Short Report: Fatal Nosocomial Spread of Crimean-Congo Hemorrhagic Fever with Very Short Incubation Period

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Abstract. Crimean-Congo hemorrhagic fever is a tick-borne viral zoonosis with the potential of human-to-human transmission with case fatality rates from 3% to 50%. The incubation period depends on host, route of infection, and viral dose. Herein, we report a nosocomial spread of the disease in a hospital at Mashhad, northeastern Iran, with a very short incubation period for one of the secondary cases. The patient was a medical student who had a negligible contact with a Crimean-Congo hemorrhagic fever patient during his admission to the hospital. The time interval between the contact and the onset of symptoms was merely 20 hours. Unfortunately, he died within 1 week of exposure.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral zoonosis that affects wide areas in Asia, Southeastern Europe, and Africa. The disease has the potential of human-to-human transmission with case fatality rates from 3 to 50%. Clinical features usually include a sudden onset of fever, myalgia, headache, and gastrointestinal symptoms. Hemorrhagic manifestations constitute a prominent symptom of late stage disease. It has been suggested that the length of the incubation period for the illness appears to depend on the mode of acquisition of the virus. The incubation period after a tick bite is 3–7 days, however it could differ depending on several factors including viral dose and route of exposure.¹ The incubation period after contact with infected blood or tissues is usually 5 to 6 days, with a documented maximum of 13 days.² Herein, we report a nosocomial spread of the disease, with a very short incubation period for one of the secondary cases.

Case presentation. *Index case.* A young man, working as a butcher at the Mashhad industrial slaughterhouse, was referred to the emergency ward at Imam Reza Hospital, Mashhad, northeastern Iran, with an unstable hemodynamic state and excessive bleeding from multiple sites after 5 days of flu-like symptoms. The butcher cut his hand while slaughtering cattle about 7 days before the onset of the illness. He was febrile but conscious. At the time of hospitalization, he had undetectable distal pulses, systolic blood pressure of 70 mm of Hg, epistaxis, hematemesis, and rectorrhagia. Considering his epidemiological link of working at a slaughterhouse, profuse bleeding, and very low platelet counts, he was isolated as a probable case of CCHF and received supportive therapy plus ribavirin. Unfortunately, he developed rapid onset of unconsciousness and respiratory failure early the next morning and died in a matter of hours as a result of hemorrhagic shock and respiratory failure.

Case A. Several hours before the death of the index case, about 20 hours after his admission to the hospital, a medical student who was in contact with the patient during his arrival reported a sudden onset of high-grade fever and severe headache. A complete blood count was performed and he had

no thrombocytopenia. Although the incubation period was improbable for the disease (< 1 day) and his blood tests were normal, he was advised to be hospitalized and treatment with ribavirin was ordered. His body temperature was 39°C and he complained of severe headache and muscle pain. Before receiving ribavirin he reported a past medical history of G6PD (Glucose-6-phosphate dehydrogenase) deficiency causing severe hemolysis, therefore the drug was not started. The day after, he was afebrile with no complaints. Again, his platelet count was in the normal range. Therefore, he was discharged. Two days later, he was readmitted with a high-grade fever, severe headache, and retro-orbital pain, nausea, and severe myalgia. His blood tests showed a mild thrombocytopenia. He was under observation for a night. However, the day after his admission the symptoms worsened and his platelet count rapidly fell (Table 1). Ribavirin was started on Day 2 of this readmission and he was kept under complete isolation with rigorous management. His blood tests showed severe thrombocytopenia, leukocytosis, and raised liver enzymes. Three days later he had mild epistaxis and gingival bleeding. The intravenous immune globulin (IVIG) with the dose of 2 g/kg divided into 5 doses every 12 hours (q12h) was started. In the morning of Day 8, he was very agitated. He became pale and had orthostatic dizziness. Within the next few hours, he developed abdominal stiffness and distention. Distal pulses could not be detected because of the low blood pressure. With a suspicious hemoperitoneum, ultrasonography was performed that revealed a moderate to severe amount of free fluid in the abdominal and pelvic cavity. Aggressive hydration and transfusion of blood products including packed cells (PC), fresh-frozen plasma (FFP), and platelet were started. Within 2 hours, the blood pressure became normal (125/70). Despite normalization of blood pressure, he remained anuric requiring fluid restriction and hemodialysis. Ribavirin and IVIG were stopped because of anuria. Two hours later the patient developed hematochezia and again became hypotensive. Again, he received IV fluids and blood products. Unfortunately, he died before receiving hemodialysis that day.

Case B and C. During this time, two nurses in contact with the index case were hospitalized with fever, headache, myalgia, and severe thrombocytopenia. One of them (Case B) was told that she had a blood splash on her conjunctiva during the resuscitation of the index case and the other (Case C) reported a needlestick injury with the index case. Both of them received ribavirin, 3 days of methyl prednisolone, IVIG, and supportive therapy with favorable recovery (Table 2). However,

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TABLE 1
Laboratory data for two deceased cases with Crimean-Congo hemorrhagic fever (CCHF)*

		May 02	May 03	May 04	May 06	May 08	May 10	
Index case	WBC (mcL)	2,700	Expired					
	PLT (mcL)	5,000						
	AST (U/L)	291						
	ALT (U/L)	533						
	LDH (U/L)	3,893						
	PT (S)	23.5						
	INR	2.92						
Case A	WBC (mcL)		8,200	Discharged	11,300	25,900	29,900	Expired
	PLT (mcL)		219,000		19,1000	9,000	7,000	
	AST (U/L)		—		65	—	1076	
	ALT (U/L)		—		73	—	923	
	LDH (U/L)		—		391	—	1973	
	PT (S)		12.5		14.9	32.8	> 60	
	INR		1.00		1.31	5.35	0.00	

*WBC = white blood count; PLT = platelet count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; INR = international normalized ratio.

†Presented with high-grade fever, headache, and myalgia < 20 hours after contact with the index case.

case B had a complicated clinical course after developing respiratory distress and hypoxemia on Day 7 of admission lasting 4 days. In addition, she received 90 bags of platelet within 10 days because of vaginal bleeding and severe thrombocytopenia, and had protracted thrombocytopenia for more than 18 days.

The molecular detection of CCHF virus in serum samples of all four cases resulted positive by qualitative real-time reverse transcription-polymerase chain reaction. The samples were taken during the first day of patients' admission and all procedures were done by trained experts according to the published protocol provided by Pasteur Institute of Iran, Laboratory of Arboviruses and Viral Hemorrhagic Fevers.³ There was no tertiary symptomatic case in this outbreak according to active clinical surveillance.

DISCUSSION

Nosocomial outbreaks of CCHF are reported now and then. However, there are several notable points in the present outbreak. First, the incubation period for case A was < 24 hours, which was shorter than the minimal incubation periods reported before. The reported time period between getting the infection and the onset of symptoms varies widely. One report⁴ stated that the interval between tick bite and the

onset of symptoms was a mean of 23.6 days (range 13–53 days). For case A, the interval between contact with the patient and the onset of symptoms was as short as < 20 hours. Apparently the patient had neither an exposure to any other possible cases/infected tissues nor a chance of a thick bite before the accident. Second, cases A and B had a biphasic pattern that started with an episode of non-specific febrile illness for about 1 day, followed by 1–2 days of a completely asymptomatic period progressing to a full blown disease with high-grade fever, severe myalgia, vomiting, and severe watery diarrhea. Third, the contact itself did not seem significant. The deceased medical student reported that at one point the index case fell down and he grabbed him with bare hands. There was visible contact of patient's blood with his intact skin. Just a venial however mortal contact that debates whether CCHF can enter through intact skin. In case B the contact was a negligible splash of blood to her conjunctiva during resuscitation of the index case. Patient C had a needlestick injury while trying to gain intravenous access for IV fluid administration. In a report of a nosocomial outbreak from Pakistan in 1980, all of the secondary nosocomial cases occurred in hospital personnel who were heavily exposed to infectious blood.⁵ In the nosocomial outbreak of CCHF in Tygerberg Hospital in 1985, of 459 listed contacts, 4 out of 46 blood contacts (8.7%)

TABLE 2
Laboratory data for two nurses exposed to the index case

		May 07	May 08	May 10	May 12	May 14	May 16	May 19
Case B	WBC (mcL)	5,700	12,100	8,000	1,400	2600	2,400	Discharged
	PLT (mcL)	57,000	11,000	14,000	31,000	18,000	36,000	
	AST (U/L)	52	211	275	240	74	57	
	ALT (U/L)	37	39	79	137	84	78	
	LDH (U/L)	598	—	1,909	—	—	510	
	PT (S)	13.9	16.8	14.4	13	13.8	12.5	
	INR	1.20	1.70	1.37	1.07	1.22	1.00	
Case C	WBC (mcL)			1,300	1,100	1,100	3,400	Discharged
	PLT (mcL)			30,000	40,000	31,000	40,000	
	AST (U/L)			502	—	285	—	
	ALT (U/L)			266	—	198	—	
	LDH (U/L)			1205	—	533	—	
	PT (S)			13.7	12.5	12.3	12	
	INR			1.17	1.00	1.01	0.96	

*WBC = white blood count; PLT = platelet count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; INR = international normalized ratio.

†Incubation period of 5 days.

‡Incubation period of 8 days.

and 3 out of 9 needle contacts (33%) developed the disease. It is not apparent that blood contacts were with intact skin or mucosa.⁶ In a report from Pakistan in 1998, two of four people exposed percutaneously and one of five with cutaneous exposure contracted CCHF. The person with cutaneous exposure was a surgeon who tore his glove during surgery and noted blood on his hand but no cut. There were no anti-CCHF antibodies or CCHF cases among persons whose skin came into contact with body fluids other than blood (0/4), who had skin-to-skin contact (0/16) with patients, or were physically close to them (0/21). Three index case relatives reported that although 10 family members had cutaneous exposure, none developed CCHF.⁷ In another report from Pakistan, contacts were divided into five subsets: percutaneous contact with blood (A), blood contact to unbroken skin (B), cutaneous contact to non-sanguineous body fluids (C), physical contact with patients without body fluids contact (D), and close proximity without touching (E). Percutaneous exposure has the highest risk of transmission. An attack rate of 50% was seen in contacts that had a percutaneous or equivalent exposure (category A) but 0% for category B and C type of contact.⁸ Mardani and others⁹ reported that seropositivity was more frequent among those healthcare workers whose intact skin had come into contact with non-sanguineous body fluids (9.52%) and those who had percutaneous contacts (7.14%). In another report from Iran, there was a tertiary case whose 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 considered a low-risk procedure for transmission of CCHF. Sexual contact was also likely in that patient because she had married a secondary case 1 month earlier¹⁰; we have previously reported a nosocomial outbreak of CCHF in Mashhad. One of the secondary cases in that report recalled a probable skin contact with the patient's blood while wearing a pair of perforated gloves.¹¹ Harxhi and others,¹² in an outbreak in Albania, concluded that the CCHF agent can be transmitted through apparently intact skin exposed to infected blood but, in the absence of skin defects or percutaneous injury with a contaminated device, exposure of mucous membranes through droplets or contaminated hands could have played a more important role.

Finally, none of the index case's first-degree relatives showed symptoms of illness, although they had significant exposure to his blood, but three healthcare workers manifested severe illness with only minimal exposures. In the study of Izadi and others,¹³ which assessed the risk of transmission of CCHF virus from human cases to first-degree relatives, nine levels of contacts were considered: percutaneous contact with the patient's blood, cutaneous contact with the patient's blood, cutaneous contact with non-sanguineous body fluids, cutaneous contact with the patient's skin, sexual contact, eating at the same table, being a roommate of the patient, being a housemate of the patient, and living with the patient in the same building. They concluded that the infectivity of the virus by usual routine contacts with patients appears to be low.¹³

CONCLUSION

The relatively negligible contact with infectious material resulted in illness and even mortality observed in cases A and B, emphasizes again the importance of complete adherence to

standard precautions and recommended barrier methods while visiting a patient with an unknown febrile illness of unknown origin. More interesting, the unusual and very short incubation period for case A, not reported before, casts doubt on the true nature of the disease and its characteristics.

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