of RA may be similar to FS. Case reports and small case series suggest low dose weekly methotrexate and leflunomide may be effective for the treatment of neutropenia in FS<sup>14,15</sup>. The evidence is limited for anti-TNF agents, although no change in neutropenia was seen in two cases after treatment with etanercept and infliximab<sup>4,16</sup>. Our clinical case illustrates also the non-response in neutropenia with etanercept.

Rituximab is a monoclonal anti-CD20 antibody, which is expressed on the surface of B-lymphocytes, causing B-cell depletion, which can suppress antibody production against circulating neutrophils and granulopoiesis<sup>17</sup>.

The use of rituximab was previously reported in pa-

tients with FS, with varying results<sup>18-22</sup>, but a systematic review showed a sustained increase in the neutrophil count in five of eight patients after one cycle of treatment, accompanied by an improvement in biological markers of inflammation and other clinical manifestations of FS<sup>23</sup>. Two patients with T-LGL leukemia associated with RA were successfully treated with rituximab and achieved complete remission<sup>24</sup>.

In RA, the effects of rituximab, on the immune system may consist not only in transient B-cell depletion, but also in changes in the microenvironment and cytokine balance capable of impairing LGL clone survival<sup>24</sup>.

The difficulties of maintaining our patient in treatment with an anti-TNF agent, despite the articular good response, due to severe leucopenia, lead us to opt for rituximab therapy.

Rituximab may be a safe and efficacious treatment in RA associated with T-LGL leukemia, but the exact role of rituximab needs further investigation. Our case report highlights the challenge of treatment of RA and associated neutropenia and the successful use of rituximab in a LGL leukemia setting.

#### CORRESPONDENCE TO

Ana Raposo  
Largo Conde de Bertandos  
4990-041, Ponte de Lima  
Portugal  
E-mail: anaeraposo@gmail.com

#### REFERENCES

- Zhang R, Shah MV, Loughran Jr TP. The root of many evils: indolent large granular lymphocyte leukaemia and associated disorders. *Hematological Oncology* 2010; 28(3):105-117.
- Bockorny B, Dasanu CA. Autoimmune manifestations in large granular lymphocyte leukemia. *Clin Lymphoma Myeloma Leuk* 2012; 12(6):400-405.
- Rose MG, Berliner N. T-cell large granular lymphocyte leukemia and related disorders. *Oncologist* 2004; 9(3):247-258.
- Shah A, Diehl LF, St Clair EW. T cell large granular lymphocyte leukemia associated with rheumatoid arthritis and neutropenia. *Clin Immunol* 2009; 132(2):145-152.
- Rebecca J, Watters, Xin Liu, Thomas P, Loughran Jr. T-cell and natural killer-cell large granular lymphocyte leukemia neoplasias. *Leuk Lymphoma* 2011; 52(12): 2217-2225.
- Sandberg Y, Almeida J, Gonzalez M, et al. TCRgammadelta + large granular lymphocyte leukemias reflect the spectrum of normal antigen-selected TCRgammadelta + T-cells. *Leukemia* 2006; 20:505-513.
- Bourgault-Rouxel AS, Loughran Jr TP, Zambello R, et al. Clinical spectrum of gammadelta+T cell LGL leukemia: analysis of 20 cases. *Leuk Res* 2008; 32:45-48.
- Lois Iglesias A, Sifuentes Giraldo WA, Bachiller Corral J, Saiz González A, Brito Brito E, Zea Mendoza A. Large granular lymphocyte leukemia as a complication of rheumatoid arthritis.

- Reumatol Clin 2012; 8(6):365-367.
9. Steinway SN, LeBlanc F, Loughran TP Jr. The pathogenesis and treatment of large granular lymphocyte leukemia. *Blood Rev* 2014; 28(3):87-94.
  10. Capsoni F, Sarzi-Puttini P, Zanella A. Primary and secondary autoimmune neutropenia. *Arthritis Res Ther* 2005; 7(5):208-214.
  11. Lamy T, Loughran Jr TP. How I treat LGL leukemia. *Blood*. 2011; 117:2764-2774.
  12. Hellmich B, Schnabel A, Gross WL. Treatment of severe neutropenia due to Felty's syndrome or systemic lupus erythematosus with granulocyte colony-stimulating factor. *Semin Arthritis Rheum* 1999; 29:82-89.
  13. Jain KK. Cutaneous vasculitis associated with granulocyte colony-stimulating factor. *J Am Acad Dermatol* 1994; 31:213-215.
  14. Wassenberg S, Herbron G, Rau R. Methotrexate treatment in Felty's syndrome, *Br. J. Rheumatol* 1998; 37:908-911.
  15. Talip F, Walker N, Khan W, et al. Treatment of Felty's syndrome with leflunomide, *J. Rheumatol* 2001; 28:868-870.
  16. Ravindran J, Shenker N, Balla AK, et al. Case report: response in proteinuria due to AA amyloidosis but not Felty's syndrome in a patient with rheumatoid arthritis treated with TNF blockade. *Rheumatology* 2004; 43:669-672.
  17. Cooper N, Arnold DM. The effect of rituximab on humoral and cell mediated immunity and infection in the treatment of autoimmune diseases. *Br J Haematol* 2010; 149:3-13.
  18. Sordet C, Gottenberg JE, Hellmich B, Kieffer P, Mariette X, Sibilia J. Lack of efficacy of rituximab in Felty's syndrome. *Ann Rheum Dis* 2005; 64: 332-333.
  19. Weinreb N, Rabinowitz A, Dellaripa PF. Beneficial response to rituximab in refractory Felty Syndrome. *J Clin Rheumatol* 2006; 12: 48.
  20. Salama A, Schneider U, Dorner T. Beneficial response to rituximab in a patient with haemolysis and refractory Felty syndrome. *Ann Rheum Dis* 2008; 67: 894-895.
  21. Lekharaju V, Chattopadhyay C. Efficacy of rituximab in Felty's syndrome. *Ann Rheum Dis* 2008; 67: 1352.
  22. Heylen L, Dierickx D, Vandenberghe P, Westhovens R. Targeted Therapy with Rituximab in Felty's Syndrome: A Case Report. *Open Rheumatol J* 2012;6:312-314.
  23. Narváez J, Domingo-Domenech E, Gómez-Vaquero C, et al. Biological agents in the management of Felty's syndrome: a systematic review. *Semin Arthritis Rheum* 2012;41(5):658-668.
  24. Cornec D, Devauchelle-Pensec V, Jousse-Joulin S, et al. Long-term remission of T-cell large granular lymphocyte leukemia associated with rheumatoid arthritis after rituximab therapy. *Blood* 2013;122(9):1583-1586.