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Short Report: Crimean-Congo Hemorrhagic Fever Virus as a Nosocomial Pathogen in Iran

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Abstract. Crimean-Congo hemorrhagic fever (CCHF) is a viral disease with several different modes of transmission. We describe the manifestations, outcome, and likely modes of transmission for three nosocomial cases. All threee cases were healthcare workers (two men and one woman). They had fever, myalgia, and petechia. Disseminated intravascular coagulation resulted in the death occurred in the woman. Because this disease is manifested with non-specific influenza-like symptoms, diagnosis can be difficult. Data for these patients can be used to investigate airborne or sexual transmission of this virus, although neither route was substantiated for these patients. Use of universal precautions and early case detection are the most helpful strategy for preventing nosocomial transmission of CCHF.

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral disease that has been reported in more than 30 countries in Africa, Asia, southeastern Europe, and the Middle East.[1] It was first described in the Crimea in 1944. Later, a virus isolated from the Congo was identified as the same virus, resulting in the name Crimean-Congo hemorrhagic fever virus (CCHFV).[2] Infection with CCHFV is manifested as an acute viral disease (fever, myalgia, and arthralgia) and in severe cases, hemorrhagic manifestations may ensue. It is transmitted mainly through tick bite or animal contact but repeatedly has caused nosocomial outbreaks.[3–7] Human-to-human transmission occurs by infected blood or secretions, but airborne transmission of the disease has not been documented.[8]

We describe the manifestations and outcomes in three confirmed cases of CCHF in healthcare workers in Iran. The risk factors and routes of transmission in a hospital setting are discussed.

INDEX CASE 1

On August 2, 1999, a 55-year-old man (a shepherd) was referred to the emergency room of a hospital with hematemesis. He had a history of animal contact. Epistaxis developed after a nasogastric tube was inserted in an attempt to control gastrointestinal (GI) bleeding. Unfortunately, he died of intractable GI bleeding and disseminated intravascular coagulation (DIC) four days later.

SECONDARY CASE 1

On August 16, 1999, a 32-year-old man (a physician) came to a clinic in Shahrekord in central Iran with severe headache, malaise, fever, vomiting, and diarrhea for one week. Petechiae, epistaxis and gum bleeding then developed, which resulted in his referral to the clinic. He was admitted to a hospital and treated with broad-spectrum antibiotics. There was no history of recent travel or contact with domestic animals. It was later discovered that he had been in contact with index case 1, who had died of severe GI bleeding two weeks before his first symptoms. The index case had coughed and splashed blood on the physician's face while he was trying to insert a nasogastric tube. Physical examination showed right cervical lymphadenopathy and a palpable spleen, but the patient was not febrile. Laboratory examinations showed leukopenia, thrombocytopenia, increased levels of aminotransferases, an increased prothrombin time (PT) and partial thromboplastin time (PTT), and hematuria. Bone marrow aspiration and biopsy were performed but results were normal. A peripheral blood smear did not show any malignant cells or parasites. During hospitalization, antibiotics and steroids were administered. After approximately one week, the patient recovered completely, all laboratory test results were normal, and he was discharged. At that time, he was not diagnosed with CCHF, but after the second nosocomial case was identified, he was suspected of having CCHF. He was diagnosed retrospectively after serum IgG and IgM enzyme-linked immunosorbent assay (ELISA) results were positive 3–4 weeks after his discharge.

TERTIARY CASE 1

On August 28, 1999, a 26-year-old woman (a physician) was admitted to the same hospital as secondary case 1. She had undulant fever, vomiting, and diarrhea for two days before admission. Vaginal bleeding developed on the day of admission. She did not have any history of recent travel or contact with domestic animals, but she had close contact with secondary case 1. This contact involved touching intact skin without gloves while trying to gain intravenous access for blood sampling. However, because there was no needlestick injury, this was a considered a low-risk procedure for transmission of CCHF. Sexual contact was likely because she had married secondary case one month earlier. Physical examination showed fever, periorbital edema, and pale mucosa. Laboratory investigations showed thrombocytopenia, leukopenia, increased levels of aminotransferases, bilirubin, and lactate dehydrogenase, increased PT and PTT, and hematuria. She was treated with broad-spectrum antibiotics, dexamethasone, and other conservative management, including platelet infusion. Two days after admission, confusion, generalized abdominal pain, and hematemesis developed in this patient. At that time, she was suspected of having viral hemorrhagic fever.

Her samples were sent for evaluation to the National Institute for Virology (NIV) in Sandringham, South Africa. After five days, the patient was transferred to a university hospital in Tehran. Coma, nystagmus, left-sided positive Babinski sign, rupture of a right ovarian cyst, and hemorrhagic cyst of the

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left ovary developed in the patient. On September 3, 1998, she died of DIC. Results of ELISAs performed at NIV showed IgG and IgM antibodies to CCHFV, and a polymerase chain reaction was positive for CCHFV RNA. Cell culture yielded CCHFV. Consequently, she was defined as a tertiary case of nosocomial CCHF with two potential routes of exposure (sexual and blood contact).

INDEX CASE 2

On April 30, 2001, a 65-year-old man (a farmer) living in the suburbs was referred to a hospital because of thrombocytopenia, severe GI bleeding, and hemoptysis. Animal contact was considered in his history. The patient died of severe bleeding (pulmonary alveolar hemorrhage) 24 hours after admission, despite attempted resuscitation.

SECONDARY CASE 2

On May 22, 2001, a 32-year-old man (a physician) was admitted to a tertiary care hospital in Isfahan in central Iran with high-grade fever, shaking chills, and severe anorexia for one week before admission, and recent development of periorbital edema, malaise, and petechiae. No history of recent travel or contact with domestic animals was found. We later found that he had resuscitated index case 2, a critically ill patient, with thrombocytopenia, severe GI bleeding, and pulmonary hemorrhage, approximately three weeks before admission. During resuscitation, he had close contact with the patient, and splashing with respiratory and GI secretions necessitated a change of clothing and a shower. On the basis of the presence of anemia (normochromic and normocytic), thrombocytopenia, and leukopenia, he was treated for suspicion of viral infection. Peripheral blood smear, bone marrow aspiration, and biopsy did not confirm any malignant disorder. He also had hematuria, proteinuria (+++), and increased levels of aminotransferases, creatine phosphokinase, and lactate dehydrogenase. He did not show any increase in PT and PTT. On May 31, 2001, he was discharged when platelet and leukocytes counts returned to normal levels. Samples obtained during hospital admission showed positive results for CCHF (IgG and IgM).

DISCUSSION

An epidemic of CCHF was first confirmed in Iran in June 1999.[9] The Center for Disease Surveillance in Iran (Ministry of Health, Iran, unpublished data) reported a peak incidence in 2002 (Figure 1). CCHF was not confirmed as an endemic disease in Iran before 1999. The most important factor in controlling the epidemic in Iran was providing persons and physicians with information about routes of transmission.[10]

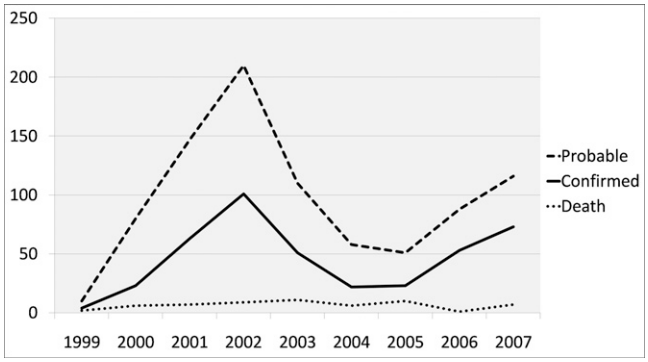

FIGURE 1. Number of probable and confirmed cases of Crimean-Congo hemorrhagic fever (CCHF) and number of deaths from CCHF in Iran (Data from Ministry of Health, Center for Disease Surveillance, Iran).

Symptoms typically include high fever, headache, malaise, arthralgia, myalgia, nausea, abdominal pain, and non-bloody diarrhea.[11] The hemorrhagic period is short (usually 2–3 days), develops rapidly, and usually begins between the third and fifth days of disease.[11] Patients may show signs of DIC and circulatory shock.[12] Community-acquired CCHF occurs through transmission of the virus by direct contact with blood or other infected tissues of livestock or from an infected tick bite.[11] A case-control study on epidemiologic characteristics of patients diagnosed with CCHF in Iran has shown that a history of tick bite is one of the most important risk factors. Other risk factors include occupation (butchers, physicians, and veterinarians), and having contact with livestock.[13]

We describe the disease course and possible routes of transmission, including sexual contact, in three cases of CCHF in healthcare workers. Laboratory (Table 1) and clinical (Table 2) manifestations were similar to those in other reports of nosocomial CCHF.[3,4,7,14]

Acute respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage, accompanied by systemic inflammatory reaction, have been reported during hemorrhagic manifestations.[15,16] Pulmonary alveolar hemorrhage was observed in index case 2, which led to ARDS and death. Intubation of this patient in such a critical condition led to splashing of blood into a physician's face, which was the probable route for virus transmission. Although alveolar hemorrhage would be a fatal manifestation of disease, rapid clinical recovery and radiologic clearance were obtained within a few days after starting oral ribavirin treatment in a study from Turkey.[16]

Nosocomial transmission has been described in reports from Pakistan, Iraq, Dubai, South Africa, and Iran.[4,14,17] Transmission of CCHFV among healthcare workers has been reported in parallel with outbreaks in the general population.[18] Although nosocomial transmission from patients to healthcare workers

TABLE 1
Laboratory findings of three nosocomial cases of Crimean-Congo hemorrhagic fever, Iran*

Case	WBC count (/L)	Hb (g/dL)	Platelet count (/L)	AST (U/L)	ALT (U/L)	LDH (U/L)	CPK (U/L)	PT (sec)	PTT (sec)	Positive serologic result, PCR, or viral culture
Secondary 1	1,900	12.0	65×10^3	550	366	NA	NA	13	30	IgG, IgM
Tertiary 1	2,100	9.0	20×10^3	3,960	1,877	1,220	NA	17	56	PCR, IgG and IgM and viral culture
Secondary 2	2,900	10.4	79×10^3	430	286	2,005	6,950	11	25	IgG, IgM

*WBC = white blood cell; Hb = hemoglobin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CPK = creatinine phosphokinase; PT = prothrombin time; PTT = partial thromboplastin time; NA = not applicable.

TABLE 2
Clinical manifestations, demographic variables, risk factors and outcome of nosocomial and index cases of Crimean-Congo hemorrhagic fever, Iran*

Case	Age, years	Sex	Bleeding manifestations	Fever	Job	Contact type/details of exposure	Outcome	Incubation period, days†
Index 1	55	M	GI bleeding, epistaxis	Yes	Shepherd	Animal contact	Dead	NA
Secondary 1	32	M	Petechia	Yes	Physician	Physical contact without gloves, blood splashing into face, performing gastric lavage	Alive	14
Tertiary 1	26	F	Hematemesis, vaginal bleeding, epistaxis, hematuria	Yes	Physician	Physical contact without gloves, blood sampling, providing intravenous access, touching skin, contact with sweat and saliva, sexual contact	Dead	12
Index 2	65	M	GI and pulmonary hemorrhage	Yes	Farmer	Animal contact	Dead	NA
Secondary 2	32	M	Petechia, purpura	Yes	Physician	Physical contact without gloves, intubation, resuscitation, blood splashing into face	Alive	22

* GI = gastrointestinal; NA = not applicable.
† Incubation period is the period between infection (first exposure to index case) and the appearance of symptoms of the disease.

accounts for hospital outbreaks worldwide, transmission of CCHFV from patient to patient has been reported recently.[19] This study signifies the importance of CCHF as a nosocomial threat, not only to healthcare workers, but also to other patients. In 1994 in Pakistan, Fisher-Hoch and others reported three healthcare workers infected with CCHFV. All three patients were severely ill but made complete recoveries.[14] In 1994 in a private hospital in Pakistan, three healthcare workers contracted CCHF after surgery on a bleeding patient who later died.[20] In 2002, a nosocomial outbreak of CCHF occurred in Rawalpindi, Pakistan. Two healthcare workers were reported; one of them died and the other was successfully treated with oral ribavirin.[3] Nosocomial transmission of this virus has been evaluated in Iran. In the summer of 2003, we studied the seroprevalence of IgG against CCHFV among healthcare workers who had come in contact with CCHF patients from three referral hospitals in disease-endemic regions. Seropositivity was more frequent among those whose intact skin had come in contact with non-sanguineous body fluids (9.52%) and those who had had percutaneous contacts (7.14%).[21]

In hospital settings, the most dangerous procedures for CCHFV transmission are interventions for controlling GI bleedings and surgery on patients who have not yet been diagnosed as having CCHF.[18] Generally, these patients will be diagnosed after these procedures, and injuries to healthcare workers during these procedures are usually underreported.[22–24]

Although reports have confirmed CCHFV transmission in a hospital setting, the exact routes of transmission have not yet been clarified. The question is whether CCHF patients should be placed in an airborne isolation setting. In the United States, the Centers for Disease Control and Prevention has classified CCHFV as a Biosafety Level 4 pathogen.[25] Human-to-human transmission occurs by infected blood or secretions but airborne transmission of the disease has not been documented.[8] All three of our nosocomial cases were involved in high-risk procedures such as inserting nasogastric and endotracheal tubes, with splashing of blood into their faces, percutaneous contact with patients' blood (intact skin), and cutaneous contact with non-sanguineous body fluids. These findings support the use of contact and droplet isolation as precautions for prevention of transmission.

The necessity for airborne isolation in hospital settings cannot be ascertained because of the low number of cases in this report. Because all three cases were in contact with blood or other highly infectious body fluids, airborne transmission cannot be concluded. Airborne isolation is almost impossible because facilities in most disease-endemic areas lack this capability. Therefore, we cannot recommend airborne isolation for CCHF patients.

Although tertiary case 1 could have acquired CCHFV nosocomially, we should not ignore the importance of sexual transmission, which has not yet been clearly described for this disease. One report of possible sexual transmission in a family member of a patient in Iran provides evidence to support this possibility.[26] We report what may be the second reported case of sexual transmission of CCHF. Although healthcare-procedure acquisition of the virus cannot be ruled out, the procedures performed were of low risk. Confirmation of sexual acquisition as a route of CCHF spread needs further study.

The time to onset of disease after exposure in our cases was reported as 12, 14, and 22 days (Table 2). In most previous studies,[25] it was found to be less than seven days. We consider that the incubation period depends mainly on the route of transmission, severity of exposure, and viral load of the case to whom a person is exposed.

The most definitive virologic diagnosis is time-consuming and is conducted in only one high-level biosafety laboratory. These factors delay early case definition and may cause nosocomial outbreaks. In our study, we were not able to detect the beginning of this epidemic. Therefore, tertiary transmission occurred. These findings indicate the potential risk to healthcare workers who are in contact with critically ill patients and perform procedures without taking standard precautions.

Ribavirin treatment has been evaluated for treatment of patients with CCHF.[14,27–30] In a historical cohort study in Iran, we concluded that oral ribavirin is an effective treatment of the hemorrhagic form of CCHF.[9] Prophylaxis is suggested after high-risk contamination.[8] In our experience, ribavirin is potentially useful and should therefore be recommended for healthcare workers who are at risk of exposure, such as by percutaneous injuries. None of our cases received prophylaxis.

We conclude that the risk of nosocomial transmission can be minimized by proper and timely infection-control measures, universal precautions including contact and droplet isolation for suspected patients, careful management of infected patients, and in some cases, administration of prophylactic therapy to healthcare workers after exposure. On the basis of data for our three cases, we do not recommend airborne isolation for CCHF patients because such isolation is not practical in most disease-endemic areas. Sexual transmission is possible but its confirmation needs more data.

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