Crimean–Congo haemorrhagic fever presenting as thrombotic microangiopathy and acute renal failure

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Introduction

Crimean–Congo haemorrhagic fever (CCHF), also known as Asian Ebola, is a fatal viral disease that is rapidly increasing worldwide [1,2]. CCHF is a tick-borne viral infection characterized by liver dysfunction, ecchymosis, extensive bleeding with shock and disseminated intravascular coagulation [3–5]. The causative agent of CCHF is the virus of genus Nairovirus and family Bunyaviridae [3–6]. The virus is transmitted to humans primarily by the bite of an infected tick of the genus Hyalomma or by direct contact with blood or secretions of an infected animal or person [3–5]. The virus is currently widely disseminated in the Russian Federation, the Balkans, the Middle East, Central Asia and Africa [3,6,7]. Small animals and birds can spread infected ticks around the world [5]. It is said that ~5 billion birds (potential tick-harbourers) fly annually from Europe to Africa, and only approximately one-half return [8]. This demonstrates how infected ticks could be transported from the East to the West. The mortality rate after infection ranges from 10 to 80% in humans [3,6]. It has been postulated that renal failure, disseminated intravascular coagulation and persistent fever are associated with higher mortality rates [7]. We report a case of CCHF that presented with symptoms suggestive for thrombotic microangiopathy and acute renal failure, and rapidly succumbed to death following extensive haemorrhages.

Case report

On 14 June 2005, a previously healthy 21-year-old female from a rural area (Chrook village, near Mianeh, East Azerbaijan, Iran) was admitted to our University Central Hospital for acute renal failure. She had noted the rapid onset of a short-lived fever, headache, nausea, severe abdominal pain, diarrhoea and decreased urination 3 days before admission (day 0). On admission [day 3 post-onset of symptoms (POS)], the physical examination revealed a girl that was slightly confused and disoriented with regard to time. Her temperature was 37.3°C and blood pressure was 105/80 mmHg. Her pulse and respiratory rates were 117 and 36/min, respectively. There were bilateral conjunctival haemorrhages. Discrete maculopapular erythematous lesions were found over the anterior thorax and axillae. The cardiac examination was normal. No signs of meningeal irritation were elicited.

On admission (day 3 POS), a complete blood count revealed a white blood cell count of 2.2 × 109/l (neutrophils 25% and lymphocytes 72%), haemoglobin of 11.6 g/dl, and a platelet count of 28 × 109/l.

Case report

Blood urea nitrogen was 142 mg/dl and serum creatinine was 4.6 mg/dl. Other findings were a blood glucose of 75 mg/dl, sodium of 136 mEq/l, potassium of 4.6 mEq/l, aspartate aminotransferase of 350 U/l, alanine aminotransferase of 250 U/l and lactate dehydrogenase of 2518 U/l (normal 225–500). Serum creatine kinase was found mildly elevated at 526 U/l (normal 24–400). The patient’s prothrombin time was 16s (normal 11–15) and partial thromboplastin time was 42s (normal 30–45). Total and direct bilirubin were 3.1 and 1.1 mg/dl, respectively. A peripheral blood smear obtained on day 3 POS revealed fragmented red blood cells (5–7% schistocytes and helmet cells per high-power field). Proteinuria (peak of which was 350 mg/day on day 5 POS) and microscopic haematuria were detected in the urinalysis throughout the patient’s hospital stay.

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Renal ultrasonography was normal. Bone marrow aspiration was performed on day 6, and it was normal appearing and showed no significant erythroid or megakaryocytic hyperplasia.

A blood culture was taken, and with the suspicion of thrombotic thrombocytopenic purpura, plasmapheresis was started on day 5 POS via centrifugation technique. This was continued up to day 7 POS, and a total of 11 of blood was withdrawn during a single 2-h session each day. A jugular vein catheter was also inserted and haemodialysis was begun. Despite these measures, the patient’s clinical status worsened rapidly on day 7 POS. Nasal, lower gastrointestinal, and vaginal bleeding as well as extensive ecchymosis and petechia were observed. The patient’s platelet count, white blood cell count, and haemoglobin further dropped to $0.5 \times 10^9$/l, $0.8 \times 10^9$/l and 6 g/dl, respectively. At this time, the prothrombin time was >30 s and partial thromboplastin time was >100 s. Blood samples were drawn on day 8 POS, and with the presumptive diagnosis of haemorrhagic fever with renal syndrome (HFRS), the patient was placed on a high dose of ribavirin (1200 mg/day, orally) and a blood transfusion was begun. Although leucopenia is not characteristic of hantavirus infection, the initial diad of acute renal failure and bleedings forwarded the diagnosis of HFRS. Despite supportive measures, the patient died due to extensive haemorrhage on day 8 POS. Necropsy of the kidneys and liver was done 24 h postmortem. Light microscopy of the renal specimens revealed rather normal-appearing glomeruli with only minimal mesangial expansion (Figure 1A). Mild tubular slugging was detected that was attributable to the delay of necropsy and postmortem autolysis (Figure 1B). The renal vasculature was normal (Figure 1C). Examination of the liver was unremarkable (Figure 1D).

The stored blood samples of the patient taken on days 3 and 8 POS were sent to the National Laboratory of Research and Diagnosis of Arboviruses and Viral Hemorrhagic Fevers Tehran. Serologic testings of both the samples were performed with enzyme linked immunosorbert assay method using mouse polyclonal IgG against recombinant nucleoprotein of the CCHF virus African strain IbAr10200 (as described previously [9]) and strain IPH 90–13 of Puumala (refer to [10] for more information on the applied serology) that were negative for anti-CCHF or anti-hantavirus (Puumala) IgM and IgG antibodies. The samples were subsequently analysed by reverse transcription polymerase chain reaction (RT-PCR) (Qiagen Kit) amplifying a 536 bp fragment of the CCHF genomic S-segment that were positive for the viral genome fragments in the patient’s sera (from both days 3 and 8 POS). For a more targeted study, a nested-PCR was performed that was also positive for CCHF virus genome in the patient’s sera. Despite the high risk of CCHF nosocomial transmission, no healthcare workers became infected.

Discussion

CCHF is becoming a global problem, because endemic areas have substantially increased in recent years, as well as the concern of its potential application in boterrorism [2,3]. The first human cases of infectious haemorrhagic fever in Iran were identified in east Azerbaijan in 1973 [9]. During the last few years, an increasing number of human CCHF virus infections have been reported from many parts of Iran [6]. The reason for this increase is still unclear. About 67% of cases have been reported from Sistan-Baluchistan, a southeastern province of Iran [6]. Between 1999 and 2004, the southeast of Iran experienced its largest number (255 cases) of recorded CCHF patients [11].

Fever, malaise, nausea and vomiting, abdominal pain, myalgia, petechia and ecchymosis are the most common manifestations of CCHF [3–5]. Diarrhoea, lymphadenopathy and hepatomegaly are also seen [4]. Thrombocytopenia, leucopenia, anaemia and elevated aspartate aminotransferase and lactate dehydrogenase have been reported in CCHF patients [4,11]. These latter two findings are associated with a poorer prognosis [4]. Although, elevated creatine phosphokinase has been reported in different series, no evidence of myositis or rhabdomyolysis has yet been found in CCHF patients [4]. Interestingly, acute appendicitis and compartment syndrome of the extremity have been reported as presenting signs of CCHF [12,13].

In the present case, the patient had an acute onset of renal failure. Thrombocytopenia, anaemia, indirect hyperbilirubinaemia and elevation of aspartate aminotransferase and lactate dehydrogenase were found. These as well as the presence of fragmented red blood cells on the peripheral blood smear initially led us to make the diagnosis of thrombotic microangiopathy. The patient’s serum creatine kinase was mildly elevated. We did not check the urine for myoglobinuria. With increasing prothrombin or partial thromboplastin time, the patient subsequently went to an extensive haemorrhage. Although the patient’s leucopenia was not characteristic [14], the clinical diad of haemorrhage and renal insufficiency initially favoured the diagnosis of HFRS, a known entity of hantavirus infection. The patient was then placed on ribavirin and supportive care. Despite these measures, she died of extensive haemorrhage. Molecular genetic analysis of the serum samples was positive for CCHF virus. However, serological testings was negative for anti-CCHF virus IgM and IgG antibodies.

In a study, positive anti-CCHF IgG and IgM antibodies were reported in only 40 and 72.9% of CCHF patients, respectively, on the first day of admission [9]. These figures only mildly increased on day 5 of admission [9]. The negative serology is mainly attributed to either the fulminant nature of the infection or blood testing ahead of seroconversion [9,15]. Burt et al. [15] revealed that the earliest time at which anti-CCHF IgM or IgG is detectable in the sera...
of CCHF patients (seroconversion) is day 4 of illness. Surprisingly, however, Keyaerts et al. [16] reported the first case of iatrogenically IgM-negative (but IgG- and IgA-positive) hantavirus infection that was due to the selective removal of heavy-weight molecules during plasmapheresis via the centrifugation technique. The CCHF serology (IgM and IgG) of our patient was negative both before (day 3 POS) and after plasmapheresis (day 8 POS). We believe that plasmapheresis could be a less possible explanation for the seronegativity of the present patient, as plasmapheresis by the centrifugation technique preferentially discards heavy-weight molecules such as pentamer IgM rather than lower weight IgG.

The hallmarks of HFRS are fever, thrombocytopenia, conjunctival haemorrhage and acute renal failure with proteinuria and haematuria [13,16,17]. Although, CCHF is generally similar to other haemorrhagic fevers, the extensive liver damage and elevated liver enzymes are the prominent findings, as well as generalized endothelial damages and disseminated intravascular coagulation [3–5]. Our patient presented with acute renal failure and thrombotic microangiopathy. Thrombotic microangiopathy (TMA) is a diverse clinicopathological entity in which there is vessel wall thickening (mainly arterioles and capillaries), intramural platelet thrombosis and partial or complete obstruction of the vessel lumen [18]. Thrombocytopenia and mechanically destroyed red blood cells featured by circulating schistocytes, and helmet cells are invariably present in patients with TMA [18]. It is said that the presence of schistocytes more than 3 per 5000 red blood cells on the peripheral blood smear (PBS) is abnormal [19]. Although we did not find any evidence of microvascular lesions or intraluminal thrombosis in the examination of the renal necropsy specimens, the initial observation of more than 5% schistocytes on PBS was highly characteristic of a diffuse endothelial injury and microangiopathic haemolysis in the present case. Intrarenal haemodynamic dysregulation due to cytokine release and extensive endothelial dysfunction are possible explanations for the acute renal failure in this case. This diffuse endothelial injury might be
due to either direct viral invasion or cytokine-mediated mechanisms.

Several features of the present case suggest a cytokine-mediated mechanism for the pathogenesis of CCHF infection: (i) as extensive liver injury is the hallmark of CCHF infection, the finding of normal liver necropsy specimen was really unexpected, and therefore the mechanism of cytokine-mediated coagulopathy similar to that of sepsis syndrome is likely here; (ii) the presence of an acute renal failure in the face of normal kidney necropsy findings highlights intrarenal haemodynamic dysregulation that is also most likely a cytokine-mediated phenomenon.

One of the major public health hazards of the haemorrhagic fevers including CCHF is person-to-person transmission [1]. Several nosocomial and community outbreaks of CCHF have been reported. As contact with infected blood is particularly associated with CCHF transmission, healthcare workers are in a high risk group for these outbreaks [1]. In June 1999, a serum sample of a medical student (in Shahrekurd, Iran) who died of extensive gastrointestinal bleeding and disseminated intravascular coagulation tested positive for the CCHF IgG antibody [9,20]. Nabeth et al. [5] reported a CCHF patient who infected 15 hospitalized individuals and four family members. One physician, one nurse, a nursing student, and two healthcare workers were infected during this outbreak [5]. It has been postulated that the ignorance of necessary precautions and an insufficient number of isolation rooms may contribute to nosocomial outbreaks of CCHF in developing countries [1]. Although the initial diagnosis of TMA and acute renal failure was by far an unexpected presentation of CCHF and misled us, fortunately, no medical personnel or other person was infected by this case.

In conclusion, clinicians should consider CCHF in the differential diagnosis of thrombotic microangiopathy and acute renal failure, particularly in areas where this infection is endemic. Early diagnosis and treatment of CCHF are potentially associated with a lower mortality and decreased chance of secondary spread of the infection.

Conflict of interest statement. None declared.

References


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