

CRIMEAN-CONGO HEMORRHAGIC FEVER: REPORT OF TWO CASES

KIRIM-KONGO KANAMALI **ATEŞİ: İKİ OLGU SUNUMU**

Şükran KÖSE, Selma GÜL, Filiz OĞUZ, Sabri ATALAY

Tepecik Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü, İZMİR, TÜRKİYE

ABSTRACT

Crimean-Congo hemorrhagic fever is a zoonotic infection and it is one of viral hemorrhagic fever syndromes. Humans usually become infected by bites of ticks, contact with a patient in the acute phase of the disease or contact with the blood or tissues of viremic livestock.

Case Report 1

A sixty year old female patient living in rural areas was admitted to the emergency service with the complaints of high fever, headache, epistaxis, generalized myalgia for three days. The patient was diagnosed with Crimean-Congo hemorrhagic fever and was hospitalized in the infectious diseases ward. The patient who received ribavirin therapy was discharged from the hospital after a full recovery.

Case Report 2

A thirty nine year old male had applied to a medical center five days ago with the complaints of weakness, sore throat, generalized body pain, bleeding gums for eight days. Laboratory test results showed bicytopenia and high levels of liver function tests. The patient was diagnosed with Crimean-Congo hemorrhagic fever and was hospitalized in the infectious diseases ward. Neither supportive treatment nor antiviral treatment was administered to the patient. The high fever resolved and liver function tests returned to the normal values from the seventh day and the patient was discharged from the hospital after making a full recovery. Crimean-Congo Hemorrhagic Fever is a endemic disease in Turkey. Early diagnosis and supportive treatment are crucial.

Key words: hemorrhagic fever, zoonosis, *Bunyaviridae*

ÖZET

Kırım-Kongo Kanamalı Ateşi, viral hemorajik ateş sendromları arasında yer alan zoonotik bir enfeksiyondür. İnsanlar çoğunlukla kenelerin ısırmasıyla, hastalığın akut safhasında hasta ile temas ya da viremik hayvanların kan ve dokularına temas yoluyla enfekte olurlar.

Olgu 1

Kırsal alanda yaşayan altmış yaşındaki kadın hasta, yüksek ateş, baş ağrısı, burun kanaması, üç gün boyunca olan kas ağrısı şikayetleri ile acil servise başvurdu. Hastaya Kırım-Kongo Kanamalı ateş tanısı kondu. Ribavirin tedavisi başlanan hasta tam iyileşme sonrası taburcu edildi.

Olgu 2

Otuz dokuz yaşında bir erkek sekiz gün boyunca diş eti kanaması halsizlik, boğaz ağrısı şikayetleri, genel vücut ağrısı, beş gün önce bir tıp merkezine başvurmuş. Laboratuvar test sonuçları bisitopeni ve karaciğer fonksiyon testleri yüksek seviyelerde gösterdi. Destekleyici tedavi veya antiviral tedavi uygulanmadı. Yüksek ateş geriledi ve karaciğer fonksiyon testleri yedinci günden itibaren normale döndü ve hasta tam iyileşme ile hastaneden taburcu edildi.

Kırım-Kongo Kanamalı Ateşi, Türkiye’de endemik bir hastalıktır. Erken tanı ve destekleyici tedavi önemlidir.

Anahtar kelimeler: hemorajik ateş, zoonoz, *Bunyaviridae*

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Yazışma adresi:

DR. Selma GÜL
Tepecik Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü
Gaziler Cd. No: 468 Yenişehir/Konak, PK:35120, İZMİR, TÜRKİYE
Tel: 0 232 4696969-1704 **Cep:** 0 506 4575455
E-Posta: selmagul75@hotmail.com

INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is a viral hemorrhagic disease associated with a severe clinical course and high mortality rates, caused by a virus belonging to the genus *Nairovirus*, family *Bunyaviridae* (1). Up to present, human being has been defined as the only host developing clinically apparent disease. Transmission to human may occur through tick bite as well as as a result of the contact with the blood of infected livestock (2). Although most patients are people living in rural areas, involving in livestock industry such as slaughter house workers, CCHF has been reported to be associated with the risk of developing nosocomial infections (3). CCHF is an acute and potentially fatal infection characterized by multiple internal organ involvement, extensive ecchymoses, disturbances in liver function.

In our country, the first cases of CCHF were reported in Tokat, Amasya and Sivas cities, in the months of May, June and July of 2002. While 50 cases were reported from Tokat during this period of time, CCHF resulted in death in six of the cases (4). The number of the cases continued to increase in the following years and the first cases of CCHF were encountered in the Aegean Region of Turkey in 2006.

In this report, two cases of CCHF were presented from Aegean Region which is a non endemic area of our country for the disease.

CASE PRESENTION 1

A sixty year old female patient, living in rural areas of Balikesir was admitted to the emergency service with the complaints of high fever, headache, generalized myalgia for three days. While the results of laboratory tests were found within normal limits, in physical examination, a tick was detected in the gluteal region and it was removed and the patient was discharged from the emergency service after recommending outpatient follow up. Two days later, the patient applied to our outpatient clinic with the complaints of bleeding from the gums and nose in addition to ongoing fever and myalgia. In the physical examination, the patient was found to be conscious, with a body temperature of 38.5°C, a pulse rate of 97/minute, a respiration rate of 30/minute. The blood pressure of the patient was found as 125/75 mmHg. Additionally to the blood oozing from the gums, nose and around the intravenous route, a skin rash in maculopapular character was detected on the abdominal skin. Other systemic examinations were unremarkable.

Laboratory test results revealed pancytopenia, coagulation disturbance and high levels of aspartate amino transferase (AST), alanine amino transferase (ALT), creatinine phosphokinase (CK) and lactate dehydrogenase (LDH). Test results of the patient on admission was shown in Table-1. The patient was diagnosed with CCHF and was hospitalized in the infectious diseases ward. Supportive care and oral ribavirin therapy were initiated. A serum sample was obtained from the patient and sent to the laboratory of virology of Refik Saydam Hifzısıhha Institute located in Ankara for the detection of CCHF virus. Daily complete blood counts were performed. Blood counts and biochemical values returned to the normal levels within 10 days. High fever dropped after the third day. CCHF IgM by the ELISA method and CCHF RNA by polymerase chain reaction in serum were found positive. The ribavirin therapy was completed in ten days and the patient was discharged from the hospital after a full recovery.

CASE PRESENTATION 2

A thirty nine year old male, beekeeper from Bodrum had applied to a medical center five days ago with the complaints of weakness, sore throat, generalized body pain, bleeding gums for eight days. Diagnosis of upper respiratory tract infection had been made and antibiotic treatment was started. Subsequently, the patient applied to the hospital for a second time, due to a high fever of 39 °C. His medical history revealed multiple contacts with ticks and he had removed a tick from his left leg ten days ago. Laboratory test results showed bicytopenia and high levels of liver function tests and he was referred to our hospital with a preliminary diagnosis of CCHF. In the admission, the physical examination of the patient was unremarkable and laboratory test results revealed thrombocytopenia and high liver function tests. Test results was shown in Table-1. A serum sample was obtained from the patient in order to investigate CCHF virus. Neither supportive treatment nor antiviral treatment was administered to the patient. The high fever resolved, thrombocytopenia improved and liver function tests returned to the normal values from the seventh day and the patient was discharged from the hospital after making a full recovery. Later on, CCHF RNA by PCR and CCHF IgM antibodies by ELISA were reported to be positive from the virology of Refik Saydam Hifzısıhha Institute laboratory.

Table 1: Laboratory findings of the patients at their first admissions

	<i>Case 1</i>	<i>Case 2</i>	<i>Range of normal values</i>
Hemoglobin (gr/dL)	15	15.5	12.0-16.0
Leukocyte (K/uL)	2100	5500	4.0-10.0
Platelet(K/uL)	6000	57000	150.0-450.0
Alanine amino transferase (U/L)	134	143	0-34.0
Aspartate amino transferase (U/L)	412	184	1.0-31
Gamma glutamyl transferase (U/L)	250	362	0-38
Creatinine phosphokinase (U/L)	1096	228	0-145
Lactate dehydrogenase (U/L)	1052	563	0-247
PTT (second)	11.3	9.4	10.1-13.6
INR	0.8	0.82	0.8-1.2
APTT (second)	44.8	29	18-28

DISCUSSION

The pathogenesis of viral hemorrhagic fevers (VHF) is not completely understood. Basic common features such as microvascular damage and hemostatic disturbances, are prominent. Endothelial injury indirectly results from endothelial activation and dysfunction of cytokines produced against the virus and/or secondly directly viral proliferation within the virus infected endothelial cells (5). Endothelial damage contributes to hemostatic failure by stimulating platelet aggregation and degranulation and activating intrinsic coagulation cascade. In cases of death, indicators of coagulation disturbances are present from the early stages of the disease and disseminated intravascular coagulation (DIC) is one of the early findings of the disease. In spite of the generally accepted opinion assuming that death may occur due to blood loss in VHF, death is generally related to septic shock and multiple organ dysfunction (6). DIC was more prominent in patients who died (7). The values concerning coagulation were found high in our first case and returned to the normal level within ten days. The normal coagulation values detected in the second case were considered to be related to the late admission of the patient to the hospital.

Incubation period changes according to the route of transmission of the virus. It is about 1 to 3 days following tick-bite and 5-6 days after transmissions due to direct contact with infected blood, body fluid or other tissues, with a maximum of 9 days (7). Fever, fatigue, headache, weakness, hypersensitivity, intense arm, leg and back pain and pronounced anorexia are the most common clinical findings. Occasionally, vomiting and diarrhea may occur. Petechia on the face and chest attracts attention on the first day. Ecchymotic areas may appear on the body and extremities. Epistaxis, hematemesis, melena and hematuria are frequent. Occasionally bleeding gums and vaginal hemorrhages may also occur. Hepatitis is usually present, hepatorenal failure and pulmonary insufficiency may develop in severe cases from the fifth day.

Body temperature may continue to rise until the 5th of 12th days then resolves by lysis between the 9th and 20th days (8). In our first case, resolution of fever occurred on the 3th day and in our second case fever resolved on the 7th day of the admission.

In the laboratory findings of CCHF, leukopenia and thrombocytopenia particularly attract attention, in addition to elevated serum levels of AST, ALT, CK and LDH. Among the hemostatic tests; prothrombin time and activated partial thromboplastin time lengthen. Serum fibrinogen level may decrease and fibrinogen degradation products may increase. Hemoglobin level may decrease even in the absence of any bleeding (8). Complete blood counts and biochemical tests values return to the normal levels in about 5 to 9 days in survivors. In our cases, blood counts and biochemical tests values returned to the normal levels in 10 days.

In CCHF disease, supportive treatment is essential. Besides, monitoring of fluid and electrolytes, blood components, and their replacement if needed, are important. Monitoring of bleeding and whole blood replacement and the use of vasopressors in shock

may be required. In the treatment of infected patients, although its mechanism of action is not clear, ribavirin is the preferred antiviral agent. Ribavirin may be used for therapeutic purposes, particularly in the earlier period of the diseases or it may be used for prophylactic purposes after a high risk exposure (9). In its report of September 2008, European Centre for Disease Prevention and Control (ECDC), clearly stated that a randomized, controlled study aimed to determine the efficacy of ribavirin could not be ethical. Ribavirin has been listed as an effective medicine against CCHF since March 2007, in the "Essential Medicines List" of the World Health Organization and it has been clearly recommended. Ribavirin was defined as beneficial by the Centers for Disease Control and Prevention (CDC) of the United States, in spite of the absence of any randomized controlled study. In the guidelines of the Epidemic Investigation Cell (EIC), Public Health Laboratories Division, National Institute of Health of Pakistan (prepared by WHO in collaboration with the Johns Hopkins Bloomberg School of Public Health), it was emphasized that ribavirin was not a specific medicine for CCHF, however it might be helpful in the management of CCHF and ribavirin therapy was recommended to be immediately started if the clinical manifestations are consistent with CCHF. In addition, it was stated that, in the event of an injury with the needle contaminated with the blood or body fluids or direct contact with the mucous membrane of a probable or confirmed case, prophylactic ribavirin treatment should be started after the initial tests. The starting dose of ribavirin is given as 15 mg/kg every 6 hours, for the adults. An initial loading dose of 2 g. on the first day of treatment followed by 1 g. every 6 hours for the first 4 days. After the 4th day ribavirin should be given at a dose of 7.5 mg/kg or 0.5 g every 6 hours in adults during the next 6 days. In prophylactic use 0.5 g every 6 hours for seven days is recommended. Ribavirin is particularly effective in the earlier periods of the disease. Data indicate that ribavirin is not effective after the patient starts to bleed. Consequently our second patient did not receive an antiviral treatment.

Although recovery takes place on the 9th and 10th days, it may occur in four weeks or more. Death mostly occurs in the second week of the disease (5th-14th days) and the rate of death may range from 5% to 30% (7,10). According to the data of the Ministry of Health, between 2008-2012, the mortality rates in our country were 4.8 % (63/1315) 4.8 % (63/1318), 5.7 % (50/868), 5.02% (54/1075) and 4.6% (37/796) respectively.

In the CCHF-endemic regions personal measures should be taken for the prevention of the disease. One should avoid areas where ticks are abundant, naked parts of the body should be covered, insect repellents should be absorbed by the skin or clothings and the body should be frequently checked for tick bites. Besides, people involving in stock-breeding should apply appropriate acaricides to their livestock and animal barns should be constructed in a way that ticks could not live.

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