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Clinico-hematological features and outcome of patients affected by Congo–Crimean hemorrhagic fever: An experience from a single center

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Abstract:

BACKGROUND: Congo–Crimean hemorrhagic fever is a tick-borne zoonotic viral disease caused by Crimean–Congo hemorrhagic fever virus (CCHFV). The outbreak in Pakistan is increased during Eid-ul-Adha. We describe a cluster of cases that presented to our hospital.

AIMS: The aim of this study was to determine the outcome of Crimean–Congo hemorrhagic fever-positive cases from January 2011 to August 2019.

MATERIALS AND METHODS: Retrospective data were retrieved using the International Classification of Diseases version 9. We received 2101 samples for testing. Polymerase chain reaction (PCR)-positive cases were included in the study. History of bleeding and animal contact was recorded. Variables analyzed were age, gender, profession, and coinfection with other viral illnesses.

RESULTS: A total of 70 PCR-positive cases were included in the study (frequency 3.3%). Sixty-one were males and nine were females. Fever was present in all cases. Epistaxis was noted in 54% of patients. Thrombocytopenia was present in all patients. Eighteen patients were butchers, six were shopkeepers, nine students, and few laborers. All females were housewives. Twenty-two patients had a history of contact with animals. Seven patients were coinfected with viral hepatitis. There were 23 (33%) deaths.

CONCLUSION: Overall mortality was 33%. Twenty-two patients had a history of contact with animals. There is a strong need for public education, especially during the month of Eid-ul-Adha.

Keywords:

Congo–Crimean fever, Eid-ul-Adha, outcome, Pakistan

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Introduction

Congo–Crimean hemorrhagic fever is a zoonotic disease transmitted infection by tick-borne virus (Nairovirus) of the Bunyaviridae family.[1] It was initially described in Soviet soldiers when they were posted in Crimea in 1944. It was first isolated in a child in 1956.[2] Approximately 1000 people die each year mainly from Asia and Europe due to this infection.[3] In Pakistan, Crimean–Congo hemorrhagic fever (CCHF) has two peaks: between March–May and August–October.[4]

In humans, tick bites are the primary mean of transmission of the virus. In one large series of 1800 patients, 69% had a history of tick bite.[5] Vertical transmission has been described with poor fetal outcomes.[6] The incubation period of CCHF ranges from 1 to 13 days.[7] In another case series of 1600 patients, fever (89%), headache (68%), and fatigue (92%) were the predominant

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symptoms. Similarly, vomiting (43%), diarrhea (25%), and hemorrhage (23%) were also noted.[5] The other findings of this viral infection include hepatomegaly, lymphadenopathy, and confusion. In severe cases, hemorrhagic manifestations are observed. After prehemorrhagic phase of the disease which lasts for one week, patients develop hemorrhagic phase in which marked coagulopathy and thrombocytopenia are noted.[8] Reported mortality ranges from 2% to 80%.[9] CCHF is an endemic disease in Pakistan with high burden in Balochistan and Sindh. In this article, we describe the hematological features and outcomes of patients who were admitted for the management of CCHF.

Materials and Methods

Study area and subjects

This was a cross-sectional retrospective analysis performed at Aga Khan University Karachi, Pakistan, in the Department of Pathology and Laboratory Medicine, Section of Haematology. Using nonprobability consecutive sampling technique, all adult patients diagnosed with CCHF who were ≥15 years of age from January 2011 to August 2019 were included in the study. Medical record data of patients were retrieved using the International Classification of Diseases version 9. The total number of samples received for testing during the study period was 2101 and of these polymerase chain reaction (PCR)-positive cases were included for analysis. The study was approved by review ethical committee of Aga Khan University Karachi. Being retrospective nature of study design, no consent form needed from the patients.

Laboratory diagnostic criteria

The diagnosis of CCHF was confirmed using a real-time qualitative PCR assay. CCHF Virus RNA was extracted from serum samples and copied into complementary DNA by the enzyme reverse transcriptase, followed by PCR amplification of target, i.e., S segment sequence of CCHF genome by real-time PCR utilizing TaqMan probe chemistry.[10] This test was performed using CFX Bio-Rad real-time PCR instrument. Serological testing for hepatitis B and C was performed using the fourth-generation chemiluminescence immunoassay, whereas nucleic acid testing for the same was performed on Cobas 6800. Tests for dengue fever (immunoglobulin M antibody done by ELISA, manual methodology) and malarial parasite species (performed on SD BIOLINE Malaria Ag P. f/Pan test) were also carried out to rule out coinfection.

Data analysis

Variables analyzed included age, gender, profession, and animal contact. The frequency of associated symptoms, e.g., nausea, vomiting, and bleeding was recorded. The outcome was assessed as mortality. Results were expressed as frequencies and percentages.

Categorical variables were compared by the use of the Chi-square test or Fisher's exact test. A P-value < 0.05 was considered statistically significant.

Results

Out of the 2101 samples received for testing, a total of 70 PCR-positive cases were included in the study (frequency 3.3%). Sixty-one were males and nine were females. The male-to-female ratio was 6.7:1 with age range between 15 and 67 years. Fever was present in all cases. Bleeding symptoms of epistaxis (38/70, 54%), gum bleeding (19/70, 27%), gastrointestinal bleeding (14/70, 20%, and hematuria (3/70, 4%) were noted. Other symptoms are given in Table 1.

Hemostatic workup revealed thrombocytopenia in all of the patients. Prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) was observed in 44% and 73%, respectively. Deranged PT and APTT were observed in all 23 patients who died of the disease [other laboratory parameters are given in Tables 2 and 3]. Regarding profession in males, 18 patients were butchers, six were shopkeepers, and nine were students. Moreover, three patients were teachers and four patients were businessmen. There were two transporters and one was from medical profession (doctor). The remaining males were laborers. All females were housewives.

Twenty-two patients had a history of contact with animals. Seven patients had a history of animal transportation. Five patients had pets. Contact with raw meat while cooking was noted in four females.

Seven patients were coinfected with viral hepatitis (four with hepatitis B and three with hepatitis C). All patients received antiviral therapy. Sixty-nine of them received ribavirin and one patient received acyclovir. Mortality was present in 23 (33%) patients. Of these, 19 were due to multi-organ failure, one patient developed intracranial

Table 1: Presenting symptoms in patients with Crimean-Congo hemorrhagic fever

Clinical symptoms	Frequency, *n* (%)
Total patients	70
Fever	68 (97)
Fatigue	39 (56)
Epistaxis	37 (53)
Gum bleeding	19 (27)
Petechial bleeding	16 (23)
Headache	15 (21)
Somnolence	9 (13)

Table 2: Laboratory parameters in patients with Crimean-Congo hemorrhagic fever

Investigations	Median (range*)
HB (g/dL)	14 (12-16)
WBC (10×10^9/L)	6.4 (3.4-8.2)
Platelet (10×10^9/L)	21 (14-43)
PT (s)	11 (10-15)
INR	1.1 (1-1.5)
aPTT (s)	47.8 (34-70)
SGPT (IU/L)	400 (190-1266)
SGOT (IU/L)	1040 (357-3864)
Creatinine (mg/dL)	1.15 (0.82.1.8)
Total bilirubin (mg/dL)	1.6 (0.8-3.2)
D-dimer (mg/L FEU)	5.85 (3.8-24)

*Lowest to highest value recorded. HB=Hemoglobin, WBC=White blood cell, PT=Prothrombin time, INR=International normalized ratio, aPTT=Activated partial thromboplastin time, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase

Table 3: Laboratory parameters predicting mortality in Crimean-Congo hemorrhagic fever

Laboratory investigation	Outcome, *n* (range)		*P*
	Alive	Expired	
HB (g/dL)	14 (12-16)	13 (12-15)	0.321
WBC (10×10^9/L)	6 (3.4-7.9)	6.5 (3.5-9.7)	0.736
Platelet (10×10^9/L)	26 (16-43)	17 (13-36)	0.292
PT (s)	10 (10-12)	15.5 (13-20.5)	<0.001
INR	1 (1-1.1)	1.6 (1.3-1.9)	<0.001
aPTT (s)	36 (31-57)	65 (57-93)	<0.001
SGPT (IU/L)	254 (103-552)	1266 (523-2282)	<0.001
SGOT (IU/L)	663 (223-1303)	4092 (1541-9185)	<0.001
Creatinine (mg/dL)	0.9 (0.7-1.3)	1.8 (1.2-3.1)	<0.001
Total bilirubin (mg/dL)	1 (0.65-2.15)	3.8 (2-4.8-2)	<0.001
D-dimer (mg/L FEU)	5.2 (2.55-5.95)	11.6 (4.8-35.8)	0.019

HB=Hemoglobin, WBC=White blood cell, PT=Prothrombin time, INR=International normalized ratio, aPTT=Activated partial thromboplastin time, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase

bleed, two patients had a myocardial infarction, and one die due to pulmonary hemorrhage.

Discussion

According to the National Institute of Health Pakistan, CCHF is prevalent in our country. Till 2008, the high burden areas included Balochistan and Khyber Pakhtunkhwa province.[11] However, in 2016, the statistics changed as most reported cases were from Punjab and Sindh provinces with higher mortality reported in the latter province.[12] Presentation of patients with symptoms of fever and bleeding diathesis encompasses a handful of differential diagnosis. In Pakistan, infection with dengue fever[13] and malarial parasite[14] is rampant in the monsoon season which coincides with Eid-ul-Adha according to the Islamic calendar. Therefore, as a differential diagnosis/coinfection, we investigated these conditions in all patients who presented with CCHF. None of the patients tested positive for dengue or malarial parasite; however, viral hepatitis was present in 10% of patients.

As reported by a study done by Mourya *et al*. in 2019,[15] males were predominantly affected by CCHFV in our study as well. The circulation of CCHFV is an enzootic-tick-vertebrae-tick cycle as a variety of domestic and wild animals serve as asymptomatic hosts.[16,17] This was also seen in our study as 31% reported a positive history of animal contact.

The most common symptom of this infection is fever and bleeding diathesis. In severe cases, neurological symptoms (e.g., agitation) may also be present.[18,19] All of our patients presented with fever along with the majority of them having hemorrhagic symptoms from one or two sites. Fifteen patients presented with headache as an associated symptom suggesting that neurological symptoms are common in these patients.

In a series of South African CCHF patients, various clinical pathologic values during the first week of illness were found to be 90% predictive of mortality. These included, leukocyte counts <10 × 10^9/L, platelet counts <20 × 10^9/L, aspartate aminotransferase (AST) of >200 U/L, alanine transaminase (ALT) >150 U/L, prolonged APTT, and hypofibrinogenemia.[20] Other studies have reported similar predictors as well.[21] Our study showed a similar trend with thrombocytopenia, deranged coagulation and liver profile which were strong predictors of a fatal outcome. A study done by Duh *et al*.[22] stipulated that CCHFV RNA level >10^7 copies/mL is also an important sign of mortality; however, the facility is not available in our center, and therefore, we performed qualitative PCR testing.

Various mortality rates, based on different geographical areas, have been reported in the literature[23] and in areas where this disease is prevalent, a rate of 80% has also been reported.[24] The mortality rate ranges from 2% to 80% in different areas; however; where the disease is prevalent, it has a mortality rate of approximately 20%. The overall mortality in our study was 33% mainly due to multisystem dysfunction secondary to cytokine release syndrome and bleeding diathesis. In comparison to other countries in the region, for example, Iran and Turkey,[21,24,25] our mortality was significantly high. We can attribute this to delayed presentation due to compromised diagnostic facilities in rural areas with a lack of trained staff and support services. Pakistan is largely an agriculture-based country, which provides an excellent habitat for the virus. It has a large border with Iran and Afghanistan and a substantial number of people have nomadic lifestyle who depend on livestock for their livelihood. There is a lack of awareness among animal breeders and butchers about this deadly and

infectious disease. Prevention is the main objective and it includes avoiding tick exposure. A study done by Saghafipour *et al*. in 2019 on domestic animals (sheep, goats, and cows) and ticks collected from these animals consolidated the fact they were infected with CCHF with an overall infection rate of 8.1% in studied ticks.[26] There is also a trend of this infectious disease to occur during the time of Eid-ul-Adha, which was also documented in a study done by Hatami *et al*., which documented that most of the recorded cases occurred during this period.[27] Travelers and residents require mass awareness and education with respect to protection against tick bites, which includes light-colored clothing and socks while working in the fields. Local application of repellants, for example, diethyl-m-toluamide and permethrin also provide protection to prevent tick bites. For country like Pakistan, the recommendations also include the establishment of dedicated slaughterhouses with slaughter animals remaining in quarantine for 14 days. All butchers should be provided with protective gloves and clothing before butchering and handling animals. In our country, there is a strong need for educating the general public about the disease through print and electronic media, especially during the month of Eid-ul-Adha when the exposure to sacrificial animals is maximum.

Conclusion

A total of 70 cases were seen in the study period with an overall mortality of 33%. There was a strong history of contact with sacrificial animals. Tick bites are important in the transmission of disease and therefore the history of tick bites should be mandatory in the evaluation of such patients. Thrombocytopenia and deranged coagulation and liver profile were strong predictors of mortality. There is a dire need for educating the public about the disease, especially during the month of Eid-ul-Adha when CCHF most commonly occurs.

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Conflicts of interest
There are no conflicts of interest.

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