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Felty's Syndrome

Vadim Gorodetskiy

Abstract

Felty's syndrome (FS) is an uncommon subset of seropositive rheumatoid arthritis (RA) complicated by neutropenia with or without splenomegaly. The pathogenesis of neutropenia in FS is still not fully understood, but it is believed that the principal cause is neutrophil survival defect. Autoantibodies against peptidylarginine deiminase type 4 deiminated histones, glucose-6-phosphate isomerase, and eukaryotic elongation factor 1A-1 antigen may contribute to neutropenia development in FS patients. Splenic histology in FS shows non-specific findings and spleen size do not correlate with neutropenia. Cases of T-cell large granular lymphocytic leukemia with low tumor burden in blood and concomitant RA are clinically indistinguishable from FS and present a diagnostic challenge. Examination of T-cell clonality, mutations in signal transducer and activator of transcription 3 gene, and the number of large granular lymphocytes in the blood can establish a correct diagnosis. Optimal approaches to therapy for FS have not been developed, but the use of rituximab seems promising. In this chapter, the epidemiology, pathogenesis, clinical manifestations, differential diagnosis, and treatment options for FS are discussed.

Keywords: Felty's syndrome, rheumatoid arthritis, neutropenia, splenomegaly, large granular lymphocyte leukemia

1. Introduction

In 1924, at Johns Hopkins Hospital, American physician Augustus Felty described five unusual cases with features of chronic arthritis, splenomegaly, and striking leukopenia [1]. In 1932, the eponym "Felty's syndrome (FS)" was first used by Hanrahan and Miller to describe these cases [2]. Currently, FS is considered an uncommon subset of seropositive rheumatoid arthritis (RA) complicated by neutropenia and splenomegaly [3]. Although splenomegaly represents one characteristic of the triad that defines FS, it is not an absolute requirement of FS diagnosis [4, 5]. T-cell large granular lymphocyte (T-LGL) leukemia in the setting of RA is the condition most likely to be confused with FS. Studies on FS should be considered with the caveat that almost all were performed without a study of T-cell clonality and, therefore, could include cases of RA-associated T-LGL leukemia (see "Diagnosis and differential diagnosis").

2. Epidemiology

About 1% to 3% of patients with RA develop FS [6]. However, with the evolution of RA pharmacotherapy, the frequency of FS has decreased substantially [7]. The mean age of the patients is 60 years, with a 1.5:1 female to male ratio [8].

3. Pathogenesis

There is firm evidence that the HLA-DRB1*04 genotype is a risk factor for FS development [9]. The exact pathophysiological mechanisms leading to development of neutropenia and splenomegaly in FS are unknown. It is believed, though, that neutrophil survival defect is the main cause of neutropenia [8, 10]. Several autoantibodies have been found in the serum of FS patients with higher frequency or at higher titers in comparison with seropositive RA patients without FS, which may contribute to neutropenia development, including:

- autoantibodies to H3, H4, and H2A histones deiminated by peptidylarginine deiminase type 4 [11];
- autoantibodies against glucose-6-phosphate isomerase [12];
- autoantibodies against eukaryotic elongation factor 1A-1 antigen [13];
- circulating immune complexes [14].

Autoantibodies against granulocyte colony-stimulating factor (G-CSF) were found in 73% patients with FS [15]. However, given that, in most cases, bone marrow in FS reveals normal myeloid cellularity or myeloid hyperplasia with increased granulopoiesis, relative excess of immature forms, and apparent lack of mature myeloid elements [8], the pathogenetic significance of anti-G-CSF antibodies in neutropenia development in patients with FS is unclear.

Some researchers question the significance of spleen sequestration/destruction in neutropenia pathogenesis [8]. However, neutrophils are found in periarteriolar lymphoid sheaths of the spleen even in patients with severe neutropenia [16]. In addition, removal of the spleen leads to restoration of normal neutrophil counts in most patients with FS.

4. Clinical manifestations

Clinical manifestations of FS and the frequency of signs/symptoms based on literature data [5, 14, 17–19] are presented in **Table 1**.

FS usually develops 10–15 years after RA presentation [14, 20], but in rare instances, neutropenia and splenomegaly may precede an arthritis history (non-articular Felty's syndrome) [21–24].

The erosive process in FS is typically severe, but this is related to the duration of RA before the onset of neutropenia and splenomegaly [6]. RA with FS is associated with more frequent and severe extra-articular manifestations than RA without FS [14, 20]. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are associated with severe extra-articular manifestations in patients with RA [25]. This is consistent with the finding that the vast majority of patients with FS have high titers of RF [14]. In our cohort of 25 patients with FS with a median duration of RA prior to FS diagnosis of 7 years, erosive arthritis at the time of FS diagnosis was detected in 77% of the patients. RF was within the normal range in only two cases, but the anti-CCP titers in these patients were highly positive [26].

Neutropenia (absolute neutrophil count of less than 1.500–2.000/ μ L) without a clearly identified cause is required, by definition, for the FS diagnosis. Neutropenia can manifest as increased frequency and severity of bacterial infections. However, despite reduced absolute neutrophil counts, patients with FS can remain free of infectious complications for extended periods of time.

Signs/symptoms	Frequency (%)
Major	
Rheumatoid arthritis	100
Neutropenia	100
Splenomegaly	90
Minor	
Rheumatoid nodules	53–82
Leg ulcers	16–41
Skin pigmentation	5–29
Hepatomegaly/portal hypertension	5–68
Serositis	0–22
Lymphadenopathy	0–34
Neuropathy	11–17
Episcleritis	0–8

Table 1.
Clinical manifestations of Felty's syndrome and the frequency of signs/symptoms.

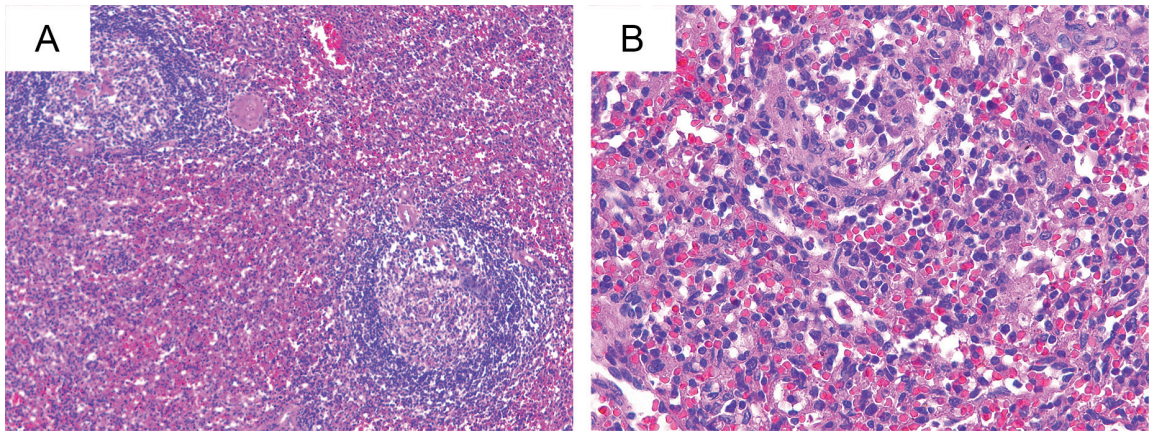


Figure 1.
Spleen histological examination in a patient with Felty's syndrome. (A) The spleen shows preservation of the white pulp with prominent germinal centers and lymphocytic infiltration of the red pulp (H&E, ×100). (B) Lymphocytes infiltrate both cords and sinusoids. The infiltration is more prominent within the splenic cords (H&E, ×400).

Splenomegaly is present in over 90% of patients with FS, but the spleen size does not correlate with neutropenia [14, 17, 19]. Splenic histology in FS shows non-specific findings (**Figure 1**). The red pulp shows expanded sinuses as well as the pulp cords, and an increased number of macrophages and plasma cells. The white pulp follicles are usually hyperplastic [18, 27, 28]. It is possible that portal hypertension secondary to nodular regenerative hyperplasia of the liver contributes to spleen enlargement in some patients with FS [29].

5. Diagnosis and differential diagnosis

FS should be suspected in a patient with RA, unexplained neutropenia, and splenomegaly. There is a wide range of pathologies in patients with RA that can manifest with neutropenia with or without splenomegaly. FS is a clinical diagnosis,

and there is no specific single diagnostic test to confirm or exclude it; therefore, FS is essentially a diagnosis of exclusion.

Neutropenia caused by drug therapy (drug-induced neutropenia) should be ruled out first. The most important treatment of drug-induced neutropenia is to withdraw the causative drug. The average time for full recovery of the neutrophil count is 9 days (range, 9–24 days) [30]. Methotrexate, cyclophosphamide, azathioprine, sulfasalazine, leflunomide, tocilizumab, tumor necrosis factor (TNF)-alpha antagonists, antimalarial medications, analgesics, and nonsteroidal anti-inflammatory drugs are the most common causes of drug-induced neutropenia in patients with RA [28]. It is important to keep in mind that unlike with other drugs, rituximab-induced neutropenia occurs after a median period of 4.5 months (range, 3–6.5 months) after the last rituximab infusion [31].

T-LGL leukemia is a rare type of mature T-cell neoplasm characterized by the clonal expansion of large granular lymphocytes (LGLs) and, in most cases, has indolent clinical course. Typical features of T-LGL leukemia include the increase in the number of peripheral blood LGLs, cytopenia (most commonly neutropenia), and variable splenomegaly. A peculiar feature of T-LGL leukemia is its association with RA, which occurs in 17–28% of patients with T-LGL leukemia [32, 33]. Historically, a definitive diagnosis of T-LGL leukemia required the increase in the number of LGLs in peripheral blood greater than $2 \times 10^9/L$, but it is now recognized that a lower count (range, $0.4\text{--}2 \times 10^9/L$) may be compatible with the diagnosis [34–36].

Cases of T-LGL leukemia in the setting of RA (RA-associated T-LGL leukemia) with low LGL count in peripheral blood and concomitant neutropenia are clinically indistinguishable from FS and diagnostically challenging. RA-associated T-LGL leukemia and FS are distinguished in clinical practice by evaluation of rearrangements of the T cell receptor (TCR) gamma and TCR beta genes in the blood and/or in the bone marrow. The monoclonal rearrangements of the TCR genes (T-cell clonality) are present in T-LGL leukemia but not in FS (**Figure 2**) [3, 8, 37]. However,

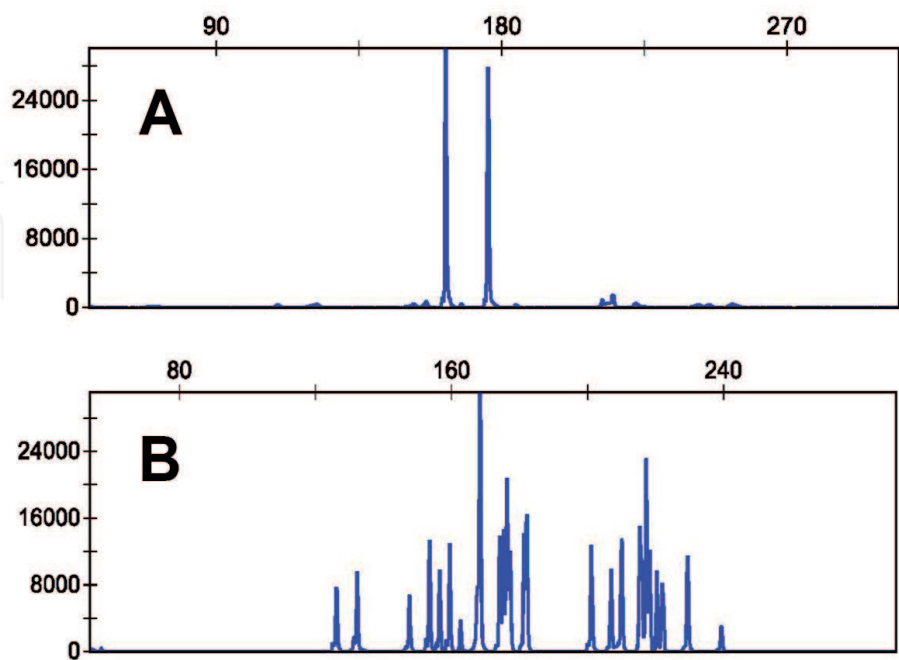


Figure 2. Evaluation of T-cell clonality based on rearrangements of the T-cell receptor (TCR) genes. (A) TCR genes show monoclonal rearrangement in T-LGL leukemia. (B) TCR genes show polyclonal rearrangement in Felty's syndrome.

there is considerable discussion regarding the significance of dominant T-cell clones as a hallmark of T-cell malignancy because clonal populations of T-cells are observed both in healthy individuals and in exuberant reactive responses [38–43]. Activating somatic mutations in the signal transducer and activator of the transcription 3 (STAT3) gene and an increase in the number of LGLs above $2 \times 10^9/L$ were detected in RA-associated T-LGL leukemia but not in FS (39% vs. 0% and 21% vs. 0%, respectively) [26]. In addition, the expression of the CD57 antigen and the aberrant (diminished or absent) expression of CD5 on cytotoxic CD3 + CD8+ T-lymphocytes are more typical for T-LGL leukemia than in the polyclonal expansion of cytotoxic T-lymphocytes in FS [26]. In contrast, it seems that the current criteria for bone marrow involvement in T-LGL leukemia do not seem to be sufficiently specific to distinguish it from FS [8, 26].

Aplastic anemia, myelodysplastic syndromes, or acute leukemia can sometimes present with isolated neutropenia. To rule out these pathologies, a bone marrow examination should be considered. In rare cases, cirrhosis, amyloidosis, lymphomas involving spleen, sarcoidosis, or infections can lead to splenomegaly in patients with RA.

6. Management

In two earlier analyzes of survival in FS, 5-year mortality ranged from 25% to 36% [5, 44]; however, recent data regarding the prognosis of FS are not available. The treatment goal in FS is a reversal of the neutropenia to prevent recurrent bacterial infections and sepsis, which is the leading cause of death in patients with FS. The treatment strategy for FS is not evidence-based because of the lack of controlled trials.

Methotrexate (MTX) is considered the first-line therapy for treatment of FS based on case reports and case series data. Low doses of MTX (up to 25 mg once a week) can improve both joint diseases and neutropenia, usually within 1–2 months.

One recent literature review supported the use of rituximab (RTX) as a second-line therapy. A sustained increase in the absolute number of neutrophils was observed in 62.5% of FS patients during the 3 months following one cycle of RTX treatment [45]. The appropriate dosing schedule of RTX for treatment of FS remains uncertain, but most often patients receive two 1000 mg doses separated by 15 days [46]. Some patients had a recurrence of neutropenia after RTX treatment, indicating that in some cases a sustained response may require maintenance therapy with RTX.

There is very limited evidence regarding the leflunomide efficacy in FS [47]. TNF-alpha inhibitors (adalimumab, etanercept, and infliximab) are ineffective in FS [45].

Splenectomy maintained normal neutrophil counts in 80% of patients with FS [10]. However, the indications for splenectomy are now limited because of effective medications and the risk of post-splenectomy sepsis.

The results of treatment with glucocorticoids (GCs) in patients with FS are variable. GCs can provide a rapid improvement in neutrophil count by stimulating the release of mature cells from the bone marrow and mobilizing them from the marginal pool, thus, creating the effect of increasing their absolute number. However, to achieve a real clinical effect, high doses and prolonged use of GCs may be required, which increases the risk of infection in patients with FS.

G-CSF can be used for treatment of FS patients with life-threatening infections.

7. Conclusion

Although nearly 100 years have passed since the first description of FS, this pathology remains a mystery in many aspects. The pathogenetic mechanisms underlying neutropenia and spleen enlargement in these patients are poorly understood. Optimal approaches to therapy for this rare disorder have not been developed, but the use of rituximab seems promising.

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Conflict of interest

The author declares no conflict of interest.

Author details

Vadim Gorodetskiy

Department of Intensive Methods of Therapy, V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia

*Address all correspondence to: gorodetskiyblood@mail.ru

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