


# T-Cell Large Granular Lymphocyte Leukemia in a Patient With Rheumatoid Arthritis

Journal of Investigative Medicine High Impact Case Reports  
Volume 8: 1–4  
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DOI: 10.1177/2324709620941303  
journals.sagepub.com/home/hic  


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## Abstract

Large granular lymphocyte leukemia (LGL) is a clonal, lymphoproliferative disorder with an indolent disease course. T-cell LGL (T-LGL) is the most common type of LGL driven from T-cell lineage (85%). The coexistence of T-LGL with several types of autoimmune disorders, mostly rheumatoid arthritis (RA), has been reported. Felty's syndrome (FS) is defined by splenomegaly, low neutrophil count, and destructive arthritis and is usually seen in <1% of patients with RA. About 30% to 40% of patients with FS have been reported to have an expansion of large granulated lymphocytes in the circulation. FS and T-LGL are similar in terms of clinical manifestations, response to immunosuppressive therapy, their smoldering course, and immunogenetic findings, proposing FS and T-LGL with RA might be different aspects of a single disease spectrum. In this article, we present a case with long-standing RA who had never been on DMARD (Disease Modifying Anti-Rheumatic Drugs) treatment found to have constitutional symptoms, neutropenia, and splenomegaly, and the patient was diagnosed with T-LGL.

## Keywords

T-cell large granular lymphocyte leukemia, large granular lymphocytes, rheumatoid arthritis, Felty's syndrome

## Introduction

Large granular lymphocyte leukemia (LGL) is a clonal, lymphoproliferative disorder with an indolent disease course. LGL can originate from either T-cells or natural killer (NK) cells. T-cell LGL (T-LGL) is the most common type of LGL derived from T-cell lineage (85%). NK LGL is very rare and derived from NK cell lineage (15%).<sup>1</sup> The coexistence of T-LGL with several types of autoimmune disorders has been reported. Among autoimmune disorders, rheumatoid arthritis (RA) is most common in patients with T-LGL.<sup>2</sup> The diagnosis of RA is mostly made before the development of T-LGL.<sup>3</sup> Up to one third of cases with T-LGL have been shown to have coexistent RA, compared with the frequency of RA in the general population, which is 0.5% to 1%.<sup>4,5</sup> T-LGL is usually diagnosed in the 50s and 60s and involves males and females equally.<sup>1</sup> Felty's syndrome (FS) is defined by the triad of variable splenomegaly, low neutrophil count, and destructive arthritis and is usually seen in <1% of patients with RA. In a study, about one third of patients had coexistence of T-LGL and RA, while another study has reported 13 out of 48 cases with T-LGL had been diagnosed with primary Sjögren's syndrome.<sup>1,6</sup> The coexistence of T-LGL and systemic sclerosis has been reported in one case.<sup>7</sup>

## Case Presentation

A 54-year-old male presented to the emergency department for shortness of breath. His past medical history was remarkable for severe emphysema/chronic obstructive pulmonary disease, asbestos exposure, and erosive RA with positive rheumatoid factor (RF) and anti-CCP antibody. He was diagnosed with RA more than 20 years ago but has only been on steroids in the past, more so for his lung problems. He had never been on DMARDs (Disease Modifying Anti-Rheumatic Drugs) treatment and never followed with a rheumatologist. His medications included Spiriva inhaler, Ventolin inhaler, and prednisone 15 mg daily. Social history was remarkable for smoking 40 years of 1.5 PPD and quit 5 months before the presentation. Family history was remarkable for RA in his mother and aunt. He admitted shortness of breath, fever, night

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Received April 26, 2020. Revised May 26, 2020. Accepted May 30, 2020.

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sweat, and unintentional weight loss about 30 lbs over the past few months. Physical examination was significant for bilateral lungs wheezing on auscultation, bilateral swan neck deformity of digits, and Z deformity of bilateral thumbs. Joints range of motion was intact with no RA nodule or active synovitis. Laboratory findings were as follows: white blood cells 710/ $\mu$ L with 76% lymphocytes, 6.0% neutrophils, 16% monocytes, 1.0% eosinophils, and 1.0% basophils; hemoglobin 10.6 g/dL; platelet 160 000/ $\mu$ L; total bilirubin 0.9 mg/dL; alkaline phosphatase 68 U/L; alanine aminotransferase 18 U/L; aspartate aminotransferase 16 U/L; and serum albumin of 2.4 g/dL. C-reactive protein 3.4 mg/dL, antinuclear antibodies (ANA) was positive, RF was 3810.0 IU/mL, and anti-CCP antibody was 250 U/mL. Serum SSB/SSA, dsDNA, C3, and C4 were within the normal limit. Chest X ray showed pulmonary emphysema, bibasilar subsegmental scarring, and pleural effusion. Bilateral hand X-ray showed carpal periarticular osteopenia, carpal bone erosions, and swan-neck deformity of the bilateral fifth digits. A computed tomography scan of the abdomen revealed mild splenomegaly (14 cm). Hematology/oncology was consulted. Peripheral blood smear revealed numerous large granular lymphocytes. Bone marrow biopsy and aspiration were reported as insufficient for diagnosis. Immunophenotyping of bone marrow revealed an increased number of T-cell lymphocytes about 91% of cells analyzed with marked aberrant loss of CD5 and moderate loss of CD7. CD4:CD8 ratio was markedly decreased (0.23) with an abnormal increase in CD8 cells. NK cells were within normal limits. Approximately 40% of the T-cell lymphocytes express a marker profile consistent with T-LGL cell lineage (positive for CD3, CD57, and CD8; negative for CD25). Clonal rearrangement of the T-cell receptor gamma (TCRG) and beta (TCRB) genes detected by polymerase chain reaction consistent with the presence of a clonal T-cell population. These results were consistent with T-LGL. The patient was diagnosed with T-LGL and started on Cytoxan 100 mg PO (per os) daily. Methotrexate was avoided due to severe lung disease. In 1-year follow-up, leukocyte count was 7860/ $\mu$ L with neutrophils of 74%.<sup>9</sup>

## Discussion

About 50 years ago, Hovig et al reported an expansion of granulated lymphocytes population in a patient who had RA and neutropenia.<sup>8</sup> Subsequently in the 1970s, McKenna et al reported 4 patients who had a lymphoproliferative disease with granulated inclusions within the lymphocytes. With the introduction of monoclonal antibodies for lymphocyte-specific antigens in the 1980s, features of lymphocytes were further revealed in these patients.<sup>9</sup> In the 1980s, 3 patients including one with RA were reported by Loughran et al, who had neutropenia and chronic lymphocytosis of large granulated lymphocytes. Given the abnormal cells infiltration into

liver, spleen, and bone marrow, and also clonal cytogenetic abnormalities, the disorder was named large granular lymphocyte leukemia.<sup>10</sup>

Originally circulating large granulated lymphocytes count  $N < 2000/\mu$ L was defined for the diagnosis of T-LGL, but recent studies revealed that about 25% of cases who met the criteria of T-LGL had circulating large granulated lymphocytes count less than this threshold.<sup>11,12</sup> Diagnosis is made by detecting the expansion of circulating large granulated lymphocytes on peripheral blood smear; immunophenotype by flow cytometry, and detection of clonal T-cell by flow cytometry, southern blot, and polymerase chain reaction.<sup>1</sup> Neutropenia occurs in about 85% of T-LGL patients, but most of them will not become symptomatic. Constitutional symptoms such as weight loss, night sweat, and fever can be seen in about one third of these patients.<sup>13</sup>

Patients with RA may have a polyclonal expansion of large granulated lymphocytes, especially if FS develops. FS, first described in 1924, is a subtype of RA and characterized by low neutrophil count and splenomegaly in the setting of RA.<sup>14,15</sup> It has a late-onset during the course of RA and can occur in 1% of RA patients especially in patients with the severe clinical picture and extra-articular involvement such as rheumatoid nodule.<sup>14</sup> FS is frequently seen in association with T-LGL.<sup>10</sup> About 30% to 40% of patients with FS have been reported to have an expansion of large granulated lymphocytes in peripheral blood, which is detected by T-cell receptor rearrangements.<sup>16,17</sup> Clinical manifestations of FS imitates T-LGL patients with RA and neutropenia.<sup>18</sup> The clonality of cytotoxic T-cells will help distinguish between T-LGL and FS associated with large granulated lymphocytes expansion; monoclonality is seen in T-LGL, while FS has polyclonality. Regardless of this difference in clonality, FS and T-LGL are similar in terms of clinical manifestations, response to immunosuppressive therapy, and their smoldering course like other chronic inflammatory disorders.<sup>19</sup>

HLA-DR4 is present in almost all patients with FS similarly to patients with simultaneous RA and T-LGL but is not seen in patients with T-LGL without the presence of RA.<sup>20,21</sup> Some studies have shown the role of activation of signal transducer and activator of transcription 3 (STAT3) in the pathogenesis of some autoimmune disorders such as Crohn's disease and RA.<sup>22,23</sup> Recent studies have shown that 30% to 40% of T-LGL patients have somatic mutations of STAT3 in lymphocytes resulting in STAT3 activation.<sup>24,25</sup> T-LGL patients with STAT3 mutations have RA more frequently (43%) compared with T-LGL patients without STAT3 mutations (6%), which represents an association between STAT3 mutations and incidence of RA in patients with T-LGL. A cohort study on 14 patients with FS has shown the presence of STAT3 mutations in 43% of cases, which is comparable with the frequency of STAT3 mutations in T-LGL.<sup>25,26</sup> These immunogenetic findings propose that FS and T-LGL with RA might be different aspects of a single disease spectrum.

Patients with T-LGL without arthritis found to have circulating ANA, RF, anti-CCP antibodies that can be seen in T-LGL and RA.<sup>11,27</sup> Mechanisms that have been proposed to describe the cause of neutropenia in FS and T-LGL are as follows: (1) impaired maturation of myeloid lineage, (2) increased apoptosis of neutrophils, (3) neutrophil destruction due to antibodies, and (4) infiltration of leukemic cells in bone marrow results in myeloid lineage damage.<sup>13</sup>

## Conclusion

We reported a case with long-standing RA with erosive changes who had never been on appropriate treatment and was diagnosed with T-LGL. To our knowledge, no study has been conducted to compare the prevalence of T-LGL in patients with well-controlled versus poor-controlled RA, which might demonstrate the effect of proper treatment on the prevention of T-LGL.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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