Case report

Felty's syndrome – a rare case of febrile neutropenia

Luís Rodrigues*,[1], Glória Nunes da Silva[2], António Pais de Lacerda[3]

[1]Thorax Department, Centro Hospitalar Universitário Lisboa Norte, Portugal; [2]Medicine 3, Medicine Department, Centro Hospitalar Universitário Lisboa Norte, Portugal; [3]Medicine Department, Centro Hospitalar Universitário Lisboa Norte and Faculty of Medicine, University of Lisbon, Portugal

Abstract

Felty's syndrome (rheumatoid arthritis with neutropenia and splenomegaly) is a rare condition with poor long-term prognosis, mainly as a result of severe infection risk. An effective treatment strategy has not been developed so far and current treatment options are based upon case reports, small series and clinical experience since no randomized clinical trials are available. The authors describe the case of a 53-year-old female patient with a 14-year history of rheumatoid arthritis presenting with fever, neutropenia and splenomegaly. Broad-spectrum antibiotics and granulocyte colony-stimulating factor were administered with good clinical outcome and low dose methotrexate for disease control was successfully initiated after discharge. We would like to highlight the importance of being aware of this syndrome in the differential diagnosis of long term rheumatoid arthritis patients presenting with febrile neutropenia.

Keywords: *Felty's syndrome; rheumatoid arthritis; febrile neutropenia*

Introduction

Felty's syndrome (FS), characterized by the triad of seropositive rheumatoid arthritis (RA), neutropenia and splenomegaly was first described in 1924 [1, 2]. Less than 1% of RA patients develop FS and usually after more than 10 years of disease progression [3], prognosis is poor, increased mortality is related to the higher incidence of severe infection, with up to 36% 5-year mortality [4].

Joint involvement is not mandatory for the diagnosis and is not present in 15-40% of cases. When present, it is usually significantly more advanced [5]. Splenomegaly can be detected in physical examination in >90% of patients [6], ultrasonography or radionuclide scanning can confirm this finding. The spleen size does not correlate either with the degree of neutropenia or with the severity of arthritis [7, 8].

Even though the complete triad is not indispensable for the diagnosis, persistent neutropenia with absolute neutrophil count below 1500/mm^3 is necessary [9] and predisposes to recurrent bacterial infection that can lead to septic shock. Pathophysiology of FS associated neutropenia is caused by diverse factors, including increased spleen sequestration, antibody and immune complex mediated peripheral destruction and bone marrow failure [5, 10-12].

Case report

The authors present the case of a 53-year-old female patient admitted to the Internal Medicine infirmary with febrile neutropenia. Patient history revealed RA diagnosis 14 years before, with no significant joint destruction. She was initially medicated with low dose MTX, but abandoned treatment and follow-up.

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*Corresponding author: Luís Rodrigues, Pulmonology - Thorax Department, Centro Hospitalar Universitário Lisboa Norte, Avenida Professor Egas Moniz, 1649-035 Lisbon, Portugal.
Email: lfr_med@hotmail.com

For the past 4 years she had low neutrophil counts (2000 – 3000/mm^3), with no history of recurrent infections. One month prior to her admission a lower neutrophil count (<500/mm^3) is detected in a routine check-up, she remained asymptomatic and the physical examination was normal. She was referred to the hematologist who performed a myelogram that showed neutrophils maturation arrest, polymorphonuclear decrease, no evidence of significant myelodysplasia and no cytological evidence of pathological infiltrates (Figure 1). Osteomedullary biopsy revealed no blasts or infiltration by foreign cells. Medullary immunophenotyping revealed neutrophil and erythroid maturation arrest, as well as non-clonal increased monocytic and T cell lines.

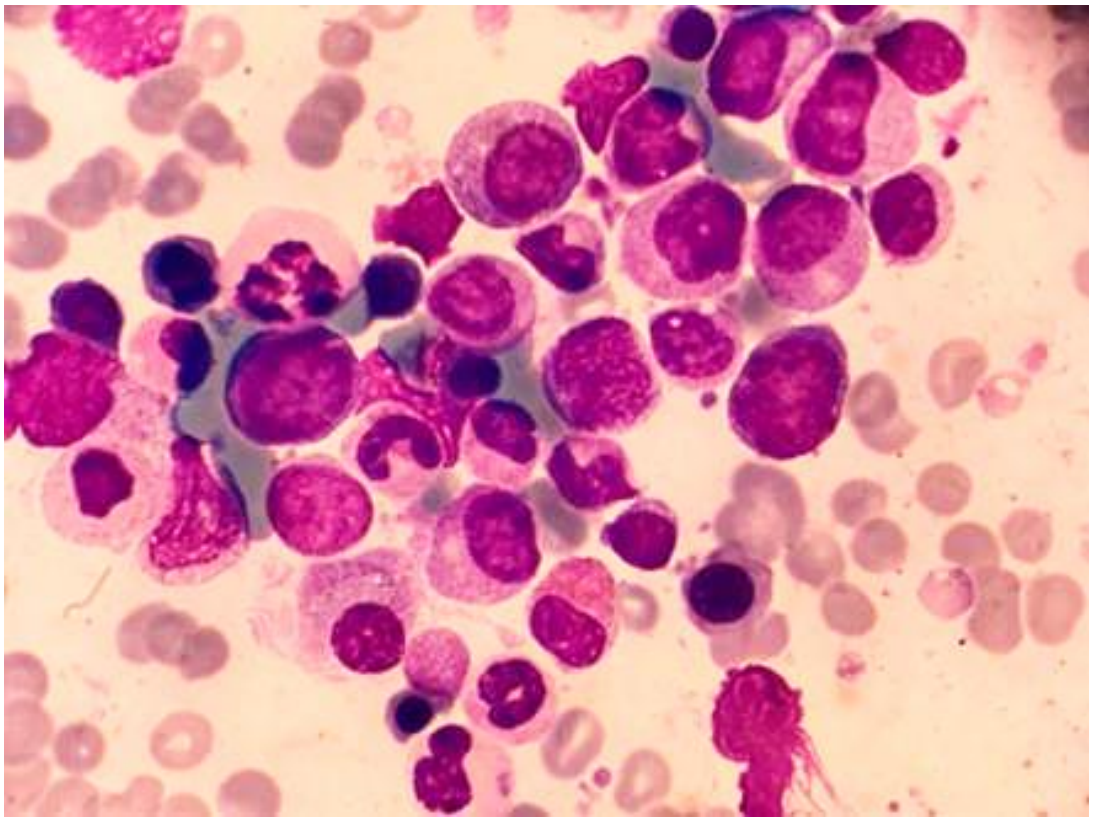

Fig. 1. Mielogram (Wright-Giemsa stain)

The patient then presented to the Emergency Department with a 3 day history of fever (38.5ºC), with no other symptoms and no alterations in the physical examination suggestive of an infectious focus. The initial laboratory evaluation revealed leucopenia (2610/mm3), neutropenia (440/mm^3) and thrombocytopenia (40000/mm^3), a slight increase in C-reactive protein (CRP) 2,81mg/dL. Urinalysis was normal, as where chest and abdominal X-rays. She was admitted to the infirmary for treatment and diagnostic investigation of febrile neutropenia.

After collection of blood and urine for microbiological examination empirical antibiotic therapy was initiated with Piperacillin/Tazobactam (4,5G 8/8h – 8 days) and Vancomycin (initial dosage 1G 8/8h and afterwards adjusted according to concentration measurements – 20 days) associated with daily G-CSF administration.

In order to investigate possible causes of infection and/or neutropenia abdominal ultrasonography was performed and revealed splenomegaly (Figure 2). Thoracic, abdominal and pelvic computed tomography confirmed the presence of splenomegaly with homogeneous density and presented no other relevant changes (Figure 3). Transthoracic echocardiography excluded lesions suggestive for bacterial endocarditis.

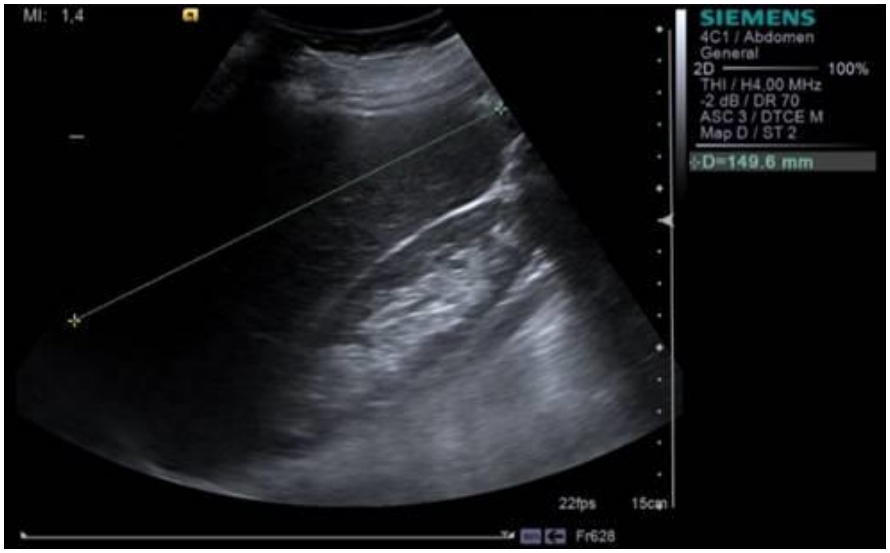

Fig. 2. Abdominal ultrasound revealing splenomegaly

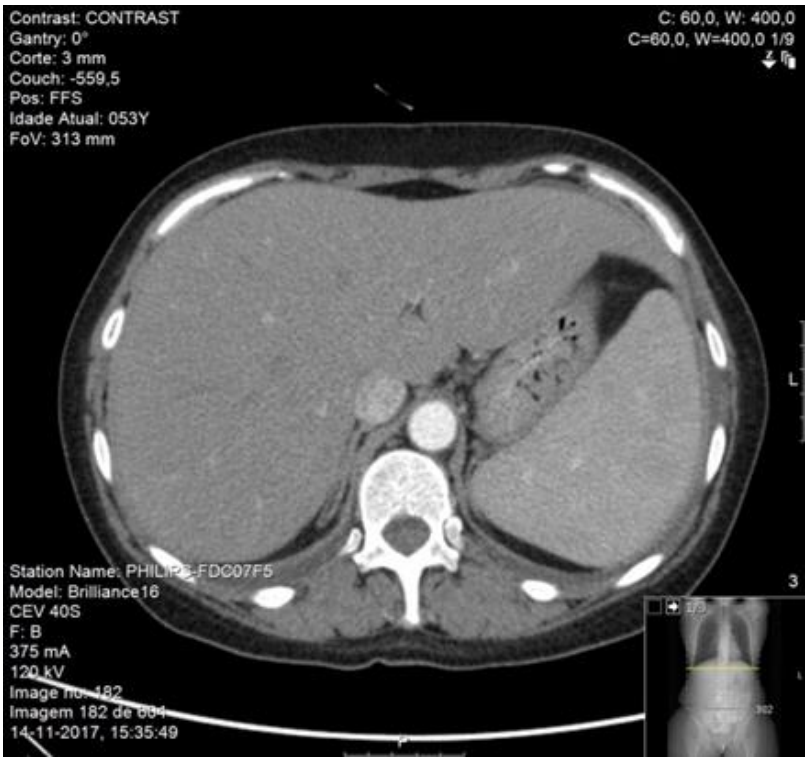

Fig. 3. Abdominal CT revealing splenomegaly

Additional laboratory data demonstrated high levels of Rheumatoid Factor (73,8IU/mL) and Anti-Citrulline Antibody (8646IU/mL). Serologies for HIV, Hepatitis, Syphilis, Q Fever, Mediterranean spotted fever, Brucellosis, Cytomegalovirus, Parvovirus and Epstein Barr Virus were negative. Seriated blood (including a medullary blood sample) and urine cultures were also negative.

Initial response to treatment was satisfactory with progressive elevation of white blood cell (WBC) and neutrophil counts, reaching normal values after 3 days of treatment; therefore G-CSF therapy was discontinued. We witnessed a new fall in WBC counts with the need for its re-introduction 7 days later, we opted this time for administration of the drug on alternate days, again witnessing a gradual rise that remained stable even after changing to a 4-day interval between administrations (Table 1).

Table 1. Laboratory results progression

Test Name	Reference range	Day 1	Day 3	Day 5	Day 8	Day 10	Day 15	Day 20
WBC	4000-11000/mm^3	2610	6950	2850	2890	2080	5710	5940
Neutrophils	1900-7500/mm^3	440	4.870	1.740	1.680	950	3.320	3.640
Hemoglobin	12,0-15,3g/dL	12,5	12,1	10,1	10,4	10,8	10,0	10,1
Platelets	150000-450000/mm^3	40000	84000	85000	99000	141000	156000	161000
CRP	<0,5mg/dL	2,81	1,62	1,18	-	0,960	0,750	0,400
Procalcitonin	<0,5ng/mL	0,26	-	-	-	0,05	-	-
Rheumatoid Factor	<14IU/mL	-	-	73,8	-	-	-	-
Anti-Citrulline Antibody	<20IU/mL	-	-	8646	-	-	-	-

(WBC: White blood cells; CRP: C-reactive protein)

The patient remained afebrile and had decreasing values of CRP during the first 7 days of treatment, on the 8th day fever reappeared, considering the high risk of infectious complications antibiotic coverage was adjusted, Piperacilin/Tazobactam was suspended and Meropenem (1G 8/8h – 12 days) was introduced maintaining Vancomycin. Fever subsided and CRP maintained a downward tendency with subsequent normalization. Procalcitonin measurements were normal throughout hospital stay (Table 1). Hospital discharge was 22 days after admission, by then patient was afebrile for over a week, had no clinical or laboratory signs suggestive of infection and normal WBC and neutrophil counts. She was referred to rheumatology and hematology consultations immediately after discharge in order to establish an appropriate outpatient therapeutic plan. Since then low dose MTX treatment (10mg once a week) has been successfully initiated, 6 months after discharge she maintained low neutrophil counts (2000–4000/mm^3), with no signs of infection and no need for G-CSF administration.

Discussions

In the presence of splenomegaly, long term neutropenia and fever in a patient with a >10 years history of RA and after exclusion of hematological disease or infection by a myelosuppressive agent the diagnosis of FS and bacterial infection by an unidentified agent was admitted.

Treatment is based upon case reports, small series and clinical experience, because no randomized clinical trials are available [5]. Glucocorticoids and granulocyte colony stimulating factor (G-CSF) are used to raise the granulocyte count and broad-spectrum antibiotics covering the most important bacterial or fungal agents to counter infection [4]. The mainstay of treatment are disease-modifying anti-rheumatic drugs (DMARDs), low dose methotrexate (MTX) is usually the initial drug of choice. Patients unresponsive or intolerant to methotrexate may be treated with an alternative agent as azathioprine, leflunomide or tumor necrosis factor inhibitors [2, 3, 13]. Splenectomy is a therapeutic alternative usually reserved for refractory patients as it can improve neutropenia but does not provide a long-lasting effect [6].

In this particular case, for safety concerns, we decided to initiate MTX only after complete recovery of the exacerbation with very satisfactory clinical outcome. A close follow-up will be maintained, in accordance to the expected poor prognosis due to high risk of infectious complications.

Conclusion

We report a rare cause of febrile neutropenia secondary to long term RA. This case highlights the importance of being aware of this syndrome in the differential diagnosis of such patients.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare to have no conflict of interest directly or indirectly related to the manuscript contents. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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