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CASE REPORT

The First Case of Felty's Syndrome Complicated by COVID-19 Infection

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Abstract: Felty's syndrome (FS) is an uncommon disorder with a poor prognosis, and most patients die from infections caused by neutropenia. Currently, there is no standardized treatment strategy, and treatment options are based on case reports and clinical experience. To date, no cases of FS complicated by coronavirus disease-2019 (COVID-19) have been reported. This article reports a successful case of FS complicated by COVID-19. We emphasized treating rheumatic diseases with immunosuppressive therapy at appropriate doses based on strong and effective anti-infection when co-infected.

Keywords: Felty's syndrome, rheumatoid arthritis, neutropenia, COVID-19, molnupiravir

Introduction

Felty's syndrome (FS) is a relatively rare type of rheumatoid arthritis (RA). In recent decades, its incidence has declined from 1.5% in 1985 to 0.5%, with a higher prevalence in Western Europe and North America than in Asia or Africa.[1] In the Han population, the incidence is less than 0.1%.[2] FS generally manifests as the triad of RA, neutropenia, and a large spleen. Large splenic size is not essential for diagnosing FS.[3] The clinical diagnosis and treatment of FS are challenging, and the lack of controlled trials renders no evidence-based drug therapy for FS.[4] Neutropenia increases the risk of infection in patients with FS, thereby increasing patient mortality. Lungs and skin are the most frequently encountered sites of infection.[5,6]

We aimed to present the case of a patient with FS diagnosed with a new, unreported coronavirus pneumonia both domestically and internationally. The clinical characteristics of FS and the optimal treatment approach for novel coronavirus infection, combined with a literature analysis, are discussed to improve clinicians' disease understanding, reduce misdiagnoses and mistreatment, and improve disease prognosis.

Case Presentation

On December 30, 2023, a 65-year-old male patient was admitted to the outpatient department of Changsha Central Hospital affiliated with the University of South China with a history of "joint pain for eight months, and diarrhea for one week". The patient complained of limb joint pain (without obvious inducement) for eight months, involving the bilateral proximal interphalangeal, metacarpophalangeal, wrist, elbow, toe, and ankle joints, accompanied by morning stiffness, mild allergy, dry mouth and eyes, and absence of alopecia. Two weeks prior, the patient was diagnosed with RA and a reduced leukocyte count during hospitalization. The patient's discomfort improved after receiving anti-rheumatoid drugs (methotrexate and Chinese patent medicine). However, he exhibited symptoms, including fever, diarrhea, absence of chills, a maximum body temperature of 39 °C, yellow watery stools occurring more than 10 times/day, along with cough, sputum, white mucus sputum, cold sores, fatigue, reduced appetite, and a weight loss of approximately 3 kg in the previous month. The patient was then referred to our hospital for further treatment. Physical examination after admission revealed the following signs: body temperature: 36.5 °C; pulse rate, 79 beats/min; respiration, 20 breaths/min; and blood pressure, 134/79 mmHg. The patient was conscious and emaciated, with multiple blisters around the lips, absence of dry and wet rales in both lungs, a soft abdomen without tenderness, absence of limb joint deformity, redness, swelling, and a lack of edema in the lower extremities. A CT scan of the lungs and abdomen performed on December 29,

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2023, revealed the following: (1) Multiple spots, nodules, and ground-glass opacities in both lungs; (2) slightly enlarged mediastinal lymph nodes; (3) diffuse edema, colon wall thickening; (4) liver cysts. Upon admission, the following diagnoses were made: (1) RA, (2) lung infection, (3) colitis-induced diarrhea, and (4) moderate malnutrition.

After admission, the patient's relevant examinations indicated improvement in blood parameters: 4.45×10^9/L white blood cell count, 85 g/L hemoglobin, 95×10^9/L platelet count, 3.9×10^9/L absolute neutrophil value, and 83.75% neutrophil percentage Liver function revealed an albumin level of 23 g/L while the electrolytes indicated 3.1 mmol/L serum potassium. Moreover, C-reactive protein(CRP) was measured at 99.6 mg/L, erythrocyte sedimentation(ESR) at 112 mm/h, rheumatoid factor(RF)at 194 U/mL, anti-cyclic citrullinated peptide(CCP) antibody at 314.7 U/mL, D-Dimer at 1.6 μg/mL, and Procalcitonin at 3 ng/mL. A positive direct anti-human globulin test and positive stool occult blood test were also observed. Furthermore, urinalysis, stool culture, renal function, random blood glucose, coagulation function, ASO, CEA, 13 antinuclear antibodies, immunoglobulin lgA/G/M/E, anti-neutrophil cytoplasmic antibody, lung prostate tumor marker, complement, antiphospholipid antibody, anti-double-stranded DNA antibody, new coronavirus nucleic acid detection, influenza A and B nucleic acid detection, tuberculosis infection T cell detection, 1.3-β-d-Glucan test, and alveolar lavage fluid X-pert results were all abnormal. Alveolar lavage fluid Next Generation Sequencing(NGS) detected human herpesviruses 1, 4, and 7, Candida albicans, and Escherichia coli. CT scans of the head, chest, and abdomen indicated diffuse patches, patchy hyperdensities, and cord shadows in both lungs, with unclear borders, particularly in the upper lungs. Moreover, bilateral pleural hypertrophy and adhesions, multiple lymphadenopathies in the mediastinum, absence of enhancement after enhancement, and a minor quantity of fluid in the bilateral chest and pericardium were observed (Figure 1a). The colorectal wall was diffusely and uniformly thickened, and the tube wall was slightly blurred with little oozing around it. No enlarged lymph nodes were observed retroperitoneally. Mild aortic valve regurgitation and normal systolic and diastolic functions were detected using cardiac ultrasonography. A nasopharyngoscopy revealed chronic pharyngitis. The superficial lymph nodes were swollen throughout the body, the skin and medullary structures remained clear, and no abnormal color flow was observed. The colorectal mucosa was granular and erosive, with easy bleeding to touch, and its nature remained unknown upon colonoscopy; ulcerative colitis was a potential diagnosis. Joint

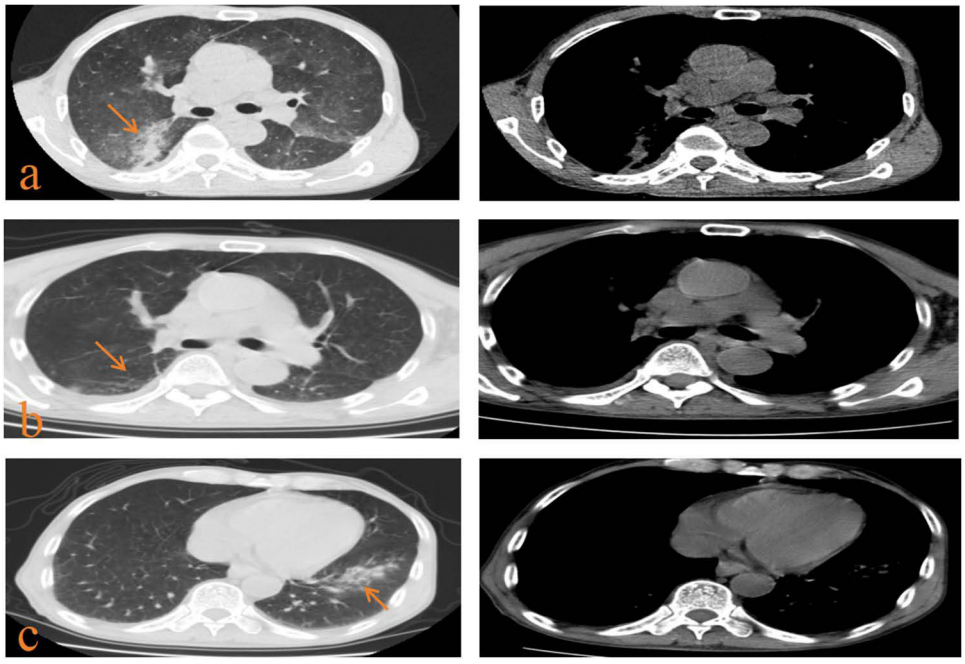

Figure 1 Changes in patient's lung lesions during treatment. (**a**) 2023.12.31 CT of the lungs at the time of admission: infectious lesions in both lungs, mainly in both upper lungs (as indicated by the arrow), right pleural effusion, multiple enlarged lymph nodes in the mediastinum. (**b**) 2024.1.29 After anti-infection and antiviral treatment, the lesions in both lungs significantly improved (as indicated by the arrow). (**c**) 2024.2.6 New infection in the left lower lung (as indicated by the arrow), improvement of lesions in the remaining lungs, and bilateral pleural effusion absorption.

color ultrasound indicated the presence of synovial hyperplasia and rich punctate color flow in the joints of fingers and wrists. Consequently, ulcerative colitis, hemolytic anemia, thrombocytopenia, and herpes were supplementary diagnoses.

The 2019 ACR/EULAR Rheumatoid Classification Scoring Criteria state that patients meeting the following conditions can achieve a score of 10 and a clear diagnosis: facet joint pain exceeding 10, high and low levels of rheumatoid factor and anti-CCP antibodies, elevated erythrocyte sedimentation rate and C-reactive protein, and symptom duration exceeding six weeks. DAS28 achieved a score of 3.2. The patient's cough and sputum improved after anti-infection (bacterial and fungal), antiviral, anti-ulcerative colitis, and symptomatic treatment. However, joint pain was aggravated, and recurrent high fever and fatigue were observed. During treatment, white blood cells and neutrophils continued to decline (Table 1). Routine blood analysis on

Table 1 Biochemical Indicators During the Patient's Treatment

Date	WBC (10^9/L)	ANC (10^9/L)	PLT (10^9/L)	Hb (g/L)	CRP (mg/L)	ESR (mm/h)	RF (U/mL)	Ati-CCP (U/mL)	IL-6 (pg/mL)
2023–12-30	4	3.5	95	85	99.6	112	194	314.7	NA
2024-1-1	3	2.1	91	77	NA	NA	NA	NA	NA
2024-1-3	2.52	1.6	145	102	NA	NA	NA	NA	NA
2024/1/6*	1.16	0.49	105	76	NA	NA	NA	NA	NA
2024-1-7	10.29	9.07	117	83	NA	NA	NA	NA	65.2
2024-1-14	2.6	1.9	57	66	148	115	NA	NA	712
2024-1-17	2.5	2	84	69	94	NA	NA	NA	NA
2024/1/19*	1.86	1.4	53	68	NA	NA	NA	NA	NA
2024-1-20	7.75	7.1	62	64	NA	NA	NA	NA	98.68
2024-1-22	2.6	1.9	56	60	76.4	128	585	291.6	NA
2024/1/23*	1.74	1	88	55	NA	NA	NA	NA	NA
2024-1-24	10.7	9.3	85	55	65.1	116	NA	NA	282.9
2024/1/27*	1.3	0.48	116	53	49.7	NA	NA	NA	NA
2024/1/30*	1.39	0.6	105	52	NA	NA	NA	NA	124.4
2024-2-1	3.88	2.7	95	61	25.9	NA	NA	NA	NA
2024/2/3*and	2.5	1.26	119	57	77.8	125	867	279	NA
2024-2-5	10.24	7.9	143	56	90.4	132	NA	NA	NA
2024/2/7*and	1.6	1.3	160	51	NA	NA	NA	NA	NA
2024-2-8	7.83	6.48	177	54	35	76	NA	NA	NA
2024-2-9	4	3.5	197	56	NA	NA	NA	NA	NA
2024-2-15	6.7	5.3	274	71	16	50	130	102	NA
2024-2-18	5.5	4.5	267	79	NA	NA	NA	NA	NA
2024-2-21	6.3	5.1	213	82	NA	NA	NA	NA	NA
2024-3-3	7.5	5.3	197	105	<8	12	NA	NA	NA

Abbreviations: WBC white blood cell, ANC neutrophil count, PLT platelet count, Hb haemoglobin, CRP c-reactive protein, ESR erythrocyte sedimentation rate, RF rheumatoid factor, CCP cyclic citrullinated polypeptide, IL-6 Interleukin-6. *Represents the subcutaneous injection of recombinant human granulocyte stimulating factor on the same day. & Represents that the new coronavirus nucleic acid test was positive on the same day, and molnolavir treatment was given at the same time.

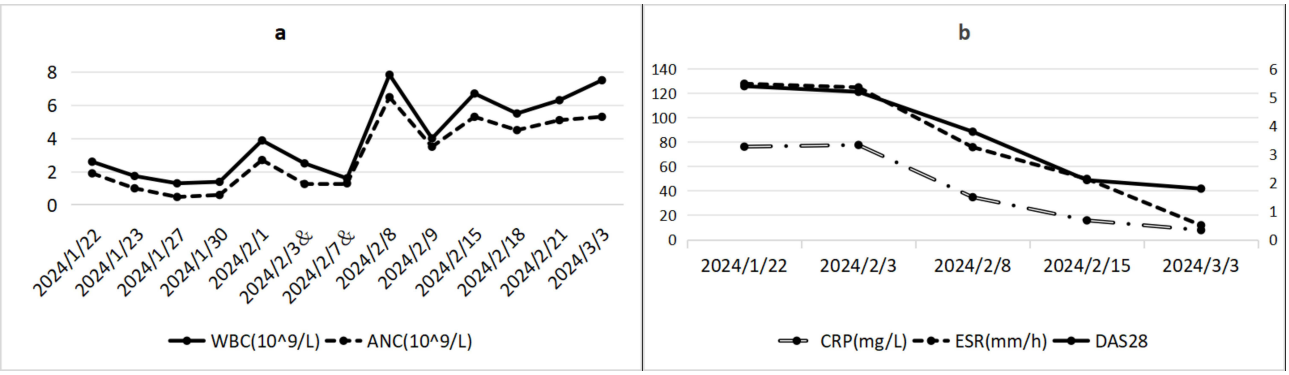

Figure 2 Changes in patient indices after treatment. (**a**) Trends in white blood cell (WBC) counts and neutrophil counts(ANC). (**b**) Trends in erythrocyte sedimentation rate (ESR), C-reactive protein(CRP) level, and Disease Activity Score 28 (DAS28) scores. & Represents that the new coronavirus nucleic acid test was positive on the same day, and molnolavir treatment was given at the same time.

January 6, 2024, included 1.16 × 10^9/L white blood cell count, 56 g/L hemoglobin, 67 × 10^9/L platelet count, 0.49 × 10^9/L absolute neutrophil value, and 42.8% neutrophil percentage. Bone marrow puncture and biopsy indicated myelmarrow suppression, underactive myeloproliferation, and the absence of hemophilic cells. A follow-up CT of the lungs was performed to improve the bilateral lung lesions (Figure 1b). The complete interleukin-6 examination assay indicated 712 pg/mL, the re-examination RF was 585 U/mL, and the anti-CCP antibody was 291 U/mL, significantly higher than before. The DAS28 score was 5.4. The patient was diagnosed with RA and agranulocytosis, considering FS. Consequently, based on anti-infective and antiviral therapy, methylprednisolone 20 mg/day intravenous infusion and MTX 10 mg QW oral treatment were prescribed for one week. After treatment, the patient's body temperature gradually decreased, and joint pain, appetite, and mood improved. DAS28 achieved a score of 4.2. Nevertheless, the leukocyte count did not increase, necessitating frequent recombinant human granulocyte-stimulating factor whitening treatment once every other day and intravenous methylprednisolone at 40 mg/day for two days. The patient reappeared with high fever, joint pain, runny nose, and fatigue, and the nucleic acid test was positive for the novel coronavirus. Molnuravir (0.8 g) was immediately administered orally every 12 h, methylprednisolone was decreased to 20 mg/day intravenously, and the patient was treated with 10 g/day immunoglobulin for five days. The patient continued to experience recurrent elevated fever. Moreover, a lung CT scan on the fourth day of antiviral therapy revealed a new cloudy lesion in the left lower lung (Figure 1c). Considering COVID-19, a respiratory consultation was requested, and due to the patient's corticosteroid requirement, agranulocytosis, and RA, a treatment course of molnupiravir capsule was recommended. After five days of antiviral therapy, the patient's body temperature gradually decreased, and joint pain, fatigue, and spirit improved significantly. Normal leukocyte levels must be maintained using granulocyte-stimulating factors. The methylprednisolone dose was readjusted to 30 mg/day of static drops. Subsequently, a routine examination revealed that the patient's white blood cells were maintained at normal levels, without fever or joint pain. The follow-up data are displayed in (Figure 2).

Discussion

In 1924, Augustus Roi Felty, an American physician, first described FS in five cases as a combination of RA, splenomegaly, and leucopenia.[3] Since then, a limited number of cases have been documented intermittently, both domestically and internationally. Due to the lack of controlled randomized trials, the current therapeutic approach for FS remains empirical. Moreover, it is based on case reports, case series, and clinical experiences.[4] Consequently, studies on the efficacy and safety of several drugs prescribed for patients with RA and FS are limited. In the future, it is imperative to conduct extensive randomized controlled clinical trials to ascertain the optimal treatment for FS. If left untreated, multiple extra-articular clinical conditions can develop, including the rare association with idiopathic noncirrhotic portal hypertension.[7] Patients with FS are generally susceptible to severe infections caused by neutropenia or slightly higher hormone doses. Overall, the prognosis is extremely poor.

FS is more prevalent in older women with active RA who have a prolonged course of disease and severe joint destruction.[4] This was demonstrated in older and more recent cohort studies, where 77% of patients with FS exhibited

joint erosion at diagnosis.[8] This finding is inconsistent with that of an elderly male patient with transient joint pain for eight months and no joint deformity. This suggests FS can also occur in the early stages of RA lesions. In the future, patients with RA who have a short course of disease, mild joint lesions, and are admitted to clinical practice will require heightened vigilance for FS in combination with agranulocytosis to avoid diagnosis and treatment delays.

Neutropenia is an indispensable feature of FS and a critical determinant in developing infection in patients with FS. Most clinicians are hesitant to use corticosteroids or anti-rheumatic medications (MTX having myelosuppressive side effects) because of agranulocytosis, and this reluctance ultimately delays treatment. This may be associated with the mechanism underlying neutropenia in FS, although some clinicians find it relatively unrelated. Although the precise mechanism of granulopenia in FS remains unclear, the following aspects have been proposed. (1) Formation of neutrophil extracellular traps (NETs).[3,9] The secretion of NETs is another defense mechanism of neutrophils alongside phagocytosis and degranulation of antimicrobial granules. NETs are antimicrobial nets formed by neutrophils upon stimulation by pathogens or inflammatory mediators. The killing of pathogens is accompanied by neutrophil death. Recent studies have demonstrated that NET formation reduces granulocyte counts in FS. During NET formation, histones can undergo post-translational modifications (acetylation, methylation, and citrullination),[10] and anti-citrullinated protein antibodies in patients with RA may react with citrullinated and acetylated histones in NETs.[11] Moreover, patients with FS have antibodies against NET components, including citrullinated histones. Overall, the connection between NET formation and granulocyte count is an area of further research. In addition to this patient's preexisting pulmonary infection (herpes simplex virus and fungus), a novel coronavirus infection emerged during hospitalization. Neutropenia was most likely caused by the stimulation of NET formation by viruses and fungi. Therefore, anti-infection therapy was administered before anti-rheumatic therapy. (2) The presence of anti-granulocyte colony-stimulating factor (anti-G-CSF) antibodies may lead to neutropenia in patients with FS. Hellmich B. professor's team observed anti-G-CSF IgG antibodies in 11 out of 15 patients with FS. However, seven patients tested positive for anti-neutrophil cytoplasmic antibodies, and the limited sample size necessitates additional mechanistic investigations to verify that anti-G-CSF is the underlying cause of granulocyte deficiency in patients with FS.[12] After additional colony-stimulating factor supplementation during treatment, leukocytes may rapidly increase to normal levels and then rapidly decline, indicating that patients with FS may have anti-G-CSF antibodies. We believe that granulocyte-stimulating factors are crucial for the treatment of patients with FS, as they provide time for DMARDs and hormones to exert their effects and significantly prevent infection. (3) Cellular and humoral immunological mechanisms may cause neutropenia in FS.[13] Furthermore, neutropenia may be accompanied by splenomegaly, which leads to sequestration and destruction of neutrophils, and bone marrow suppression caused by interferon γ. In conclusion, the cause of granulocyte deficiency in patients with FS requires further investigation. The most common sites of infection in patients with FS are the lungs and skin.[5,6] This finding was consistent with the characteristics of the present case. The patient developed new coronavirus pneumonia during treatment. Considering the diagnosis and treatment protocol for novel coronavirus infection and the side effects of the drugs and anti-coronavirus treatment drugs,[14,15] molnupiravir capsules were selected. Molnupiravir capsules have few side effects and do not impair the efficacy of the other drugs. After five days of antiviral therapy, the patient's COVID-19 nucleic acid test results remained positive. Although studies have indicated that the median time of nucleic acid conversion of the new coronavirus is 10 days after molnupiravir treatment,[16] the patient's persistent fever and lung CT suggested that additional investigation of new infection foci is warranted. Relevant research suggests that extending molnupiravir administration for up to 10 days may be necessary for effective treatment or prevention of infection caused by RNA viruses.[17] Therefore, we extended the duration of molnupiravir administration to 10 days. Molnupiravir antiviral therapy was administered while simultaneously suppressing the immune response at half the hormone dose. Finally, the patient's condition was effectively managed.

Currently, there are no empirical guidelines for FS treatment. The primary objectives of treatment are elevated neutrophil count and infection control. Splenectomy has been the mainstay of treatment for the past few decades; however, with the extension of follow-up, splenectomy has provided only short-term neutrophil maintenance and has failed to reduce the incidence of infection in patients with FS.[18] Although FS is associated with immune complex formation, the effectiveness of plasmapheresis remains unsatisfactory.[19] MTX is currently the first-line treatment for FS. It increases neutrophil counts in patients with FS and promotes the healing of vasculitis-related ulcers.[20] Multiple ulcer changes have been detected in the colon during colonoscopy, and the possibility of vasculitis-mediated ulcer formation cannot be disregarded. Unfortunately, no follow-up colonoscopy was performed after treatment. However, case reports have indicated that MTX treatment may cause a further decline in neutrophil counts in patients with FS,[21] which may be

attributed to the myelosuppressive side effects of MTX. Therefore, neutrophil levels should be carefully monitored during treatment.

Case reports have documented the use of hydroxychloroquine alone, without hormonal therapy, for treating FS. However, hydroxychloroquine was administered at a higher dose (1200 mg/day).[22] Considering the involvement of cellular and humoral immunity in FS pathogenesis, rituximab has been proposed as a potential alternative when MTX alone fails to elicit a satisfactory response. Approximately 65% of cases report a rapid increase in neutrophil levels after rituximab treatment.[4] Case reports of poor response to rituximab in patients with refractory FS have also been documented.[23] Abatacept and tocilizumab may be effective options when the response to MTX and rituximab remains unsatisfactory.[24,25] As MTX and immunosuppressants have a slow onset of action, using glucocorticoids and human granulocyte-stimulating factors is crucial. Moreover, studies have revealed that prednisone may significantly ameliorate agranulocytosis during FS therapy at 30 mg/day. However, agranulocytosis may remain uncorrected at doses below 7.5 mg/day without additional immunosuppressants.[26,27] Due to recurrent lung infections, we continuously adjusted the hormone dosage according to the patient's condition, timely administered human granulocyte-stimulating factor, and used immunoglobulin to boost immunity and bind pathogenic antibodies, ultimately leading to satisfactory outcomes. Upon discharge, the patient was treated with methylprednisolone (24 mg) for maintenance.

This is the first case report of a novel coronavirus coinfection with FS. We did not refrain from using corticosteroids throughout the treatment period because of concerns about aggravating the infection. Instead, we confidently utilized hormones to suppress the immune response through the agranulocytosis mechanism of FS based on potent antiviral therapy. Ultimately, a clinical cure was achieved, however, this has not been reported in the literature. This case implies that a future balance is possible between using anti-infective therapy-based hormones and treating FS complicated by various pathogenic infections. This case review and the relevant literature suggest that biologics, including rituximab and tocilizumab, could be the preferred option in the future if the patient experiences relapses based on anti-rheumatic therapy and during the gradual tapering of corticosteroids. In conclusion, the number of reported cases of FS domestically and internationally is relatively low, and clinicians require additional experience in treating FS. Medical professionals must meticulously evaluate, contemplate, and evaluate data concerning FS to implement personalized treatment. If the emphasis is placed on anti-rheumatism over anti-infection, the patient is at higher risk of dying from a severe infection. Conversely, if the focus is on anti-infection, rheumatism may exacerbate the patient's systemic damage.

Conclusion

FS is a rare and distinctive form of RA that is challenging to diagnose and treat. Agranulocytosis predisposes patients to infection with various pathogens. We are the first to document a case of COVID-19-complicated FS. Based on the successful treatment of this case, we believe that when FS is complicated by an acute infection, patients should be administered an appropriate dose of hormones to suppress the immune response while fighting the infection. We also believe MTX should be administered promptly, considering its myelosuppressive side effects. Further clinical randomized controlled trials are required to validate the role of biologics in FS treatment.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This de-identified observational study protocol was reviewed, and the need for approval was waived by the University of South China Affiliated Changsha Central Hospital Review Board. The patient's written consent for participation was obtained.

Consent for Publication

Written informed consent for publication of the clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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