Case Report

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Significance of Differential Diagnosis for Febrile and Fatigued Patients in an Endemic Area During The COVID-19 Pandemic: Consideration of COVID-19, Brucellosis, and Crimean-Congo Hemorrhagic Fever

Orçun Barkay[1], Faruk Karakeçili[1], Umut Devrim Binay[1], Betül Sümer[1]

[1]Erzincan Binali Yıldırım University Faculty of Medicine, Mengücek Gazi Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Erzincan, Turkey.

Abstract

Brucellosis and Crimean-Congo Hemorrhagic Fever are diseases that can present with similar clinical and laboratory findings to those of COVID-19. This can delay diagnosis and increase the risk of nosocomial transmission in the case of Crimean-Congo Hemorrhagic Fever. Although misdiagnosis of Brucellosis and Crimean-Congo Hemorrhagic Fever, and even a case of coinfection have been reported in the literature, no case report mentioning Crimean-Congo Hemorrhagic Fever and Brucellosis coinfection hospitalized with the pre-diagnosis of COVID-19 was found. A 35-year-old female patient presented to the emergency service with complaints of fever and fatigue. The patient was evaluated in the emergency triage and was taken to the area where COVID-19 pre-diagnosed patients were being examined. A thorax computed tomography without intravenous contrast usage was reported as normal, and the patient was discharged after being informed about COVID-19 transmission routes. The patient re-applied to the emergency service with complaints of fever, fatigue, headache, and myalgia four days later. The laboratory findings showed a white-cell count of 1600/mm^3, haemoglobin of 12,8 g/liter, platelet of 146000/mm^3, urea of 21,5 mg/dl, creatinine of 0,81 mg/dl, alanine aminotransferase of 134 U/liter, aspartate aminotransferase of 303 U/liter, lactate dehydrogenase of 714 U/liter, creatine kinase of 1796 U/liter, C-reactive protein of 3 mg/liter, D-dimer of 2000 µg/liter, and a thorax computed tomography showed minimal ground-glass opacity. The patient was hospitalized with a preliminary diagnosis of COVID-19 by the chest diseases clinic. This case highlights the importance of considering other diseases with similar clinical and laboratory findings in endemic regions of Brucellosis and Crimean-Congo Hemorrhagic

Keywords: Brucellosis, COVID-19, Crimean-Congo Hemorrhagic Fever

Introduction

We are still dealing with the COVID-19 disease, which is affecting the entire world and is caused by SARS-CoV-2 (1). Brucellosis is one of the common zoonotic diseases and is generally transmitted by contact with infected animal tissues or by consuming the products of these animals. The disease, which is endemic in our country, is especially common in people living in rural areas and dealing with animal husbandry (2). Crimean-Congo Hemorrhagic Fever (CCHF), another common disease in this population, is one of the viral hemorrhagic fevers with endothelial damage (3). Patients with brucellosis and CCHF in endemic regions can also present with similar clinical and laboratory findings to those of COVID-19 (4), leading to misdiagnosis or confusion by visiting multiple departments. In addition, the diagnosis of the patient can be delayed, and the risk of nosocomial transmission may increase in the case of CCHF. Although misdiagnosis of Brucellosis and CCHF, and even a case of coinfection have been reported in the literature (5), no case report mentioning CCHF and brucellosis coinfection hospitalized with the pre-diagnosis of COVID-19 was found. In this report, we present a case of a patient who was admitted to the clinic with a preliminary diagnosis of COVID-19 and was detected to have brucellosis and CCHF coinfection.

Case Report

A 35-year-old female patient presented to the emergency service with complaints of fever and fatigue that had been ongoing for two days. The patient was evaluated in the emergency triage and was taken to the area where COVID-19 pre-diagnosed patients were being examined. There was no pathological finding in the physical examination of the patient, and no pathological finding was found in the serum

Corresponding Author: Orçun Barkay
e-mail: o.barkay1985@gmail.com
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parameters, except for an absolute lymphocyte count of 310/mm³. A thorax computed tomography (CT) without intravenous contrast usage was reported as normal. The patient was informed about COVID-19 transmission routes and discharged.

The patient re-applied to the emergency service with complaints of fever, fatigue, headache, and myalgia four days later. The laboratory findings of the patient, who was again evaluated in the area reserved for COVID-19 patients at the emergency department, showed a white-cell count of 1600/mm³ (reference range, 4490 to 12680), haemoglobin of 12,8 g/liter (reference range, 12 to 16), platelet of 146000/mm³ (reference range, 150000 to 450000), urea of 21,5 mg/dl (reference range, 17 to 43), creatinine of 0,81 mg/dl (reference range, 0,66 to 1,09), alanine aminotransferase (ALT) of 134 U/liter (reference range, 0 to 35), aspartate aminotransferase (AST) of 303 U/liter (reference range, 0 to 35), lactate dehydrogenase (LDH) of 714 U/liter (reference range, 0 to 248), creatine kinase (CK) of 1796 U/liter (reference range, 0 to 145), C-reactive protein (CRP) of 3 mg/liter (reference range, 0 to 5), D-dimer of 2000 µg/liter (reference range, 80 to 583). A low-dose thorax CT was performed and showed a minimal ground-glass opacity with a peripheral location limited to the fissure in the left lobe basal segment (Figure 1).

The patient was hospitalized with a preliminary diagnosis of COVID-19 by the chest diseases clinic. We evaluated the patient in the chest diseases service. The general state was good, with the patient being conscious, cooperative, and oriented. The temperature was 39,2 °C, blood pressure was 110/70 mmHg, and the heart rate was 102 beats per minute. Systemic examination was normal. We learned that the patient resided in a rural area and engaged in animal husbandry. Although the patient had no history of tick bites, she reported catching ticks on her body several times and disposing of them. The patient was transferred to our infectious diseases service with a pre-diagnosis of CCHF. Serum samples were sent to the Public Health Agency Microbiology Reference Laboratory Department for CCHF diagnostic tests, and supportive treatment was initiated. Detailed viral hepatitis diagnostic tests were performed due to high serum aminotransferase levels. Brucella Rose Bengal and standard tube agglutination tests were also requested, given the patient's engagement in animal husbandry, history of consuming fresh milk and dairy products, and residence in an endemic region for brucellosis. The patient's SARS-CoV-2 polymerase chain reaction (PCR) test was negative. On the second day of hospitalization, laboratory tests revealed leukopenia (white-cell count: 1200/mm³), a hemoglobin level of 12,2 g/liter, a platelet count of 114000/mm³, a urea level of 14 mg/dl, a creatinine level of 0,74 mg/dl, elevated ALT levels of 130 U/liter, AST levels of 196 U/liter, LDH levels of 523 U/liter, CK levels of 887 U/liter, a CRP level of 3 mg/liter, an international normalized ratio (INR) of 1,07 %, and blood type A Rh positive. Acute viral hepatitis was not detected, but the Brucella Rose Bengal test was positive, and the standard tube agglutination and Coombs' immunocapture agglutination tests were positive at 1/320 titers. Two sets of blood cultures were collected from the patient whose fever persisted. On the third day of hospitalization, laboratory tests showed leukopenia (white-cell count: 1600/mm³), a hemoglobin level of 13 g/liter, a platelet count of 86000/mm³, ALT levels of 111 U/liter, AST levels of 138 U/liter, LDH levels of 451 U/liter, CK levels of 510 U/liter, and an INR of 1,2 %. At the reference laboratory, the immunofluorescence method detected the presence of CCHF specific IgM antibodies (CCHFV Mosaic 2, Euroimmun Labordiagnostika AG, Germany). The diagnosis was also confirmed by real-time reverse transcriptase PCR (RT-PCR). Viral RNA isolation was performed using the High Pure Viral Nucleic Acid Kit (Roche Diagnostics GmbH, Germany), and the presence of viral RNA was tested using TaqMan-based single-stage RT-PCR. The Perkin-Elmer 7700 Sequence Detection System (Applied BioSystems, USA) was used for detection, with a combination of reverse transcriptase (MBI Fermentas, Germany) and Hot Start Taq DNA polymerase (Bioron GmBH, Germany). On the third day of hospitalization, specific treatment was initiated for brucellosis (rifampicin 600 mg per day and doxycycline 100 mg twice a day per oral). The patient's clinical course was closely monitored, and serum parameters were followed closely. Along with treatment for brucellosis, supportive treatment was given for CCHF. The patient's fever showed regression after the fourth day of follow-up; serum parameters such as leukopenia and aminotransferase levels began to improve (Table 1), and the patient's complaints were alleviated.

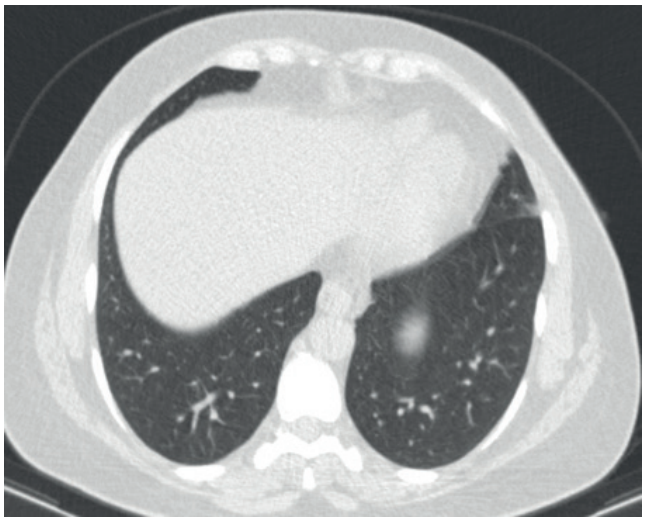

Figure 1. Axial CT Image of the Chest Showing A Minimal Ground-glass Opacity.

Table 1: Laboratory data

	Hospitalization Period				
Variable	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**
WBC (/mm³)	1600	1200	1600	2600	4500
Hb (g/liter)	12,8	12,2	13	13,1	13
Platelet (/mm³)	146000	114000	86000	74000	149000
Urea (mg/dl)	21,5	14	-	-	20
Creatinine (mg/dl)	0,81	0,74	-	-	0,7
ALT (U/liter)	134	130	111	100	32
AST (U/liter)	303	196	138	113	34
LDH (U/liter)	714	523	451	353	220
CK (U/liter)	1796	887	510	348	120
INR (%)	-	1,07	1,2	1,04	1,04

On the eighth day of hospitalization, all serum parameters were within normal limits, and the patient's symptoms had significantly improved. Blood cultures obtained on the second day of hospitalization were negative. The patient was hospitalized for ten days and then discharged with instructions for oral brucellosis treatment. The patient's follow-up is currently ongoing on an outpatient basis. Informed consent was obtained from the patient during their hospitalization in our facility.

Discussion

During the current COVID-19 pandemic, patients may present with many non-specific symptoms such as fever, fatigue, myalgia, headache, and back pain (1). The symptoms of brucellosis and CCHF patients also have a wide range, many of which are similar to those of COVID-19.

Brucellosis is a zoonosis caused by an intracellular bacterium and can therefore affect many organs and systems. The most common findings are fatigue, fever, night sweats, myalgia, and arthralgia (6, 7). None of these findings are specific to brucellosis. Hematological abnormalities such as leukopenia, anemia, and thrombocytopenia can occur due to bone marrow involvement and hypersplenism. Diseases causing bone marrow involvement and hypersplenism should be considered in the differential diagnosis (8, 9). Another disease that often causes similar findings is CCHF. The clinical presentation and laboratory findings of CCHF resemble those of brucellosis, and they can be differentiated by visible skin, mucous membranes, and other organ bleeding at the advanced stage of the disease (10). Both diseases are more common in people engaged in animal husbandry and living in rural areas (11). Similar clinical and laboratory findings have been reported in different studies (12, 13).

COVID-19 can also manifest as similar clinical (fever, fatigue, headache, etc.) and laboratory (cytopenia, aminotransferase elevation, D-dimer, INR elevation) findings. Rural residents have also been affected by the COVID-19 pandemic. In addition, SARS-CoV-2 and Nairovirus are RNA viruses. Brucella is also an intracellular pathogen, like viruses. Symptoms and clinical findings of infections caused by viruses and intracellular pathogens can be very similar. In such cases, a careful differential diagnosis is essential.

Our patient, who lives in a rural area and works with animal husbandry, presented with leukopenia, thrombocytopenia, and elevated levels of AST, ALT, LDH, and CK. Based on these findings, we diagnosed CCHF. To confirm the diagnosis, we sent a serum sample taken on the second day of hospitalization to the reference laboratory and closely monitored routine laboratory values. Brucellosis was also suspected, based on a previously reported case by Karakeçili et al. (5), and Brucella Rose Bengal, standard tube agglutination (1/320), and Coombs' immunocapture (1/320) tests were positive. The results from the reference laboratory showed that IgM and RT-PCR tests were positive for CCHF. Consequently, we diagnosed our patient with co-infection of brucellosis and CCHF, who was initially hospitalized with a pre-diagnosis of COVID-19. We considered the brucellosis as acute, given the sudden onset of the patient's symptoms and the absence of a previous history of the disease. The lack of long incubation period was suspected as the reason for the negativity of the two blood cultures gathered during hospitalization. The patient received rifampicin and doxycycline therapy for brucellosis, and we closely monitored the serum parameters after the positive PCR result for CCHF. With specific brucellosis treatment and supportive treatment for CCHF, the patient's symptoms improved, and serum parameters returned to normal.

To our knowledge, no case of co-infection of brucellosis and CCHF with a pre-diagnosis of COVID-19 has been reported previously. Our case underscores the importance of considering CCHF and brucellosis in the differential diagnosis of patients presenting with similar symptoms, particularly in endemic regions during the COVID-19 pandemic. Our case also highlights that the two diseases can coexist. Fortunately, the droplet and contact isolation precautions applied for the preliminary diagnosis of COVID-19 were also sufficient to prevent the transmission of CCHF. Early diagnosis of CCHF in these patients can prevent nosocomial transmission and ensure appropriate diagnosis and treatment.

In conclusion, a careful differential diagnosis is crucial in patients pre-diagnosed with COVID-19 who present with vague symptoms, particularly in regions where both brucellosis and CCHF are endemic

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