Rare disease

Severe Crimean–Congo haemorrhagic fever presented with massive retroperitoneal haemorrhage that recovered without antiviral treatment

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Summary

Crimean-Congo haemorrhagic fever (CCHF) is a tickborne viral zoonosis with up to 50% mortality in humans caused by CCHF virus belonging to the genus *Nairovirus*, family *Bunyaviridae*. The geographical distribution of CCHF cases corresponds closely with the distribution of principle tick vectors that is species of *Hyalomma*. The disease presents with non-specific febrile symptoms, but progress to a serious haemorrhagic syndrome that, soon after, a full blown multi organ failure may develop with prominent features of liver damage and bleeding diathesis. The authors present a case of a 39-year-old man with severe CCHF with retroperitoneal haemorrhage that recovered without ribavirin administration. The case was confirmed for CCHF by serological and molecular tests.

BACKGROUND

Crimean-Congo haemorrhagic fever (CCHF) is a zoonotic and viral haemorrhagic fever disease with a mortality in humans ranging 3% to 50%. The agent virus called CCHF virus belongs to the genus *Nairovirus* and family *Bunyaviridae*. The virus is transmitted to humans through the bite of *Ixodid* ticks or by contact with blood or tissues from infected livestock,^{1 2} the latter being the most significant transmission route to humans in Iran.³ In addition to this zoonotic transmission, CCHF virus (CCHFV) can also be spread from person to person through close contact with patients and or nosocomial transmission.^{4–8} The main course of CCHF includes four distinct phases including incubation, prehaemorrhagic, haemorrhagic and convalescence. After a brief incubation period, the patient has sudden onset of fever, myalgia, nausea and severe headache. Within 3–6 days of the onset of illness, development of a petechial rash and haemorrhagic symptoms such as epistaxis, haematemesis and melena may be apparent. The most extremely ill patients enter multiorgan failure characterised by shock, haemorrhage and coma.^{9–11} In this way, the role of detailed patient's history taking and timely use of virus detection assays could not be overemphasised.¹² There are controversies regarding the prescription of a specific antiviral drug, the route of administration and the best time interval. Once there was a strong belief that early administration of ribavirin may save the patients.^{4 13–15} Here, we report a case of severe CCHF that presented with fever, severe thrombocytopenia and massive retroperitoneal haemorrhage who fully recovered without specific antiviral therapy.

Serological assay; serum samples were analysed by specific ELISA for IgM and IgG detection. For IgM ELISA, the ELISA plates are coated with the goat IgG fraction to human

IgM (anti μ chain). The patient serum and recombinant or native antigen and immunoascite were respectively added. Then peroxidase-labeled antimouse immunoglobulin is added. Finally, hydrogen peroxide and TMB (3, 3', 5, 5' tetra methyl benzedrine) were added, the enzymatic reaction was stopped by the addition of 4N sulfuric acid. Then, the plates were read by an ELISA reader at 450 nm. For IgG ELISA, the wells were coated with the mouse immunoascite. While adding the native or the recombinant antigen, the patient serum was added. Peroxidase-labeled antihuman immunoglobulin was added. After 10 min of incubation with the TMB substrate (KPL, Gaithersburg, Maryland, USA), the optical density was read at 450 and 620 nm.^{5 16–18}

Molecular Assay; viral RNA is extracted from phenol-extracted tick suspensions using QIAamp RNA mini kit according to the instructions of the manufacturer (QIAGEN GmbH, Hilden, Germany). The extracted viral RNA is analysed subsequently by gel-based and real-time (RT-PCR) with one-step RT-PCR kit (QIAGEN GmbH, Hilden, Germany) and using specific primers F2 5' TGGACACCTTCACAACTC 3' and R3 5' GACAATTCCTACACC 3' which amplify a 536 bp fragment of the S-segment of the CCHFV genome.^{3 17 19 20}

CASE PRESENTATION

He was a 39-year-Iranian man, working in a slaughterhouse in Tehran. He separated the fat strands from the cattle carcass with a sharp card. Five days prior to his admission, he felt a severe headache, sense of imbalance and presyncope. Soon he developed fever, prominent conjunctive suffering and generalised body pain, especially over his flank on left side. The severity of pain over this area was to such an extent that it interfered with walking and getting up of

Figure 1 (a,b) Sections of enhanced CT scan of abdomen showing $\sim 9 \times 12$ cm retroperitoneal haemorrhage involving psoas sheath on left side.

bed. He was too ill to manage himself without aid. There was no significant response to narcotic drugs.

INVESTIGATIONS

On admission, he was febrile, pale, edematous and agitated. He had severe thrombocytopenia (platelet count: $6000/\mu\text{l}$). Serum levels of creatine phosphokinase and lactate dehydrogenase level (LDH) were significantly elevated (>7000 IU/l, >3000 IU/l respectively). Increase in the level of liver

enzymes was consistent with the existence of an acute hepatocellular injury (aspartate aminotransferase: 4160 IU/l, alanine aminotransferase: 3500 IU/l). Immunologic assays revealed no evidence of viral hepatitis. Prothrombin time, partial thromboplastin time and fibrinogen values were all normal. On serial examination of blood smear, there was no diagnostic clue in favour of malaria, spirochete and bacterial infection. In spite of decrease in platelet count and increase in LDH level, there were very few

numbers of fragmented red blood cells (RBCs). No circulating blast was seen. He had also borderline hypotension and tachycardia. He had continuous intractable pain over his flank that surprisingly was diagnosed to be derived from a massive retroperitoneal haemorrhage involving the psoas sheath on left side (figure 1a,b).

The discrepancy between the extent of anaemia and thrombocytopenia in addition to paucity of fragmented RBCs in blood smear led us not to consider thrombotic thrombocytopenic purpura as the underlying disease, therefore appropriate amount of platelet and packed RBC was transfused to halt bleeding. Regarding the increased level of muscle injury biomarkers, he was at risk of developing acute renal failure due to myoglobinuria. Crystalloid infusion and urine alkalinisation were soon started. The results of arboviral and spirochete infection were pending. CT guided aspiration of retroperitoneal fluid collection was performed to rule out any superimposed bacterial infection. Antibiotics, anti pyretic and narcotic drugs were administered on manner of needed base. Examination of bone marrow aspiration samples revealed no abnormality except increased numbers of megakaryocytes. It seemed that destruction of platelets occurred outside of the bone marrow. The result of serological (IgM and IgG specific ELISA) and RT-PCR (gel-based and real-time RT-PCR) assays confirmed Crimean-Congo haemorrhagic fever disease definitely. Once, the results of microbiology testing of retroperitoneal aspiration revealed no bacterial growth, the administered antibiotics were discontinued. Leukocytosis replaced initial leucopenia.

DIFFERENTIAL DIAGNOSIS

Thrombotic thrombocytopenic purpura, Leptospirosis, Ehrlichiosis, leukaemia, viral hepatitis

TREATMENT

Soon he recovered from the disease crisis and the amount of required platelet and RBCs decreased. He no longer had headache, dizziness and especially flanks pain, so we did not administer any specific antiviral therapy.

OUTCOME AND FOLLOW-UP

In a few days, he was discharged from the hospital and supposed to be followed on an outpatient base. Two weeks later he regained his weight loss to some extent and was able to resume his daily activities. The retroperitoneal haemorrhage was also decreased in size.

DISCUSSION

Crimean-Congo haemorrhagic fever is a highly contagious zoonosis caused by a viral agent from *Bunyaviridae* family. The ticks from *Hyalomma* genus play the central role in disease transmission. The infected animals as the reservoir are usually asymptomatic. Yet, the disease may also be acquired through contact with tissue and blood of infected livestock. The disease is characterised by a constellation of symptoms such as fever, headache and bleeding diathesis-related complaints. Elevated biomarkers of liver damage and muscle injury are not uncommon in the course of the disease. Laboratory values show disseminated intravascular coagulation along with thrombocytopenia; the latter is

a common finding in the course of the disease. In addition, early onset thrombocytopenia and its severity are in direct relation to the disease death. The average death rate is often 30–50%,^{21 22} but mortality from 10% to 80% have been reported in various outbreaks, for example 72.7% and 80% from the United Arab Emirates and China, respectively.^{23 24} Mortality of nosocomial infections are often much higher than those acquired naturally through tick bite, and may be related to the level of viremia.⁹ From 2000 to 2009, evidence showed that the CCHF disease has been during all years with different mortality, ranging from 20% in 2000 to significant decrease in the recent years. However, this declining trend may be due to presence of a precise and rapid laboratory detection system and national surveillance and control program founded in 1999 as National Expert Committee on Viral Haemorrhagic Fevers.^{3 17}

As there is no specific prognosis finding, considering the patients' demographic features and possible exposures might be helpful in early disease recognition. Then, specific diagnosis should be performed with specific detection of anti-CCHFV antibodies through sandwich ELISA and also of the virus genome in the patient's serum through specific primers and RT-PCR techniques.^{17 25}

It seems that there is wide variety in clinical severity and outcome among the patients with CCHF over the world that may be in part due to considerable variation among strains of a given infecting serotype. The role of host immune system cannot be overemphasised in pathogenesis. It seems that defects in interferon γ receptor may be responsible for overwhelming infection in interferon deficient animal models.^{26 27} Patients who have dysregulated immune response and increased levels of tumour necrosis α , interleukin-10 (IL-10) and γ interferon have been reported to have higher levels of viral loads and poorer outcomes.^{28 29}

There is no widely practiced severity prediction score; the extent of thrombocytopenia, anaemia and liver damage is mostly used to predict the outcome.³⁰ In this way, it is not yet clear which patients benefit more from specific antiviral therapy. Once there was such a belief that early administration of specific antiviral therapy was critical in saving patients from fatal outcome. However, reports of patients who recovered from the disease uneventfully without antiviral agents underscored the primary notion.³¹ The results of a recent meta analysis and systematic reviews have not brought a clear message indicative of absolute efficacy of ribavirin in these patients.³² Our patient is a typical example of severe Crimean-Congo haemorrhagic fever that defeated his grave disease without the aid of antiviral agents.

Learning points

- ▶ To consider the demographic features of the patient in preparing a list of differential diagnosis.
- ▶ To emphasise that we are doctors and not computers; so try to enhance our skills of communication, history taking, physical examination and clinical reasoning.
- ▶ Crimean-Congo haemorrhagic fever may be treated without administration of specific antiviral therapy.

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Competing interests None.

Patient consent Obtained.

REFERENCES

1. Camicas JL, Cornet JP, Gonzalez JP, *et al.* [Crimean-Congo hemorrhagic fever in Senegal. Latest data on the ecology of the CCHF virus]. *Bull Soc Pathol Exot* 1994;**87**:11–6.
2. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. *J Med Entomol* 1979;**15**:307–417.
3. Chinikar S, Goya MM, Shirzadi MR, *et al.* Surveillance and laboratory detection system of Crimean-Congo haemorrhagic fever in Iran. *Transbound Emerg Dis* 2008;**55**:200–4.
4. Fisher-Hoch SP, Khan JA, Rehman S, *et al.* Crimean Congo-haemorrhagic fever treated with oral ribavirin. *Lancet* 1995;**346**:472–5.
5. Garcia S, Chinikar S, Coudrier D, *et al.* Evaluation of a Crimean-Congo hemorrhagic fever virus recombinant antigen expressed by Semliki Forest suicide virus for IgM and IgG antibody detection in human and animal sera collected in Iran. *J Clin Virol* 2006;**35**:154–9.
6. van Eeden PJ, Joubert JR, van de Wal BW, *et al.* A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital. Part I. Clinical features. *S Afr Med J* 1985;**68**:711–7.
7. Vorou R, Pierrotsakos IN, Maltezos HC. Crimean-Congo hemorrhagic fever. *Curr Opin Infect Dis* 2007;**20**:495–500.
8. Joubert JR, King JB, Rossouw DJ, *et al.* A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital. Part III. Clinical pathology and pathogenesis. *S Afr Med J* 1985;**68**:722–8.
9. Whitehouse CA. Crimean-Congo hemorrhagic fever. *Antiviral Res* 2004;**64**:145–60.
10. Ergonul O. Crimean-Congo haemorrhagic fever. *Lancet Infect Dis* 2006;**6**:203–14.
11. Swanepoel R, Gill DE, Shepherd AJ, *et al.* The clinical pathology of Crimean-Congo hemorrhagic fever. *Rev Infect Dis* 1989;**11** Suppl 4:S794–800.
12. Fisgin TN, Doganci L, Tanyel E, *et al.* Initial high rate of misdiagnosis in Crimean Congo haemorrhagic fever patients in an endemic region of Turkey. *Epidemiol Infect* 2010;**138**:139–44.
13. Izadi S, Salehi M. Evaluation of the efficacy of ribavirin therapy on survival of Crimean-Congo hemorrhagic fever patients: a case-control study. *Jpn J Infect Dis* 2009;**62**:11–5.
14. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2008;**78**:125–31.
15. Elaldi N, Bodur H, Ascioglu S, *et al.* Efficacy of oral ribavirin treatment in Crimean-Congo haemorrhagic fever: a quasi-experimental study from Turkey. *J Infect* 2009;**58**:238–44.
16. Chinikar S, Mirahmadi R, Mazaheri V, *et al.* A serological survey in suspected human patients of Crimean-Congo hemorrhagic fever in Iran by determination of IgM specific ELISA method during 2000–2004. *Arch Ir Med* 2005;**8**:52–5.
17. Chinikar S, Ghiasi SM, Hewson R, *et al.* Crimean-Congo hemorrhagic fever in Iran and neighboring countries. *J Clin Virol* 2010;**47**:110–4.
18. Marriott AC, Polyzoni T, Antoniadis A, *et al.* Detection of human antibodies to Crimean-Congo haemorrhagic fever virus using expressed viral nucleocapsid protein. *J Gen Virol* 1994;**75** (Pt 9):2157–61.
19. Papa A, Bozovi B, Pavlidou V, *et al.* Genetic detection and isolation of Crimean-Congo hemorrhagic fever virus, Kosovo, Yugoslavia. *Emerging Infect Dis* 2002;**8**:852–4.
20. Chinikar S, Persson SM, Johansson M, *et al.* Genetic analysis of Crimean-Congo hemorrhagic fever virus in Iran. *J Med Virol* 2004;**73**:404–11.
21. Ergonul O, Whitehouse C.A. *Crimean-Congo Hemorrhagic Fever. A Global Perspective*. Netherlands: Springer 2004.
22. Nichol ST. Bunyaviruses. In: Knipe DM, Howley PM, editors. *Fields Virology*. Philadelphia, PA: Lippincott Williams and Wilkins 2001:1603–33.
23. Yu-Chen Y, Ling-Xiong K, Ling L, *et al.* Characteristics of Crimean-Congo hemorrhagic fever virus (Xinjiang strain) in China. *Am. J. Trop. Med. Hyg* 1985;**34**:1179–82.
24. Schwarz TF, Nsanze H, Ameen AM. Clinical features of Crimean-Congo hemorrhagic fever in the United Arab Emirates. *Infection* 1997;**25**:364–7.
25. Hewson R, Chamberlain J, Mioulet V, *et al.* Crimean-Congo haemorrhagic fever virus: sequence analysis of the small RNA segments from a collection of viruses world wide. *Virus Res* 2004;**102**:185–9.
26. Bereczky S, Lindegren G, Karlberg H, *et al.* Crimean-Congo hemorrhagic fever virus infection is lethal for adult type I interferon receptor-knockout mice. *J Gen Virol* 2010;**91**(Pt 6):1473–7.
27. Papa A, Bino S, Velo E, *et al.* Cytokine levels in Crimean-Congo hemorrhagic fever. *J Clin Virol* 2006;**36**:272–6.
28. Saksida A, Duh D, Wraber B, *et al.* Interacting roles of immune mechanisms and viral load in the pathogenesis of Crimean-Congo hemorrhagic fever. *Clin Vaccine Immunol* 2010;**17**:1086–93.
29. Drosten C, Kümmerer BM, Schmitz H, *et al.* Molecular diagnostics of viral hemorrhagic fevers. *Antiviral Res* 2003;**57**:61–87.
30. Yilmaz G, Koksali I, Topbas M, *et al.* The effectiveness of routine laboratory findings in determining disease severity in patients with Crimean-Congo hemorrhagic fever: severity prediction criteria. *J Clin Virol* 2010;**47**:361–5.
31. Yilmaz R, Kundak AA, Ozer S, *et al.* Successful treatment of severe Crimean-Congo hemorrhagic fever with supportive measures without ribavirin and hypothermia. *J Clin Virol* 2009;**44**:181–2.
32. Soares-Weiser K, Thomas S, Thomson G, *et al.* Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. *BMC Infect Dis* 2010;**10**:207.

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