CASE REPORT / OLGU SUNUMU

DOI: 10.4274/mjima.galenos.2022.2022.36
Mediterr J Infect Microb Antimicrob 2022;11:36
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2022.2022.36

Increased Mortality with Co-existence of Crimean-Congo Hemorrhagic Fever and COVID-19

Kırım-Kongo Kanamalı Ateşi ve COVID-19 Koenfeksiyonu Sonucu Artan Mortalite

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral disease with fever and bleeding caused by a tick-borne virus belonging to the *Bunyaviridae* family. Coronavirus disease-2019 (COVID-19) is a novel disease caused by Severe Acute Respiratory Syndrome Coronavirus Type 2, which can lead to acute respiratory distress syndrome (ARDS). Here, we present a case with CCHF and COVID-19 co-infection to draw attention to the increased mortality in co-infection cases. A 77-year-old female patient with known hypertension was admitted to the emergency department with complaints of fever, nausea, vomiting, diarrhea, and myalgia for two days. There was no history of tick bite or contact with a patient with COVID-19. Current anamnesis and clinical and laboratory findings pre-diagnose the patient with CCHF, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura, leading to a ward admission. Crimean-Congo hemorrhagic fever was diagnosed after receiving a positive CCHF immunoglobulin M (indirect fluorescent antibody) result. A nasopharyngeal swab sample for COVID-19 real-time polymerase time reaction was sent due to a continuous fever and the development of shortness of breath on day three of hospitalization, which revealed positive results; thus, the patient was started on favipiravir treatment. The patient was transferred to the intensive care unit on day four due to increased oxygen demand and ARDS diagnosis. The patient died due to respiratory failure on the seventh day of hospitalization. COVID-19-related ARDS that overlapped on top of CCHF caused her to develop a cytokine storm and died despite her clinical parameter improvement due to CCHF. Crimean-Congo hemorrhagic fever and COVID-19 symptoms or findings can be confused because of their similarities, but the possibility of being seen together should not be overlooked. Concurrently, some similarities in the pathogenesis of these two diseases suggest that co-infection may worsen the clinical course; hence, new studies are needed on this subject.

Keywords: COVID-19, Crimean-Congo hemorrhagic fever, coinfections

Öz

Kırım-Kongo kanamalı ateşi (KKKA), *Bunyaviridae* familyasına ait kene kaynaklı bir virüsün neden olduğu, ateş ve kanama ile seyreden akut viral bir hastalıktır. Koronavirüs hastalığı-2019 (COVID-19), Şiddetli Akut Solunum Yolu Sendromu Koronavirüs tip 2'nin neden olduğu ve akut solunum sıkıntısı sendromuna (ARDS) yol açabilen yeni bir hastalıktır. Bu olgu sunumunda KKKA ve COVID-19 koenfeksiyonu olan bir olgu sunulmuş ve koenfeksiyon durumunda artan mortaliteye dikkat çekmek amaçlanmıştır. Yetmiş yedi yaşında, hipertansiyonu olduğu bilinen kadın hasta, iki gündür

Cite this article as: Şimşek M, Tayşi MR, Karaman İ, Yıldırım F, Sezgi A, Şencan İ. Increased Mortality with Co-existence of Crimean-Congo Hemorrhagic Fever and COVID-19. Mediterr J Infect Microb Antimicrob. 2022;11:36.

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Received/Geliş Tarihi: 19.05.2022 **Accepted/Kabul Tarihi:** 12.08.2022

Published: 12 August 2022

ateş, bulantı, kusma, ishal ve miyalji şikayetleri ile acil servise başvurmuştu. Daha önce bir COVID-19 hastasıyla temas öyküsü veya kene ısırığı öyküsü yoktu. Mevcut anamnez, klinik ve laboratuvar bulgularına göre hasta KKKA, hemolitik üremik sendrom ve trombotik trombositopenik purpura ön tanıları ile servise yatırıldı. Kırım-Kongo kanamalı ateşi tanısı, pozitif KKKA IgM (dolaylı floresan antikor) ve pozitif polimeraz zincir reaksiyonu (PCR) sonucu alındıktan sonra konuldu. Hastanın yatışının üçüncü gününde ateşinin devam etmesi ve nefes darlığı gelişmesi nedeniyle COVID-19 PCR için nazofaringeal sürüntü örneği gönderildi ve sonuç pozitif çıktı, sonrasında hastaya favipiravir tedavisi başlandı. Yatışının dördüncü gününde oksijen ihtiyacının artması üzerine yoğun bakıma alınan hastaya ARDS tanısı kondu. Yatışının yedinci gününde hasta solunum yetmezliği nedeniyle kaybedildi. Hastamızın KKKA nedeniyle klinik parametrelerinin iyileşmesine rağmen, KKKA'nın üzerine COVID-19 ile ilgili ARDS, sitokin fırtınası geliştirmesine neden oldu ve ölüm ile sonuçlandı. Kırım-Kongo kanamalı ateşi ve COVID-19 semptom/bulguları birbirine benzediği için karıştırılabilse de birlikte görülme ihtimali de gözden kaçırılmamalıdır. Aynı zamanda bu iki hastalığın patogenezindeki bazı benzerlikler, koenfeksiyonun klinik seyri kötüleştirebileceğini düşündürmekte ve bu konuda yeni çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: COVID-19, Kırım-Kongo kanamalı ateşi, koenfeksiyonlar

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute and severe viral disease characterized by fever and bleeding caused by a tick-borne virus belonging to the *Bunyaviridae* family[1]. Increased vascular permeability is caused by the release of large amounts of cytokines, chemokines, and proinflammatory mediators from virus-infected monocytes and macrophages and intrinsic coagulation system activation. Disseminated intravascular coagulopathy, hemophagocytosis, and liver dysfunction are responsible for CCHF pathogenesis[2]. Coronavirus disease-2019 (COVID-19) is a disease caused by Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2), leading to acute respiratory distress syndrome (ARDS), with high mortality and morbidity[3]. Coronavirus disease-2019 may contribute to the development of ARDS by activating the excessive and dysregulated host immune response[4]. Cellular and humoral hyperactivation and increased inflammatory cytokines and chemokines play an important role in ARDS pathogenesis[5].

Coronavirus disease-2019 and CCHF have many similar clinical findings. Common symptoms in CCHF are fever, malaise, headache, abdominal pain, and myalgia, whereas common symptoms in COVID-19 are fever, dry cough, myalgia, weakness, shortness of breath, and loss of taste or smell. Common laboratory findings between these two diseases include thrombocytopenia, lymphopenia, increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK)[1,6]. Here, we present a case with CCHF and COVID-19 co-infection to draw attention to the increased mortality in co-infection cases.

Case Report

A 77-year-old female patient with known hypertension was admitted to the emergency department with complaints of fever, nausea, vomiting, diarrhea, and myalgia for two days. The patient had no contact with anyone with a COVID-19 diagnosis in the last 14 days and no history of tick infestation. The patient was engaged in agriculture and animal husbandry in Çankırı. There was no history of raw milk and cheese consumption. At admission, her vital signs were as follows: body temperature: 36.3 °C; blood pressure: 160/100 mmHg; respiratory rate: 20/min; heart rate: 87 beats/min; and SpO_2: 92%. Physical examination revealed a conscious, oriented, and cooperative patient. There were petechial rashes and ecchymoses distributed all over her body. Other system examinations were unremarkable. The detailed inspection revealed no ticks on her body. Laboratory findings at admission were as follows: leukocyte count: 26410/mm^3; neutrophil count: 24840/mm^3; lymphocyte count: 940/mm^3; hemoglobin: 8.1 g/dl; hematocrit: 23.8%; platelet: 7000/mm^3; urea: 197 mg/dl; creatinine: 4.1 mg/dl; AST: 162 U/L; ALT: 37 U/L; CK: 121 U/L; LDH: 2503 U/L; C-reactive protein: 132.4 mg/L; international normalized ratio: 1.15; activated partial thromboplastin time: 30.4 s; prothrombin time (PT): 9.62 s (Table 1).

Current anamnesis and clinical and laboratory findings pre-diagnosed the patient with CCHF, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura, leading to a ward admission. A blood culture was taken and ceftriaxone of 2×1 g (IV) was empirically started. Crimean-Congo hemorrhagic fever was diagnosed after receiving a positive CCHF immunoglobulin (Ig) M (indirect fluorescent antibody) result. Pooled thrombocyte, fresh frozen plasma, and erythrocyte suspensions were replaced in the patient. Hemodialysis and ultrafiltration were performed because there was no urine output. In the follow-up, the patient did not have any signs of active bleeding, and platelet values progressively increased. Ribarivin treatment was not considered for the patient who showed clinical improvement with supportive treatment and with increased platelet count.

The patient did not have a history of contact with a patient with COVID-19, but a nasopharyngeal swab sample for COVID-19 real-time polymerase time reaction (RT-PCR) was sent due to the current pandemic circumstances and the continuous fever and development of shortness of breath on day three of hospitalization, which revealed a positive result. Concurrently, the PCR sent for CCHF was positive. The patient was started on favipiravir at 2×1600 mg TB loading and 2×600 mg maintenance (PO) treatment. The patient was transferred to the

Table 1. Laboratory findings of patient

Blood parameters	Admission days			
	Day 1	Day 3	Day 5	Day 7
Leukocyte count (/mm^3)	26410	15290	13340	19590
Neutrophil count (/mm^3)	24840	12320	10120	19120
Lymphocyte count (/mm^3)	940	1400	1760	340
Platelet count (/mm^3)	7000	73000	132000	220000
Hemoglobin (gr/dl)	8.1	8.9	9.4	8.4
PT (seconds)	9.62	8.97	9.05	10.2
aPTT (seconds)	30.4	22.6	21.9	33.8
INR	1.07	1	1.01	1.13
Fibrinogen (mg/dl)	-	537	-	539
D-dimer (µg/ml)	8.2	8.54	4.28	2.17
Urea (mg/dl)	197.1	170	128	148
Creatinine (mg/dl)	4.1	5.21	4,7	2.56
AST (U/L)	162	42	15	21
Lower (U/L)	37	39	17	16
LDH (U/L)	2503	1257	444	465
CK (U/L)	121	-	57	48
CRP (mg/dl)	132.4	14	81	155.8

PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, AST: Aspartate aminotransferase, CK: Creatine kinase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

intensive care unit (ICU) due to the increased oxygen demand on day four of hospitalization, and she was diagnosed with ARDS. Ceftriaxone was stopped in the ICU because her fever continued and she was empirically started with piperacillin-tazobactam 3×2.25 g (iv), levofloxacin 1×500 g every 48 h (IV) (at hemodialysis dose). Chest X-ray and thorax computed tomography (CT) images taken in the ICU are shown in Figures 1 and 2. When the interleukin-6 result was >1000 pg/ml, 400 mg of tocilizumab (IV) treatment was started, whereas at the time PaO_2/FIO_2 was 80 mmHg, and methylprednisolone of 2×40 mg IV treatment was added. High flow nasal oxygen therapy was started with 60 L/min flow and 80% FIO_2. She was switched to non-invasive mechanical ventilation because her hypoxemia worsened, and elective intubation was performed on day five of hospitalization. The patient died due to respiratory failure seven days after her hospitalization.

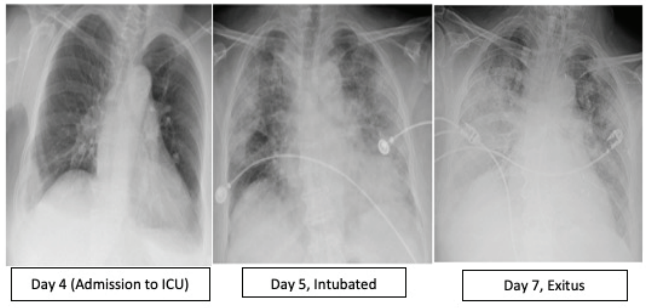

Figure 1. Chest X-ray images taken in the intensive care unit of the patient

ICU: Intensive care unit

Discussion

This study presented a mortal case with CCHF and COVID-19 co-infection, followed by ARDS. Our patient met most of the clinical and laboratory findings that are seen in CCHF, was engaged in agriculture and animal husbandry, applied to our clinics during summer, had petechiae and ecchymosis, and our region was endemic in terms of CCHF, which made us consider CCHF in the differential diagnosis and the patient was diagnosed with CCHF IgM positivity. Later, the development of dyspnea was a clue for COVID-19 diagnosis, and the diagnosis was made with the COVID-19 RT-PCR positivity.

acute respiratory distress syndrome development occurs on an average of 8-9 days after the onset of symptoms in severe COVID-19 cases[7,8]. In CCHF, the prehemorrhagic (symptomatic) period lasts approximately 1-7 days, while the hemorrhagic period lasts 2-3 days[1]. The presence of hemorrhagic findings, such as petechiae and ecchymosis, on the 3rd day of the onset of symptoms in our patient and the development of ARDS on the 7th day of the onset of symptoms, suggest that these two diseases deteriorated each other and rapidly worsen the patient's condition. Most of the deaths in CCHF occur due to active bleeding usually during the hemorrhagic phase, but deaths

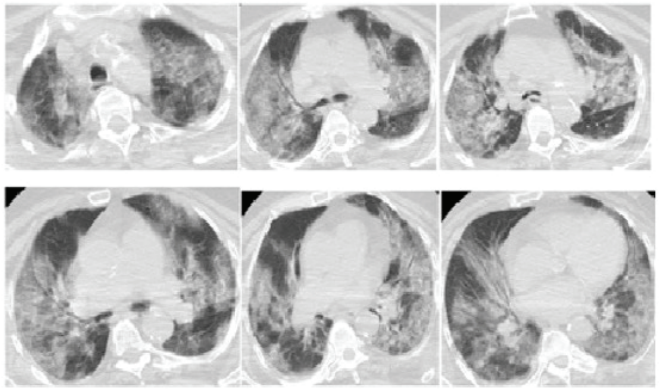

Figure 2. Thorax CT on the 2nd day of the patient's admission to the intensive care unit, and the 5th day of hospitalization. Thorax CT showed bilateral, diffuse ground glass areas, alveolar consolidation, and air bronchograms

CT: Computed tomography

due to COVID-19 occur as a result of respiratory failure[1,9]. Our patient died not because of hemorrhage, but because of respiratory failure due to COVID-19.

There were only two reported cases of COVID-19 and CCHF co-infection from Turkey, which is a rare occurrence[10,11]. Both cases were successfully treated with favipiravir although CCHF or COVID-19 have no specific antiviral treatment. Patients in both cases reported having similar symptoms and history, which was also remarkable for living in areas that are endemic to CCHF. This shows that two viral infectious diseases can be seen together and should be considered in the differential diagnosis in patients with similar clinical presentations. In contrast to our case, favipiravir was successful in the treatment of these patients, with improved patient clinical and laboratory parameters after five days of treatment, and without complications during their follow-up. Additionally, reported patients with CCHF and COVID-19 co-infection were younger, had fewer comorbidities, had a less severe clinical presentation at admission, and had favipiravir started earlier. In our case, COVID 19-related ARDS that overlapped on top of CCHF caused her to develop a cytokine storm and died despite her improved clinical parameters due to CCHF.

Virus interference is a phenomenon in which two viruses interact within a host, thereby affecting the outcome of infection of at least one of such viruses. Recently, different situations of virus-virus interactions were analyzed, and one of them was the immunological interactions occurring only in animals with adaptive immune systems[12]. However, there are no *in vivo* studies on viral interference with SARS-CoV-2. Therefore, this study points out that SARS-CoV-2 and CCHF negatively interacted in terms of clinical interference in our case, in which mortality increased due to excess immune system activation.

Conclusion

Clinically and pathologically, CCHF and COVID-19 show some similarities, and initially, there may be confusion in the diagnosis. Ground glass opacities, the most typical CT finding of COVID-19, are also seen in CCHF. Elevated liver enzymes and impaired liver function are seen in both diseases. Cytokine storm syndromes are also a common feature of both diseases which result in increased morbidity and mortality but have different outcomes. Crimean-Congo hemorrhagic fever results in hemorrhage, while COVID-19 can cause thrombosis[13]. Crimean-Congo hemorrhagic fever and COVID-19 symptoms or findings can be confused because of their similarities, but the possibility of being seen together should not be overlooked. Concurrently, some similarities in the pathogenesis of these two diseases suggest that co-infection may worsen the clinical course; thus new studies are needed on this subject.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ş., M.R.T., İ.K., F.Y., A.S., İ.Ş., Design: M.Ş., M.R.T., İ.K., F.Y., A.S., İ.Ş., Data Collection or Processing: M.Ş., M.R.T., İ.K., F.Y., A.S., İ.Ş., Analysis or Interpretation: M.Ş., M.R.T., İ.K., F.Y., A.S., İ.Ş., Literature Search: M.Ş., M.R.T., İ.K., F.Y., Writing: M.Ş., M.R.T., İ.K., F.Y., A.S., İ.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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