A Case of Crimean-Congo Hemorrhagic Fever with Pleural Effusion

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SUMMARY: Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral zoonosis with the potential of human-to-human transmission that affects wide areas in Asia, Southeastern Europe, and Africa. Hemorrhagic manifestations constitute a prominent symptom of late stage disease with case fatality rates from 3 to 50%. We present a case of CCHF complicated by hemorrhagic pleural effusion and resulting in resolution without chest tube drainage in a 9-year-old boy. The diagnosis of CCHF was confirmed by enzyme-linked immunosorbent assay tests. Both serum and pleural fluid CCHF IgM were positive at titers of 1/1,600 and 1/6,400, respectively.

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal viral infection found in parts of Africa, Asia, Eastern Europe, and the Middle East. The virus belongs to the genus Nairovirus in the Bunyaviridae family and causes severe diseases in human beings, with a reported mortality rate of 3-50%. CCHF viruses are transmitted by Hyalomma genus ticks, particularly by Hyalomma marginatum marginatum. Fever, malaise, nausea and vomiting, abdominal pain, myalgia, petechia, and ecchymosis are the most common manifestations of CCHF. Diarrhea, lymphadenopathy, and thrombotic microangiopathy with acute renal failure have been reported as presenting signs of CCHF (3-5). Laboratory findings include leucopenia and thrombocytopenia, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT) (1.2). IgM and IgG antibodies are detectable by enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assays from approximately 7 days after the onset of the disease. Recent infection is confirmed by demonstrating seroconversion, or a fourfold or greater increase in antibody titer in paired serum samples, or IgM antibodies with IgM antibody in a single sample. Reverse transcriptase-polymerase chain reaction (RT-PCR) is the method of choice for rapid laboratory diagnosis of CCHF virus infection because this method is highly specific, sensitive, and rapid and allows early diagnosis (2). The World Health Organization (WHO) recommends intravenous or oral ribavirin based on the experience of apparent benefit (6). Suspected or diagnosed patients with CCHF should be isolated in a private room, preferably in a negative-pressure room. Patients should be cared for by a minimum number of health care workers, and barrier precautions should be strictly implemented. Postexposure prophylaxis with ribavirin may be considered for health care workers potentially exposed to CCHF virus (7). Cases infected with CCHF virus were first reported in Turkey in 2002. There were 17 reported cases in 2002, 133 cases in 2003, 249 cases in 2004, 266 cases in 2005, 438 cases in 2006, and 717 cases in 2007 according to the Ministry of Health of Turkey. Ninety-two (5%) of them died. The six provinces in Kelkit Valley, northeastern Turkey, are the most strongly affected (Tokat, Sivas, Gümüşhane, Amasya, Yozgat, and Corum provinces) (8). We have diagnosed and treated 42 pediatric cases of CCHF since 2006. Thirteen of them were presented in a congress (9), while the remaining 29 pediatric cases were unpublished. A case of CCHF with hemorrhagic pleural effusion is presented here.

A previously healthy 9-year-old boy, living in the village of Kislacik, Corum, was admitted to our hospital with the complaints of fever, weakness, and vomiting in May 2007. His father said that the boy had removed a tick from his navel 3 days before the onset of the disease. The patient visited a pediatrician in the regional hospital in Corum when his complaints began. Laboratory values were remarkable for thrombocytopenia, leukopenia, and elevated liver enzymes at this time. The patient was referred to a tertiary care center for CCHF, since Corum is an area in which CCHF was endemic. Because of the suspicion of CCHF the patient was immediately isolated, and barrier nursing was implemented to prevent nosocomial transmission on admission. There was no history of cough, abdominal pain or myalgia during the course of the disease. On admission, physical examination revealed that the patient was slightly lethargic, disoriented, and listless. His temperature was 36.6°C and his blood pressure was 90/60 mmHg. Pulse rate and respiratory rate were 108 and 32/min, respectively. Oral mucosa was dry, and diminished respiratory sounds were detected on the basal part of the right lung. The examination of other systems showed them to be normal. Laboratory studies showed hemoglobin 16 g/dL, hemocrit 46.1%, platelet 28 x 10^9/L, leukocytes 2.1 x 10^9/L with a differential count of 68% neutrophils, 32% lymphocytes. Serum ALT was 166 U/L (5-40 U/L), AST 370 U/L (8-33 U/L), LDH 976 U/L (110-295 U/L), CK 243 U/L (<247 U/L), blood urea nitrogen 28 mg/dL (0-23 mg/dL), creatinine 0.78 mg/dL (0.3-1.2 mg/dL), sodium 129 mEq/L (138-145 mEq/L), potassium 3.21 mEq/L (3.4-4.7 mEq/L), glucose 112 mg/dL, PT 12.3 s (11-13.2 s), aPTT 32.4 s (20-31 s), erythrocyte sedimentation rate 5 mm/h (0-10 mm/h), and C-reactive protein level 6.44 mg/L (0-8 mg/L). Total protein, albumin, and bilirubin levels were normal. The patient’s laboratory data and chest radiographies on admission and for the following days are shown in Table 1 and Figure 1, respectively. The patient developed respiratory distress on the 3rd day; repeated chest x-rays showed right pleural effusion (Figure 1). Ultrasonographic examination of the chest revealed...
anechoic pleural fluid collection in the right hemithorax which had a 35-mm thickness. Thoracentesis was not performed because of thrombocytopenia and prolonged aPTT at this time. It could be attempted on the 6th day of admission, and 60 mL serohemorrhagic pleural fluid was drawn. Pleural fluid showed plenty of erythrocytes and 50/mm³ leucocytes, the glucose level was 95 mg/dL, and the protein level was 4 g/dL. Gram stain, acid-fast bacilli stain, and bacterial cultures were negative. Initial fluid therapy started with 2,500 mL/m² of body surface. Ribavirin therapy was given to the patient (30 mg/kg as the initial dose, followed by 15 mg/kg every 6 h for 4 days, and then 7.5 mg/kg every 8 h for 6 days per oral). He also received fresh frozen plasma and thrombocyte transfusions in view of the bleeding manifestation. After the hemorrhagic period of 5 days, the patient showed dramatic clinical improvement and resolution of pleural effusion without chest tube drainage. This was proven by chest radiographies and is shown in Figure 1. The diagnosis of CCHF was confirmed by using IgM capture ELISA tests. Heat inactivated serum and pleural fluid samples were tested with the Centers for Disease Control and Prevention ELISA kits. Tests were carried out in the national reference laboratory of CCHF, Virology Laboratory, Communicable Diseases Research Center, Refik Saydam National Institute of Health, Ankara, Turkey. Both serum and pleural fluid CCHF IgM were positive at titers of 1/1,600 and 1/6,400, respectively. CCHF IgG and RT-PCR tests were not performed.

The patient who came from Corum (CCHF-endemic region), presented with complaints of fever, weakness, and vomiting. He had thrombocytopenia, leukopenia and raised levels of AST, ALT, and LDH on initial laboratory tests. The history of tick bite and the incubation period of 3 days were both compatible with CCHF. Based on these clinical, laboratory, and epidemiological findings, a diagnosis of CCHF infection was suspected, and the diagnosis of CCHF was confirmed by the detection of IgM antibodies in a single specimen with ELISA on the 4th day of symptoms. Pleural effusion was detected on a chest x-ray on the 3rd day of admission and was confirmed by ultrasound. Progressive increases of effusion during the next 3 days and gradual improvements during the following days were observed. The x-ray presentation was also correlated with laboratory findings (leukocyte count, platelet levels, aPTT levels).

CCHF has four distinct phases: incubation, prehemorrhagic, hemorrhagic, and convalescence. The incubation period depends on the host, route of exposure, and viral inoculum, and is estimated to last from 1 - 3 days after a tick bite, 5 days after contact with livestock blood or tissue, and 5 - 6 days after contact with human blood. The prehemorrhagic period lasts 3 - 6 days and is characterized by sudden onset of fever (39 - 41°C), rigor, severe headache, myalgia, lower backache, abdominal pain, and photophobia. Gastrointestinal symptoms are also common (7). The hemorrhagic period develops from various sites 3 - 6 days following the onset of illness and lasts 2 - 3 days. On mucous membranes and skin, hemorrhagic manifestations range from petechiae to large ecchymoses. Bleeding from the nose, gums, and buccal cavity occurs frequently. In severe cases of CCHF, gastric, uterine, intestinal, genitourinary, cerebral and pulmonary hemorrhages occur with decreasing frequency. In patients with profuse hemorrhage, tachycardia, shock and death may ensue. For patients who survive, the convalescence period begins 15 - 20 days after the onset of illness and is characterized by prolonged and pronounced weakness, weak pulse, and occasional hair loss, polyneuritis, sweating, headache, dizziness, nausea, and poor appetite. Poor vision, loss of hearing, and loss of memory may

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<th>Date</th>
<th>Hb (g/dL)</th>
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Hb, hemoglobin; PLT, platelet; PT, prothrombin time; PTT, partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

Fig. 1. Chest radiographies of the patient on admission and on the following days.
Thrombocytopenia, disseminated intravascular coagulation, shock, vascular endothelial injury, and liver dysfunction can lead to bleeding tendencies in CCHF (11). Pleural effusion, pneumonitis, hemoptyisis, and pulmonary hemorrhage have been reported in cases with other viral hemorrhagic fevers. Viral hemorrhagic fevers share some pathophysiologic, clinical, and laboratory features. Capillary fragility is a common feature of viral hemorrhagic fevers, suggesting that infection of the endothelium plays a major role (12). Dengue hemorrhagic fever (DHF) is known to be characterized by plasma leakage into the chest and abdominal cavities and bleeding diathesis. In addition to the common manifestations, pleural effusion, pneumonitis, hemoptyisis, and pulmonary hemorrhage have been seen rarely in cases with DHF (13). In a study conducted in patients with DHF, 468 chest x-rays were obtained from 363 patients. The authors reported abnormalities after the 3rd day in more than half of chest x-rays with infiltration only and small pleural effusion as the major findings. Progressive changes during the 1st week and improvements during the 2nd week were observed in these abnormal chest x-rays. The chest x-rays presentation was also significantly correlated with laboratory findings (leukocyte count, platelet levels, aPTT, ALT, and albumin levels), as well as with the clinical course (14). In parallel with these findings; hemorrhagic pleural fluid developed in our patient concurrently with the lowest platelet count and longest PTT. In our patient, hemorrhagic pleural fluid developed during the hemorrhagic period. The patient showed a dramatic clinical improvement and spontaneous resolution of the pleural effusion was seen after the hemorrhagic period.

In conclusion, we present this case to show that self-limited hemorrhagic pleural effusion may be seen during the course of CCHF. There is no clear explanation for why pleural effusion may develop in CCHF. The possible mechanism of pleural effusion is considered to be bleeding or vascular leakage as in some of the other viral hemorrhagic fevers.

REFERENCES