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Case Report Open Access

Early onset of Felty syndrome or leukemia: A case report

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Felty syndrome is a form of rheumatoid arthritis (RA) that usually presents with neutropenia and splenomegaly. It usually occurs in the setting of long-lasting (RA)and rarely as an early manifestation of RA.

Case presentation: A 47-year-old female patient presented to the emergency department with a history of fever and arthralgia. She was found to have splenomegaly and pancytopenia. After ruling out hematologic malignancies by bone marrow biopsies, she was diagnosed with RA. Rheumatoid factor (RF) and cyclic citrullinated peptide antibody (Anti-CCP) levels were elevated. The patient was ultimately diagnosed with early-onset Felty syndrome in the course of RAand an occult hepatitis B infection. Despite the low incidence rate of Felty syndrome, it should be considered as a differential diagnosis of patients with arthralgia, fever, neutropenia, and splenomegaly.

Keywords: Felty syndrome; Hepatitis B virus; Pancytopenia; Rheumatoid arthritis

Introduction

"Chauffard-Still-Felty syndrome," or "Felty syndrome," is a form of rheumatoid arthritis (RA) that usually presents with neutropenia and splenomegaly. The classic triad of Felty syndrome is neutropenia, splenomegaly, and arthralgia, and it usually occurs in the setting of long-lasting RA [1].The average age of patients is 40 years old, and this syndrome is present in approximately 1-3% of female patients with a minimum 20-year history of RA [2][3]. As a consequence of neutropenia, severe infection is a major cause of mortality [4]. Herein, we report Felty syndrome in a patient with no history of RA. The patient had concomitant hepatitis B infection.

Case presentation

A 47-year-old female patient presented with complaints of arthralgia for about five years, fever, and low back pain. Four months earlier, she had presented to the local hospital with fever (38.5°C), weakness, weight loss of approximately 7 kg in 6 months(approximately 10%), aphthous ulcers in the mouth, and asymmetric arthralgia. She was referred to their internal medicine clinic . Medical assessment revealed she had splenomegaly, lymphadeno-pathy (a 6-millimeter lymph node in the left anterior chain of cervical lymph nodes), and

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vesiculated squamous lesion on both lips.

The available data showed the patient had pancytopenia (white blood cell (WBC) = $1600*10^9$/L (reference rang, 4-11.), platelet count = $30*10^9$/L), Hemoglobin (Hb) =10.6 g/dl (reference rang, 11- 16 g/dl)). The patient did not inform us of any other diseases, allergy history, family history of diseases, or smoking or opioid consumption. Leukemia was considered her primary diagnosis after performing a peripheral blood smear that showed large granulocytes. The patient refused further medical evaluation. She used herbal medications to relieve articular pain until she was referred to the rheumatology department of our tertiary hospital. Upon presentation, physical examination revealed fever (39°C), tachycardia (heart rate = 120), tachypnea (respiratory rate > 30), and a palpable spleen. Cardiac and respiratory sounds and oxygen saturation were normal. No phalangeal arthritis was notable. Because of the Covid-19 pandemic and non- specific symptoms of the patient, a chest computed tomography scan was obtained, but it did not show any abnormality. The Covid-19 polymerase chain reaction (PCR) was also negative. Urine analysis results were normal, and blood culture did not show any microorganisms. Lichtman body or large lymphocytes were not found in the peripheral blood smear, and abdominal ultrasound sonography demonstrated splenomegaly (spleen size > 170 mm). Moreover, according to the previous diagnosis of leukemia, a bone marrow aspiration was obtained which showed no abnormality. Human immune deficiency virus protein 24, Wright and 2mercaptoetahnol, and tuberculin tests were all negative. Hepatitis laboratory tests revealed negative results for hepatitis B surface antigen and antibody; however, hepatitis core antibody immuno-globulin (Ig)G was positive. PCR tests for cytomegalovirus, Epstein bar virus, and parvovirus, which could cause splenomegaly, were negative. An anti-nuclear antibodies laboratory test was sent for consideration of autoimmune disease, and it revealed negative results. High rheumatoid factor = 512 (positive of > 20 IU/ml) and high anti-cyclic citrullinated peptide = 2803 (positive of > 30 U/ml) were reported. Furthermore, erythrocyte sedimentation rate was 113/h, and c-reactive protein was 23 (positive of > 6 mg/dl) . Lumbar and bilateral palmar x-ray plain graphs found no erosions or bone defects (Figures 1 and 2).

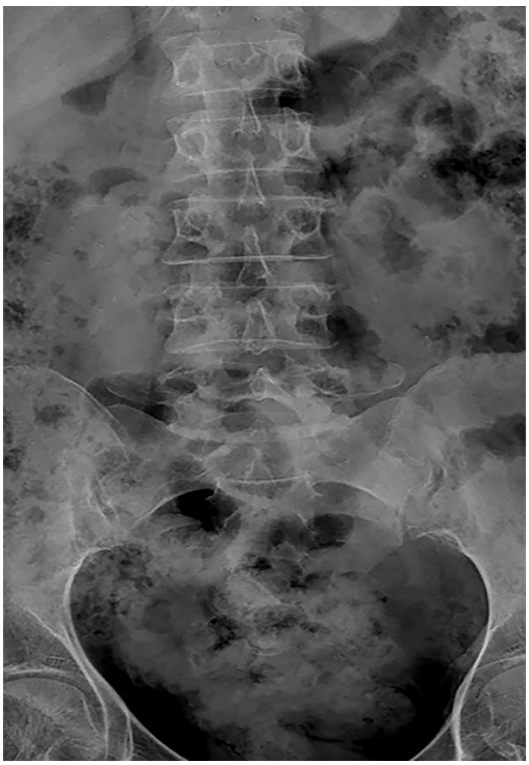

Figure 1. Lumbar Xray showed no vertebral erosion or articular defect.

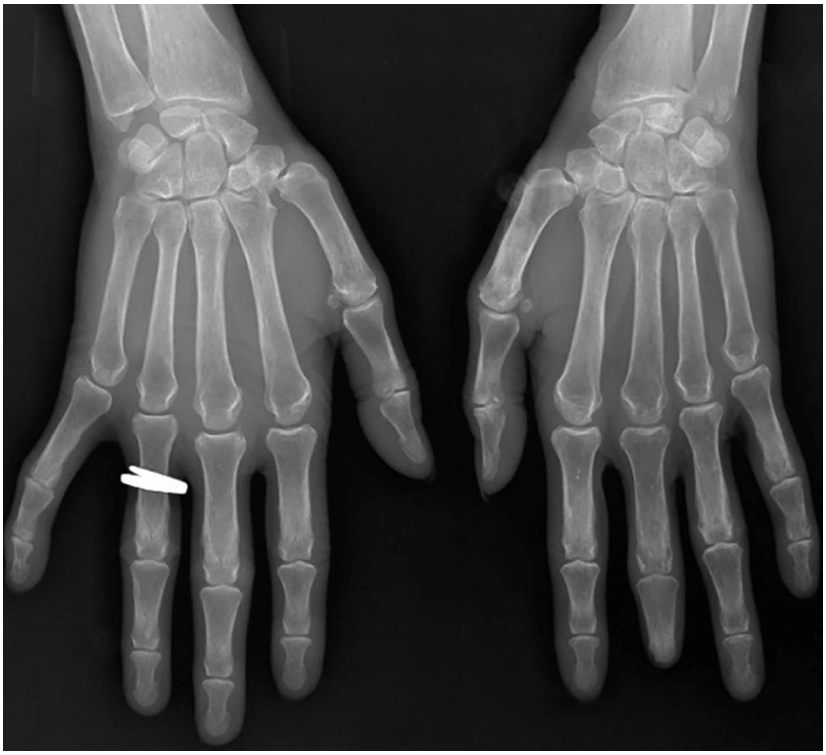

Figure 2. Bilateral palmar X-ray showed no erosion or bone defect. Noticeably, the white mark was golden ring.

Eventually, the patient was diagnosed with Felty syndrome as an early manifestation of RA. For further treatment, Hepatitis B virus deoxyribonucleic acid PCR was performed, which showed a positive results, and thus, simultaneous occult hepatitis B infection was diagnosed. Considering the patient's fever and neutropenia, she was initially treated with cefepime and vancomycin. In addition, granulocyte stimulating factor was administered. After her symptoms were alleviated, the patient was discharged with tenofovir 300 mg/d. After four weeks, she received rituximab, methotrexate 15 mg/week (subcutaneous), cyclosporine 100 mg/d, prednisolone 5 mg/d, pantoprazole 40 mg/d, hydroxychloroquine 200 mg/d, and folic acid 1 mg/d. Further follow-up was done after the alleviation of symptoms by anti-inflammatory drugs. The patient was referred to a surgeon for consideration of splenectomy, but she refused the operation.

Discussion

RA is a chronic disease characterized by symmetric joint involvement. Extra-articular manifestations are vasculitis, pericarditis, and interstitial lung disease [5]. Felty syndrome is asevere form of RA that occurs in long-lasting diseases. It can be asymptomatic or manifest with skin ulcers, recurrent infections, or idiopathic portal hypertension. Prognosis is poor, mainly due to severe recurrent infection as a result of neutropenia. It could be misdiagnosed with any systematic condition causing splenomegaly and neutropenia, like infections with Epstein–bar virus, tuberculosis, malaria, or HIV. It should not be misdiagnosed with systemic lupus erythematosus, large granular lymphocytic leukemia (LGL), amyloidosis, sarcoidosis, or autoimmune disorders causing leukemia or lymphoma [6]. As mentioned, our patient was initially misdiagnosed with LGL. We would like to emphasize differentiating Felty syndrome with LGL, which is also called "Pseudo Felty", which can alter the treatment of the patient. LGL causes neutropenia in approximately 80% of patients [7], and splenomegaly is seen in 40% of patients [8]. The challenging distinction between LGL and Felty syndrome relates to the mutation of STAT3 and HLA-DR4 in both diseases. Otherwise, the diagnostic procedure for leukemia is a peripheral blood smear. LGL is confirmed if at least 0.5 × 109 LG cells are observed in PBS [9, 10] and immunohistochemistry shows positive results of CD 2, 3, 4, 8, 16, and 57-related T-cells [7]. The

interesting presentation of Felty syndrome in a 47-year-old female without considerable arthritis, neutron penic fever, and concomitant HBV infection makes our patient unique. Although hepatitis B causes symmetric articular involvement and can be found in RA patients who receive immunosuppressive drugs [11], there is no clinical data that relates hepatitis B infection to neutropenia or splenomegaly in RA or as a risk factor for Felty syndrome [12]. Moreover, no active hepatitis infection had been confirmed for the patient except for HBV DNA PCR replication without any increase in liver enzymes. Occult hepatitis B infection is characterized by HBV DNA presence in serum without HBS Ag. It is divided into two categories: seropositive, which includes anti-HBC and/or anti-HBs positive patients which comprises about 1–20% of patients similar to our patient, and seronegative, in which anti-HBC and anti-HBs are negative [13]. Occult hepatitis B infectionis prevalent in Africa and Asia in populations who have HIV and Hepatitis C [14]. Notably, the prevalence of occult hepatitis B infection in the Islamic Republic of Iran has been estimated at 2.49% in anti-HBC positive patients [15]. In the present case, we started tenofovir with a dose of 300 mg with a normal range of liver enzymes. The potentially harmful condition while using an anti-CD-20 immuno-suppressive drug like rituximab is the risk of reactivation of HBV [16]. Buti et al. found no HBV DNA replication in a patient who received tenofovir before beginning chemotherapy drugs like rituximab [17]. We administered rituximab at a four-week interval to tenofovir and observed no HBV DNA replication or increase in hepatic enzymes. Methotrexate modulates STAT-3 mutation and is a first-line therapy of LGL and Felty syndrome related to neutropenia [18]. Neutropenia may be associated with the presence of granulocyte-specific anti-nuclear factor (GS-ANF), which is positive in more than 75% of FS patients. IgG-like granulocyte antibodies can destroy granulocytes, decreasing their ability to phagocytose immune complexes, and T-cell activation can inhibit granulocyte production. Accordingly, cyclosporine can induce gran-ulocyte production by inhibiting calcineurin, which activates T-cells [19].

Conclusion

To the best of our knowledge, this is the first case of FS with occult hepatitis B infection to ever be reported. Although the main diagnosis was challenging, patient history, and consideration of immunoglobulin and HBV DNA before using immunosuppressive drugs moved us directly toward the diagnosis. So, Felty syndrome should be noticed as an early manifestation of RA, which causes a severe infection that makes management difficult.

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Conflict of interest

The authors declare no conflicts of interest in drafting this manuscript.

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