INTRODUCTION

Crimean Congo Hemorrhagic Fever (CCHF) is a tick-borne disease caused by Nairovirus of the family Bunyaviridae. The major reservoirs of this infection are both wild and domestic animals. The virus is transmitted to humans through either tick bite or body fluids of the infected animals. Human-to-human transmission has also been reported amongst those in close contact with body fluids of infected persons.\(^1\)

CCHF typically courses through four phases: incubation, pre-hemorrhagic, hemorrhagic and convalescence periods.\(^2\) The incubation period usually depends on the mode of transmission of the virus and viral dose. Pre-hemorrhagic phase presents with a fever and other flu-like symptoms.\(^2\) Additional symptoms of non-bloody diarrhea, abdominal pain, vomiting, depression and lassitude may be present.\(^2,3\) Signs such as conjunctivitis, pharyngitis, cutaneous flushing, hypotension, bradycardia, tachypnea and hepatomegaly may also be noted.\(^2,3\) The hemorrhagic period is generally short, lasting 2 - 3 days, and begins 3 - 7 days after disease.\(^1,2\) Progressive hemorrhagic diathesis rapidly develops in the form of petechial bleeding, mucosal bleeding, hematuria, hematemesis or melena.\(^1,2\) This may be followed by Disseminated Intravascular Coagulation (DIC) and circulatory shock in severe cases. Death usually occurs in this phase. If the patient survives, he begins convalescing 10-20 days after disease onset.\(^1\)

Here, we describe a case of CCHF that presented with prolonged hemorrhage.

CASE REPORT

A 62-year male patient without any comorbid conditions was admitted to JPMC, Karachi in December 2014 with a history of fever, chills, cough and flu-like symptoms since 6 days and bleeding gums since 3 days. He was referred to JPMC from a private hospital in the city, where he had been managed supportively for 2 days and a complete blood count (CBC), coagulation profile and liver function tests were ordered. He belonged to an urban neighbourhood but had the history of exposure to a small flock of lambs that he reared at home. However, he could not recall a tick bite. He reported no previous history of bleeding diathesis.

Upon admission, his blood picture revealed a dropping hemoglobin (Hb) from 12 mg/dl to 9.7 mg/dl while platelet count rose from 10 x 10^9 to 30 x 10^9 since initial presentation at the private hospital.  His Total Leukocyte Count (TLC) was also noted to be significantly decreased at 1.86 x10^9 (neutrophils 46%, lymphocytes 44%). Other work up revealed activated partial thromboplastin time=59 seconds, international normalized ratio=1.01, alanine transaminase=107 U/I, creatinine=1.0 mg/dl, and urea=32 mg/dl. Dengue serology for acute infection and blood smear for malarial parasite were negative. Two units of packed red cells and 4 units of Fresh Frozen Plasma (FFP) were arranged and transfused the same day. His Total Leukocyte Count (TLC) was also noted to be significantly decreased at 1.86 x10^9 (neutrophils 46%, lymphocytes 44%). Other work up revealed activated partial thromboplastin time=59 seconds, international normalized ratio=1.01, alanine transaminase=107 U/l, creatinine=1.0 mg/dl, and urea=32 mg/dl. Dengue serology for acute infection and blood smear for malarial parasite were negative. Two units of packed red cells and 4 units of Fresh Frozen Plasma (FFP) were arranged and transfused the same day. A clinical picture typical of hemorrhagic fever, a positive history of contact with domestic animals, and awareness of an ongoing CCHF epidemic prompted suspicion for CCHF. His blood sample was sent on the admission day, for a Polymerase Chain Reaction (PCR) test for CCHF virus RNA, to a laboratory in Karachi. Based on high suspicion, a loading dose of 2 gm of oral ribavirin was initiated before CCHF virus RNA was detected.

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Following the confirmation of CCHF the next day, ribavirin was continued at 4 gm/day in four divided doses for the next 6 days and subsequently at 2 gm/day in 4 divided doses for another 6 days. The patient was kept isolated with barrier nursing. Antibiotic treatment with Amoxicillin-clavulanate 625 mg/125 mg orally BD, was initiated for prophylaxis of chest infections. Over the course of four days following admission and ribavirin therapy, the patient had two prominent fever spikes (102°F) and continued to bleed through gums with large volumes of blood collecting repeatedly in the oral cavity. Oral hygiene was noted to be poor and regular antisepctic mouthwash use was begun. Prolonged bleeding was also witnessed through puncture sites, but no hematuria, hematemesis or melena was reported. His blood counts monitored through daily CBC worsened progressively. Hb/Hct decreased to 7.2 mg/dl/21.4% and platelets declined to a minimum 11 x 10⁹ on the fourth day while TLC rose to 9.1 mg/dl with neutrophilia (75%). This was managed aggressively with replacement of two units of packed cells and a single mega unit of platelets, following which platelet count and Hb improved transiently to 83 x 10⁹ and 8.2 g/ dl, respectively. Another marked drop in Hb (7.1g/dl) was witnessed on CBC performed on the 9th day post-admission whilst more small oral bleeds continued. Thereon no further bleeds occurred, and platelets gradually rose to 179 x 10⁹ on 12th day post-admission at JPMC. Dosing of ribavirin was stopped on 12th day, coinciding with a stable platelet count.

Throughout admission, the patient was kept in an isolation unit and strict barrier nursing protocols were followed, involving use of gloves, gowns and N-95 respirators at each patient encounter. The patient was discharged on the 12th day of admission.

**DISCUSSION**

Pakistan, along with neighbouring Iran and Afghanistan, is endemic to CCHF with the first confirmed case occurring in the country in 1976.¹⁻² Seasonal variations in incidence have been witnessed in the region. Traditionally, more cases are seen in rural areas and in a biannual pattern between March and May and again between August and October.²⁻⁶ Recently, however, cases have been reported throughout the year.⁴ The index case was one of 7 CCHF cases that presented at JPMC, Karachi between November 2014 - January 2015 and belonged to an urban neighbourhood. This supports the slowly changing geographical and epidemiological patterns with some cases being reported from urban areas and throughout the year.

CCHF is a severe hemorrhagic disease with frequent extensive bleeding, DIC and multiorgan failure. A wide range of case fatality rate ranging from 10 - 40% has been reported.³ CCHF has been shown to be susceptible to ribavirin in vitro but controlled trials have failed to establish any benefit. A number of uncontrolled studies have reported good response to oral or parenteral ribavirin in CCHF patients.⁷⁻⁸ Patients usually present in the pre-hemorrhagic phase with flu-like symptoms, or just after the first bleeding episode. This case presented relatively later; once gingival bleeding had begun while diagnosis and antiviral treatment were further delayed by 2 days as the patient underwent transfer of care. While this patient survived, the most unusual aspect of this case was the duration of bleeding. While it is rare for bleeding to last more than 3 - 4 days with platelet counts rising over 150 x 10⁹ by the 7th day, this patient took twice that time to reach those platelet counts and stop bleeding.²⁻⁸ This was despite the ribavirin dosage as recommended in the updated WHO/NIH guidelines.⁹ The total hospital stay for this patient was 14 days compared to the mean length of stay of 8 days for all CCHF patients who presented during the same period and survived. In a study conducted by Tasdelen et al., earlier administration of ribavirin to CCHF patients (< 4 days since onset of symptoms) resulted in significantly higher mean platelet counts at days 5 - 10 of disease onset when compared to later administration (> 4 days since onset).¹⁰ While the authors are uncertain about what caused the slower improvement of platelet counts and prolonged bleeding, it is possible this could have been prevented by earlier initiation of ribavirin.

In a background of changing geographical and epidemiological patterns as well as year-round occurrence, it is imperative that a high index of suspicion of CCHF is maintained when managing viral fevers. Attempts for earlier diagnosis and initiation of ribavirin therapy should be made to improve mortality from hemorrhagic episodes in CCHF.

**REFERENCES**


