Case Report Haemophagocytosis in a patient with Crimean–Congo haemorrhagic fever

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Crimean–Congo haemorrhagic fever (CCHF) is a severe disease with a case fatality of 2.8 to 80%. A patient dwelling in an endemic region for CCHF was admitted with fever preceding bleeding diathesis and pancytopenia. Despite no history of tick exposure, CCHF was highly suspected. With an oral ribavirin therapy, clinical and laboratory improvements were obtained. The diagnosis was confirmed by detection of IgM antibody to CCHF virus and positive RT-PCR. Although the main pathogenesis of CCHF infection is not elucidated yet, haemophagocytosis, a symptom rarely reported in viral haemorrhagic fevers, was observed in this case. Haemophagocytosis is suggested to have a role in the development of pancytopenia in CCHF, the mechanism of which still needs to be investigated, probably with cytokine studies. Together with clinical symptoms and patient history, haemophagocytosis may be an indicator for CCHF.

Introduction
Crimean–Congo haemorrhagic fever (CCHF) is an acute illness affecting multiple organ systems and characterized by extensive ecchymosis, visceral bleeding and hepatic dysfunction; and it has a case-fatality of 2.8 to 80% (Ergonul et al., 2004; Williams et al., 2000). CCHF was first clinically described in 1944 in Crimea of the former Soviet Union during a large outbreak of over 200 cases. CCHF virus, belonging to the genus Nairovirus (family Bunyaviridae), was identified in 1967 from a patient in Uzbekistan, and was found to be similar to a virus isolated in 1956 in the Congo, hence the name Crimean–Congo (Hoostraal, 1979; Centers for Disease Control, 1983). CCHF is a potentially fatal fever that has been described in parts of Africa, Asia, eastern Europe and the Middle East (Hoostraal, 1979). It may be transmitted by the bite of infected ticks, contact with infected animals, or person-to-person transmission by exposure to blood or other infected body fluids (Nabeth et al., 2004).

In Turkey, CCHF cases were first published in 2004 (Ergonul et al., 2004; Karti et al., 2004). Clinical cases, however, go back to 2001 (Bakir et al., 2005). Here we report a severe case of CCHF with haemophagocytosis in bone marrow aspiration, in a patient living in an endemic region but without any history of tick exposure.

Case report
A 26-year-old woman living in a city in north-eastern Anatolia was admitted to a local healthcare setting with fever, frontal headache, malaise, arthralgia and myalgia. Initially she was given symptomatic therapy and sent home. On the seventh day after the first symptoms, she developed nasal and vaginal bleeding (at an expected time for menstruation but much higher amounts than usual). Because thrombocytopenia was noticed, she was referred to our hospital with a differential diagnosis of haematological malignancy. On admission, a single ecchymose at the site of venopuncture, haemorrhagic crusts on her nostril without any active bleeding and a normal body temperature (no fever after the fourth day following initial symptoms) were detected. Laboratory results were found as follows: 3300 white blood cells mm–2, 12.7 g haemoglobin dl–1, 7000 platelets mm–3, 581 IU alanine aminotransferase l–1, 319 IU aspartate aminotransferase l–1, 1657 IU lactate dehydrogenase l–1, 583 IU creatinine kinase l–1, 245 mg fibrinogen dl–1, and 1405 ng ferritin ml–1. A peripheral blood smear revealed reactive lymphocytes, and platelets in decreased number. Bone marrow aspiration to
exclude haematological malignancy revealed haemophagocytosis of neutrophils, erythrocytes and thrombocytes by histiocytes (Fig. 1). No blastic infiltration was noticed. Coagulation test results were in the normal range. Considering both the geographical location the patient came from and the high fever preceding bleeding diathesis, CCHF was highly suspected. Despite no history or physical sign of tick exposure, oral ribavirin (an initial loading dose of 2 g followed by 0.8 g four times a day for 4 days, and 0.4 g four times a day for the last 6 days) was given from the eighth day following initial symptoms. Later a formal diagnosis of CCHF was obtained with a positive test for anti-CCHF IgM antibody by ELISA and the isolation of the CCHF genome by RT-PCR. Vaginal bleeding decreased, and platelet count increased gradually. A slow but gradual decrease was noticed in haemoglobin values, with a level of 8.4 mg dl\(^{-1}\) on the day of discharge. After a 10 day oral ribavirin therapy, the laboratory results were as follows: 5400 white blood cells mm\(^{-3}\), 353 000 platelets mm\(^{-3}\), with a normal biochemical panel. Following discharge, the anaemia recovered, as monitored during outpatient visits.

Discussion

CCHF has been described in parts of Africa, Asia, eastern Europe and the Middle East (Hoogstraal, 1979). Although serological evidence indicated the existence of CCHF virus in Turkey several decades ago (Serter, 1980), a number of patients with CCHF was first reported during 2004 (Ergonul et al., 2004; Karti et al., 2004).

CCHF is a haemorrhagic syndrome presenting with fever, nausea, vomiting, myalgia and bleeding from various sites. Leucopenia, thrombocytopenia, high levels of alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase are commonly detected (Swanepoel et al., 1989). It is defined as a tick-borne disease (Hoogstraal, 1979). In many studies, however, CCHF cases with a positive serology but without any history of tick exposure are reported (Ergonul et al., 2004). Though clinical symptoms and patient history, especially travel to endemic areas or exposure to tick bites are the first indicators of CCHF, the definitive diagnosis is by virus isolation, immunological assay (e.g. ELISA) and/or molecular diagnostic assays, such as RT-PCR (Whitehouse, 2004). A positive IgM antibody result and detection of CCHF genome by RT-PCR were obtained in the case presented here.

The patient characteristics were assessed according to the 90 % fatality outcome criteria described by Swanepoel et al. (1989), by which this case was defined as ‘severe’. Ribavirin therapy was given as soon as the diagnosis of CCHF was previewed. Although there are studies (Fisher-Hoch et al., 1995) reporting the success of ribavirin therapy in CCHF, there is still lack of a rational approach to CCHF infection.

The main pathogenesis of CCHF infection has not been elucidated. However, haemophagocytosis, in bone marrow aspiration, was observed in our case (Fig. 1). This condition describes the pathological finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets and their precursor cells. Histopathologically, it may be observed in bone marrow, spleen, and lymph nodes (Favara, 1992), and may be seen secondary to viral, bacterial, fungal, parasitic and collagen vascular diseases (Fisman, 2000). However, it is rarely reported in viral haemorrhagic fevers. Karti et al. (2004) firstly reported haemophagocytosis in seven patients with CCHF. Additionally, only three case reports demonstrated haemophagocytosis with hantaan and puumala viruses, and dengue virus among all the haemorrhagic fever viruses (Lee et al., 2002; Baty et al., 1998; Lu et al., 2005). Excessive activation of monocytes attributable to stimulation by high levels of Th1 cytokines, such as gamma interferon, tumour necrosis factor alpha, interleukin (IL)-1 or IL-6, were reported to be a possible immunopathological mechanism of haemophagocytic lymphohistiocytosis (Favara, 1992). Haemophagocytosis is suggested to play a role in the pathogenesis of pancytopenia observed in CCHF (Karti et al., 2004), the mechanism of which still needs to be investigated, probably with cytokine studies.

CCHF should be considered in evaluation of patients admitting with high fever preceding bleeding diathesis, and with a history of living or travelling in endemic regions, especially in spring and summer. Regarding the case’s referral with a prediagnosis of only haematological malignancy, physicians working in risky areas should be alert about this kind of infection. Together with clinical symptoms and patient history, haemophagocytosis may be an indicator for CCHF.

References


