
Chronic Neutropenia Associated With Autoimmune Disease

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Chronic neutropenia with autoimmune diseases is associated mainly with rheumatoid arthritis (RA), as Felty's syndrome or large granular lymphocyte (LGL) leukemia, and with systemic lupus erythematosus (SLE). Recent advances have allowed better understanding regarding the mechanism of neutropenia and improved options for treatment. Target antigens for antineutrophil antibodies have been identified for both Felty's syndrome and for SLE. The role of soluble Fas-ligand (FasL) in inducing apoptosis of neutrophils has been clarified for LGL leukemia and increased neutrophil apoptosis has been described in neutropenic patients with SLE. The role of immune complexes in affecting neutrophil traffic and function continues to be studied. Treatments of neutropenia have included methotrexate, cyclosporine A, and granulocyte colony-stimulating factor (G-CSF) as well as granulocyte-macrophage colony-stimulating factor (GM-CSF). The efficacy of both GM- and G-CSF in reversing neutropenia and decreasing the risk of infections in Felty's syndrome and SLE has been well documented. Of concern, however, have been flares of symptoms or development of leukocytoclastic vasculitis in some patients following the use of these cytokines. Recent results suggest that in these patients G-CSF should be administered at the lowest dose effective at elevating the neutrophil count above 1,000/ μ L.

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CHRONIC NEUTROPENIA with autoimmune diseases is associated mainly with rheumatoid arthritis (RA), as Felty's syndrome or large granular lymphocyte (LGL) leukemia, and with systemic lupus erythematosus (SLE). Recent advances have allowed better understanding regarding the mechanism of neutropenia and the target autoantigens in these disorders and have improved treatment. More aggressive early treatment of RA may result in a decreased incidence of Felty's syndrome. Treating the patient who develops severe neutropenia often requires close collaboration between the rheumatologist and hematologist for optimum results.

Chronic Neutropenia in RA

As originally described by Felty, patients had chronic leukopenia with arthritis and splenomegaly.¹⁹ Several refinements to the original description include the designation of RA as the associated form of arthritis, recognition of neutropenia as the principal cytopenia, and the finding that neutropenic RA patients with and without splenomegaly were indistinguishable, indicating that splenomegaly should not be considered an essential feature of this disorder.¹⁰ Finally, patients with clonal expansions of T-cell LGL with chronic neutropenia frequently have RA.³⁸ Similar to Felty's syndrome, nearly 90% of RA patients with the LGL syndrome are HLA-DR4-positive.^{6,51} The similar findings for immunogenetic background, clinical features, and response to treatment (see below) of both disorders suggest that Felty's syndrome and LGL leukemia plus RA are parts of a single disease process.⁶

Clinical Features

Patients who develop Felty's syndrome often have severe, long-standing RA, with nodules, ulcers, splenomegaly, and hyperpigmentation of lower extremities; they may also develop vasculitis, neuropathy, pulmonary fibrosis, hepatomegaly, and Sjögren's syndrome. Synovitis may not be active, perhaps reflecting the neutropenia.

Patients with Felty's syndrome tend to have high levels of rheumatoid factor, immune complexes, shown by elevated C1q binding, and hypergammaglobulinemia and antinuclear antibodies (ANAs). The neutrophil count is generally less than 1,500/ μ L; mild anemia, thrombocytopenia, and modest lymphopenia with decreased CD4 counts are also seen. The marrow is typically normo- to hypercellular.

The mortality rate in patients with Felty's syndrome is increased due to recurrent pyogenic infections or overwhelming sepsis. The risk of infection is particularly increased when the neutrophil count is less than 200/ μ L,⁷ but may also reflect functional abnormalities of the circulating neutrophils. The risk

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of developing non-Hodgkin lymphoma is increased 12-fold in men with Felty's syndrome.²⁵

The Pathogenesis of Neutropenia in Felty's Syndrome

Both humoral and cellular immune mechanisms operate,⁵³ with disordered granulopoiesis as well as increased margination and peripheral destruction. Immune complexes or antibodies to neutrophil antigens are thought to be responsible for the neutropenia in Felty's syndrome.^{8,24} Sera of patients with Felty's syndrome have elevated levels of immune complexes, and circulating neutrophils from most patients show increased cell-bound IgG, due mainly to immune complexes but also containing antineutrophil antibodies.⁵⁰ Infusing immune complexes into the circulation of animals or even patients induces neutropenia.⁸ Such cell-bound immune complexes may cause functional disturbances of neutrophils¹⁵ or increase adherence of neutrophils to endothelial cells.²⁸ Immune complexes also affect neutrophil apoptosis, an effect dependent on the nature of the immune complexes. Precipitating immune complexes increase apoptosis whereas soluble immune complexes reduce it.²² Activation of neutrophils occurs with both types of immune complexes, but is greater with precipitating immune complexes.^{22,54} The ability of activated complement, particularly C5a, to induce neutropenia, has been recognized for many years.¹² These results suggest that immune complexes in Felty's syndrome and SLE can induce neutropenia and functional disorders of neutrophils.

Recently, a target antigen of antineutrophil antibodies in a patient with Felty's syndrome was identified. An antibody phage display library followed by an antigen expression library was used to isolate a neutrophil-reactive monoclonal antibody, ANA15, and subsequently to identify the target antigen. The investigators probed a λ gt11 expression library from a myeloid cell line and identified the eukaryotic elongation factor 1A-1 (eEF1A-1) as a novel autoantigen. Screening of a large panel of sera revealed that 66% of patients with Felty's syndrome had elevated levels of anti-eEF1A-1 antibodies whereas none of 22 healthy donor sera and 23% of sera from uncomplicated RA patients had low levels of the antibody. Translocation of the antigen from the nucleus to the cell surface of neutrophils during induced apoptosis of the cells occurred *in vitro*, suggesting how this autoantibody could bind to the cell surface of neutrophils. Further study of this antibody-antigen pair should permit evaluation of pathogenicity resulting from the interaction and its significance in neutropenia.¹⁷

A subset of antibodies to endothelial cells from SLE patients reacted with the eEF1A-1 antigen²¹; sera

of ANA-positive patients with atopic dermatitis also reacts to this antigen. These patients tended to have leukopenia and a facial rash similar to that seen in lupus.⁴¹

Treatment of Neutropenia in Felty's Syndrome

Neutropenia appears to reflect an active "rheumatoid" process; hence, several effective treatments for RA are also effective in treating Felty's syndrome, including gold,¹⁶ methotrexate (see below), cyclosporine A,¹¹ and leflunomide.⁵⁵ Splenectomy also benefits some patients³³ but the risk of postsplenectomy sepsis may be increased.¹ Variations on surgical splenectomy for Felty's syndrome and other conditions have included splenic artery embolization, laparoscopic splenectomy, and splenic radiation.⁹

Methotrexate in Felty's Syndrome

Several patient series reports suggest that methotrexate is the treatment of first choice in Felty's syndrome.^{20,58} The rise in neutrophils may occur promptly although some patients respond slowly. Hepatic dysfunction during methotrexate therapy may be due to underlying nodular regenerative hyperplasia.

Granulocyte or Granulocyte-Macrophage Colony-Stimulating Factor

Patients with Felty's syndrome may respond to granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) with a rise in neutrophil counts and decreased infections.⁴⁸ In general, after stopping short-term administration of G- or GM-CSF, the neutrophil count promptly falls to pretreatment levels. However, long-term hematopoietic growth factor administration in Felty's syndrome may increase patients' neutrophil counts above 1,000/ μ L and reduce infections. The frequency of G-CSF may be tapered to two or three times per week. Some patients require treatment with G-CSF in combination with methotrexate, cyclophosphamide, or prednisone to correct the neutropenia.

Side Effects of CSFs

Some patients with Felty's syndrome have developed a flare of arthritis or leukocytoclastic vasculitis following treatment with either G-CSF or GM-CSF. Other complications of these therapies include anemia and thrombocytopenia. A review of case reports of cutaneous vasculitis from the adverse reaction database of Amgen (Thousand Oaks, CA), the manufacturer of filgrastim, one form of G-CSF, indicated six cases of leukocytoclastic vasculitis in approxi-

mately 200,000 patients treated for malignant disease. In contrast, of the approximately 200 patients treated for chronic benign neutropenia, including Felty's syndrome and LGL leukemia, 6% developed cutaneous vasculitis. Thus, treating Felty's syndrome or neutropenic SLE patients with G- or GM-CSF may increase the risk of developing vasculitis compared to their use in malignant disorders or in normal donors.³¹

Since elevated levels of neutrophil-binding immune complexes are present in patients with both Felty's syndrome and SLE, it is possible that administering G- or GM-CSF could both increase the number of circulating neutrophils and amplify activation of neutrophils,⁵⁴ leading to endothelial injury and leukocytoclastic vasculitis in some patients. Recent studies suggest that such complications are diminished if G-CSF is administered at the lowest dose effective at elevating the neutrophil count above 1,000/ μ L.²⁹

Based on these considerations, the following approach to treating Felty's syndrome is suggested: (1) Attempt to exclude drug toxicity, usually by stopping a suspected agent. The absence of splenomegaly does not diminish the probability of Felty's syndrome. (2) Perform a bone marrow examination: the marrow should be cellular or hypercellular; serologies are helpful and usually demonstrate high titer rheumatoid factor, often positive ANA and elevated immune complexes (C1q binding). If possible, it is helpful to demonstrate elevated neutrophil-reactive IgG. (3) Treat patients who have infections regardless of the neutrophil count. Use low doses of G-CSF, 3 μ g/kg/d, to decrease the risk of flare of arthritis or vasculitis, and low to medium doses of prednisone (20 to 30 mg/d) while starting G-CSF for the same reason. (4) If the patient responds to G-CSF, add methotrexate, starting at 5 to 7.5 mg/wk (confirm that the patient's renal function is normal). Increase the dose by 2.5 mg/wk every 3 to 4 weeks to a maximum dose of 15 to 20 mg/wk, with folic acid 1 mg/d. Thus, it may take several months for the patient to reach the maximum dose of methotrexate. The goal is to induce a stable remission and eliminate the need for chronic G-CSF administration. (5) In asymptomatic patients without infections, the decision when to treat may be more difficult. If the neutrophil count is persistently less than 200/ μ L, however, begin treatment, given the high risk of serious infections; use methotrexate, 5 mg/wk and slowly increase the dose as described above. In patients with renal insufficiency or hepatic disease, in whom methotrexate is contraindicated, use G-CSF on a long-term basis or perform splenectomy. (6) In all patients, splenectomy should be considered if there is no response to therapy or if complications such as disease flare or vasculitis occur.

Neutropenia in LGL Leukemia

A 1968 report of a patient with RA and chronic neutropenia who had an expanded population of lymphocytes with granular inclusions³⁰ was later followed by the description of two cases with neutropenia and lymphocytosis of T-gamma lymphocytes.³ During the 1980s, with the availability of monoclonal antibodies to lymphocyte antigens, investigators further characterized the phenotypic features of the lymphocytes in these patients; the typical albeit not universal pattern was CD3⁺, CD4⁻, CD8⁺, CD16 variable, and CD57⁺, consistent with activated cytotoxic T cells. A 1985 report described three patients, one with RA, who had chronic lymphocytosis of LGL and neutropenia.³⁶ Based on the presence of clonal cytogenetic abnormalities and infiltration of the bone marrow, liver, and spleen by the abnormal cells, the disorder was termed LGL leukemia. The clonal nature of the expansion of the LGL is now routinely confirmed by showing rearrangement of the T-cell receptor (TCR) genes in these cells.

Clonally expanded LGL appear to correspond to normal activated cytotoxic T cells. Many normal people have minor but stable populations of clonally expanded CD8⁺, CD57⁺ T cells, and the frequency of these expansions may be increased in the elderly and non-neutropenic patients with RA.⁴³ Thus the term "T-cell clonopathy of undetermined significance" has been suggested, comparable with the term "benign monoclonal gammopathy." On the other hand, patients with LGL leukemia have a clonal proliferation of CD8⁺ LGL that is clinically evident and chronic, although usually nonprogressive. The term LGL leukemia has been adopted in the World Health Organization classification of B- and T-cell lymphocyte disorders.

Neutropenic patients with RA fall into two distinct groups: those who have and those who do not have expansion of LGL, rather than there being a continuous distribution of the number of these cells.⁴ These findings imply that the marked clonal expansion of LGL in RA is a form of transformation.

The mechanism leading to chronic expansions of LGL is unknown. The V β and J β genes expressed by the leukemic cells reflect a normal pattern of distribution. The residues corresponding to the third complementarity-determining region of the TCR- β chain were different in all cases, suggesting that leukemic CD3⁺ LGL cells have been clonally transformed in a random fashion, and showing no evidence for a superantigen effect.¹⁴ TCR- α and - β chain usage in LGL RA patients demonstrate a restricted junctional region motif that differs significantly from control sequences, observations consistent with an antigen-driven, rather than a superantigen-driven, process in LGL RA patients.⁴

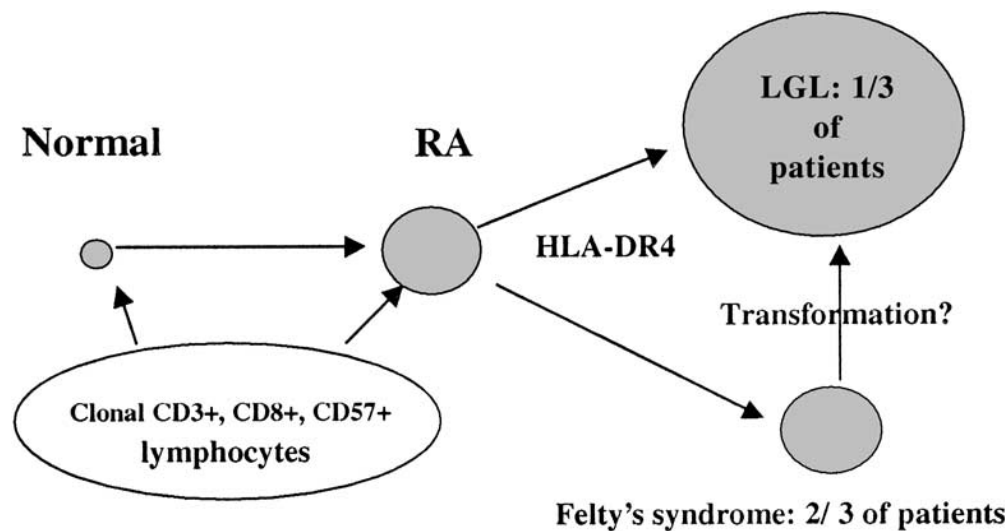


Figure 1. Clonal populations of LGL or related lymphocytes in the circulation of normal subjects and patients with RA, Felty's syndrome, or LGL leukemia. The size of the circle relates roughly to the population of these cells.

An association between RA and LGL leukemia has been noted by many investigators.^{2,30} The presence of chronic neutropenia and splenomegaly closely resembles Felty's syndrome. Among 55 patients with RA who had neutropenia, 17 had evidence of LGL leukemia whereas 32 did not; the remaining six had indeterminate findings.⁵ Nearly all patients with Felty's syndrome are HLA-DR4-positive, similar to LGL leukemia and RA. In contrast, patients with LGL leukemia not associated with RA have a normal prevalence of HLA-DR4.^{6,51} These immunogenetic findings support the concept that Felty's syndrome and LGL leukemia with RA are part of a single disease process (Fig 1).

Neutropenia in LGL is not due to humoral immune mechanisms such as antineutrophil antibodies.⁵⁷

Role of Fas-Ligand

The Fas-ligand (FasL), a member of the tumor necrosis factor family, induces apoptosis in Fas-bearing target cells. FasL is expressed on the surface of cytotoxic T cells but only after activation. Membrane-bound human FasL can be converted to a soluble form by the action of a matrix metalloproteinase-like enzyme. Recent studies indicate that in patients with LGL leukemia, constitutive expression of FasL on circulating LGL as well as elevated levels of soluble FasL in serum could play an important role in the neutropenia of this disorder. Sera from patients with LGL leukemia and natural killer (NK) cell lymphoma contain elevated levels of soluble FasL. Malignant cells from these patients constitutively express FasL, whereas peripheral NK cells from healthy subjects

express FasL only on activation.⁵⁶ Additional work has shown that circulating LGL from each of seven patients with LGL leukemia had constitutive expression of FasL gene transcripts.⁴² High levels of circulating FasL were found in 39 of 44 serum samples from patients with LGL leukemia.³⁵ In contrast, FasL was undetectable in 10 samples from healthy donors. In vitro, serum from the LGL patients triggered apoptosis of normal neutrophils that depended partly on the Fas pathway. Finally, measurements of FasL performed on serial serum specimens during methotrexate treatment indicate that resolution of neutropenia was associated with the disappearance of or marked reduction in FasL levels in 10 of 11 treated patients. These data suggest that shedding of FasL from leukemia LGL results in high serum levels of soluble FasL, which is a pathogenic mechanism in this disorder. Not yet explained is why the neutrophil appears to be the principal target of elevated FasL since other cells also express cell-surface Fas.

Treatment of Neutropenia Due to LGL Leukemia

Ten patients with LGL leukemia, both with and without RA, responded to methotrexate in one study.³⁷ Complete clinical remissions were observed in five patients, and an additional patient had a partial response. Complete and partial responses were maintained on therapy, with a follow-up period ranging from 1.3 to 9.6 years. This beneficial effect of methotrexate was confirmed in three of four LGL RA patients in another trial.²⁷ Some patients with T-cell LGL leukemia and chronic neutropenia have also responded to hematopoietic growth factors.⁴⁷

Cyclosporine can also be effective in treating the neutropenia associated with LGL leukemia.²³ Among five patients with LGL leukemia, severe neutropenia, and recurrent infections treated with cyclosporine, four attained normal neutrophil counts; one required the addition of low-dose GM-CSF. Attempts to taper and withdraw cyclosporine resulted in recurrent neutropenia. Three patients maintained normal neutrophil counts on continued cyclosporine therapy for 2, 8, and 8.5 years. Despite resolution of neutropenia, increased populations of clonally expanded LGLs persisted in all patients during cyclosporine therapy. Thus, cyclosporine may inhibit T-cell LGL secretion of as yet unidentified mediators of neutropenia.⁴⁶

Cyclosporine could inhibit secretion of FasL, similar to the action of methotrexate.³⁵ Supporting this hypothesis, one study found that cyclosporine treatment was effective in a patient with LGL leukemia who had pure red blood cell aplasia, neutropenia, and thrombocytosis. The serum soluble FasL concentration was very high, whereas the serum levels of tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), interleukin-1 β (IL-1 β), interleukin-2 (IL-2), and thrombopoietin were normal. After treatment with cyclosporine, the neutropenia, anemia, and thrombocytosis were improved, and the LGL number and elevated soluble FasL concentration decreased.⁴⁵ These results strongly suggest that treating LGL leukemia with cyclosporine or methotrexate reduces the elevated levels of FasL, resulting in improvement of the chronic neutropenia.

Neutropenia in SLE

Neutropenia is common in SLE although recurrent infections due to severe neutropenia are rare. Among 126 prospectively studied patients with SLE, hemolytic anemia occurred in 13%, neutropenia in 47%, lymphocytopenia in 20%, and thrombocytopenia in 27%. Patients with hemolytic anemia were less likely to have serositis, but no differences in the incidence of renal or cerebral manifestations were found between the various groups. Infections were mainly associated with the use of corticosteroid therapy and not related to neutropenia itself. Life-table analysis showed no adverse influence on survival of hemolytic anemia, neutropenia, or lymphocytopenia, but late-onset thrombocytopenia was associated with a decreased survival. No relationship was found between thrombocytopenia and the presence of antiphospholipid antibodies or the occurrence of thromboembolic events.⁴⁰

Mechanism of Neutropenia in SLE

Three principal mechanisms have been described: neutrophil-reactive IgG, increased neutrophil apo-

ptosis, and marrow dysfunction. Antineutrophil antibodies were described in a patient with lupus in whom the intravascular half-life of neutrophils was shortened.⁵² In other studies, increased levels of neutrophil-bound IgG were found in 50% of lupus patients, but some did not have neutropenia. Gel-filtration and pepsin-digestion studies indicated that the neutrophil-binding IgG consisted of both IgG antineutrophil antibodies as well as neutrophil-binding immune complexes.⁴⁹

In one study, sera from 22 of 31 SLE patients bound IgG to neutrophil cell membranes and/or to nuclei, but only membrane-binding antibodies opsonized the cells for recognition by monocytes. There was no correlation between neutrophil count and the level of neutrophil-binding IgG as measured by indirect immunofluorescence. In contrast, opsonic activity and neutrophil count were inversely correlated ($r = 0.5$, $P < .05$). However, opsonic activity was also present in sera from most non-neutropenic patients. The investigators suggested that the impaired reticuloendothelial system function in SLE may allow sensitized neutrophils to remain in the circulation.²⁶

Another recent study of SLE patients found that the specific autoantibodies to ribonucleoprotein particles, anti-Ro (or SSA), were associated with neutropenia. The anti-Ro autoantibodies bind the surface of granulocytes and fix complement. Binding is a property of anti-Ro Fab fragments and can be inhibited by 60-kd Ro. However, the antigen bound on the surface of granulocytes is a 64,000 molecular weight protein and a novel autoantigen in SLE. As suggested by inhibition studies, sequence identity between 60-kd Ro and eight tandem repeats in the 64-kd antigen may be responsible for serologic cross-reactivity. These data imply that anti-Ro antibodies that also bind the 64-kd protein mediate neutropenia in patients with SLE.³²

Finally, the frequency of circulating apoptotic neutrophils in lupus and control patients and their relationship with disease activity and neutropenia have been measured. Patients with RA and inflammatory bowel disease served as disease controls. The percentage of apoptotic neutrophils, determined by annexin V binding, was increased nearly threefold in the peripheral blood of SLE patients compared with normal healthy donors and disease controls. SLE neutrophil apoptosis correlated positively with lupus disease activity and with antibodies to double-stranded DNA. Increased neutrophil Fas expression compared with normal controls was observed in the SLE patients and in the disease controls; thus, although neutrophil Fas expression is increased nonspecifically in inflammatory disease, the increased circulating apoptotic neutrophils in SLE correlated positively with disease activity.¹³

Marrow Dysfunction in SLE

Marrow findings are often unpredictable and reflect the diverse causes of cytopenias in patients with connective tissue disorders.⁴⁴ Bone marrows may show histiocytes phagocytosing hematopoietic cells.³⁹ Potent IgG inhibitors of hematopoiesis were identified in sera from six of 20 SLE, all of whom had leukocytopenia and/or anemia. These IgG bound to CD34⁺ hematopoietic progenitor cells, but not to CD33⁺ cells.³⁴

Treatment With G-CSF

One study treated nine patients with SLE who had associated neutropenia and refractory infections using G-CSF at 6.6 $\mu\text{g}/\text{kg}/\text{d}$ subcutaneously for an average of 6 days (range, 1 to 17 days) as an adjunct to antibiotic treatment. In one case of impaired wound healing, long-term G-CSF was applied over 148 days. In each case, the average neutrophil count increased within 2 days from 1,300/ μL (range, 700 to 2,400) to 8,400/ μL (range, 3,200 to 19,400). In three of nine cases, however, lupus-associated symptoms flared, including exacerbation of central nervous system symptoms in two patients and leukocytoclastic vasculitis in one.¹⁸ These results are reminiscent of the adverse events seen with Felty's syndrome. Although G-CSF induces a rapid increase in neutrophil counts in patients with lupus-associated neutropenia and normal or hyperplastic granulopoiesis, worsening the disease is a real risk. Based on findings described above, it is recommended that in treating SLE patients G-CSF be administered at the lowest dose needed to raise the neutrophil count above 1,000/ μL .²⁹

Conclusion

Chronic neutropenia associated with RA and with SLE results from a complex interplay involving cell-binding immunoglobulins, both antibodies and immune complexes, complement components, and changes in adhesion molecules, in concert with increased apoptosis related to the Fas/FasL system and alterations in marrow function. Many of these factors appear to result from active underlying RA and SLE, so that treating the active disease often improves the neutropenia. Both methotrexate and cyclosporine may be effective in LGL leukemia by reducing levels of FasL. Recent studies demonstrate that G- or GM-CSF can increase neutrophil counts and reduce the risk of infections in both disorders. Because of an increased risk of inducing a disease flare or leukocytoclastic vasculitis, however, these biologic agents should be used judiciously.

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