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What Could Lead to the Production of Anti-Rheumatoid Antibodies in Patients with Brucellosis Spondylodiscitis: Possible Causes

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Abstract

Background: High titers of specific antibodies to cyclic citrulline peptide (ACCP) are often present in the serum of patients with rheumatoid arthritis (RA) and, together with rheumatoid factor (RF), are a diagnostic marker of RA. Brucellosis is a zoonotic infection in which osteoarticular involvement occurs in 10-85% of patients. RF in brucellosis patients is significantly higher than in healthy people.

Methods: We presented 2 cases of brucellosis spondylodiscitis with positive results for RF and ACCP, which aroused great interest among the rheumatologists of our center.

Results: Both patients described were men (27 and 60 years old) with arthritis, back pain, and high levels of rheumatoid arthritis-specific antibodies. These patients were suspected of having tuberculous spondylitis, but the tuberculous process was excluded using specific tests. During antibacterial therapy, there is a dynamic decrease in antirheumatoid antibodies. X-rays of the hand joints revealed no signs of erosive arthritis.

Conclusion: All cases of arthritis, spondylitis, and spondylodiscitis in endemic areas require careful analysis and comparison of patients' clinical and laboratory-instrumental data to prevent misdiagnosis. With brucellosis infection, against the background of adequate antibacterial therapy, inflammation of the joints and spine is reversible.

Keywords: Rheumatoid Arthritis, Antibodies to Cyclic Citrulline Peptide (ACCP), Chronic Brucellosis, Spondylodiscitis, Differential Diagnosis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease of the joints that affects cartilage and bones, leading to joint destruction and disability (1). Many bacterial and viral infections that involve the musculoskeletal system (MSS) can mimic early RA (2). Anti-cy clic citrulline peptide (ACCP) antibodies are a marker of RA, and we are accustomed to believing that a positive result for this antigen increases the probability of having a diagnosis of RA by 80% with a specificity of 98% (3, 4). It has been proven that ACCP increases both in blood serum and in the synovial membrane of the joints. This indicates the local production

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↑What is "already known" in this topic:
Rheumatoid factor (RF) is a diagnostic marker of rheumatoid arthritis. Damage to the musculoskeletal system is one of the most common manifestations of chronic brucellosis (ChB). Almost a third of patients with brucellosis arthritis have positive RF.

→What this article adds:
The detection of antibodies to cyclic citrullinated peptide (ACCP) in patients with brucellosis spondylodiscitis and arthritis has not previously been described. Symmetrical arthritis and positivity for RF and ACCP make it difficult to diagnose brucellosis arthritis. The positivity of RF and ACCP in brucellosis infection is probably associated with macrophage activation syndrome and the arthritic ability of Brucella.

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of anti-citrulline peptide in the focus of inflammation, regulated by genes predisposing to RA (5). In the clinical practice of a rheumatologist, there are patients with a positive test for ACCP without classical manifestations of RA. In the endemic zone for brucellosis, like Kazakhstan, we faced the problem of the similarity of clinical manifestations of chronic brucellosis (ChB) with the symptoms of RA. We met patients who, in addition to general infectious symptoms (wave-like sub-febrile fever, chills, night sweats, lymphadenopathy, general weakness, fatigue, pain in muscles and bones), had a picture of polyarthritis of the small joints of the hands with morning stiffness and a positive rheumatoid factor (RF) and ACCP, which confused rheumatologists, since the correct verification of the diagnosis, a priori, determines the choice of therapy. Given the opposite pathogenetic mechanisms of developing these two diseases, therapy is multidirectional. We are aware of the polymorphism of the clinical manifestations of ChB, and the most frequently involved system is the MSS, which occurs in 10–85% of patients with ChB (6, 7). The musculoskeletal disorders in ChB include arthritis, bursitis, tenosynovitis, sacroiliitis, spondylitis, and osteomyelitis. Due to the similarity of symptoms of lesions of the MSS in ChB and seronegative spondyloarthritis (SpA) (8-13), it is not easy to differentiate between these conditions (14). We encountered two clinical cases of brucellosis spondylodiscitis with sharply positive indicators of RF and ACCP without clinical manifestations of RA. The presented patients were not previously observed with a diagnosis of RA and, accordingly, did not receive basic immunosuppressive therapy.

Purpose

To report two clinical cases of brucellosis spondylodiscitis with positive RA markers without clinical manifestations of this erosive-destructive arthritis.

Case report

Case №1: Man, 27 years old, city dweller, a doctor by profession. The patient complains of pain and movement restrictions in the thoracic and lumbar spine, pain around the entire circumference of the chest associated with the act of breathing, aggravated by physical exertion, sometimes at rest, arthritis in the knee and right ankle joints, aches all over the body, chills, sweating, sub-febrile undulating fever, depression, emotional lability, weight loss of 5 kg in 2 months. The patient was examined (Table 1): ESR - 51-66 mm/hour; CRP - 15.45 mg/l, RF-47-103-53 U/l, ACCP-602 IU/l, HLA B27 - negative; feces for calprotectin - negative; X-ray of the hands - no pathology was found (Figure 1); chest x-ray - lung pathology not found; An MRI of the lumbar spine (LSP) was made (Figure 2). A TB doctor consulted the patient, specific tests were performed (sputum smear microscopy - negative, Interferon Gamma Release Assay -negative, Mantoux tuberculin skin test - negative) tuberculous spondylitis was excluded. Further, the patient was examined for brucellosis infection; the results were positive, and the infectious disease specialist was diagnosed with ChB, decompensation stage, spondylodiscitis, spondylitis, arthritis, polyarthralgia, myalgia asthenic syndrome (sweating, hyperhidrosis of the palms, weight loss, weakness), psycho-brucellosis, Wright agglutination test 1:400, Huddlson agglutination test 3+, ELISA for brucellosis IgG + IgA +. The infectious disease specialist prescribed antibacterial therapy: rifampicin 150 mg + doxycycline 200 mg once daily for 48 days. During treatment, back pain, symptoms of intoxication syndrome (chills, weakness, fatigue), and emotional instability persisted. Therefore, after 3 months, a second course of treatment was prescribed - ciprofloxacin 1000 mg/day and doxycycline 200 mg/day for 45 days with a decrease in joint and intoxication syndromes. After 3 months, the patient underwent control tests

Table 1. Laboratory analyses of the first patient in dynamics

Indicators	September 2021 (before treatment)	December 2021 - before the 1st course of treatment (RP*+DCC*)	May 2022 - before the 2nd course (CPF*+DCC)	October 2022 (before the 2nd course (LVF*+ RHI-2*)	July 2024 (after the treatment)
Hemoglobin, g/l	143	133	148	149	151
Erythrocytes, 10*12	5,0	4,4	5,2	5,5	4,9
Platelets, 10*9	271	329	257	249	198
Leukocytes, 10*9	5,6	5,3	6,8	5,1	7,3
Lymphocytes, %	35	39	27	39,8	19,8
ESR, mm/h	5	42	2	14	8
CRP, mg/l	0,6	15	0,8	1,9	3,4
RF, U/l	57	103	35	53,4	15
ASL-O, IU/ml	55	101	290	155	Negative
HLAB27	negative	-	-	-	-
ACCP*, U/l	602	-	-	75	34
Wright agglutination reaction	-	1:400	Positive	1:100	1:50
Huddleson agglutination reaction	-	+++	++	-	-
ELISA IgG	-	Positive	-	Positive	Positive
ELISA IgA	-	Positive	-	Negative	Negative

*ACCP - antibodies to cyclic citrullinated peptide
*RP - Rifampicin, *DCC - Doxycycline, *CPF – Ciprofloxacin, * LVF - Levofloxacin
*RHI-2 - Recombinant human interleukin-2

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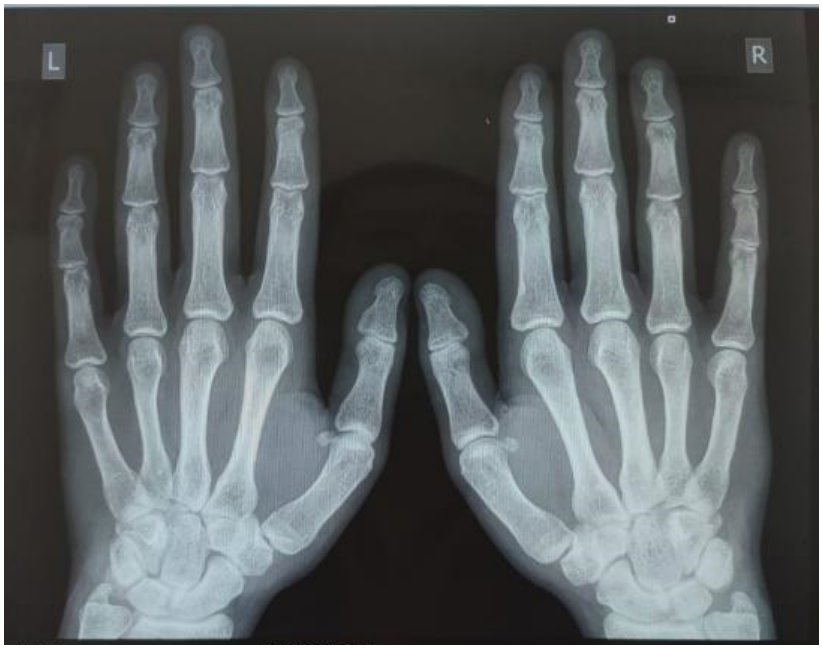

Figure 1. X-ray of the hands in the patient No. 1.

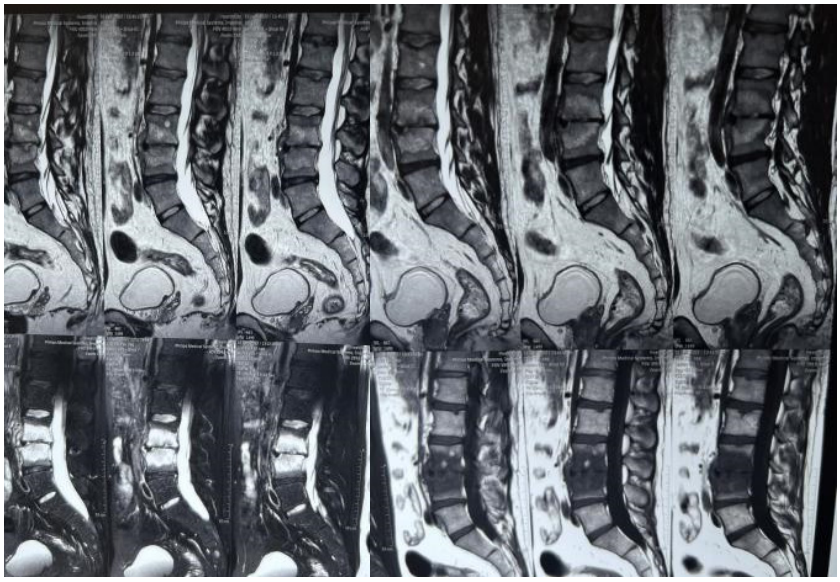

Figure 2. MRI of the spine patient No. 1, 01.2022. (before the first course of treatment). Picture of spondylodiscitis L3-L4 in the subacute phase, L3 retrolisthesis, ossification, and edema of the anterior longitudinal ligament.

after treatment: ELISA for brucellosis IgG+, Wright agglutination test 1:100. The patient continues to have emotional lability, anxiety, and unmotivated fatigue, and he repeatedly turns to an infectious disease specialist with the desire for complete healing. The infectious disease specialist prescribed levofloxacin 1000 mg daily with a dosage form of recombinant human interleukin-2 500,000 U 1 ml subcutaneously 1 time in 3 days (72-hour intervals), course of treatment 5 injections. During therapy, signs of inflammation normalized, rheumatoid antibodies (RF and ACCP) and titers of serological reactions decreased, as well as improvements in the MRI picture (Figure 3)

Case №2. Man, 60 years old, village resident, shepherd. The patient complains of severe back pain with irradiation to the right leg, pain and limitation of movement in the right hip joints, pain and restriction of movement in the knee joints, severe night sweats, undulating febrile fever, and weight loss of 18 kg in 6 months. Twenty years ago, there was an episode of arthritis of the knee joints, febrile fever for two months, and weight loss. Blood analysis: Hb - 130 -107 g / l, leukocytes - 18.97-10.8 * 10^9 / l, platelets - 490 * 10^9 / l, ESR - 28-37 mm / h; CRP-20.37 mg/l, RF - 61.0-40.8 IU/ml, ACCP-4690 -2750 IU/l, ferritin - 491

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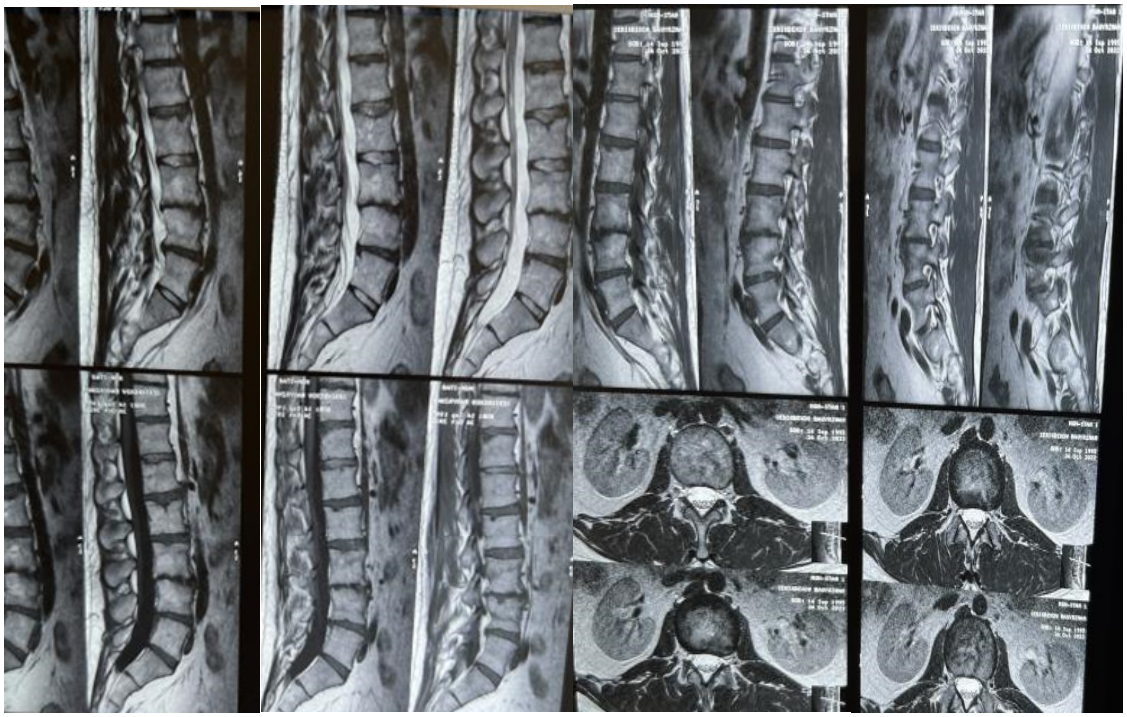

Figure 3. MRI of the spine patient No. 1, 10.2022. (after treatment) – osteochondrosis, central hernia L5-S1. Right-sided paramedian protrusion of the L1-L2 disc. Signs of spondylodiscitis at the level of L4-L5.

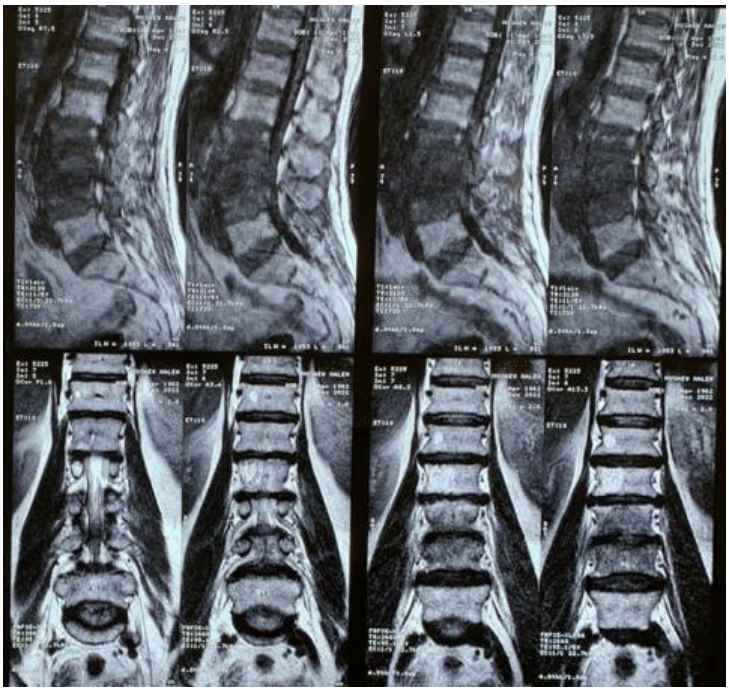

Figure 4. MRI image of patient No. 2. Signs of spondylodiscitis at the level of L3-L4 with the formation of an esophagus along the posterior contour of the L4 vertebra (brucellosis? tuberculosis?). Circular protrusion of the intervertebral discs L2-L3, L3-L4, L4-L5 with compression of the dural sac, narrowing of the intervertebral foramen. Hemangioma of bodies L1, L2 of the vertebrae;

ng/ml, PCT values <0.10 ng/ml (negative); ELISA for brucellosis IgG+, Wright agglutination test - negative, Huddlson agglutination test - negative, HLA B27 - negative; Ultrasound of the abdominal organs - hepatomegaly; an MRI of the spine was taken (Figure 4); x-ray of the hands - no pathology was detected; x-ray of the knee joint - deforming osteoarthritis of the knee joints two x-ray stage. A TB doctor consulted the patient; tuberculous spondylitis was excluded based on laboratory and instrumental data (sputum smear microscopy negative, Interferon Gamma Release Assay -negative, GeneXpert MTB/RIF – negative,

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Chest radiograph - pathology not found). Chronic human brucellosis was diagnosed based on serological tests, clinical manifestations, and epidemiological information. Serum agglutination test (SAT) and Elisa IgG are positive (positivity rate – 2.9) were utilized for brucellosis diagnosis. An infectious disease doctor prescribed levofloxacin 500 mg 2 times a day for 45 days and doxycycline 200 mg/day for 21 days to relieve acute inflammation, and dexamethasone 8 mg 2 times a day with a dose reduction every two days. The patient was transferred to the infectious department.

Discussion

Brucellosis is a highly virulent, zoonotic infection that primarily affects animals, and humans can become infected through contact with infected animals or through the consumption of contaminated animal products (15, 16). From the point of view of the difficulty of differential diagnosis of rheumatological diseases with lesions of the musculoskeletal system, the chronic forms of brucellosis infection cause a problem since they are characterized by variability in clinical manifestations and a recurrent course. In a large-scale meta-analysis of musculoskeletal lesions in ChB, the incidence of arthralgia, arthritis, spondylitis, and sacroiliitis were 65%, 26%, 12%, and 36%, respectively (10). In ChB, the spine is affected with a 2-54% frequency and manifests as spondylitis, spondylodiscitis, and discitis (7, 17, 18). Spondylodiscitis is the most severe form of musculoskeletal disease as it causes a high rate of neurological complications (7).

Symmetrical polyarthritis in the small joints of the hands, the positivity of RA and ACCP makes it difficult to diagnose ChB in favor of RA, but in the case of brucellosis, arthritis is reversible and disappears without a trace after treatment (19). In 2022 Leu Agelii et al. examined the differences between actual and misdiagnosed RA cases in a long-term cohort of patients and proved that in some misdiagnosed patients, the cause of arthritis was a chronic infection (20).

The standard agglutination test (SAT) is the most accepted serological diagnostic test for human brucellosis (21). Enzyme-linked immunosorbent assays (ELISAs) allow better interpretation of the clinical situation and eliminate false negative/positive results that can occur with an SAT (22). In the early stages of infection, pathological signs on the joint X-ray may not be detectable (23). Therefore, MRI has several advantages over other imaging methods and is very useful for the differential diagnosis of brucellosis lesions of the spine (spondylitis, spondylodiscitis, sacroiliitis) and other pathologies of the spine (24).

In the cases we provided, the patients did not have the classic symptom - polyarthritis with morning stiffness in the joints, but they had high titers of anti-rheumatoid antibodies. We suggest two possible reasons for the increase in ACCP in ChB:

1. Syndrome of polyclonal activation of lymphocytes. We know that each lymphocyte can respond to only one antigenic determinant. After interacting with the antigen, the lymphocyte actively multiplies and gives rise to a whole population (clone) of lymphocytes, each of which remains specific to this antigenic determinant. Moreover, the antibodies synthesized by these lymphocytes are specific to this antigen. Subsequently, it was found that when an antigen enters the body again (re-infection or exacerbation of chronic infection), the clone of lymphocytes specific to this antigen is activated again and begins synthesizing antibodies. This is a normal immune system reaction in the form of monoclonal activation of lymphocytes to a certain "normal" antigen. If the antigen is "complex," the so-called "superantigen" - then a pathological process occurs - polyclonal activation of lymphocytes – this is the ability of the bacterium to cause the activation of several different clones of lymphocytes and, accordingly, the polymorphism of clinical manifestations as in ChB. These abilities of Brucella spp. Being a "superantigen" is likely due to the following bacterial virulence factors:

- Brucella spp lives in the cell vacuole (brucella-containing vacuole), which transforms into a replicative compartment - thus evading intracellular digestion (25, 26)
- Brucella spp inhibits apoptosis of infected mononuclear cells (27)
- Brucella spp prevents dendritic cell maturation, antigen presentation, and activation of naive T cells (28)
- Brucella spp produces a soluble inhibitor of tumor necrosis factor-α (27)

2. Arthritogenic ability of Brucella. Brucella spp. is likely to cause autoimmune reactive arthritis. Brucella spp, probably like other trigger infectious agents like Salmonella, Yersinia, and Shigella, causing HLA-B27-associated reactive arthritis, produce so-called arthritogenic peptides, whose epitopes are presented by phagocytes to cytotoxic T lymphocytes on the synovial membrane (29). Furthermore, we know that citrulline autoantibodies are localized in the synovial membrane and demonstrate active inflammation of the synovial tissue in patients (3, 4). On the other hand, autoimmune involvement in ChB demonstrates the response of antigens of the major histocompatibility complex. Data on the association of brucellosis arthritis with the HLA-B39, HLA-A2, and HLA-B27 antigens have been obtained from HLA-B27 (30-32).

However, we must discuss another logical point of view. There are multiple studies (33-36) that discuss the production of anti-CCP antibodies and RF in the preclinical phase of RA, where immune dysregulation and autoantibody production occur several years before the onset of clinical symptoms of RA, making them valuable biomarkers for predicting the development of RA (35, 36). In 2018, a study showed that 21.5% of anti-CCP-positive healthy individuals eventually developed RA. The risk of progression to RA increased with the level of anti-CCP antibodies, with 46.0% of patients with high levels of anti-CCP developing RA within five years (37), and even up to 10 years before the onset of symptoms (34). Detecting rheumatoid antibodies in the preclinical phase may help identify high-risk individuals and implement early intervention strategies.

A thorough and detailed history taking is critical to the timely diagnosis of brucellosis infection. Obtaining an epidemiological history (contact with infected animals, eating contaminated animal products, or visiting endemic areas)

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facilitates the diagnostic search (38).

Conclusion

The polymorphism of the musculoskeletal lesion in ChB in the form of arthritis, back pain, picture of unilateral or bilateral sacroiliitis, and tenosynovitis makes it difficult to make a differential diagnosis of similar diseases in the clinic. The positivity of RF and ACCP in brucellosis infection is probably associated with macrophage activation syndrome and the arthritic ability of Brucella. This proves a significant reduction and/or disappearance of autoantibodies during antibacterial therapy with restoration of the functional activity of the joint.

On the other hand, it is necessary to remember that the presence of one disease does not exclude the addition of another, so one patient can be diagnosed with both RA and ChB. Correct verification of the diagnosis determines the choice of therapy since the treatment of infectious and autoimmune diseases is fundamentally different from each other, and a diagnostic error will lead to incorrect treatment tactics, which, when using biological immunosuppressive therapy, can cause a tragic outcome.

The above clinical cases have shown the need to study other reasons for the production of anti-rheumatoid antibodies in addition to RA, and the authors hope that the pathogenesis of these conditions will become better understood over time.

Authors' Contributions

Yulduz Khaidarova and Madina Omarova researched the literature and conceived the study. A.F.A. was involved in conception and data collection and wrote the first draft. Professor Gaukhar Kurmanova and professor Gulzada Nurgaliyeva reviewed and edited the manuscript and approved the final version.

Ethical Considerations

This study was conducted in compliance with all the principles of professional and scientific ethics.

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Conflict of Interests

The authors declare that they have no competing interests.

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