

# Clinical And Pathophysiological Perspectives On Felty Syndrome: Implications For Advanced Healthcare Practice

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## Abstract:

**Background:** Felty syndrome is a rare but severe extra-articular complication of long-standing seropositive rheumatoid arthritis (RA), classically defined by the triad of RA, neutropenia, and splenomegaly. Its pathogenesis reflects complex immune dysregulation, genetic predisposition—particularly HLA-DR4—and impaired neutrophil homeostasis.

**Aim:** This review aims to synthesize current clinical, genetic, and pathophysiological knowledge about Felty syndrome and highlight implications for advanced nursing practice and multidisciplinary management.

**Methods:** A comprehensive analysis of epidemiological data, immunogenetic studies, pathophysiological mechanisms, diagnostic strategies, and management approaches was conducted based on existing clinical research and observational evidence summarized in the article.

**Results:** Findings indicate strong genetic associations with HLA-DRB1\*0401, a prevalence of 1–3% among RA patients, and a typical latency of over 16 years after initial RA diagnosis. Pathophysiology involves impaired granulopoiesis, splenic sequestration, autoantibodies against G-CSF, and overlap with large granular lymphocyte (LGL) leukemia. Diagnosis requires integration of hematologic, immunologic, imaging, and bone marrow findings. Management relies on methotrexate as first-line therapy, rituximab for refractory disease, and G-CSF for severe neutropenia, with splenectomy reserved for selected cases.

**Conclusion:** Felty syndrome represents a complex immuno-hematologic condition requiring early recognition, interprofessional collaboration, and individualized therapeutic strategies. Advances in DMARDs, biologics, and neutropenia management have substantially improved outcomes, although infection risk remains a major concern.

**Keywords:** Felty syndrome; rheumatoid arthritis; neutropenia; splenomegaly; HLA-DR4; G-CSF; methotrexate; rituximab; LGL leukemia; multidisciplinary care.

## Introduction:

Felty syndrome, also referred to as Chauffard-Still-Felty disease, represents a rare extra-articular complication of seropositive rheumatoid arthritis (RA), clinically defined by the triad of RA, neutropenia (absolute neutrophil count  $<1500 \text{ mm}^3$ ), and splenomegaly. The genetic marker HLA-DR4 has been identified in over 90% of individuals affected by this condition, suggesting a strong immunogenetic predisposition [1]. The syndrome was initially described in 1924 by the American physician Augustus Felty at Johns Hopkins Hospital, who reported five unique cases exhibiting chronic arthritis of approximately four years' duration, pronounced splenomegaly, and notable leukopenia. The eponymous term “Felty

syndrome” was first adopted by Hanrahan and Miller in 1932 when they documented the positive outcomes of splenectomy in a patient demonstrating clinical features analogous to Felty’s original cases. Although Felty syndrome is traditionally recognized through the constellation of chronic arthritis, splenomegaly, and neutropenia, the presence of all three elements is not strictly required for diagnosis. Neutropenia remains the pivotal diagnostic criterion and is invariably observed in affected individuals, whereas arthritis and splenomegaly may vary in presentation [2]. This variability in clinical manifestations contributes to diagnostic complexity, as the syndrome’s infrequency limits routine recognition among healthcare practitioners. Consequently, the condition often requires heightened clinical vigilance and a thorough understanding of its subtle presentations to ensure timely identification and intervention. Management of Felty syndrome necessitates an integrated, multidisciplinary approach due to its systemic involvement and potential complications. Optimal care extends beyond the role of rheumatologists and hematologists, incorporating the expertise of advanced practice nurses, clinical pharmacists, and allied healthcare professionals to address both immunological and hematological aspects of the disease. Nurses play a critical role in monitoring neutropenia, preventing infections, and coordinating patient-centered care plans that mitigate risk while supporting long-term management. Pharmacologic interventions, immunosuppressive strategies, and, in select cases, surgical options such as splenectomy require careful collaboration among the care team to balance efficacy with patient safety. The complex interplay of genetic susceptibility, chronic autoimmune activity, and hematological compromise underscores the importance of comprehensive, evidence-based strategies in achieving favorable clinical outcomes for patients with Felty syndrome [1][2].

### **Etiology**

The etiology of Felty syndrome is closely linked to genetic and immunological factors, with a particular emphasis on the role of HLA-DRB1 alleles. Evidence indicates that the presence of the shared epitope within HLA-DRB1 significantly increases the likelihood of developing anticyclic citrullinated peptide (CCP) antibodies, which are highly specific markers for rheumatoid arthritis (RA), exhibiting a specificity of approximately 96% [3]. These antibodies, along with rheumatoid factor (RF), are strongly associated not only with RA but also with the increased risk of extra-articular manifestations, commonly referred to as ExRA [4]. The HLA-DRB1 gene comprises several alleles, including DRB101 and DRB104, with DRB1\*04 homozygosity being particularly correlated with severe, erosive forms of RA. Multiple studies have highlighted the role of HLA-DRB10401 in the pathogenesis of Felty syndrome. A large multicenter investigation assessing the influence of HLA-DRB1 alleles in patients presenting with ExRA demonstrated a robust association between the HLA-DRB10401 allele and the development of Felty syndrome, underscoring the specific contribution of this genetic factor to the disease phenotype. Interestingly, the same study found no significant relationship between ExRA and either HLA-DQB1 alleles or DRB1-DQB1 haplotypes, which emphasizes the predominant influence of HLA-DRB1 in predisposing individuals to Felty syndrome [5]. These findings suggest that the immunogenetic profile of a patient, particularly the presence of HLA-DRB1\*0401, not only predisposes to the development of RA but also influences the emergence of its extra-articular complications, including neutropenia and splenomegaly characteristic of Felty syndrome. Understanding this genetic association is essential for identifying high-risk populations, guiding early screening strategies, and informing personalized management approaches that integrate both rheumatologic and hematologic care considerations.

### **Epidemiology**

Felty syndrome is an uncommon complication of rheumatoid arthritis (RA), with prevalence estimates ranging from 1% to 3% among patients diagnosed with RA [6]. Over recent decades, the widespread adoption of disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), along with biologic therapies, has contributed to a noticeable decline in the incidence of Felty syndrome, suggesting that the true prevalence may now be substantially lower [7]. Typically, Felty syndrome manifests many years after the onset of RA, with an average latency period of approximately 16.1 years from initial RA diagnosis. The risk is further elevated in individuals with a positive family history of RA, indicating a heritable component to disease susceptibility. Genetic predisposition is further underscored by the frequent

association of Felty syndrome with the HLA-DR4 allele, which is more prevalent in affected individuals [2]. The demographic pattern of Felty syndrome closely mirrors that of RA itself. The condition disproportionately affects females, with a female-to-male ratio of approximately 3:1, and is most commonly diagnosed during middle age. Epidemiological data also indicate a higher occurrence among White populations compared to non-White populations [8][9]. These patterns reflect both genetic and environmental contributions to disease development. The combination of chronic autoimmune activity, genetic susceptibility, and demographic factors contributes to the observed epidemiological trends and informs risk stratification in clinical practice. Awareness of these epidemiologic characteristics is essential for healthcare providers, particularly nurses and advanced practice clinicians, to identify at-risk patients, implement early monitoring strategies, and optimize long-term management of RA and its rare but serious extra-articular complications, including Felty syndrome.

### **Pathophysiology**

The pathophysiology of Felty syndrome remains incompletely understood, with current evidence suggesting a complex, multifactorial process involving both humoral and cellular immune mechanisms. Central to the disease is neutropenia, which represents the hallmark clinical abnormality and drives much of the syndrome's morbidity. Neutropenia in Felty syndrome appears to result from a combination of impaired neutrophil production and accelerated peripheral destruction. Bone marrow infiltration by cytotoxic lymphocytes may limit granulopoiesis, leading to inadequate neutrophil output, while splenomegaly contributes to increased sequestration and peripheral clearance of neutrophils. This dual mechanism is supported by clinical observations demonstrating marked improvement in neutrophil counts following splenectomy, indicating the spleen's significant role in neutrophil turnover [10]. Humoral immune mechanisms also contribute to neutrophil abnormalities in Felty syndrome. A case-control study examining the presence of antibodies against granulocyte-colony stimulating factor (G-CSF) found that 73% of patients with Felty-associated neutropenia had IgG anti-G-CSF antibodies. These antibodies were associated with elevated serum G-CSF levels and persistent neutropenia, suggesting that both an exaggerated cytokine response and hyposensitivity of myeloid progenitor cells to G-CSF contribute to defective neutrophil homeostasis [11]. In addition, autoantibodies in Felty syndrome have been shown to bind deaminated histones and neutrophil extracellular chromatin traps (NETs), facilitating neutrophil sequestration and peripheral destruction. This finding emphasizes the role of immune-mediated clearance of neutrophils in the pathogenesis of the syndrome, alongside impaired production [12].

The relationship between Felty syndrome and large granular lymphocyte (LGL) leukemia has also been explored, as both conditions share clinical features, immunogenetic profiles, and pathogenic mechanisms. Approximately one-third of Felty syndrome patients exhibit a clonal population of CD3+/CD8+ LGLs. In LGL leukemia, neutropenia has been attributed to elevated circulating Fas ligand, which triggers neutrophil apoptosis. The frequent co-occurrence of RA in LGL leukemia patients, alongside elevated Fas ligand levels, parallels mechanisms observed in Felty syndrome, suggesting overlapping pathogenic pathways [13][14][15][16]. Epidemiologic data indicate that roughly 20% of patients with T-cell LGL leukemia also have RA, further reinforcing the conceptual link between the two disorders [17][18]. This overlap has led researchers to hypothesize that Felty syndrome and T-cell LGL leukemia represent entities along a disease spectrum, with shared immunogenetic predisposition, particularly HLA-DR4, underlying both conditions [19]. The spectrum concept is supported by the observation that both conditions exhibit neutropenia, autoimmune phenomena, and clonal lymphocyte expansions, highlighting the convergence of autoimmunity and hematologic dysregulation in their pathogenesis. Chronic immune stimulation, combined with genetic susceptibility, appears to drive both aberrant neutrophil apoptosis and dysregulated lymphocyte function, ultimately manifesting as the characteristic features of Felty syndrome, including RA, splenomegaly, and persistent neutropenia.

In summary, the pathophysiology of Felty syndrome involves an intricate interplay of impaired neutrophil production, peripheral neutrophil destruction, humoral autoimmunity, and

clonal lymphocyte expansion. Defective granulopoiesis, immune-mediated clearance of neutrophils, autoantibody-mediated interference with cytokine signaling, and shared pathogenic mechanisms with LGL leukemia collectively contribute to disease development. These insights underscore the importance of understanding Felty syndrome not solely as an extra-articular manifestation of RA but as a complex hematologic-immune disorder requiring integrated clinical management. The multifactorial nature of its pathophysiology explains the variability in clinical presentation and highlights potential therapeutic targets, including immunomodulatory agents, biologics, and splenectomy, aimed at correcting both autoimmune and hematologic abnormalities.

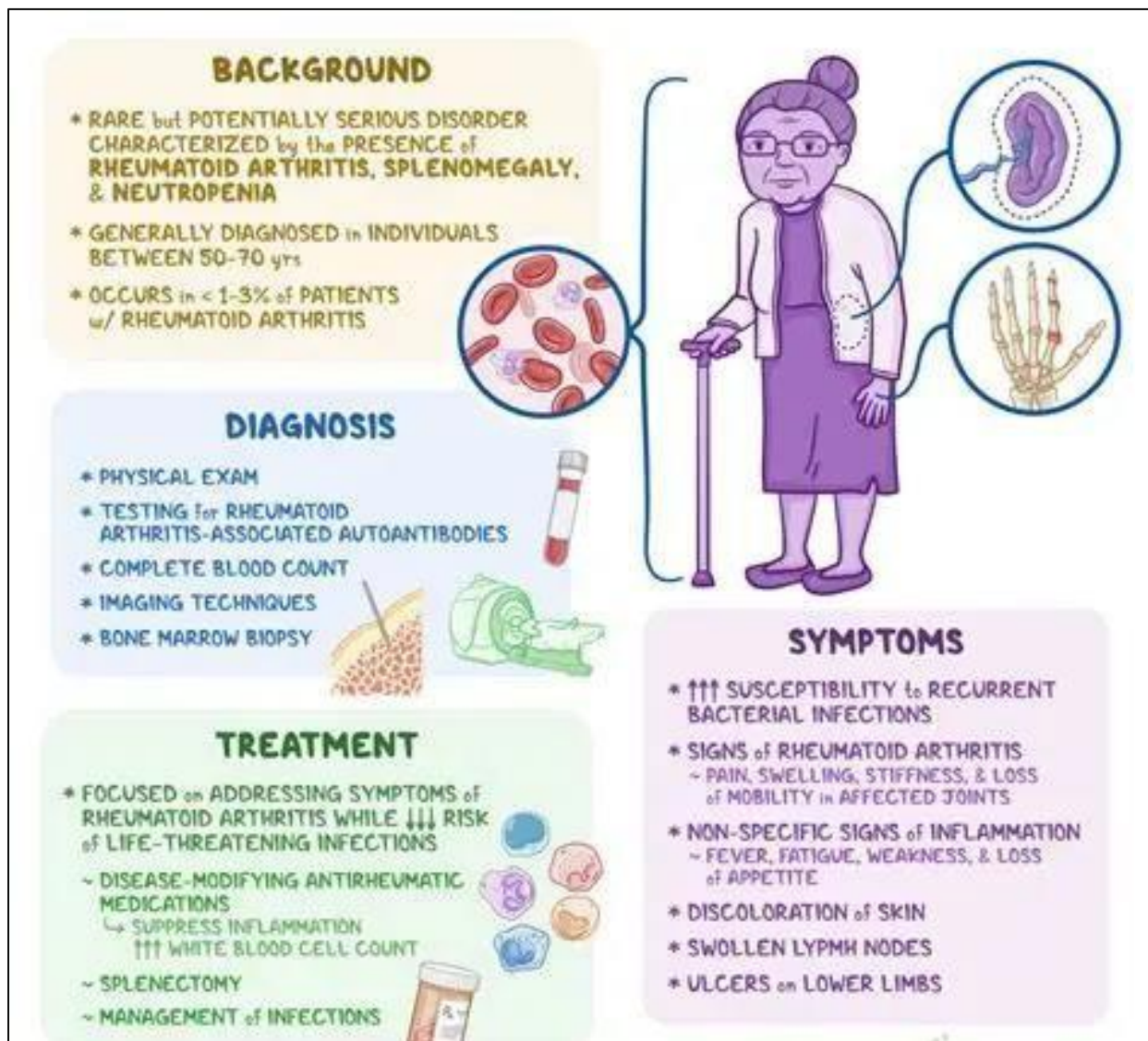


Fig. 1: Felty Syndrome.

### History and Physical

Felty syndrome is predominantly recognized as a severe extra-articular manifestation of long-standing rheumatoid arthritis (RA), typically arising in patients with chronic, erosive, and

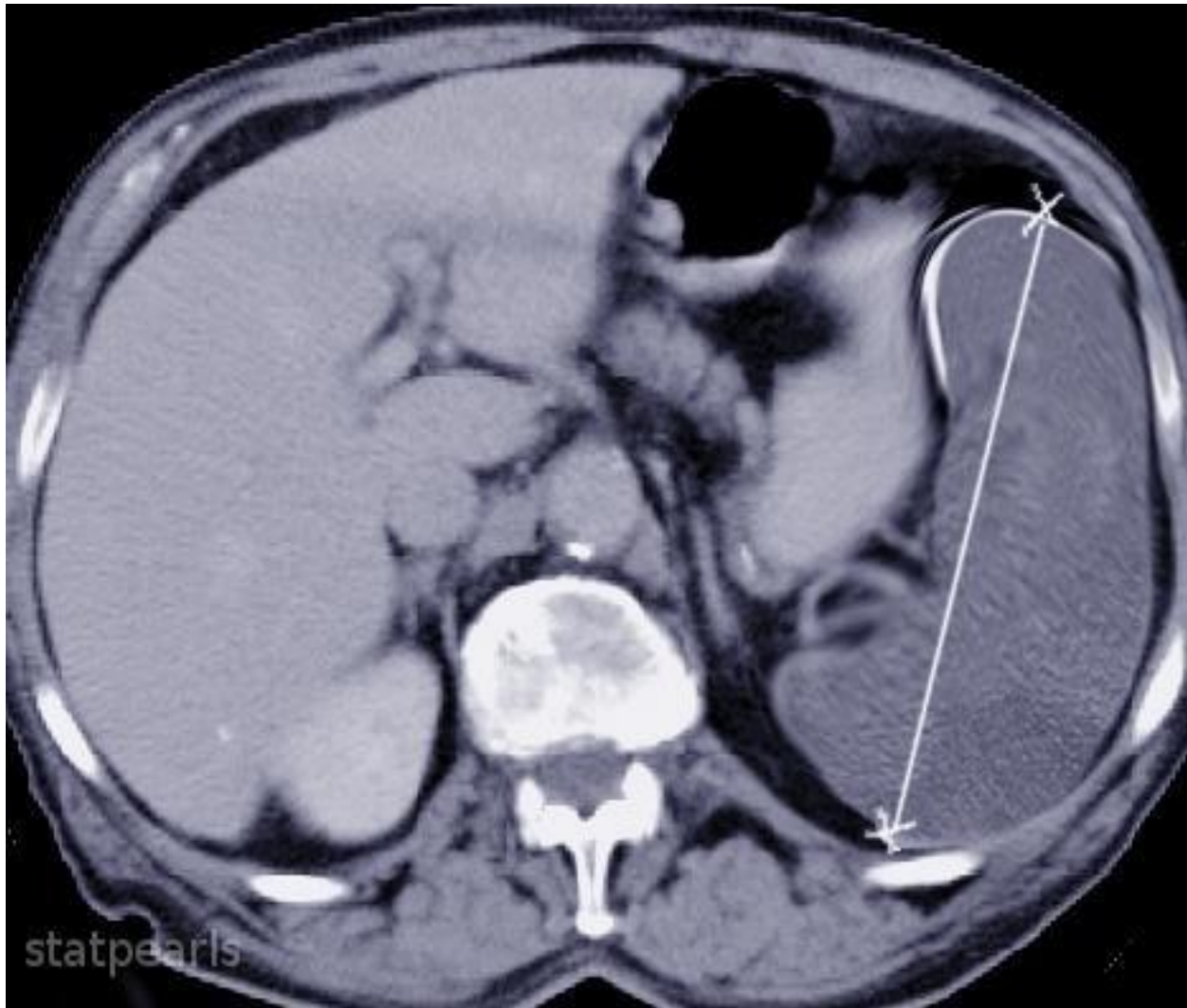
seropositive forms of the disease. Nonetheless, the diagnosis of Felty syndrome can occasionally precede the onset of clinically apparent arthritis, underscoring the variability in its presentation and the importance of considering it in patients with unexplained neutropenia or recurrent infections [20][21]. When articular involvement is present at the onset, it may be either subtle or overt; however, the majority of patients demonstrate radiographic evidence of erosive joint disease. Synovial effusions are relatively common, occurring in approximately 75% of cases, and may serve as an early clinical indicator in the evaluation of suspected Felty syndrome [22]. Clinical presentation is often dominated by recurrent infections, reflecting the profound neutropenia that defines the syndrome. These infections frequently affect the skin and respiratory tract, though any organ system may be involved depending on immune status and environmental exposures [14][23]. Because Felty syndrome can remain asymptomatic outside of infectious episodes, clinicians must maintain a high index of suspicion, particularly in patients with a history of RA who present with unusual or recurrent infections. Extra-articular manifestations are common and diverse, reflecting the systemic nature of the disease. Rheumatoid nodules are observed in up to 74% of patients, while hepatomegaly occurs in approximately 68%. Lymphadenopathy is present in about 42% of cases, and autoimmune phenomena such as Sjogren syndrome are reported in 48% of patients. Pulmonary complications, including fibrosis and pleuritis, affect 50% and 22% of patients, respectively. Peripheral neuropathy and leg ulcers are less common but clinically significant, occurring in 14% and 16% of cases, respectively [24]. Systemic symptoms, including fever and unintentional weight loss, may also accompany these manifestations, further complicating the clinical picture [25]. Splenomegaly, a classic feature of Felty syndrome, is typically palpable on physical examination; however, its presence is not a mandatory criterion for diagnosis. Some patients may also develop idiopathic non-cirrhotic portal hypertension, which carries the risk of variceal bleeding and adds another dimension to clinical management. Collectively, the constellation of infections, extra-articular manifestations, systemic symptoms, and splenomegaly highlights the need for comprehensive clinical evaluation, careful history-taking, and thorough physical examination in patients suspected of having Felty syndrome. The variability in presentation underscores the critical role of multidisciplinary assessment, including rheumatology, hematology, and nursing care, to ensure timely diagnosis and appropriate intervention.

### **Evaluation**

The evaluation of Felty syndrome relies on a combination of hematologic, serologic, imaging, and histopathologic assessments, reflecting the complex interplay between autoimmune mechanisms, chronic inflammation, and hematologic dysregulation. Complete blood count (CBC) with differential remains the cornerstone of initial evaluation, with an absolute neutrophil count (ANC) of less than 2000/ $\mu$ L serving as a hallmark feature required for diagnosis. This neutropenia predisposes patients to recurrent and potentially severe bacterial infections, often prompting further investigation [26]. In some cases, Felty syndrome may be detected incidentally during routine surveillance of blood counts, such as in monitoring for cytotoxic drug toxicity, highlighting the importance of careful longitudinal hematologic assessment. Notably, the degree of neutropenia does not correlate with the extent of splenic enlargement, emphasizing that laboratory findings must be interpreted independently of clinical splenic assessment. Additional hematologic abnormalities may include anemia and thrombocytopenia, particularly in patients with splenomegaly, while anemia of chronic inflammation is nearly ubiquitous among affected individuals. Moreover, Felty syndrome demonstrates a higher prevalence of autoimmune hemolytic anemia, as indicated by a positive Coombs test, compared with rheumatoid arthritis alone [14].

Serologic testing provides important diagnostic and prognostic information. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, which are characteristic of RA, are almost universally present in Felty syndrome. Additional immunologic markers, such as antinuclear antibodies, anti-histone antibodies, and HLA-DR4, may also be detected. Anti-histone antibodies are reported in approximately 83% of patients, and their presence in individuals with RA is considered highly suggestive of Felty syndrome [14]. These serologic findings support the diagnosis and may aid in differentiating Felty syndrome from other autoimmune or hematologic conditions. Imaging studies complement laboratory evaluation, particularly in the assessment of joint and splenic involvement. Plain radiographs of small peripheral joints often demonstrate severe erosive changes, reflecting the chronicity and intensity of RA in

these patients [27]. Splenic imaging, including ultrasound or radionuclide scanning, is useful in detecting splenomegaly and monitoring structural changes. Although splenomegaly is common, it is not a diagnostic requirement, but imaging can provide a baseline for future management, including surgical considerations such as splenectomy. Bone marrow biopsy is a critical component in the evaluation of Felty syndrome, particularly to differentiate it from hematologic malignancies such as large granular lymphocyte (LGL) leukemia. The marrow typically exhibits myeloid hyperplasia with increased granulopoiesis and a relative excess of immature forms, a pattern often described as “maturation arrest” [25]. A hypoplastic marrow should prompt consideration of alternative diagnoses. Immunophenotyping of bone marrow cells further aids in identifying clonal lymphocyte populations, with T-cell LGL leukemia defined by CD3+/CD8+/CD57+ markers and natural killer cell variants by CD3-/CD56+ expression [14]. Histologic examination of the spleen, obtained either at autopsy or post-splenectomy, generally demonstrates nonspecific findings, including congestion of venous sinusoids, reticular cell hyperplasia, and germinal center hyperplasia. These changes reflect the chronic immune activation and hematologic stress characteristic of Felty syndrome rather than a unique pathognomonic pattern. Collectively, the integration of hematologic, serologic, imaging, and histologic data forms the foundation for accurate diagnosis, risk stratification, and management planning in patients with Felty syndrome, emphasizing the need for a comprehensive, multidisciplinary evaluation.



**Fig. 2:** CT scan of splenomegaly.

### **Treatment / Management**

Management of Felty syndrome focuses on dual objectives: controlling the underlying rheumatoid arthritis (RA) and addressing neutropenia to prevent recurrent infections. Achieving an absolute neutrophil count (ANC) above 2000/ $\mu\text{L}$  is a primary goal in patients with clinically significant neutropenia. Importantly, the presence of neutropenia alone, without evidence of infection or systemic symptoms, does not warrant immediate intervention. However, in patients with RA, neutropenia may guide adjustments in disease-modifying antirheumatic drugs (DMARDs), with improvement in neutrophil counts often serving as an indirect indicator of the responsiveness of Felty syndrome to RA-targeted therapies [1]. Patients presenting with neutropenia should undergo comprehensive evaluation for latent or active infections, and systemic symptoms such as fever or malaise should prompt immediate treatment. Preventive measures, including rigorous oral hygiene, appropriate immunizations, and general neutropenic precautions, are essential components of management, and consultation with infectious disease specialists may be indicated in complex cases [26]. Although no randomized controlled trials specifically guide

Felty syndrome treatment, observational studies support the use of low-dose oral methotrexate (MTX) as first-line therapy. MTX, administered with folic acid supplementation to mitigate anti-folate toxicity affecting the liver, bone marrow, and gastrointestinal tract, has demonstrated efficacy in both improving neutrophil counts and reducing the frequency of infections. Doses below 7.5 mg per week have been reported to produce measurable neutrophil recovery within four to six weeks, although the dose-response relationship necessitates an adequate trial at the maximum tolerated dose before classifying a patient as nonresponsive [28][29][30].

Other DMARDs have shown variable effectiveness in isolated cases. Leflunomide, for example, has been associated with improved neutrophil counts in patients intolerant to MTX or biologics such as etanercept, although these observations are largely anecdotal [31]. Historical therapies, including parenteral gold salts, have fallen out of favor due to adverse effect profiles [32]. Cyclosporine has demonstrated some efficacy in select reports, but its use is limited due to toxicity and the availability of more effective alternatives [33][34]. Biologic agents, particularly rituximab, a monoclonal antibody targeting CD20-positive B cells, have shown consistent and sustained improvements in neutrophil counts without major adverse events. Rituximab is considered for patients who fail to respond to conventional DMARD therapy, whereas anti-tumor necrosis factor (TNF) agents, including infliximab, adalimumab, and etanercept, generally do not improve neutrophil levels [35][36]. Glucocorticoids may provide rapid improvement in neutrophil counts, particularly during acute exacerbations or active infections. However, their long-term use is limited by immunosuppressive effects, and administration is contraindicated in patients with ongoing infections [37]. Granulocyte-colony stimulating factor (G-CSF) represents another key therapeutic option, particularly for patients with ANC below 1000/ $\mu\text{L}$  and recurrent or severe infections who are unresponsive to DMARDs or biologic therapy. Systematic reviews indicate that G-CSF administration significantly increases neutrophil counts within one week, stabilizes ANC above pretreatment levels, and reduces infectious complications. Short-term use during acute infections aims for ANC levels above 1000/ $\mu\text{L}$ , enhancing neutrophil function while mitigating infection risk. Long-term G-CSF therapy, however, carries the potential to exacerbate underlying autoimmunity and should be reserved for refractory cases [38].

Surgical management in Felty syndrome, primarily splenectomy, was historically a mainstay following the first documented procedure by Hanrahan and Miller. The patient, a 50-year-old woman, exhibited marked improvement in both neutropenia and arthritis over five months of follow-up [39][26]. In contemporary practice, the indications for splenectomy are limited due to the efficacy of DMARDs, biologics, and G-CSF. Surgery is reserved for patients with severe, recurrent infections refractory to medical therapy or for rare complications, including transfusion-dependent anemia or life-threatening hemorrhage from thrombocytopenia. Postoperative recurrence of neutropenia occurs in approximately 25% of patients, and while G-CSF can provide temporary improvement, anti-G-CSF antibodies in RA or Felty syndrome may complicate response and limit long-term efficacy [3][40]. In clinical practice, management of Felty syndrome requires a nuanced, multidisciplinary approach. Rheumatologists must tailor DMARD therapy

to optimize both joint and hematologic outcomes, while hematologists monitor neutrophil counts and manage complications. Nurses play a critical role in patient education, infection prevention, and adherence to neutropenic precautions, while infectious disease specialists provide guidance on prophylaxis and management of recurrent infections. Biologic therapies, particularly rituximab, should be considered for refractory cases, whereas G-CSF offers short-term support for patients with severe neutropenia and active infection. Surgical intervention is reserved for carefully selected patients, and long-term follow-up is essential to monitor disease progression, complications, and treatment response. Overall, the management of Felty syndrome integrates immunomodulation, infection prevention, hematologic support, and, when necessary, surgical intervention. Treatment strategies must be individualized, balancing efficacy, safety, and patient-specific comorbidities to achieve optimal outcomes in this rare but potentially severe complication of RA. The evolving therapeutic landscape, including biologics and targeted immunotherapies, has shifted the management paradigm from surgical predominance to a comprehensive, multidisciplinary medical approach, with a primary focus on controlling RA activity and preventing life-threatening infections.

### **Differential Diagnosis**

The differential diagnosis of Felty syndrome requires careful evaluation, particularly in patients presenting with rheumatoid arthritis (RA) accompanied by neutropenia and, in some cases, splenomegaly. One of the most critical conditions to distinguish from Felty syndrome is large granular lymphocyte (LGL) leukemia, sometimes referred to as “pseudo-Felty syndrome.” LGL leukemia frequently presents with neutropenia, which may occur with or without splenomegaly, closely mimicking the hematologic features of Felty syndrome. The clinical overlap is further complicated by the frequent coexistence of autoimmune disorders in LGL leukemia, particularly RA, making differentiation challenging [41][42]. Precise immunophenotyping is essential, as LGL leukemia is characterized by a clonal population of cytotoxic T lymphocytes expressing surface markers such as CD2, CD3, CD8, CD16, and CD57. Bone marrow biopsy and peripheral blood smears typically demonstrate increased numbers of LGL cells, providing further diagnostic confirmation. Many researchers and clinicians regard Felty syndrome and LGL leukemia as part of a disease continuum rather than completely separate entities, reflecting the shared immunogenetic and pathophysiologic mechanisms underlying both conditions. In this context, the involvement of a hematologist is crucial to exclude hematologic malignancies and ensure accurate diagnosis of neutropenia in RA patients. Beyond LGL leukemia, other potential causes of neutropenia and splenomegaly must be systematically considered and excluded. Drug-induced neutropenia represents a common iatrogenic factor, particularly in patients receiving disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), which can cause bone marrow suppression. Similarly, tumor necrosis factor (TNF) inhibitors may lead to neutropenia in susceptible individuals. Observing worsening neutropenia following temporary cessation of these medications can provide important diagnostic clues, suggesting an underlying Felty syndrome rather than medication toxicity [43].

Infectious etiologies must also be evaluated, as viral infections such as Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) can produce neutropenia and splenomegaly resembling Felty syndrome. In suspected cases, serologic testing is vital to exclude these viral infections. Furthermore, other autoimmune disorders, including systemic lupus erythematosus (SLE), may manifest with features overlapping with extra-articular RA, such as cytopenias and splenic enlargement. Clinical assessment and targeted serologic evaluation, including antinuclear antibody (ANA) testing and disease-specific markers, allow for differentiation between these autoimmune conditions and Felty syndrome. In summary, establishing a diagnosis of Felty syndrome requires meticulous exclusion of alternative causes of neutropenia and splenomegaly, with particular attention to LGL leukemia, medication effects, viral infections, and other autoimmune disorders. Accurate differentiation is essential for guiding treatment decisions and determining appropriate therapeutic strategies, emphasizing the need for a multidisciplinary approach that includes rheumatology, hematology, and infectious disease expertise. Prompt recognition and careful evaluation prevent misdiagnosis, facilitate appropriate management, and improve patient outcomes.

## **Prognosis**

The prognosis of Felty syndrome has improved significantly over the past several decades due to advances in the treatment of rheumatoid arthritis (RA) and supportive management of neutropenia. Historically, the extra-articular manifestations of RA, including Felty syndrome, were associated with considerable morbidity and mortality. Prior to the introduction of methotrexate (MTX) and biological therapies, RA patients who developed Felty syndrome frequently experienced severe complications such as persistent neutropenia, recurrent infections, and organ involvement, which contributed to a reported five-year mortality rate of approximately 36%, with infections being the leading cause of death [45]. The availability of DMARDs and biologic agents has altered the natural history of the disease by controlling systemic inflammation, reducing the severity of joint destruction, and mitigating extra-articular manifestations [7]. The incorporation of granulocyte-colony stimulating factor (G-CSF) into clinical practice has also improved outcomes by providing targeted support for neutropenic patients. By stimulating neutrophil production and enhancing functional capacity, G-CSF reduces the incidence and severity of infections, which historically accounted for a substantial proportion of Felty syndrome-related mortality [44]. Additionally, widespread use of MTX has decreased the reliance on splenectomy as a treatment modality, further reducing surgical morbidity and mortality. Although contemporary large-scale studies are limited, observational data suggest that the prognosis for patients with Felty syndrome is considerably better in the current era, particularly for those who receive timely and comprehensive immunomodulatory therapy. Early recognition, aggressive infection prevention, and careful monitoring of neutrophil counts are key determinants of long-term outcomes. Nevertheless, the rarity of the condition, combined with the absence of randomized controlled trials, highlights the need for individualized treatment strategies and close interdisciplinary collaboration to optimize patient prognosis.

## **Complications**

Felty syndrome is associated with multiple complications, the most clinically significant of which is severe or recurrent infection due to chronic neutropenia. Patients are particularly vulnerable to dermatologic and respiratory infections, which may be severe, recurrent, and occasionally life-threatening [14][23]. The degree and persistence of neutropenia strongly influence the frequency and severity of these infections, making close monitoring and timely intervention critical. Secondary bacterial infections can complicate the management of RA and may precipitate hospitalizations or require intravenous antibiotic therapy. Hematologic complications are also common. Anemia may occur as a consequence of chronic inflammation or splenic sequestration, and severe thrombocytopenia can lead to spontaneous hemorrhage. Patients with Felty syndrome may develop variceal bleeding due to non-cirrhotic portal hypertension, a rare but serious complication of chronic splenic enlargement. Therapeutic interventions carry additional risks; splenectomy, historically a mainstay for refractory neutropenia, can increase post-operative infection risk, sometimes with fatal outcomes. Similarly, G-CSF therapy, while generally effective, carries a small risk of exacerbating underlying autoimmune conditions, including RA or other autoimmune cytopenias [38]. The presence of these complications underscores the need for a proactive, multidisciplinary approach. Regular hematologic surveillance, infection prevention strategies, and patient education are essential to mitigate complications. Clinicians must balance aggressive treatment of neutropenia with the potential risks associated with immunomodulatory therapies and surgical interventions. The heterogeneity of complications highlights the systemic nature of Felty syndrome and necessitates individualized care plans tailored to the patient's clinical status and comorbidities.

## **Patient Education**

Given its rarity, Felty syndrome is often under-recognized, yet early identification is critical due to the potentially fatal consequences of delayed treatment. Clinicians should maintain a high index of suspicion in any patient with RA presenting with neutropenia, even if the neutropenia is asymptomatic or temporarily masked during acute infections. Early recognition allows timely intervention to prevent life-threatening complications and supports better long-term outcomes. Patient education plays a central role in the management of Felty syndrome. Because no universally accepted curative therapy exists, preventive measures are essential. Patients should receive guidance on maintaining good oral and dental hygiene to

reduce the risk of mucosal infections, adhere to recommended immunizations, and promptly report signs of infection. Clinicians should emphasize routine monitoring of neutrophil counts and careful adjustment of anti-rheumatic therapies to support immune function and minimize neutropenia. In non-acute settings, these strategies allow for early detection of complications and proactive management to prevent infections. Therapeutic management presents unique challenges, particularly in acute settings or resource-limited environments. The lack of randomized controlled trials and the reliance on observational data mean that treatment decisions often require individualized judgment, particularly for patients with refractory neutropenia. Collaborative care involving rheumatologists, hematologists, infectious disease specialists, and nursing teams is essential for optimizing treatment, monitoring complications, and providing comprehensive patient education. Patient engagement, adherence to preventive measures, and awareness of early warning signs are crucial to reducing morbidity and mortality. Overall, prevention, monitoring, and education form the cornerstone of Felty syndrome management, supporting both immediate and long-term patient safety and quality of life [38].

### **Enhancing Healthcare Team Outcomes**

Felty syndrome is a rare and complex condition that necessitates a high index of clinical suspicion for early diagnosis and prevention of severe complications. Because of its rarity and multifaceted presentation, an interprofessional approach is critical to optimize patient outcomes. A collaborative, multidisciplinary team ensures that all aspects of care—from diagnosis to long-term management—are addressed efficiently, with each healthcare professional contributing their specialized knowledge to deliver patient-centered care. Physicians and advanced practice providers are primarily responsible for establishing an accurate diagnosis and developing a comprehensive treatment plan. In addition to a rheumatologist overseeing disease-modifying antirheumatic drug (DMARD) therapy, a hematologist's input is essential to differentiate Felty syndrome from hematologic malignancies such as large granular lymphocyte (LGL) leukemia. Early consultation with an infectious disease specialist can further reduce morbidity by guiding infection prevention, prompt diagnosis, and targeted antimicrobial therapy in neutropenic patients. These collaborative efforts ensure that patients receive timely and precise interventions, reducing the risk of recurrent infections and other complications. Nurses play a vital role in both assessment and ongoing management. They assist in obtaining detailed histories, focusing on recurrent infections, gastrointestinal bleeding, and splenic discomfort, which may signal disease activity or emerging complications. Nurses also monitor treatment adherence, evaluate patient responses to therapy, and communicate changes in clinical status to the broader team. By maintaining close patient contact, nurses act as frontline observers who can identify early warning signs and facilitate prompt interventions [38].

Pharmacists complement this care by overseeing medication safety, particularly in patients receiving DMARDs such as methotrexate, where dosing errors or drug interactions can have significant consequences. Pharmacists also provide patient education regarding the benefits and potential adverse effects of medications, reinforcing adherence and promoting understanding of complex treatment regimens. Monitoring hematologic parameters, reviewing laboratory trends, and advising on therapy modifications are additional responsibilities that pharmacists bring to the interprofessional team. Effective communication is a cornerstone of high-functioning care teams. Clear, timely sharing of patient information, laboratory results, and treatment updates ensures that each professional can contribute optimally. Interdisciplinary meetings allow for coordinated decision-making, minimize duplication of services, and enhance continuity of care across clinical settings. This collaboration is particularly important in Felty syndrome, where rapid changes in neutrophil counts or acute infections require immediate, coordinated responses. Ongoing

education and professional development are also crucial for maintaining high-quality care. Healthcare providers must remain current on advances in diagnostic tools, treatment strategies, and evidence-based interventions for Felty syndrome. Coordinated team efforts not only enhance patient safety but also reduce errors, streamline workflow, and improve overall healthcare outcomes. By integrating the expertise of physicians, advanced practitioners, nurses, pharmacists, and other specialists, a cohesive interprofessional approach ensures that patients with Felty syndrome receive comprehensive, safe, and effective care. Through collaboration, continuous communication, and shared responsibility, interprofessional teams can significantly improve clinical outcomes, reduce complication rates, and enhance quality of life for patients with this rare and challenging disorder [38].

### **Conclusion:**

Felty syndrome remains a rare but clinically significant extra-articular manifestation of rheumatoid arthritis, marked by profound neutropenia, heightened infection risk, and systemic immune dysregulation. As highlighted in the article, the historical burden of morbidity and mortality has decreased substantially due to the availability of methotrexate, biologics, and supportive therapies such as G-CSF, all of which have transformed long-term prognosis. Despite these advances, timely diagnosis continues to be challenging, particularly because symptoms may be subtle or overshadowed by chronic RA activity. Persistent neutropenia, recurrent infections, and extra-articular features necessitate vigilant clinical assessment and early consideration of Felty syndrome in at-risk patients. Effective management requires an integrated, multidisciplinary approach involving rheumatology, hematology, infectious disease specialists, pharmacists, and nursing teams to ensure comprehensive monitoring, immunomodulatory therapy optimization, and rigorous infection prevention. The overlap between Felty syndrome and LGL leukemia further underscores the importance of detailed hematologic evaluation to guide appropriate treatment decisions. Ultimately, improved patient education, adherence to preventive measures, and close interprofessional communication are essential for reducing complications and enhancing quality of life. Continued research and clinical awareness remain critical to further improving outcomes in this complex immunologic-hematologic disorder.

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