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The spectrum of LGL and Felty's Syndrome

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Abstract

Purpose of review—Patients with chronic large granular lymphocyte (LGL) leukemia often have rheumatoid arthritis, neutropenia and splenomegaly, thereby resembling the manifestations observed in patients with Felty's syndrome (FS), which is a rare complication of rheumatoid arthritis (RA) characterized by neutropenia and splenomegaly. Both entities have similar clinical and laboratory presentation, as well as common genetic determinant HLA-DR4, indicating they may be part of the same disease spectrum. This review paper seeks to discuss the underlying pathogenesis and therapeutic algorithm of RA, neutropenia and splenomegaly in the spectrum of LGL leukemia and Felty's syndrome.

Recent findings—We hypothesize that there may be a common pathogenic mechanism between LGL leukemia and typical FS. Phenotypic and functional data have strongly suggested that CD3⁺ LGL leukemia are antigen-activated. Aberrations in the T cell repertoire with the emergence of oligoclonal/clonal lymphoid populations have been found to play a pivotal role in pathogenesis of rheumatoid arthritis. The biologic properties of the pivotal T cell involved in rheumatoid arthritis pathogenesis are remarkably similar to those in leukemic LGL.

Summary—RA-associated T-LGL leukemia and articular manifestations of typical Felty's syndrome are not distinguishable. A common pathogenetic link between LGL leukemia and RA is proposed.

Keywords

large granular lymphocyte leukemia; Felty's syndrome; autoimmune disease

Introduction

Large granular lymphocyte (LGL) leukemia is a clonal disease representing a spectrum of biologically distinct lymphoproliferative diseases originating either from mature CD3⁺ T cells or CD3[−] natural killer (NK) cells [1]. Both CD3⁺ and CD3[−] LGL function as cytotoxic lymphocytes. The 2008 World Health Classification of mature T- and NK- cell neoplasms continues to distinguish T-cell LGL leukemia (T-LGL leukemia) from aggressive NK-cell leukemia based on their unique molecular and clinical features [2]. Furthermore, a new provisional entity of chronic lymphoproliferative disorder of NK cells (also known as

chronic NK cell lymphocytosis or chronic NK-LGL leukemia) was created to distinguish it from much more aggressive NK-cell leukemia [2]. The T cell form of LGL leukemia was first described in 1985 as a clonal disorder including blood, marrow and spleen [3]. One of these initial patients had rheumatoid arthritis (RA) and indeed had been characterized previously as Felty's syndrome. Subsequently, rheumatoid arthritis was recognized as a characteristic finding of T cell LGL leukemia [4]. RA is only rarely associated with the NK type of LGL leukemia; consequently, this manuscript will focus on the T cell form of LGL leukemia. LGL leukemia is diagnosed in the clinical context of cytopenia, lymphocytosis, splenomegaly and autoimmune conditions such as RA. LGL leukemia patients show excess of LGL $>0.5 \times 10^9/L$ with $CD3^+CD8^+CD57^+$ immunophenotype. Furthermore, a main criterion for T-LGL leukemia is the detection of a clonal T-cell-receptor (TCR) rearrangement with a typical phenotype of $TCR\alpha\beta$.

First described in 1924, Felty's syndrome, a specific sub-category of RA featuring the co-occurrence of RA, neutropenia and splenomegaly [5], is frequently associated with LGL leukemia [6]. In fact, approximately 30–40% of FS patients have peripheral blood expansions of large granular lymphocytes [7]. The clinical presentation in FS patients closely resembles LGL leukemia patients with neutropenia and RA [6]. Importantly, patients with FS may have a clonal proliferation of LGLs characterized by TCR rearrangements [8]. Due to the prevalence of the immunogenic marker HLA-DR4 in both diseases [9–11], it has been suggested that Felty's syndrome and LGL leukemia with RA are part of a single disease process [12].

Rheumatoid arthritis in LGL leukemia and Felty's syndrome

Chronic LGL leukemia is known to be associated with a wide spectrum of autoimmune disorders. Rheumatoid arthritis (RA) is the most common autoimmune disease associated with LGL leukemia in the western world [12–14]. RA is mostly diagnosed prior to the onset of LGL leukemia [15•]. RA is present in 11 to 36% of patients with LGL leukemia [1,15•, 16], compared to its presence in 0.5–1% adult population worldwide [17]. Notably, Asian patients with LGL leukemia were around seven times less likely than Western patients to develop RA [18••]. Chronic activation by an exogenous antigen such as virus or endogenous autoantigen has been proposed as a possible initial trigger leading to an expansion of LGL [19]. It has also been suggested that T-cell LGL leukemia could represent an autoimmune disorder caused by chronic antigenic stimulation leading to extreme expansion of only one clone of $CD8^+$ cytotoxic T cells [20,21]. An association of T-cell LGL leukemia with several different autoimmune conditions supports this hypothesis. Interestingly, RA is a chronic inflammatory disease in which T cells play an essential role in joint destruction. As a rare extra-articular manifestation of RA, Felty's syndrome (FS) occurs in less than 1% of RA patients [22]. The mean duration of arthritis is ten to fifteen years prior to the onset of neutropenia and splenomegaly [23,23]. FS is clinically characterized by severe joint destruction contrasting with moderate or absent joint inflammation and severe extra-articular disease, including a high frequency of rheumatoid nodules, lymphadenopathy, hepatomegaly, vasculitis, leg ulcers, Sjögren's syndrome and pulmonary fibrosis [15,22]. Articular involvement is usually significantly more severe in patients with FS than in typical RA, with regard to the extent of synovitis and clinical and radiographic deformity [22].

Neutropenia in LGL leukemia and Felty's syndrome

Neutropenia is the most common finding in LGL leukemia, occurring in 70–80% patients [1,24]. Neutropenia-induced infections are indications for seeking medical attention in patients with LGL leukemia and FS. Interestingly, neutropenia is less prevalent in Asian LGL leukemia patients; instead, pure red cell aplasia (PRCA), which is caused by cytotoxic activity of leukemic LGL against erythroid progenitors in marrow [25], is most common complication in Asian LGL leukemia patients [18••]. These findings suggested that differential genetic backgrounds and immune insults might render differential susceptibilities towards clinical manifestations in LGL leukemia [18••].

Neutropenia in LGL leukemia may be caused by survival (enhanced neutrophil destruction) and proliferation defects (deregulated neutrophils production), which can be mediated by humoral and cell-mediated mechanisms respectively [26,27•]. Neutrophil production defects do not appear to be prominent in LGL leukemia and FS based on the observations of mild hypercellularity with left-shifted myeloid maturation in marrow [28,29]. Production of immune complexes can result in decreased neutrophil survival, as can production of soluble Fas ligand [30,31]. These humoral and cell-mediated pathways induce granulocytic apoptosis through independent intracellular mechanisms that are not mutually exclusive and may be observed concurrently in individual patients with either LGL leukemia or FS. Indeed, immunosuppression is often effective in alleviating neutropenia, in patients with LGL leukemia and FS [1,15•], giving insight into the nature of aberrant immune response in these two entities contributing to the pathogenesis of neutropenia. Clinical response in LGL leukemia is often associated with reduction in levels of circulating Fas ligand [31].

Splenomegaly in LGL leukemia and Felty's syndrome

Mild to moderate splenomegaly is seen in 20%–60% LGL leukemia patients [30,32]. Diffuse infiltration of red splenic pulp by leukemic LGL with frequent presence of reactive germinal centers are characteristic findings in T-cell LGL leukemia [33]. Splenomegaly is also a diagnostic hallmark of FS, ranging from mild to massive on imaging [22]. The structural basis for splenomegaly in FS is predominantly an increase in the red pulp, with associated sinus hyperplasia and an increased macrophage population [34]. Notably, the degree of splenomegaly bears no relationship to the degree of hematological abnormalities including neutropenia in both entities [1,35].

Pathogenesis of LGL leukemia and Felty's syndrome

Aberrations in the T cell repertoire with the emergence of oligoclonal/clonal lymphoid populations have been found to play a pivotal role in pathogenesis of both LGL leukemia and rheumatoid arthritis [20,36]. There are remarkable phenotypic and functional similarities noted when comparing findings seen in leukemic LGL to those observed in the clonally expanded lymphoid subset in RA. A minor difference is that LGL from patients with RA usually co-express CD3 and CD8, whereas co-expression of CD4 and CD8 in LGL leukemia is less common. A major difference appears to be that there is a dominant clone detected in LGL leukemia as manifested by markedly increase numbers of LGL in the periphery whereas the clonal size of individual T cell clones observed in typical RA is small.

Importantly, LGL leukemia and RA with LGL expansion share the following features in common: 1. Clonal expansion of unusual T cells of an effector and/or memory-effector phenotype, being CD3+, CD28–, CD57+ [37–39]. 2. Expression of inhibitory and activating NK receptors on LGL [40,41]. 3. Constitutive overexpression of cytotoxic effector molecules, such as perforin, soluble granzymes, and Fas ligand [42–44]. 4. Constitutive production of proinflammatory chemokines such as RANTES, MIP-1 α , MIP-1 β and IL-8 [45,46]. 5. Dysregulated apoptosis characterized by high levels of both Fas receptor and Fas ligand on LGL but resistance to Fas-mediated death [47,48].

Patients with T-LGL leukemia or RA can exhibit substantial expansion of CD8+ T cells. These CD8+ T cells can display oligoclonality in the peripheral blood and synovial fluid of RA patients [49–52]. The antigen driving the expansion of these CD8+ clones in RA is not known. Using tetramer staining, one study demonstrated EBV-specific CD8+ T cells in synovial fluid from RA patients. However, these findings were not restricted to RA as there was also an enrichment of these cells in synovial fluid from patients with osteoarthritis and psoriatic arthritis [53].

Many lines of evidence suggest that clonal expansion of leukemic LGL may be antigen-driven, perhaps as result of as yet unknown viral antigen [54–59]. Serologic findings in LGL leukemia patients are suggestive of infection with members of the HTLV (Human T-lymphotropic virus Type I)/BLV (Bovine leukemia virus) genus of retroviruses. 21% of LGL leukemia sera are reactive in a HTLV-I ELISA compared to 0.17% of normal blood donors [59]. In Western blot testing against HTLV-I viral lysate, LGL leukemia sera show a similar cross reactivity pattern as seen when testing HTLV-II or BLV positive sera, i.e., reactivity to gag p24 and env p21e [39]. Similar antibody reactivity to the env p21e has been observed in sera from patients with typical rheumatoid arthritis [60]. Further work has shown that this p21e reactivity is directed at a 34 amino acid fragment designated BA21 [54,61]. These results raise the possibility that exposure to a protein with homology to BA21 may be a common inciting stimulus in both LGL leukemia and typical rheumatoid arthritis. Collectively, the biologic features of the LGL expansion involved in rheumatoid arthritis pathogenesis are remarkably similar to those for leukemic LGL.

Treatment of LGL leukemia and Felty's syndrome

The majority of patients with LGL leukemia have a clinically indolent course with a median survival time over 10 years. The most common indications for therapy include recurrent infections due to severe neutropenia, anemia, or less frequently, symptomatic splenomegaly and severe B symptoms [15,32]. Systemic immunosuppressive treatment is considered to be the most appropriate form of treatment for both LGL leukemia and FS. First-line, single-agent therapy with low-dose methotrexate (10 mg/m² per week), cyclophosphamide (50–100mg orally daily), and cyclosporine A (5–10 mg/kg per day) can control symptoms and cytopenias in approximately 50%–60% of LGL leukemia patients [15,62–64], but this approach is not curative. Neutropenia of FS can be effectively treated with disease-modifying anti-rheumatic drugs (DMARDs), the widest experience being with methotrexate (MTX) [65]. Low dose oral pulse therapy of MTX results in improvement in most FS patients [66,67]. It is recommended that 4 months of treatment be given before a decision is

made to change to an alternative agent because of no response [15•]. Responders usually require indefinite therapy to prevent relapses. Therapy with low-dose methotrexate can control both LGL leukemia and rheumatoid arthritis [15•,62]. Cyclosporine A is sometimes used as an initial therapy; however, toxicities of long-term treatment are usually greater than the side effects of methotrexate or cyclophosphamide. Upon achieving best response, the dose of cyclosporine A should be tapered down to obtain the lowest effective maintenance dose [68]. Corticosteroids as monotherapy appear less effective than methotrexate, cyclosporine A or cyclophosphamide. However, in combination with other immunosuppressants, steroids may improve B symptoms and hematologic features more quickly [15•,32]. Hematopoietic growth factors (G-CSF, GM-CSF) have also been used successfully as first-line monotherapy for neutropenia or as a supportive treatment together with immunosuppressive therapy [69,70]. It is noteworthy that correction of cytopenias with cyclosporine therapy may be achieved without reduction of the clone [68]. Complete normalization of the neutrophil count is not necessary for significant clinical improvement [15•].

Patients with LGL leukemia who fail first-line therapy may benefit from second-line therapy with nucleoside analogues, including fludarabine, 2'-deoxycoformycine, and 2-chloroxyadenosine [71]. The frequent expression of CD52 on malignant LGL supports the potential efficacy of utilization of targeted therapy with a humanized anti-CD52 antibody (alemtuzumab) in T-LGL leukemia patients [72]. Recently, there has been a growing interest in the biologic agent rituximab in the treatment of FS [73–75]. Rituximab, a monoclonal antibody specific for human CD20, which recognizes and depletes CD20⁺ B lymphocytes, led to a sustained neutrophil response and marked symptomatic improvement as evidenced by decreased size of rheumatoid nodules and better pain control, in a subset of FS patients [73–75].

Splenectomy has been used for therapy of both LGL leukemia and FS and has been beneficial for some patients in both entities. Splenectomy can have a favorable impact on refractory and symptomatic cytopenias in patients with LGL leukemia [76,77], and can result in an immediate improvement of neutropenia in 80% of the FS patients, with decrease infection rate [65]. Splenectomy can also relieve the gastrointestinal-related symptoms of nausea, early satiety and pain related to splenomegaly [76]. However, the procedure is not curative.

Response to treatment in LGL leukemia must be determined by periodic clinical and blood count assessments [15•]. The primary response criteria are defined using blood count results four months after starting therapy. Hematological complete response (CR) is defined as the complete normalization of blood counts (hemoglobin >12g/dL, platelets >150×10⁹/L, absolute neutrophil count >1.5×10⁹/L, and lymphocytosis <4×10⁹/L), and circulating LGL in the normal range (0.25×10⁹/L) [15•]. Complete molecular remission is determined by the disappearance of T cell clone [15•].

Conclusion

We initially described LGL leukemia as a clonal disorder characterized by tissue invasion of LGL in marrow, spleen, and liver. Such patients often have chronic neutropenia and splenomegaly, thus meeting clinical criteria for Felty's syndrome. We hypothesize that Felty's syndrome and LGL/rheumatoid arthritis are the same disease. Multiple lines of evidence including clinical presentation, immunologic, pathologic, and genetic data support this contention. The clinical features of rheumatoid arthritis occurring in LGL leukemia patients cannot be distinguished from the clinical features of typical rheumatoid arthritis. A similar effective clinical response to low dose oral methotrexate in LGL leukemia patients and Felty's syndrome patients also suggests a common pathogenesis. Pathologic findings in splenectomy specimens are also similar with prominent reactive germinal follicles frequently observed in both conditions. Almost all patients with Felty's syndrome have inherited a DR4 haplotype, and 90% of patients with LGL/rheumatoid arthritis also have this genetic background. These immunogenetic findings lend further credence to the idea that LGL leukemia with rheumatoid arthritis and Felty's syndrome are part of the same disease process.

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References

Papers of particular interest, published with the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

1. Sokol L, Loughran TP Jr. Large Granular lymphocyte leukemia. *Oncologist*. 2006; 11:263–273. [PubMed: 16549811]
2. Lim MS, de Leval L, Quintanilla-Martinez L. Commentary on the 2008 WHO classification of mature T- and NK-cell neoplasms. *J Hematop*. 2009; 2:75–76. [PubMed: 19684869]
3. Loughran TP Jr, Kadin ME, Starkebaum G, Abkowitz JL, Clark EA, Distech C, Lum LG, Slichter SJ. Leukemia of large granular lymphocytes: association with clonal chromosomal abnormalities and autoimmune neutropenia, thrombocytopenia, and hemolytic anemia. *Ann Intern Med*. 1985; 102:169–175. [PubMed: 3966754]
4. Wallis WJ, Loughran TP Jr, Kadin ME, Clark EA, Starkebaum GA. Polyarthritis and neutropenia associated with circulating large granular lymphocytes. *Ann Intern Med*. 1985; 103:357–362. [PubMed: 4026084]
5. Felty A. Chronic arthritis in the adult, associated with splenomegaly and leukopenia. *Bull Johns Hopkins Hosp*. 1924; 35:16.
6. Burks EJ, Loughran TP Jr. Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty syndrome. *Blood Rev*. 2006; 20:245–266. [PubMed: 16530306]
7. Bowman SJ, Bhavnani M, Geddes GC, Corrigan V, Boylston AW, Panayi GS, Lanchbury JS. Large granular lymphocyte expansions in patients with Felty's syndrome: analysis using anti-T cell receptor V beta-specific monoclonal antibodies. *Clin Exp Immunol*. 1995; 101:18–24. [PubMed: 7621587]

8. Loughran TP Jr, Starkebaum G, Kidd P, Neiman P. Clonal proliferation of large granular lymphocytes in rheumatoid arthritis. *Arthritis Rheum.* 1988; 31:31–36. [PubMed: 3345230]
9. Lanchbury JS, Jaeger EE, Sansom DM, Hall MA, Wordsworth P, Stedeford J, Bell JI, Panayi GS. Strong primary selection for the Dw4 subtype of DR4 accounts for the HLA-DQw7 association with Felty's syndrome. *Hum Immunol.* 1991; 32:56–64. [PubMed: 1685490]
10. Bowman SJ, Sivakumaran M, Snowden N, Bhavnani M, Hall MA, Panayi GS, Lanchbury JS. The large granular lymphocyte syndrome with rheumatoid arthritis. Immunogenetic evidence for a broader definition of Felty's syndrome. *Arthritis Rheum.* 1994; 37:1326–1330. [PubMed: 7945496]
11. Starkebaum G, Loughran TP Jr, Gaur LK, Davis P, Nepom BS. Immunogenetic similarities between patients with Felty's syndrome and those with clonal expansions of large granular lymphocytes in rheumatoid arthritis. *Arthritis Rheum.* 1997; 40:624–626. [PubMed: 9125243]
12. Starkebaum G. Leukemia of large granular lymphocytes and rheumatoid arthritis. *Am J Med.* 2000; 108:744–745. [PubMed: 10924655]
13. Samanta A, Grant I, Nichol FE, Pringle JH, Wood JK, Campbell AC. Large granular lymphocytosis associated with rheumatoid arthritis. *Ann Rheum Dis.* 1988; 47:873–875. [PubMed: 2848461]
14. Loughran TP Jr, Starkebaum G. Large granular lymphocyte leukemia. Report of 38 cases and review of the literature. *Medicine (Baltimore).* 1987; 66:397–405. [PubMed: 3626848]
15. Lamy T, Loughran TP Jr. How we treat LGL leukemia. *Blood.* 2010 *ePub*. This article describes the update on how authors diagnose and treat LGL leukemia.
16. Loughran TP Jr. Clonal diseases of large granular lymphocytes. *Blood.* 1993; 82:1–14. [PubMed: 8324214]
17. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature.* 2003; 423:356–361. [PubMed: 12748655]
18. Kwong YL, Au WY, Leung AY, Tse EW. T-cell large granular lymphocyte leukemia: an Asian perspective. *Ann Hematol.* 2010; 89:331–339. [PubMed: 20084380] This article reports that Asian LGL leukemia patients are more frequent to have rheumatoid arthritis but less frequent to have neutropenia than Western patients.
19. Epling-Burnette PK, Loughran TP Jr. Survival signals in leukemic large granular lymphocytes. *Semin Hematol.* 2003; 40:213–220. [PubMed: 12876670]
20. O'Keefe CL, Plasilova M, Wlodarski M, Risitano AM, Rodriguez AR, Howe E, Young NS, Hsi E, Maciejewski JP. Molecular analysis of TCR clonotypes in LGL: a clonal model for polyclonal responses. *J Immunol.* 2004; 172:1960–1969. [PubMed: 14734782]
21. Wlodarski MW, O'Keefe C, Howe EC, Risitano AM, Rodriguez A, Warshawsky I, Loughran TP Jr, Maciejewski JP. Pathologic clonal cytotoxic T-cell responses: nonrandom nature of the T-cell-receptor restriction in large granular lymphocyte leukemia. *Blood.* 2005; 106:2769–2780. [PubMed: 15914562]
22. Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndromes. *Semin Arthritis Rheum.* 1991; 21:129–142. [PubMed: 1788550]
23. Goldberg J, Pinals RS. Felty syndrome. *Semin Arthritis Rheum.* 1980; 10:52–65. [PubMed: 7414334]
24. Rose MG, Berliner N. T-cell large granular lymphocyte leukemia and related disorders. *Oncologist.* 2004; 9:247–258. [PubMed: 15169980]
25. Mori KL, Furukawa H, Hayashi K, Sugimoto KJ, Oshimi K. Pure red cell aplasia associated with expansion of CD3+ CD8+ granular lymphocytes expressing cytotoxicity against HLA-E+ cells. *Br J Haematol.* 2003; 123:147–153. [PubMed: 14510958]
26. Breedveld FC, Lafeber GJ, de Vries E, van Krieken JH, Cats A. Immune complexes and the pathogenesis of neutropenia in Felty's syndrome. *Ann Rheum Dis.* 1986; 45:696–702. [PubMed: 3740999]
27. Zhang R, Shah MV, Loughran TP Jr. The root of many evils: indolent large granular lymphocyte leukaemia and associated disorders. *Hematol Oncol.* 2010; 28:105–117. [PubMed: 19645074] The article discusses T-LGL leukemia has significant overlap with other autoimmune diseases and hematological disorders.

28. Berliner N, Horwitz M, Loughran TP Jr. Congenital and acquired neutropenia. *Hematology Am Soc Hematol Educ Program*. 2004;63–79. [PubMed: 15561677]
29. Morice WG, Kurtin PJ, Tefferi A, Hanson CA. Distinct bone marrow findings in T-cell granular lymphocytic leukemia revealed by paraffin section immunoperoxidase stains for CD8, TIA-1, and granzyme B. *Blood*. 2002; 99:268–274. [PubMed: 11756181]
30. Lamy T, Loughran TP Jr. Current concepts: large granular lymphocyte leukemia. *Blood Rev*. 1999; 13:230–240. [PubMed: 10741898]
31. Liu JH, Wei S, Lamy T, Epling-Burnette PK, Starkebaum G, Djeu JY, Loughran TP. Chronic neutropenia mediated by fas ligand. *Blood*. 2000; 95:3219–3222. [PubMed: 10807792]
32. Lamy T, Loughran TP Jr. Clinical features of large granular lymphocyte leukemia. *Semin Hematol*. 2003; 40:185–195. [PubMed: 12876667]
33. Osuji N, Matutes E, Catovsky D, Lampert I, Wotherspoon A. Histopathology of the spleen in T-cell large granular lymphocyte leukemia and T-cell prolymphocytic leukemia: a comparative review. *Am J Surg Pathol*. 2005; 29:935–941. [PubMed: 15958859]
34. van Krieken JH, Breedveld FC, te Velde J. The spleen in Felty's syndrome: a histological, morphometrical, and immunohistochemical study. *Eur J Haematol*. 1988; 40:58–64. [PubMed: 3277856]
35. Fishman D, Isenberg DA. Splenic involvement in rheumatic diseases. *Semin Arthritis Rheum*. 1997; 27:141–155. [PubMed: 9431585]
36. Bowman SJ, Hall MA, Panayi GS, Lanchbury JS. T cell receptor alpha-chain and beta-chain junctional region homology in clonal CD3+, CD8+ T lymphocyte expansions in Felty's syndrome. *Arthritis Rheum*. 1997; 40:615–623. [PubMed: 9125242]
37. Vallejo AN, Schirmer M, Weyand CM, Goronzy JJ. Clonality and longevity of CD4+CD28null T cells are associated with defects in apoptotic pathways. *J Immunol*. 2000; 165:6301–6307. [PubMed: 11086066]
38. Schirmer M, Vallejo AN, Weyand CM, Goronzy JJ. Resistance to apoptosis and elevated expression of Bcl-2 in clonally expanded CD4+CD28– T cells from rheumatoid arthritis patients. *J Immunol*. 1998; 161:1018–1025. [PubMed: 9670983]
39. Melenhorst JJ, Brummendorf TH, Kirby M, Lansdorp PM, Barrett AJ. CD8+ T cells in large granular lymphocyte leukemia are not defective in activation- and replication-related apoptosis. *Leuk Res*. 2001; 25:699–708. [PubMed: 11397476]
40. Bigouret V, Hoffmann T, Arlettaz L, Villard J, Colonna M, Ticheli A, Gratwohl A, Sami K, Chapuis B, Rufer N, et al. Monoclonal T-cell expansions in asymptomatic individuals and in patients with large granular leukemia consist of cytotoxic effector T cells expressing the activating CD94:NKG2C/E and NKD2D killer cell receptors. *Blood*. 2003; 101:3198–3204. [PubMed: 12480700]
41. Namekawa T, Snyder MR, Yen JH, Goehring BE, Leibson PJ, Weyand CM, Goronzy JJ. Killer cell activating receptors function as costimulatory molecules on CD4+CD28null T cells clonally expanded in rheumatoid arthritis. *J Immunol*. 2000; 165:1138–1145. [PubMed: 10878393]
42. Perzova R, Loughran TP Jr. Constitutive expression of Fas ligand in large granular lymphocyte leukaemia. *Br J Haematol*. 1997; 97:123–126. [PubMed: 9136951]
43. Oshimi K, Shinkai Y, Okumura K, Oshimi Y, Mizoguchi H. Perforin gene expression in granular lymphocyte proliferative disorders. *Blood*. 1990; 75:704–708. [PubMed: 2297572]
44. Gulan G, Ravlic-Gulan J, Strbo N, Sotosek V, Nemec B, Matovinovic D, Rubinic D, Podack ER, Rukavina D. Systemic and local expression of perforin in lymphocyte subsets in acute and chronic rheumatoid arthritis. *J Rheumatol*. 2003; 30:660–670. [PubMed: 12672182]
45. Kothapalli R, Nyland SB, Kusmartseva I, Bailey RD, McKeown TM, Loughran TP Jr. Constitutive production of proinflammatory cytokines RANTES, MIP-1 β and IL-18 characterizes LGL leukemia. *Int J Oncol*. 2005; 26:529–535. [PubMed: 15645140]
46. Lisignoli G, Toneguzzi S, Grassi F, Piacentini A, Tschon M, Cristino S, Gualtieri G, Facchini A. Different chemokines are expressed in human arthritic bone biopsies: IFN-gamma and IL-6 differently modulate IL-8, MCP-1 and rantes production by arthritic osteoblasts. *Cytokine*. 2002; 20:231–238. [PubMed: 12550108]

47. Lamy T, Liu JH, Landowski TH, Dalton WS, Loughran TP Jr. Dystregulation of CD95/CD95 ligand-apoptotic pathway in CD3(+) large granular lymphocyte leukemia. *Blood*. 1998; 92:4771–4777. [PubMed: 9845544]
49. Fitzgerald JE, Ricalton NS, Meyer AC, West SG, Kaplan H, Behrendt C, Kotzin BL. Analysis of clonal CD8+ T cell expansions in normal individuals and patients with rheumatoid arthritis. *J Immunol*. 1995; 154:3538–3547. [PubMed: 7897233]
50. Wang EC, Lawson TM, Vedhara K, Moss PA, Lehner PJ, Borysiewicz LK. CD8high+(CD57+) T cells in patients with rheumatoid arthritis. *Arthritis Rheum*. 1997; 40:237–248. [PubMed: 9041935]
51. Masuko-hongo K, Sekine T, Ueda S, Kobata T, Yamamoto K, Nishioka K, Kato T. Long-term persistent accumulation of CD8+ T cells in synovial fluid of rheumatoid arthritis. *Ann Rheum Dis*. 1997; 56:613–621. [PubMed: 9389223]
52. Kang YM, Zhang X, Wagner UG, Yang H, Beckenbaugh RD, Kurin PJ, Goronzy JJ, Weyand CM. CD8 T cells are required for the formation of ectopic germinal centers in rheumatoid synovitis. *J Exp Med*. 2002; 195:1325–1336. [PubMed: 12021312]
53. Tan LC, Mowat AG, Fazou C, Rostron T, Roskell H, Dunbar PPR, Tournay C, Romagne F, Peyrat MA, Houssaint, et al. Specificity of T cells in synovial fluid: high frequencies of CD8(+) T cells that are specific for certain viral epitopes. *Arthritis Res*. 2000; 2:154–164. [PubMed: 11062606]
54. Loughran TP Jr, Hadlock KG, Perzova R, Gentile TC, Yang Q, Fong SK, Poiesz BJ. Epitope mapping of HTLV envelope seroreactivity in LGL leukaemia. *Br J Haematol*. 1998; 101:318–324. [PubMed: 9609528]
55. Loughran TP Jr, Coyle T, Sherman MP, Starkebaum G, Ehrlich GD, Ruscetti FW, Poiesz BJ. Detection of human T-cell leukemia/lymphoma virus, type II, in a patient with large granular lymphocyte leukemia. *Blood*. 1992; 80:1116–1119. [PubMed: 1355373]
56. Pandolfi F, Shriver K, Scarselli E, Fiorelli V, Semenzato G, Zambello R, Chisesi T, de Rossi G, Strong DM. HTLV-I antibodies and lymphoproliferative disease of granular lymphocytes. *Lancet*. 1987; 2:1527. [PubMed: 2892087]
57. Starkebaum G, Loughran TP Jr, Kalyanaraman VS, Kadin ME, Kidd PG, Singer JW, Ruscetti FW. Serum reactivity to human T-cell leukaemia/lymphoma virus type I proteins in patients with large granular lymphocytic leukaemia. *Lancet*. 1987; 1:596–599. [PubMed: 2881134]
58. Levitt LJ, Reyes GR, Moonka DK, Bensch K, Miller RA, Engleman EG. Human T cell leukemia virus-I-associated T-suppressor cell inhibition of erythropoiesis in a patient with pure red cell aplasia and chronic T gamma-lymphoproliferative disease. *J Clin Invest*. 1988; 81:538–548. [PubMed: 2892860]
59. Loughran TP Jr, Sherman MP, Ruscetti FW, Frey S, Coyle T, Montagna RA, Jones B, Starkebaum G, Poiesz BJ. Prototypical HTLV-I/II infection is rare in LGL leukemia. *Leuk Res*. 1994; 18:423–429. [PubMed: 8207960]
60. Starkebaum G, Shasteen NM, Fleming-Jones RM, Loughran TP Jr, Mannik M. Sera of patients with rheumatoid arthritis contain antibodies to recombinant human T-lymphotrophic virus type I/II envelope glycoprotein p21. *Clin Immunol Immunopathol*. 1996; 79:182–188. [PubMed: 8620624]
61. Sokol L, Agrawal D, Loughran TP Jr. Characterization of HTLV envelope seroreactivity in large granular lymphocyte leukemia. *Leuk Res*. 2005; 29:381–387. [PubMed: 15725471]
62. Loughran TP Jr, Kidd PG, Starkebaum G. Treatment of large granular lymphocyte leukemia with oral low-dose methotrexate. *Blood*. 1994; 84:2164–2170. [PubMed: 7919331]
63. Battiwalla M, Melenhorst J, Sauntharajah Y, Nakamura R, Molldrem J, Young NS, Barrett AJ. HLA-DR4 predicts haematological response to cyclosporine in T-large granular lymphocyte lymphoproliferative disorders. *Br J Haematol*. 2003; 123:449–453. [PubMed: 14617004]
64. Matrai Z, Lelkes G, Milosevits J, Paldine HP, Pecze K. T-cell large granular lymphocytic leukemia associated with pure red cell aplasia, successfully treated with cyclophosphamide. *Orv Hetil*. 1997; 138:2075–2080. [PubMed: 9304100]
65. Balint GP, Balint PV. Felty's syndrome. *Best Pract Res Clin Rheumatol*. 2004; 18:631–645. [PubMed: 15454123]
66. Tan N, Grisanti MW, Grisanti JM. Oral methotrexate in the treatment of Felty's syndrome. *J Rheumatol*. 1993; 20:599–601. [PubMed: 8478888]

67. Wassenberg S, Herborn G, Rau R. Methotrexate treatment in Felty's syndrome. *Br J Rheumatol*. 1998; 37:908–911. [PubMed: 9734684]
68. Sood R, Stewart CC, Aplan PD, Murai Hk Ward P, Barcos M, Baer MR. Neutropenia associated with T-cell large granular lymphocyte leukemia: long-term response to cyclosporine therapy despite persistence of abnormal cells. *Blood*. 1998; 91:3372–3378. [PubMed: 9558395]
69. Lamy T, LePrise PY, Amiot L, Drenou B, Fauchet R, Genetet N, Semana G. Response to granulocyte-macrophage colony-stimulating factor (GM-CSF) but not to G-CSF in a case of agranulocytosis associated with large granular lymphocyte (LGL) leukemia. *Blood*. 1995; 85:3352–3353. [PubMed: 7538825]
70. Weide R, Heymanns J, Koppler H, Tiemann M, Huss B, Pfluger KH, Havemann K. Successful treatment of neutropenia in T-LGL leukemia (T gamma-lymphocytosis) with granulocyte colony-stimulating factor. *Ann Hematol*. 1994; 69:117–119. [PubMed: 7522057]
71. Sternberg A, Eagleton H, Pillai N, Leyden K, Turner S, Pearson D, Littlewood T, Hatton C. Neutropenia and anaemia associated with T-cell large granular lymphocyte leukaemia responds to fludarabine with minimal toxicity. *Br J Haematol*. 2003; 120:699–701. [PubMed: 12588360]
72. Osuji N, Del Giudice I, Matutes E, Morilla A, Owusu-Ankomah K, Morilla R, Dunlop A, Catovsky D. CD52 expression in T-cell large granular lymphocyte leukemia--implications for treatment with alemtuzumab. *Leuk Lymphoma*. 2005; 46:723–727. [PubMed: 16019510]
73. Lekharaju V, Chattopadhyay C. Efficacy of rituximab in Felty's syndrome. *Ann Rheum Dis*. 2008; 67:1352. [PubMed: 18697782]
74. Weinreb N, Rabinowitz A, Dellaripa PF. Beneficial response to rituximab in refractory Felty Syndrome. *J Clin Rheumatol*. 2006; 12:48. [PubMed: 16484886]
75. Chandra PA, Margulis Y, Schiff C. Rituximab is useful in the treatment of Felty's syndrome. *Am J Ther*. 2008; 15:321–322. [PubMed: 18645332]
76. Subbiah V, Viny AD, Rosenblatt S, Pohlman B, Lichtin A, Maciejewski JP. Outcomes of splenectomy in T-cell large granular lymphocyte leukemia with splenomegaly and cytopenia. *Exp Hematol*. 2008; 36:1078–1083. [PubMed: 18550263]
77. Gentile TC, Loughran TP Jr. Resolution of autoimmune hemolytic anemia following splenectomy in CD3+ large granular lymphocyte leukemia. *Leuk Lymphoma*. 1996; 23:405–408. [PubMed: 9031124]

Key points

- LGL leukemia/rheumatoid arthritis and Felty's syndrome are part of the same disease.
- LGL leukemia/rheumatoid arthritis and Felty's syndrome share similarity in clinical presentation, immunologic, pathologic, and genetic features.
- Low dose of immunosuppressive treatment is effective in both patients with LGL leukemia and Felty's syndrome.