CASE REPORT

Neutropaenia and splenomegaly without arthritis: think rheumatoid arthritis

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SUMMARY

Felty syndrome (FS) is an uncommon, but severe, extra-articular manifestation of rheumatoid arthritis (RA). It occurs in patients with longstanding RA. It is extremely rare for RA to present as FS or develop after initially presenting as neutropaenia and splenomegaly. We describe a case of 47-year-old woman who was diagnosed simultaneously with FS and possible RA after testing positive for anticyclic citrullinated peptide antibody, but a negative rheumatoid factor. She had an excellent response to methotrexate. We review the existing literature of such cases and emphasise the importance of serological testing for RA in patients presenting with neutropaenia and splenomegaly, even in the absence of joint symptoms or prior diagnosis of RA.

BACKGROUND

This case identifies the very rare presentation of Felty syndrome (FS), also known as Felty's syndrome, as the initial presentation of rheumatoid arthritis (RA). We aim to highlight the importance of considering RA as a diagnosis in patients with neutropaenia and splenomegaly, even in the absence of symptoms or previous history of arthritis. The case is relevant to the disciplines of internal medicine, haematology and rheumatology.

CASE PRESENTATION

A 47-year-old woman presented to her primary care provider with a 1 week history of low-grade fever, fatigue and a sore throat. She also complained of new onset pain and swelling in her hands, pain in her feet and shoulders accompanied by morning stiffness for up to 60 min. Initial workup revealed pancytopenia and an elevated C reactive protein (CRP). A complete blood count (CBC) 1 year prior to this was normal. Azithromycin was prescribed for possible pharyngitis and she was referred to haematology for the pancytopenia. While on antibiotics, she developed light-headedness, joint pain and presyncope requiring evaluation in our emergency department. Her medical history was significant for well-controlled asthma, treated hypothyroidism and history of herpes zoster. She worked as a veterinary technician, but there was no history of any zoonotic diseases, tuberculosis or animal or tick bites. Family history was negative for autoimmune diseases. She did not smoke. Examination revealed pallor, tachycardia, hypertension and

a systolic ejection murmur. Synovitis and rheumatoid nodules were absent and hepatosplenomegaly was not detected.

INVESTIGATIONS

Laboratory testing again showed pancytopenia. Her haemoglobin was 9.4 g/dL (normal: 13.5–17.5), platelet count was $131 \times 10^9/L$ (normal: 151–355) and absolute neutrophil count (ANC) was $0.14 \times 10^9/L$ (normal: 1.4–6.6). Mild hypokalaemia was present. Urinalysis and chest X-ray were normal. She was admitted for further evaluation with suspicion of a viral illness. Labs including liver function tests, renal function, ferritin and serological tests for Parvovirus B19, Epstein–Barr virus, hepatitis B and C virus, HIV, cytomegalovirus, coccidioidomycosis, histoplasmosis and Brucella were negative. Peripheral smear showed polychromasia without schistocytes. Antinuclear antibodies (ANA), extractable nuclear antigens, antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, CRP and rheumatoid factor (RF) were negative. Anticyclic citrullinated peptide antibody (anti-CCP) was strongly positive. Bone marrow biopsy showed hypercellular bone marrow (50%–80% cellular) with trilineage haematopoiesis and showed no evidence of large granular lymphocytic (LGL) leukaemia. Patient was discharged for outpatient follow-up with haematology and rheumatology. X-rays of hands and feet did not reveal any erosions. Abdominal ultrasound revealed marked splenomegaly (19 cm) without hepatomegaly or adenopathy, which was then confirmed on physical examination as well. Positron emission tomography scan was done to evaluate for an infiltrative process since no other cause for the splenomegaly was discernible. It did not reveal any abnormal organ uptake or marrow involvement. Flow cytometry of the peripheral blood and bone marrow aspirate and bone marrow cytogenetic studies were unremarkable.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses included infections, myeloproliferative syndromes, systemic lupus erythematosus and sarcoidosis. Extensive workup was done to cover common causes of neutropaenia as well as infectious causes due to her exposure to animals. Fungal workup was done since coccidioidomycosis is endemic in Arizona. Infections were ruled out in the absence of fever and extensive negative testing. Normal lung imaging, bone marrow and positron emission tomography scanning excluded sarcoidosis and myeloproliferative

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syndromes. Autoimmune labs including ANA, RF and anti-CCP were done to see if the pancytopenia and the new-onset joint pain were reflective of any underlying autoimmune disorder. Since the blood smear lacked any signs of hypersplenism, for example, spherocytes, hypersplenism was considered unlikely. In the absence of an identifiable cause of neutropaenia, the positive anti-CCP and arthralgias, led to an abdominal ultrasound that revealed splenomegaly.

TREATMENT

The presence of arthralgias, splenomegaly, anti-CCP and neutropaenia, in the absence of any other identifiable cause for her symptoms despite an extensive workup, led to a diagnosis of RA presenting as FS. There was some spontaneous improvement in the haemoglobin and platelet count (while still remaining below normal) but the ANC continued to decline. The declining ANC, risk of infection and ongoing arthralgias prompted the initiation of treatment with methotrexate 10 mg weekly.

OUTCOME AND FOLLOW-UP

On subsequent follow-up, all her blood counts had normalised and the arthralgias resolved. At 6-month follow-up, she continued to do well clinically and her CBC remained normal.

DISCUSSION

FS consists of the triad of RA, splenomegaly and neutropaenia. It is a rare and severe extra-articular manifestation of RA affecting about 1% of patients with RA.¹ Patients with FS have an increased risk for developing life-threatening bacterial infections and increased mortality. The pathophysiology of neutropaenia in FS is multifactorial, including increased neutrophil sequestration in the spleen, peripheral destruction of neutrophils and failure of bone marrow to produce neutrophils.² Patients with RA and FS are reported to have elevated levels of antibodies against granulocyte colony-stimulating factor (G-CSF) that can contribute to the neutropaenia.³ A role for immune complexes and proinflammatory cytokines through functional inhibition of neutrophils and bone marrow inhibition of cell formation has been found as well.^{4,5} FS develops after an average of 16 years of RA⁶ and is more common in patients with a phenotype of destructive erosive RA. Global incidence of FS is decreasing due to better control of RA. It is extremely rare for RA and FS to present simultaneously. However, it is important to consider RA as a possible cause of neutropaenia with splenomegaly if no other aetiology is identified even if they do not have a prior diagnosis of RA and have no arthritis signs or symptoms. We present one such case and briefly review the existing literature to better guide approaching such cases.

Since FS is a late manifestation of severe active RA, a high index of suspicion and awareness is needed in patients presenting with neutropaenia and splenomegaly with no identifiable cause. LGL leukaemia must be considered, since 30%–40% of FS cases may have LGL expansions.⁷ However, this was not reported in any of the cases we reviewed. Other differential diagnoses include viral illnesses, myeloproliferative syndromes, systemic lupus erythematosus and sarcoidosis. Table 1 provides a summary of the reported cases in the English literature, including our case, of RA presenting as FS or RA developing after the occurrence of FS.

FS is more common in females, as is RA. Ages at presentation ranged from 21 to 76 years, but the fifth decade was the modal age group. All patients presented with neutropaenia and splenomegaly. Most did not have arthritis symptoms at presentation, but a majority developed RA symptoms during follow-up with

Table 1 Review of cases of FS without prior active RA

Number	Year	Author/Reference	Age	Gender (M/F)	RF	CCP	Splenomegaly/Neutropaenia	Arthritis/arthralgia at presentation	Erosive disease	Treatment	Follow-up	Developed arthritis
1	1974	Cornwell ¹⁶	56	M	+	NA	+/+	None	NA	Cyclophosphamide	3 years	None
2	1982	Heyn, case #1 ¹⁷	76	F	+	NA	+/+	None	Yes	Lithium carbonate	NA	NA
3	1982	Heyn, case #2 ¹⁷	55	M	+	NA	+/+	None	Yes	NA	1 year	Yes
4	1983	Armstrong, case #1 ¹⁸	73	F	+	NA	+/+	None	Yes	NA	4 years and 7 months	Yes
5	1983	Armstrong, case #2 ¹⁸	57	F	+	NA	+/+	Yes*	Yes	NA	2 years	Yes
6	1983	Armstrong, case #3 ¹⁸	72	F	+	NA	+/+	None	Yes	NA	10 years	Yes
7	1983	Bradley ¹⁸	66	F	+	NA	+/+	None	NA	Splenectomy	10 months	Yes
8	1984	Fitzgerald ¹⁹	58	M	+	NA	+/+	None	Yes	Splenectomy	1 year	No
9	1989	Cycowitz ²⁰	34	F	+	NA	+/+	None, previous RA diagnosis	Yes	Prednisone	15 months	No
10	2009	Chavalitthamrong ²¹	31	M	+	+	+/+	None	No	Methotrexate, G-CSF	NA	No
11	2010	Muroi ²²	52	F	+	+	+/+	Yes, prior RA suspicion	No	Splenectomy	NA	Persisted
12	2013	Rozin ²³	57	M	+	+	+/+	None	No	Prednisone, Methotrexate	NA	NA
13	2015	Jain ²⁴	73	F	+	+	+/+	None	No	Prednisone	NA	NA
14	2016	Lagrutta ²⁵	56	F	+	+	+/+	None, previous RA diagnosis	Yes	Splenectomy, Prednisone, Colchicine, Azathioprine, Methotrexate	Within 1 year	Yes
15	2018	Our case	47	F	-	+	+/+	Yes	No	Methotrexate	6 months	Treated

*Had extensor tendon sheath swelling.

CCP, cyclic citrullinated peptide; FS, Felty syndrome; G-CSF, granulocyte colony stimulating factor; NA, not available; RA, rheumatoid arthritis; RF, rheumatoid factor.

one case developing arthritis 10 years after the initial presentation.⁸ Of note, erosive disease was present on X-rays despite the absence of arthritic symptoms. With greater availability of ultrasound and MRI, presence of synovitis could be detected much earlier, perhaps even in patients who have no clinical symptoms.

All patients were positive for RF except our case. After anti-CCP testing became available, all patients tested positive for anti-CCP including our patient. Therefore, testing for both RF and anti-CCP should be done in such cases rather than relying on the RF alone. Anti-CCP antibodies are a highly specific marker for RA with an estimated specificity of around 96%.⁹ A significant number of patients may not have a positive RF. As expected in an early phase RA disease presentation, no other extra-articular features such as vasculitis were present.

Some of these patients did not fulfil the 2010 classification criteria for RA¹⁰ at presentation, but then some patients subsequently developed synovitis and had erosive disease, making any competing diagnosis, if any, unlikely. It is also well established that RF and anti-CCP can predate the onset of clinical RA by many years¹¹ and these cases are likely representative. Our patient also did not fulfil the RA criteria. The European League against Rheumatism has recently identified patient characteristics predictive of future development of RA. They have labelled such patients as having clinically suspect arthralgia.¹² Our patient also fits in this category.

Multiple physical examinations failed to detect the splenomegaly until after the ultrasound identified it. It is not clear from the medical records if percussion was used to assess for splenomegaly. The physical examination notes simply stated 'no hepatosplenomegaly'. Percussion is more sensitive than palpation for detecting splenomegaly. Overall clinical examination has a low sensitivity and high specificity for splenomegaly.¹³ Imaging should be used for clinical suspicion of splenomegaly. It would be a matter of speculation to state how an earlier detection of splenomegaly would have altered, if at all, our case. This case, however, does emphasise the importance of a directed and proper physical examination.

Since neutropaenia remains a very common and important feature of FS, management is directed towards reversal of granulocytopenia to facilitate resolution of ongoing infections and to prevent recurrent infections. General treatment principles follow that of RA. Methotrexate is the most common and widely used drug with good results as in our case.¹⁴ Other options include corticosteroids, hydroxychloroquine, leflunomide and azathioprine. Of the biological agents, rituximab remains a possible therapeutic option.¹⁵ Tumour necrosis factor inhibitors have no role in the management of FS.¹⁵ There is no role for prophylactic splenectomy,

although it may be indicated in severe cases with frequent infections. Neutropaenia may recur in 25% of patients even after splenectomy.² G-CSF has no effect on RA activity, but is effective to treat the neutropaenia, when indicated.

FS is not a very common entity, but can lead to serious life-threatening infections and therefore, understanding its possible association with RA is important. Our case serves to highlight the importance of testing for RA by checking both RF and anti-CCP even in the absence of articular symptoms. Such patients should then be referred to rheumatologists for evaluation since they may already manifest findings of RA or may develop it in the future.

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Learning points

- Felty syndrome (FS) can be a cause of neutropaenia and splenomegaly in patients without a prior diagnosis of rheumatoid arthritis (RA) or active joint symptoms.
- Rheumatoid factor (RF) alone is not a sufficient screening test for RA in suspected FS cases.
- Testing for RF and anticyclic citrullinated peptide antibody (anti-CCP) should be a part of the workup for neutropaenia and splenomegaly even in the absence of joint symptoms once other causes have been ruled out.
- Those patients who do test positive for RF and anti-CCP should have baseline X-rays of the hands and feet and referred to a rheumatologist as an inflammatory arthritis may develop in the future.

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