Atypical Presentation of Felty Syndrome: Successful Management with Rituximab Therapy: A Case Report and Review of Literature Abstract:

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Introduction:

Felty syndrome, also known as Chauffard-Still-Felty syndrome, was first described by Augustus Felty. It is a rare condition diagnosed in patients with longstanding seropositive rheumatoid arthritis (RA) characterized by an enlarged spleen and neutropenia (1). Neutropenia, defined as absolute neutrophil count <1500/mm, is Felty syndrome's hallmark feature. In RA, the patient usually presents initially with arthritis, and the felty syndrome commonly develops after many years. However, in highly uncommon instances, felty syndrome can manifest before or without any signs of arthritis. Only a few case reports have been published highlighting this unusual presentation of the Felty syndrome (Table 2). We present a similar case of a young female who initially presented with felty syndrome without arthritis. This case report emphasizes the clinical and diagnostic approach to rule out alternate causes of neutropenia with splenomegaly and timely recognition of the atypical presentation of Felty syndrome.

Case Report:

Case History and Presentation:

A 24-year-old female with a history of migraines and menorrhagia presented to an urgent care center in late summer 2020, complaining of fever, fatigue, and unintentional weight loss. The review of systems was positive for generalized weakness and dizziness. She denied bone pain, chronic diarrhea, recurrent infections, Raynaud's, pleurisy, palpitations, skin rashes, photosensitivity, alopecia, seizures, sicca, or palpable adenopathy. Her social history was remarkable for drinking alcohol every other day from October 2019 to the end of the summer of 2020, cocaine use in the past, and being a former smoker. Her past surgical history is remarkable for bilateral adenoidectomy. Her vital signs were typical. The physical exam was grossly unremarkable.

Methods (Differential Diagnosis, Investigations and Treatment):

A complete blood count (CBC) showed leukopenia at the expense of severe neutropenia, mild normocytic anemia, and normal platelets.

Table 1 shows the initial lab results for the patient. (separate File)

Differential Diagnosis included infections, sarcoidosis, systemic lupus erythematosus, and myeloproliferative syndromes. Further workup was carried out to determine the cause of decreased neutrophil count. A chemistry panel showed paraproteinemia, normal kidney function, and normal liver enzymes. The infectious

panel showed a negative rapid COVID test, HIV negative, hepatitis C antibody test non-reactive, and serologic testing for hepatitis B suggested passive immunity. She was found to have a positive antinuclear antibody (ANA) test and a positive rheumatoid factor. The anti-cyclic citrullinated peptide (anti-CCP) was high >340. A peripheral flow cytometry was unremarkable. The patient had a bone marrow biopsy, and aspiration showed a norm cellular marrow with maturing trilineage hematopoiesis, a preserved marrow reserve pool on the two occasions. In addition, there was no morphologic evidence of overt or advanced myelodysplasia, acute leukemia, metastatic neoplasm, plasma cell dyscrasia, or lymphoma.

An ultrasound of the abdomen showed a slightly enlarged liver due to possible fatty infiltration, and the spleen measured 11.8 x 4.5 x 13.6 cm, which was mildly enlarged (Figure 1) (separate File)

Due to the positive RF factor, she was evaluated by rheumatology due to features of Felty syndrome and diagnosed with rheumatoid arthritis. She initially started Prednisone 10 mg daily and later transitioned to Hydroxychloroquine 200 mg qd. Despite treatment, the patient reported only mild improvement in her body aches, but her neutropenia and severe fatigue persisted.

Due to her dropping neutrophil count and peak COVID infection, a joint decision to treat her was made with a trial of prednisone 1 mg/kg daily for two weeks, resulting in the normalization of the absolute neutrophil count (ANC). This response was sustained for four months before relapsing. After stopping steroids, the ANC level again dropped. Rituximab was then considered as an alternative for long-term management of autoimmune neutropenia in the setting of Felty syndrome.

Figure 2 and Figure 3 show the trend of absolute neutrophil count and white blood cell count after treatment with steroids and Rituximab. (In separate Files)

Results (Outcome and Follow up):

After the treatment started, her neutrophil count improved. On her follow-up appointments, her CBC and WBC remained normal, and she reported improvement in her fatigue symptoms. She has not had any hospital admissions or life threatening infections, and nonspecific symptoms improved considerably.

Discussion :

Felty syndrome is an extracellular articular manifestation of rheumatoid arthritis. The lifetime risk of developing Felty syndrome (FS) for a patient with rheumatoid arthritis (RA) has been estimated to be approximately 1-3 percent (1). It is primarily diagnosed through clinical evaluation based on the presence of persistent neutropenia and enlarged spleen in chronic RA. It is crucial to emphasize this criterion because diagnosing the condition can be challenging when arthritis symptoms are absent (4,8). Arthritis usually occurs for almost ten or more years before neutropenia is diagnosed (6). Beyond this triad, clinical presentations of Felty's syndrome can involve anemia, low platelet counts (thrombocytopenia), recurrent bacterial infections, skin ulcers, unexplained portal hypertension, and an elevated risk for the development of blood-related cancers like non-Hodgkin's and Hodgkin's lymphoma (3). Though uncommon, documented cases in the literature highlight instances of FS occurring without concurrent articular RA (Table 2). We have presented such a case and briefly reviewed the existing literature.

Table 2 shows a few cases, including ours, in which Felty syndrome was diagnosed before or simultaneously with the onset of arthritis symptoms. (Separate File)

Felty syndrome was found to be more common in females. All the patients presented with neutropenia and splenomegaly, and some of them had arthritis initially as well, as shown in the table.

Pathophysiology of neutropenia in Felty syndrome involves both cellular and humoral immunity. It includes the development of autoantibodies against granulocyte colony-stimulating factor (G-CSF) and polymorphonuclear neutrophils (PMN), resulting in apoptosis of neutrophils and neutropenia (13).

There are no specific criteria for diagnosing felty syndrome. It is a clinical diagnosis of rheumatoid arthritis with splenomegaly and neutropenia. In patients who present without arthritis, positive RF and anti-CCP

antibodies can point towards the possibility of rheumatoid arthritis, like in our patient. High-titer RF and anti-CCP have a specificity of 99.5% for RA (15). When the patient tested positive for both factors, she was referred to rheumatology and diagnosed with RA.

Felty syndrome does not have a specific curative treatment. Literature needs guidelines in the management of Felty syndrome, although a few articles have highlighted the different strategies. Treatment primarily focuses on improving neutropenia with the treatment of rheumatoid arthritis, which is the underlying cause (8). Methotrexate and rituximab are the preferred DMARDs in patients with FS (11). Numerous case reports have demonstrated that rituximab can induce a sustained and complete response in autoimmune cytopenias, particularly in cases of Felty's Syndrome (7, 10, 14). In our case, the patient responded well to the Rituximab treatment. Glucocorticoids can temporarily increase neutrophils as they cause the release of non-segmented neutrophils into the circulation (12). The role of splenectomy is small, although it has been used in refractory cases.

Our patient did not have arthritis; instead, she presented with remarkable fatigue, severe neutropenia in labs, and mild splenomegaly on imaging. Further workup showed high-titer rheumatoid factor and positive anti-CCP antibody. The neutropenia normalized with the use of a high dose of steroids but later relapsed. She was then started on rituximab therapy, which improved her neutrophils. However, the patient needs to be closely monitored for neutrophils and the development of arthritis.

While our case report and brief literature review provide valuable insights into Felty syndrome's atypical presentation and management, it is essential to acknowledge that these findings may only sometimes apply. This limits our report, as it may not apply to all the cases due to individual differences in presentation and response to treatment.

Felty syndrome is a rare presentation of RA, but persistent neutropenia can lead to life-threatening infections. Therefore, it is necessary to check for RA and early refer to rheumatology even in the absence of arthritis symptoms. Early detection of Felty syndrome is crucial for further management and prevention of life-threatening infections.

Conclusions :

In conclusion, this case highlights the present atypical manifestation of Felty Syndrome, underscoring the challenges in managing this rare condition. The case findings emphasize the importance of considering diverse clinical manifestations of FS. We also emphasize the importance of ruling out other causes of neutropenia and splenomegaly. If left untreated, neutropenia can lead to the development of life-threatening infections. Awareness among healthcare professionals, particularly hematologists, is crucial for timely recognition and appropriate intervention, ensuring optimal care for patients with this complex autoimmune condition.

Key Clinical Message:

The atypical presentation of Felty syndrome, even without arthritis symptoms, needs further evaluation. Timely diagnosis of neutropenia and splenomegaly in patients with rheumatoid arthritis without joint symptoms is crucial for a better prognosis. Despite the rarity of the condition, clinicians should have a high index of suspicion, and multidisciplinary collaboration between rheumatology, hematology, and other specialists is required for accurate diagnosis.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Consent :

Verbal consent was taken from the patient

References :

1-Gupta A, Abrahimi A, Patel A. Felty syndrome: a case report. J Med Case Rep. 2021 May 27;15(1):273. doi: 10.1186/s13256-021-02802-9. PMID: 34039422; PMCID: PMC8157748.

2-Chavalitdhamrong D, Molovic-Kokovic A, Iliev A. Felty's syndrome as an initial presentation of rheumatoid arthritis: a case report. Cases J. 2009 Nov 18;2:206. doi: 10.1186/1757-1626-2-206. PMID:

3-Akhtari M, Curtis B, Waller EK. Autoimmune neutropenia in adults. Autoimmun Rev. 2009 Sep;9(1):62-6. doi: 10.1016/j.autrev.2009.03.006. Epub 2009 Mar 14. PMID: 19293004; PMCID: PMC2783155.

4-Saeed H, Ejikeme C, Tucktuck M, Jawed Q, Kessler W. Non-Articular Felty Syndrome Refractory to Granulocyte Colony-Stimulating Factor Therapy. Cureus. 2021 Aug 15;13(8):e17206. doi: 10.7759/cureus.17206. PMID: 34540433; PMCID: PMC8440238.

5-Jakez-Ocampo J, Atisha-Fregoso Y, Llorente L. Pancytopenia as manifestation of nonarticular felty syndrome. J Clin Rheumatol. 2021;27:0–4.

6-Jain T, Mittal C, Sengupta R, Rubin B. Non-articular Felty's syndrome: an uncommon diagnosis. Neth J Med. 2015;73:435–436.

7-Bigot W, Viallard JF, Sellam J, Dellal A, Retbi A, Gobert D, Malard F, Mohty M, Mekinian A, Fain O. Efficacy and safety of rituximab for autoimmune neutropenia: a French case series and literature review. Rheumatology. 2020 Sep;59(9):2637-2640. doi: 10.1093/rheumatology/keaa045.

8-Serrano Santiago VE, Morgan Z. The Diagnosis Felt(y) Right: A Case Report of Felty Syndrome With Limited Articular Involvement. Cureus. 2022 Apr 29;14(4):e24593. doi: 10.7759/cureus.24593. PMID: 35602797; PMCID: PMC9113736.

9-Owlia MB, Newman K, Akhtari M. Felty's Syndrome, Insights and Updates. Open Rheumatol J. 2014 Dec 31;8:129-36. doi: 10.2174/1874312901408010129. PMID: 25614773; PMCID: PMC4296472.

10-Narváez J, Domingo-Domenech E, Gómez-Vaquero C, et al. Biological agents in the management of Felty's syndrome: a systematic review. Semin Arthritis Rheum. 2012;41:658–668.

11-Fiechtner JJ, Miller DR, Starkebaum G. Reversal of neutropenia with methotrexate treatment in patients with Felty's syndrome. Correlation of response with neutrophil-reactive IgG. Arthritis Rheum. 1989;32:194–201.

12-Bishop CR, Athens JW, Boggs DR, Warner HR, Cartwright GE, Wintrobe MM. Leukokinetic studies. A non-steady-state kinetic evaluation of the mechanism of cortisone-induced granulocytosis. J Clin Invest. 1968;47:249–260.

13-Hellmich B, Csernok E, Schatz H, Gross WL, Schnabel A. Autoantibodies against granulocyte colony-stimulating factor in Felty's syndrome and neutropenic systemic lupus erythematosus. Arthritis Rheum. 2002;46:2384–2391.

14-Sarp U, Ataman S. A beneficial long-term and consistent response to rituximab in the treatment of refractory neutropenia and arthritis in a patient with Felty syndrome. J Clin Rheumatol. 2014;20:398.

15-Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155-63.

16-Cornwell GG, Zacharski LR. Neutropenia, elevated rheumatoid factor, splenomegaly, and absence of rheumatoid arthritis. Ann Intern Med. 1974;80(4):555-6.

17-Bradley JD, Pinals RS. Felty's syndrome presenting without arthritis. Clin Exp Rheumatol. 1983 Jul-Sep;1(3):257-9.

18-Armstrong RD, Fernandes L, Gibson T, Kauffmann EA. Felty's syndrome presenting without arthritis. Br Med J (Clin Res Ed). 1983;287(6405):1620.

19-Aslam F, Cheema RS, Feinstein M, Chang-Miller A. Neutropaenia and splenomegaly without arthritis: think rheumatoid arthritis. BMJ Case Rep. 2018 Jul 11;2018:bcr2018225359.

20-Cycowitz Z, Heller I, Burke M, et al. Felty's syndrome without concomitant arthritis: a variant. Clin Exp Rheumatol. 1989;7:301–3.

21-Muroi K, Sakuma Y, Izumi T, Sato K, Tanaka A, Ozawa K. A long course of leukocytopenia and splenomegaly with extramedullary hematopoiesis in the absence of clinically manifested rheumatoid arthritis. J Clin Exp Hematop. 2010;50:163–166.

22-Rozin A, Hoffman R, Hayek T, et al. Felty's syndrome without rheumatoid arthritis? Clin Rheumatol. 2013;32:701–4.

23-Lagrutta M, Alle G, Parodi RL, et al. Severe extra-articular manifestations of rheumatoid arthritis in absence of concomitant joint involvement following long-term spontaneous remission. A case report. Reumatol Clin. 2016;12:223–5.

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