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Crimean Congo Hemorrhagic Fever Case Report

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Abstract

Crimean Congo Hemorrhagic Fever (CCHF) is a zoonotic disease caused by Nairovirus from the *Bunyaviridae* family carried through ixodid ticks. CCHF virus is transmitted by tick bite, crushing infected ticks or contact with blood or body fluids of patient with CCHF or viremic animals. The disease is characterized by serious morbidity and mortality as well as multi-systemic involvement. Diagnosis is based on the story, laboratory findings and microbiological evidence. Supportive treatment is the mainstay of CCHF treatment. In this study, two cases of CCHF from Bitlis, Turkey presenting with different symptoms after tick bite are reviewed.

Keywords: Pediatric; Ticks; Crimean-congo hemorrhagic fever; Thrombocytopenia

Introduction

Crimean Congo Hemorrhagic Fever (CCHF) is a zoonotic disease transmitted by the ixodid ticks caused by viruses from the Nairovirus group of the *Bunyaviridae* family. The mortality rate around the world varies between 3% to 30% [1-2]. Initially it was seen around Tokat, Turkey in 2002 and over time has spread to the central Anatolia and eastern black sea regions [3]. According to the Turkish Ministry of health, the total number of cases from 2008 to 2017 is 8,742, the number of deaths is 409, and the mortality rate is 4.67% [4].

The CCHF virus is transmitted by tick bite, crushing infected ticks or contact with the infected animal blood and other body fluids. Another way of transmission is the vertical transition from mother to baby. The clinical symptoms are sudden onset of fever, headache, diffuse muscle pain, weakness, nausea-vomiting and varying degrees of skin and mucosal bleeding [3].

The treatment approach consists mainly of supportive and antiviral therapy. As part of the supportive therapy, fluid and electrolyte replacements and blood products are given; ribavirin is used as anti-viral treatment [3]. In this study, we aimed to present the clinical course, management and outcomes of two distinct pediatric CCHF cases together with the current literature in the field.

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Case Series

Case 1

A 14-year-old male patient without any significant past medical history presented to the emergency department twice with the complaints of 3 days of fever and abdominal pain, and was discharged following symptomatic treatment with the recommendation of outpatient follow-up. One day after his initial emergency department visit, he was presented again with bloody urine, nose bleeds and drowsiness and was found to have a platelet count of 20,000/mm^3, White Blood Cell (WBC): 3200/mm^3, Urea: 112 mg/dL and he was admitted to intensive care unit with the presumed diagnosis of Hemolytic Uremic Syndrome (HUS). Despite the treatment given the patient's condition worsened in his follow-ups and patient was referred to our health institution on the 3rd day of his admission. It was learned that the patient was bitten by the tick and removed the tick by his hand 6 days before his hospitalization. In his initial evaluation in our institution, fever: 38.3°C Respiratory Rate (RR): 17/min, Blood Pressure (BP): 85/60 mmHg, Heart Rate (HR): 76/min, peripheral oxygen saturation (SpO_2): 96%. Patient's condition was poor in physical exam, patient was confused, lung sounds were with diffuse bilateral rales, abdominal tenderness was present, spleen was palpated 2 cm under the cost as, had 3 ecchymoses at the left arm antecubital region, the largest approximately 2 cm × 3 cm, diffuse petechiae were present around lower extremities and vascular access sites. Wide spread active bleeding was present at the intervention sites and gums.

In hemogram and biochemical tests, hemoglobin: 17 g/dL, WBC: 3830 /mm^3, PLT: 44000 /mm^3, Urea: 100 mg/dL, Cr: 1.42 mg/dL, Na: 126 meq/L, K: 3.5 mEq/L, AST: 907 U/L, ALT: 253 U/L, LDH: 2313 U/L, Creatine Kinase (CK): 1240 U/L, C-Reactive Protein (CRP): 2 mg/L, Ferritin: >16500

ng/mL, Triglyceride:156 mg/dL. INR: 2.77, Fibrinogen: 85.17 mg/dL, Prothrombin time (PTZ): 33.1 sec, activated Partial Thromboplastin Time (aPTT): 82.1, D-Dimer: >7.5 mg/L. He was admitted to pediatric intensive care unit following initial evaluation. On the chest radiograph, there was an infiltrative appearance and pleural effusion on the right side. Portal vein Doppler ultra Sonography showed no flow in the main portal vein, right and left portal vein and splenic vein, Portal Vein Thrombosis (PVT) was detected. Serum sample for CCHF was sent to the reference laboratory at the Ankara Refik Saydam Medical Center. As the patient continued to have active bleeding, the patient was made NPO and given fluid, platelet, Fresh Frozen Plasma (FFP) support; intravenous Vitamin K and N-acetylcysteine infusion was started. Pediatric hematology was consulted with suspected CCHF-induced hemophagocytosis. The patient was started on Documentation Sheet for the Initial Therapy in HLH 2004 protocol. As the test result was positive for CCHF virus Ig M, ribavirin treatment was started on the second day of intensive care hospitalization. On the third day of hospitalization, hemoglobin: 8.6 g/dL, WBC: 5900/mm^3, PLT: 28000/mm^3, Urea: 152 mg/dL, Creatine: 2.07 mg/dL, Na: 143 meq/L, K: 4 mEq/L, Ca: 7.57 mg/dL, AST: 10742 U/L, ALT: 1726 U/L, LDH: 7457 U/L, CK: 3214 U/L, INR: 2.51, PTZ: 30.3 sec, aPTT: 79.9 sec. As the Absolute Neutrophil Count (ANS): 640/mm^3, Granulocyte-Colony Stimulating Factor (G-CSF) was given. Plasmapheresis was initiated due to persistent bleeding and coagulopathy despite the daily FFP and platelet suspension transfusion. In the fourth day of the follow-up, the patient's general condition worsened, and inotropic support was initiated upon the development of hypotension and bradycardia. The pH in the arterial blood gas was 7.19 pCo_2: 68 mmHg, pO_2: 38.4 mmHg HCO_3: 14.8 mmol/L, Lactate: 5 mmol/L. The patient was intubated and mechanical ventilator support was provided. The patient had decreased urine output and kidney function tests deteriorated, was in the stage of kidney damage according to the pRIFLE (pediatric Risk, Injury, Failure, Loss, End stage renal disease) criteria. Intravenous Immunoglobulin (IVIG) was given to suppress macrophage activation and cytokine storm. The clinical course remained poor with worsening gum bleeding and nasal bleeding and pulmonary hemorrhage and hemodynamic instability and eventually resulted in exitus on the eighth day of the follow-up. Written informed consent was obtained from the family of the patient.

Case 2

A 13-year-old male patient with no known past medical history was presented to the outside hospital with complaints of fever and abdominal pain for the past three days. Patient had history of tick bite ten days before his admission. During the patient's initial evaluation; White Blood Cell count (WBC): 2000/mm^3, Platelets (PLT): 30000/mm^3, ALT: 274 U/L, AST: 496 U/L then patient was referred to our health care organization with pre-diagnosis of CCHF. After the initial evaluation of the case, he was admitted to the pediatric intensive care unit with the diagnosis of CCHF. Fever: 37°C, respiratory rate: 17/min, Blood Pressure (BP): 110/75, Heart Rate (HR): 66/min, peripheral oxygen saturation (SpO_2): 92%. On the physical exam, overall condition was fair, had petechiae right arm flexor. On laboratory evaluation Hemoglobin: 13.9 g/dL, WBC: 2400/mm^3, PLT: 24000/mm^3, glukoz: 95 mg/dL, BUN: 19 mg/dL, Cr: 0.65 mg/dL, Na: 141 meq/L, K: 4.2 mEq/L, AST: 395 U/L, ALT: 262/L, LDH: 712 U/L, CK 543 U/L, INR: 0.94, PTZ:11.9 sec, aPTT: 22.8 sec, D-Dimer: 0.228 mg/L, CRP: 1.97 mg/L. Serum sample CCHF test was sent to the reference laboratory, Ankara Refik Saydam Medical Center. Platelet suspension was given to the patient, as the result for CCHF virus IgM came back positive ribavirin treatment began on the day 3 of the hospitalization. Patient's biochemical and hematological evaluations were stable on the day 6 of the hospitalization. Ribavirin treatment was completed to total of 10 days and patient was discharged home. Written informed consent was obtained from the family of the patient.

Discussion

Crimean Congo Hemorrhagic Fever is the most common viral hemorrhagic fever. In our country, it was first seen in the province of Tokat, Turkey in 2002, and then the case was eventually reported in all over the country. The most important way of transmission of the disease is due to infected tick bite. The disease is closely associated with tick ecology and shows seasonal characteristics. In the Northern Hemisphere, the cases are first seen in March/April, reaching the highest level in June and July, and trending down and eventually disappearing in September and October [3]. Our cases were those who applied to the health institution as a result of tick bite in the month of May, when the CCHF disease showed seasonal characteristics in Bitlis province where the tick was seen endemically.

Typical course of CCHF infection includes incubation, prehemorrhagic, hemorrhagic and convalescent periods. Incubation period is the time between tick bite and disease development and takes 3 to 7 days on average. Pre-hemorrhagic period is characterized by sudden fever (39°C to 41°C), headache, myalgia, dizziness, nausea, vomiting and diarrhea. The fever lasts on average 4 to 5 days. Hyperemia in the face, neck and chest, and conjunctivitis can be seen during this period. This period lasts 1 to 7 days at total. The hemorrhagic period is short; it develops quickly and usually begins on the 3rd and 5th days of the disease. The bleeding findings are variable; petechiae, large hematomas on the skin and mucosal membranes can be seen. Convalescent period starts 10 to 20 days after the disease is first detected. Variable pulse, tachycardia, transient hair loss, polyneuritis, dyspnea, xerostomy, poor vision, hearing and memory loss have been reported in the convalescent period [3]. Our first case that was admitted to our health care institution was in the hemorrhagic period and this cond case was in the pre-hemorrhagic period. Therefore, it should be taken into account that CCHF cases can present with different clinical findings.

Laboratory findings of CCHF infection are mainly leukopenia, elevation of levels of AST, ALT, LDH and CPK, PT, aPTT, low fibrinogen level, increase in fibrin degradation products and also as a typical finding of thrombocytopenia. In patients with clinical improvement, laboratory findings return to normal limits in about 5 to 9 days [3]. In one of our cases, there were DIC (Disseminated Intravascular Coagulation), findings and PVT was detected in portal vein Doppler ultrasonography. The possible mechanisms behind these problems are thought to be the direct endothelial damage caused by the virus or the indirect endothelial activation by the cytokines developing against the virus and dysfunction. PVT findings have not been previously mentioned in CCHF cases published to date, and possible thrombotic complications should also be considered in cases where DIC findings followed the CCHF diagnosis.

Dilber et al. found findings consistent with hemophagocytosis in approximately 30% of patients in their study including 21 pediatric cases [5]. Fisgin et al. [6] detected hemophagocytosis in the bone marrow examination of 5 patients, 3 of who were diagnosed with

CCHF in a study conducted in 2007. Karti et al. [7] involving 14 adult cases in their study, detected reactive hemophagocytosis in 7 (50%) of the cases. One of our cases also had findings compatible with hemophagocytosis.

While the mortality rate of the disease reaches up to 30% around the world, it is 4% to 5% in our country [4,8]. Clinically defined poor prognosis criteria are confusion, stiff neck, bleeding from multiple areas, prolonged fever, unconsciousness, splenomegaly, somnolence, hematemesis, melena, high fever, DIC, presence of kidney failure, and laboratory findings associated with poor outcome are the white blood cell count above 10000/mm^3, the platelet count below 20.000/mm^3, the AST level above 200U/L, the ALT level above 150 U/L, the activated PTT longer than 60 sec, or the fibrinogen level lower than 110 mg/dL [9,10]. When our cases were evaluated, our case resulted with exitus had all the poor prognostic findings as compatible with the literature.

Crimean-Congo Hemorrhagic Fever is diagnosed serologically and molecularly. It is serologically established by detection of IgM and IgG antibodies 7 days after the onset of the disease by ELISA and IFA tests. Specific IgM level decreases and becomes undetectable by the 4 months after the infection, but IgG levels can be determined for 5 years. Molecularly, the diagnosis is made using the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) method. PCR method is more specific, sensitive and faster than serological diagnosis [11,12]. The diagnosis of both of our cases was determined serologically.

There is no specific treatment for CCHF disease but the main approach is supportive treatment [3]. Support therapy should provide respiratory, circulatory, and parenteral nutrition support and dialysis; fluid-electrolyte balance should be monitored. In the inpatient clinical follow-up of our cases, respiratory and cardiovascular support was provided for our first case, and plasmapheresis and hemodiafiltration treatment were applied from extra corporeal support systems since multi organ failure was developed. Both of our cases were supplemented with blood products, and our case requiring high amount of transfusion resulted in exitus.

There is no specific antiviral therapy approved for the treatment of CCHF in humans, but WHO reports that ribavirin is used in CCHF disease and its oral form is effective both intravenously. Although there are no randomized control studies showing that ribavirin is useful in its clinical use, initiation of ribavirin treatment in the first 7 days in observational studies is important for the effectiveness of treatment [13,14]. However, there are also publications reporting that it is ineffective. Elaldı et al. [15] in their study comparing 126 cases diagnosed with CCHF and treated with ribavirin and 92 cases diagnosed with CCHF and not treated with ribarivin. The mortality rate of ribavirin treatment group was 7.1% and the mortality rate of that non-treatment group was 11.9%. In addition, they reported that ribavirin had no significant effect on mortality, and even its use in the first 8 days increased mortality. Ribavirin treatment was used in both of our cases and no observational clinical evidence was detected for the effectiveness of ribavirin treatment during our inpatient follow ups.

Protection and control measures in CCHF management are reviewed under two categories: Social level and health-care institutions. Personal protection measures should be emphasized, which are at the forefront of social protection and will minimize contact with ticks. For example, avoiding the areas where ticks are widespread, wearing light and coverage clothing, checking the whole body for ticks, applying tick repellent medication to the skin and clothes during high risk activities and taking other measures to prevent skin contact. In health care institutions, health care professionals working in the hospital in endemic areas are at serious risk especially during the inpatient care of patients with external bleeding from various sites. Any staff with possible contact with infected person and their body secretions and blood must be trained in this regard. Patients should be isolated and strict infection control measures should be implemented at every stage. Barrier isolation with disposable gloves, long gowns, masks and goggles should be used. Simple barrier measures have been reported to be effective. When leaving the patient room, all protective equipment should be removed, safely disposed, or disinfected [3].

In conclusion CCHF is a wide spread condition and cases can be seen in almost every region of our country. The complaints of the cases may not be specific, but they may appear with severe clinical presentations including death due to massive bleeding. Crimean-Congo Hemorrhagic Fever should be considered in the differential diagnosis of the patients presenting with fever, headache, and weakness and with leucopenia and thrombocytopenia. Since there is no specific treatment for CCHF disease increasing awareness for protection and prevention is the most crucial step. The efficacy of Ribavirin on treatment and mortality in patients who presented at the later stages of the disease is controversial and its benefit is not clear in patients with bleeding. Clinical observational studies on this issue gain importance for ethical reasons as randomized clinical trials cannot be conducted.

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