INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is endemic in Pakistan with sporadic outbreaks. The virus is one of the five genera in the family Bunyaviridae and mainly affects mononuclear phagocytes, endothelial cells, and hepatocytes, causing a severe hemorrhagic fever.1

It was first described in Crimea in the Soviet Union in 1944.2 In Pakistan, it was initially reported in 1976, when a laparotomy was performed on a patient with abdominal pain, hematemesis, and melena in a general hospital in Rawalpindi.3 Since then 12 outbreaks, mainly in western and northwestern regions of the country, have been reported.4 Outbreaks have also been reported from western province of Saudi Arabia,5 the United Arab Emirates,6 Kuwait,7 and Iraq.8 Case fatality is reported between 15% and 100%.1,9−11 Nosocomial outbreaks have been reported with a high mortality rate.3,6,8,12,13 Treatment of CCHF is with oral/intravenous ribavirin.14−21 Because of its transmissibility from domestic ruminant animals such as cattle, sheep, and goats, prevention is best achieved by educating the farming community and hospital staff.22 Duration of contact and type of exposure determine transmissibility.23

INDEX CASE

On February 12, 2002, a 25-year-old Kashmiri woman from Bagh in Azad Jammu and Kashmir, 100 km northwest of Rawalpindi/Islamabad, presented at a local health outlet with high grade fever accompanied with chills, rigors, and severe myalgias persisting for one week. Two days later, following the initial symptoms, she developed features of generalized coagulopathy with vaginal bleeding, hematemesis, and melena. After admission to a local hospital, her condition deteriorated and she was referred to Holy Family Hospital, a tertiary care center in Rawalpindi. At the time of her presentation, she was drowsy and febrile (temperature = 102°F), tachypneic with a respiration rate of 44/min, and hypotensive (blood pressure = 90/50 mm of Hg). There were multiple petechiae on her body, especially around the intravenous access sites and purpuric rashes on both forearms. A chest examination revealed bilateral coarse crepitations extending up to mid chest with decreased air entry at the bases. She responded only to painful stimulus (grade III coma) with no focal neurologic signs. Laboratory investigations revealed pancytopenia with a platelet count of 12 × 10^9/L (normal = 150−300 × 10^9/L), a serum urea level of 60 mg/dL (normal = 8−20 mg/dL), marked derangement of coagulation profile (prothrombin time [PTT] = 25 seconds [control = 13 seconds]; activated partial thromboplastin time [aPTT] = 78 seconds, [control = 26 seconds]; fibrinogen = 100 mg/dL [normal = 200−400 mg/dL]; and fibrin degradation products [FDPs] = 40 μg/mL [normal = <10 μg/mL]), and normal serum electrolytes. A chest radiograph was reported as normal and peritoneal ascites was seen on an abdominal ultrasonogram.

A provisional diagnosis of septicemia leading to disseminated intravascular coagulation (DIC) was made and the subject was treated accordingly. After transfusions of fresh frozen plasma (FFPs), platelets, and red blood cell concentrates, her platelet count improved to 29 × 10^9/L. However, no improvement was observed in the coagulation profile (PTT, aPTT, fibrinogen, and FDPs). Twenty four hours after admission, the patient developed respiratory arrest and was placed on artificial ventilation, but four hours later she died. Since no suspicion of CCHF arose for this patient, no sample of serum was saved for retrospective detection of antibodies against CCHF virus.

SECONDARY CASE 1

During the period of stay of the index case in the intensive care unit, an attending intern physician, a 25-year-old woman, looked after the patient. At the time of respiratory arrest on the evening of February 12, the index case was revived successfully, during which time the intern also administered mouth-to-mouth resuscitation. She also had multiple contacts with blood and vomitus of the patient, but no needle stick injury was reported. The intern spent rest of the evening and night managing the patient until her death on the morning of February 13. She remained generally asymptomatic for the next four days except for mild fatigue. On the morning of February 18, she developed fever, shivering, and generalized weakness. She was taken to the emergency room and on suspicion of an acute malarial episode, was prescribed a course of an antimalarial and then discharged. Throughout the night she vomited and complained of mild generalized abdominal pain. In the early hours of February 19, she developed drowsiness and was admitted to the isolation room with a provisional diagnosis of enteric fever leading to septicemia.

At the time of admission, her clotting profile, liver functions (bilirubin = 0.3 mg/dL, alanine aminotransferase [ALT] = 32 units/L, and aspartate aminotransferase [AST] = 48 units/L), and platelet count (170 × 10^9/L) were within normal range. A provisional diagnosis of septicemia leading to disseminated intravascular coagulation (DIC) was made and the subject was treated accordingly. After transfusions of fresh frozen plasma (FFPs), platelets, and red blood cell concentrates, her platelet count improved to 29 × 10^9/L. However, no improvement was observed in the coagulation profile (PTT, aPTT, fibrinogen, and FDPs). Twenty four hours after admission, the patient developed respiratory arrest and was placed on artificial ventilation, but four hours later she died. Since no suspicion of CCHF arose for this patient, no sample of serum was saved for retrospective detection of antibodies against CCHF virus.
ranges. Vomiting improved by evening and she slept well throughout the night. A repeat of the coagulation profile on February 20 revealed deranged PT, aPTT (42 seconds and 45 seconds more than the controls, respectively), and a low platelet count ($80 \times 10^9/L$). Levels of FDPs were elevated (28 $\mu$g/mL); however, the fibrinogen level was normal (250 mg/dL). Ten bags (each bag contains approximately 70–80 mL) of FFPs were transfused over the next 24 hours to correct the biochemical coagulation abnormalities. She remained afebrile, but by the evening of February 21 she started bleeding from multiple sites. Family attendants also reporting a single episode of aggressive behavior. The coagulation profile carried out on that day showed further derangements ($PT = 64$ seconds [control = 12 seconds]; $aPTT = 77$ seconds [control = 32 seconds]; platelet count = $28 \times 10^9/L$; FDPs = 1000 $\mu$g/mL; and fibrinogens = 100 mg/dL). Ultrasonography of the lower pelvis and abdomen showed peritoneal ascites and multiple cysts in the adnexa. Subsequent abdominal paracentesis revealed hemorrhagic fluid, and based on this evidence viral hemorrhagic fever was now thought of as a strong possibility. On the morning of February 22, she developed respiratory difficulty and marked drowsiness. She was shifted to the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan. The intern remained on an artificial respirator in the intensive care unit of the Pakistan Institute of Medical Sciences, an advanced tertiary care center, and intravenous ribavirin therapy was initiated after consultation with the epidemic investigation cell of the National Institutes of Health of Pakistan.

The test results were positive for IgM antibodies against CCHF virus and were confirmed by a polymerase chain reaction for this virus.

SECONDARY CASE 2

Before the transfer of the index case to the intensive care unit from the general ward, she had profuse bleeding from oral cavity, rectum, vagina, and nasal orifices. An intern physician, a 27-year-old man, looked after the index case in the general ward, where he performed gastric lavage on her. The intern used latex gloves, but no face mask or eye shields were used. He reported contact with respiratory secretions of index case over his face while performing this procedure, which took approximately 45 minutes. He also reported soaking of sleeves of his white coat with patient’s blood. On February 17 (five days after initial contact with the index case), he developed generalized aches, pain, and malaise. A day later, he reported weakness, exhaustion, and severe generalized lower limb pain. By February 19, he had a fever (temperature = 101°F) and an episode of epistaxis, followed by severe drenching sweats four hours later. These symptoms persisted from February 19 to February 22, and during this whole period he remained on a liquid diet. Baseline investigations showed a total leukocyte count (TLC) of $2.3 \times 10^9/L$ (neutrophils = 54%, lymphocytes = 41%) and a platelet count of $80 \times 10^9/L$. A coagulation screening was done at that time, which revealed a normal PTT and aPTT. He remained in state of fatigue and exhaustion from February 23 to February 26. He also reported bleeding gums on awakening in the morning. Further coagulation profiles done on February 26 showed a TLC of $3.7 \times 10^9/L$, a platelet count of $87 \times 10^9/L$, a prolonged aPTT of 50 seconds (control = 32 seconds), and a normal PTT.

Crimean-Congo hemorrhagic fever was suspected, and antiviral therapy (oral ribavirin) was started on February 26 and continued for 10 days (a loading dose of 2 grams, followed by 4 grams/day for 4 days and 2 grams/day for 6 days). The family effectively isolated the intern at home. Investigations done on day 7 of the treatment showed normalization of the TLC, platelet counts, and coagulation abnormalities. Samples dispatched to the National Institute of Virology in Johannesburg, South Africa tested positive for IgM and IgG antibodies to CCHF virus. The male intern is the only known secondary case of CCHF who survived this outbreak.

DISCUSSION

Crimean-Congo hemorrhagic fever virus can infect a wide range of domestic and wild animals, including sheep and cattle. Animals are infected with CCHF virus from the bite of infected ticks. Seroprevalence has been observed to be between 13% and 36% among animals. A number of tick genera are capable of becoming infected with CCHF virus, but the most efficient and common vectors for CCHF appear to be members of the genus *Hyalomma*. The most important source for acquisition of the virus by ticks is believed to be infected small vertebrates on which immature *Hyalomma* ticks feed. Once infected, the tick remains infected throughout its life, and the mature tick may transmit the infection to large vertebrates, such as livestock. Domestic ruminant animals, such as cattle, sheep, and goats remain viremic for one week after becoming infected. Humans may become infected with CCHF through transmission of virus from direct contact

![Figure 1. Crimean-Congo hemorrhagic fever (CCHF) in Pakistan, 1976–2002: Infected and fatal cases.](image)
with blood or other infected tissues of livestock or from an infected tick bite. The majority of human cases have occurred in workers associated with livestock industry, agriculture, slaughterhouses, and veterinary practice. Seroprevalence is reported to be 13.1% among rural farmers in the northern Senegal and South Africa.27

Thirteen outbreaks of CCHF have been previously reported in Pakistan (Figure 1).3,4 The presently reported cases represent the fourteenth (eighth nosocomial) outbreak of CCHF in Pakistan and the second in Rawalpindi. Since January 1976, CCHF has caused 43 reported deaths.4 Rarely diagnosed, CCHF is known and feared among the medical staff in Pakistan.3

The index case spent 36 hours in our hospital. There was no reported history of tick bite; however, she was a member of a shepherd’s family. The possibility of a Hyalomma tick bite or contact with infected animal blood cannot be ruled out. The patient may also have contracted the virus by handling infected meat of livestock. Blood samples of the index case for CCHF antibody testing were not taken since there was no suspicion of CCHF. Since viremia is more profound and intense in fatal cases, they have the greatest potential for nosocomial transmission.28,29 The secondary cases were most likely exposed to the index case in the hospital. Both of the secondary cases became symptomatic within five days of the exposure to index case. From her admission until her death, the index case was looked after by 12 health care workers. The physical contact of the female secondary case with the index case was of longer duration than any other.

Deaths have been reported to occur on days 5–14 of CCHF fever.30 The onset of DIC is unique to CCHF among the viral hemorrhagic fevers.31 The index case died of DIC-related complications on day 8 of the illness and both secondary cases developed DIC early in their disease.

During the first five days of illness, occurrence of any of the following clinical pathology values is ≥90% predictive of a fatal outcome as calculated by method of Galen and Gambino: TLC ≥ 10 × 10^9/L, platelet count ≤ 20 × 10^9/L, AST ≥ 200 units/L, ALT ≥ 150 units/L, aPTT ≥ 60 seconds, and fibrinogen ≤ 110 mg/dL.30

Almost all pathologic parameters of the first secondary case had reached critical levels by day 5 of her illness. In comparison, these parameters for the other secondary case remained within normal limits during the same period (Table 1).

An ELISA is currently the most sensitive test for the detection of antibodies against CCHF virus. However, it is cumbersome and time-consuming, which make it unsuitable for rapid diagnosis.33 We collected 50 samples from high-risk contacts of the index and secondary cases and sent them to the National Institute of Virology in Johannesburg, South Africa for detection of antibodies against CCHF virus. Two samples turned out to be positive for IgG and IgM antibodies against CCHF virus. No secondary cases were seen in the index case family. There were no tertiary cases noted.

In our experience, the post-exposure prophylaxis and treatment with oral/intravenous ribavirin in recommended doses has been found to be effective. Surveillance of cattle, control of ticks, rapid identification and isolation of cases, barrier nursing of the cases, and tracing and surveillance of contacts are necessary for best achieving prevention. There is a need to estimate the seroprevalence of CCHF among herds and shepherds because they have a high probability of being involved in an outbreak.

Table 1

<table>
<thead>
<tr>
<th>Laboratory assay*</th>
<th>90% or more predictive of fatal outcome†</th>
<th>Index case</th>
<th>Secondary case 1</th>
<th>Secondary case 2</th>
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<tr>
<td>TLC</td>
<td>≥10 × 10^9/L</td>
<td>12 × 10^9/L</td>
<td>24 × 10^9/L</td>
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<td>28 × 10^9/L</td>
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<tr>
<td>Fibrinogen</td>
<td>≤110 mg/dL</td>
<td>100 mg/dL</td>
<td>100 mg/dL</td>
<td>300 mg/dL</td>
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</tbody>
</table>

* TLC = total leukocyte count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time.
† Derived from 50 laboratory-confirmed patients with CCHF.30

REFERENCES


