Felty's syndrome

What is Felty's syndrome?[1]

Felty's syndrome refers to a severe form of rheumatoid arthritis (RA) that often presents clinically with splenomegaly and neutropenia. This triad of features do not have to be complete in all patients, but neutropenia (absolute neutrophil count of less than 1500/mm3) must be present for the diagnosis. Felty's syndrome was first described by Dr Augustus Felty in 1924.

How common is Felty's syndrome? (Epidemiology)[1]

- Felty's syndrome is a rare condition that has been reported to present in 1–3% of patients with rheumatoid arthritis.
- It is more prevalent in women, often diagnosed during the fifth to seventh decade of life.
- The incidence is higher in Caucasian populations.
- Felty's syndrome is also often seen in patients having chronic active RA for 10 or more years, positive for rheumatoid factor (RF), and positive for HLA-DR4.

Aetiology

The precise cause is unknown.

- Felty's syndrome is an autoimmune disease. The loss of immunological tolerance to self-antigens can cause neutropenia through both peripheral immunological destruction and impaired granulopoiesis. This is traditionally described as a cell-mediated destruction. However, humoral immunity might be important as well in causing neutropenia.[2]

- Felty's syndrome is associated with the HLA-DR4 genotype. This genotype is a marker for more aggressive RA with greater extra-articular manifestations.[3]
- **NB**: there is a considerable clinico-laboratory overlap between T-cell large granular lymphocytic (T-LGL) leukaemia associated with RA and Felty's syndrome.[4] This suggests that they are just different eponyms for the same clinical entity.[3]

Felty's syndrome symptoms (presentation)[1]

Overview

- Felty's syndrome may be asymptomatic but serious local or systemic infections may be the first clue to the diagnosis.[5]
- As a result of neutropenia, affected persons are increasingly susceptible to infections (see 'Complications', below).
- The clinical picture of RA in this scenario is usually one of severe joint destruction contrasting with moderate or absent joint inflammation; and severe extra-articular disease - eg, including rheumatoid nodules, lymphadenopathy, hepatopathy, vasculitis, leg ulcers and skin pigmentation.
- Additional features associated with Felty's syndrome include anaemia and thrombocytopenia.

Symptoms

- Fatigue.
- Anorexia.
- Weight loss.
- Fever.
- Mucosal and skin ulceration.
- Eye symptoms (including dry eyes and irritation due to Sjögren's syndrome and red and painful eyes due to episcleritis).
- Recurrent infections due to neutropenia (lung and skin infections are most common).

- Left upper quadrant pain (due to splenomegaly or splenic infarcts).
- Symptoms related to RA, including joint swelling, pain, stiffness and deformity.

Signs

- Splenomegaly.
- Hepatomegaly.
- Lymphadenopathy.
- Typical RA joint deformities ± active synovitis causing joint swelling and tenderness.
- Pallor.
- Rheumatoid nodules.
- Features of vasculitis - leg ulcers, brown pigmentation on the legs, periungual infarcts, ischaemia of the extremities.
- Peripheral neuropathy.
- Eye involvement, including episcleritis.

Investigations and diagnosis

There is no specific diagnostic criterion for Felty's syndrome. It is a clinical diagnosis in patients with RA with unexplained neutropenia and splenomegaly.[6]

Relevant investigations may include:

- Blood tests:
    - FBC - for neutropenia ± anaemia of chronic disease.
    - Autoantibodies - rheumatoid factor and anti-CCP antibody.
    - Inflammatory markers (ESR and CRP) may be elevated.
    - LFTs - may be raised if there is liver involvement (see 'Complications', below).

- Radiology:
    - Ultrasound or CT scan to evaluate splenomegaly.
- Bone marrow biopsy:
    - May be required to differentiate Felty's syndrome from haematological malignancies - eg, non-Hodgkin's lymphoma.

Felty's syndrome treatment and management

As Felty's syndrome is rare, information about management relies on small studies and case reports. This condition is difficult to treat and associated with a poor prognosis due to the substantial risk of infections.

Treatment to improve neutropenia

- Immune-modulating drugs: some of these may be the same drugs used to treat the underlying RA.
- Methotrexate is usually first choice, as there is most experience with this drug.
- Various disease-modifying antirheumatic drugs (DMARDs) have been used with mixed success and few data are available on the use of biological agents that might even increase the infection risk.[2]
- Other DMARDs, including hydroxychloroquine, ciclosporin A, sulfasalazine, leflunomide, azathioprine and cyclophosphamide, have also been used in the treatment of Felty's syndrome.[7]
- Rituximab has been used with encouraging results.[2] [8] [9] It is usually reserved for use as a second-line treatment in those patients with refractory Felty's syndrome.[10]
- Other biological agents include the anti-tumour necrosis factor alpha agents, etanercept, infliximab and adalimumab.
- Treatment with granulocyte colony-stimulating factor is a safe and effective treatment in the management of neutropenia associated with Felty's syndrome.[11]

- The dose and frequency of the recombinant human granulocyte colony-stimulating factor should be adjusted at the lowest effective dose.
- Splenectomy is generally reserved for those not responding to medical treatment. Splenectomy is also the treatment of choice for complications of portal hypertension in patients with Felty's syndrome. [12]
- Prevention of infection:
    - Immunisation against influenza and pneumococcus.
    - Patient awareness to seek immediate treatment for symptoms of infection.
    - Splenectomy patients require additional measures for prevention of infection (see separate article Splenectomy, Hyposplenism and Asplenia).

Management of splenomegaly

Advise patients about activities, depending on their infection risk and spleen size. For example, advise patients to avoid any activity that could result in blunt trauma to the left upper quadrant (re the risk of splenic rupture).

Management of infectious complications

The most common infections in this scenario affect the skin, mouth, and upper and lower respiratory tract. Any infection should be identified and treated promptly (eg, take swabs/cultures, give appropriate antibacterial or antifungal treatment, etc).

Prognosis

- Overall, patients with Felty's syndrome have a poorer prognosis than those with uncomplicated RA. They have increased morbidity and mortality from infections and malignancy.
- Serious infection is the main cause of death.
- As with all patients with RA, patients with Felty's syndrome also have an increased risk of cardiovascular disease.

- The degree of neutropenia in Felty's syndrome varies with time, and spontaneous remission of neutropenia can occur in up to 40% of patients without specific treatment. However, these patients remain at increased risk of infection despite normal neutrophil counts.

Further reading

- Patel R, Akhondi H; Felty Syndrome. StatPearls, July 2022.
- Klein A, Molad Y; Hematological Manifestations among Patients with Rheumatic Diseases. Acta Haematol. 2021;144(4):403-412. doi: 10.1159/000511759. Epub 2020 Nov 20.

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