

Hematological aspects of Crimean-Congo hemorrhagic fever

Kırım-Kongo kanamalı ateşinin hematolojik yönleri

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral disease transmitted to humans by Hyalomma ticks or by direct contact with the blood of infected humans or domestic animals. In certain areas of the world, including Africa, Asia, South East Europe and Middle East, sporadic cases or outbreaks of CCHF have been reported. During the last six-year period from 2003 to 2009, CCHF has also occurred endemically in Turkey, particularly during spring and summer, with a case-fatality rate of approximately 5%. The disease is characterized by acute fever, nausea, vomiting, headache, myalgia, elevated liver enzymes and hemorrhagic manifestations ranging from mucocutaneous bleeding to life-threatening massive hemorrhage with disseminated intravascular coagulation (DIC) and hemophagocytosis. As with other viral hemorrhagic diseases, activation of lymphocytes, monocytes, macrophages and oversecretion of cytokines play a pivotal role in the pathogenesis and prognosis of CCHF. Recently an increasing number of publications on CCHF have been emerging in the literature, majority of which have been written by infection specialists. In this article, recent literature on CCHF has been reviewed, with particular emphasis on hematological manifestations, pathogenesis and therapeutic approaches in CCHF from the hematologist's point of view. (*Turk J Hematol 2009; 26: 161-6*)

Key words: Crimean-Congo hemorrhagic fever, hematological manifestation, hemophagocytosis

Received: May 11, 2009

Accepted: August 4, 2009

Özet

Kırım-Kongo kanamalı ateşi (KKKA) insanlara Hiyalom keneleri aracılığıyla ya da enfekte veya evcil hayvanların kanlarına doğrudan temas aracılığıyla insanlara geçen akut bir kene yoluyla bulaşan viral hastalıktır. Afrika, Asya, Güney Doğu Avrupa ve Orta Doğu da dahil dünyanın belirli bölgelerinde KKKA'ya ait sporadik vakalar yada salgınlar rapor edilmiştir. 2003'ten 2009 yılına kadar geçen altı yıllık süre boyunca özellikle bahar ve yaz aylarında yaklaşık %5'lik bir vaka-ölüm oranıyla endemik olarak Türkiye'de de görülmüştür. Hastalık akut ateş, bulantı, kusma, baş ağrısı, miyalji, karaciğer enzimlerinin yükselmesi ve mukokütanöz kanamadan yaşamı tehdit eden yaygın damar içi intravasküler koagülasyon (DIC) ve hemofagositozla birlikte masif kanamalara kadar bir yelpazede hemorajik manifestasyonlar ile karakterizedir. Diğer viral hemorajik hastalıklarda olduğu gibi, lenfositlerin, monositlerin, makrofajların aktivasyonu ve sitokinlerin aşırı sekresyonu KKKA'nın patojenez ve prognozunda kilit bir rol oynar. Son zamanlarda literatürde KKKA ile ilgili olarak daha çok enfeksiyon uzmanları

tarafından yazılan yayınlarda artma olduğu görülmektedir. Bu makalede hematologun bakış açısıyla özellikle KKKA'daki hematolojik belirtiler, patojenez ve tedavi yaklaşımları üzerine vurgu yapılarak KKKA hakkında yayınlara gözden geçirilmiştir. (Turk J Hematol 2009; 26: 161-6)

Anahtar kelimeler: Kırım-Kongo hemarajik ateşi, hematolojik belirtiler, hemafagositoz

Geliş tarihi: 11 Mayıs 2009 Kabul tarihi: 4 Ağustos 2009

Epidemiology

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral disease that is transmitted to humans by Hyalomma ticks or by direct contact with the blood of infected humans or domestic animals. Nosocomial spread of infection mostly among healthcare personnel has also been reported. The causative virus is a member of the Nairovirus genus of the family Bunyaviridae and has a viral envelope [1-3]. Sporadic or endemic occurrence of the disease has been reported in some regions of Africa, Asia, southeastern Europe, and the Middle East. The estimated fatality rate is between 5% and 50%, reaching up to 72.2% in an outbreak in the United Arab Emirates [4-7]. Turkey is one of the countries where CCHF has occurred endemically in the spring and summer seasons of the past six years. The majority of cases were from the central northern and eastern regions of Turkey [8-15]. Between 2002 and 2007, 1820 cases with a confirmed diagnosis by enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) were identified, and 92 of these died of the disease [8]. According to the most recent data published by the Turkish Ministry of Health for the period between 2002 and 2008, a total of 3135 cases were diagnosed with CCHF, and 155 (5%) of these died [9,10].

As its name implies, CCHF virus often results in severe hemorrhagic disease in humans, although not all patients develop the classic form of hemorrhagic disease. Viral load, acquisition route, and nature of host defense may play a major role in disease presentation. Nosocomial spread of infection carries higher risk than exposure through tick bite [5,6,16,17].

Clinical and Laboratory Findings

Clinically, CCHF consists of four phases, i.e. incubation, prehemorrhagic, hemorrhagic, and convalescence phases (Figure 1). The duration of the incubation period usually depends on the route of acquisition and extent of virus contamination. Following an incubation period of 3-7 days, the prehemorrhagic phase starts with acute-onset fever and nonspecific symptoms such as headache, photophobia, back and abdominal pain, myalgia, arthralgia, nausea, vomiting, and diarrhea. Fever generally subsides within 4-5 days but may persist up to 12 days. The hemorrhagic phase usually begins on the 4th-6th days of the disease, and during this phase, patients show signs of hemorrhagic diathesis ranging from mucocutaneous bleeding to fatal massive hemorrhage and disseminated intravascular coagulation (DIC). Bleeding symptoms may occur in 34 to 90% of the patients with CCHF. In addition to massive hemorrhage and hepatorenal failure, myocardial infarction, cardiorespiratory arrest and central nervous system dysfunction may develop with a fatal outcome. Laboratory findings of the disease include cytopenias (anemia

and/or leukopenia and/or thrombocytopenia); elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), ferritin, bilirubin and fibrin degradation products; prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT); and decreased fibrinogen. It is noteworthy to mention that fibrinogen levels do not decrease in all cases since it is an acute phase reactant. For surviving patients, the convalescence period begins 15-20 days after the onset of disease. Weakness, weak pulse, sweating, dizziness and poor appetite have been reported in this period [2,5,6,12-18]. Hair, hearing or memory loss has also been reported in some patients [2,5,6]. Clinical and laboratory findings of CCHF are shown in Table 1.

Hematological Manifestations of CCHF Virus Infection

Epistaxis, gingival bleeding, petechiae, large ecchymoses, hematemesis, melena, hemoptysis with alveolar hemorrhage, hematuria, vaginal bleeding, and bleeding from venipuncture sites may occur due to thrombocytopenia and prolonged PT and aPTT in the hemorrhagic phase of CCHF [2,5,6,18-20]. Ocular findings with subconjunctival and retinal hemorrhage and without visual symptoms have also been reported in 73.7% of 19 patients [21]. Remarkably, a single patient was operated on the suspicion of acute appendicitis, but during the operation, hemorrhages in the oblique muscles and cecum were identified without any evidence of appendiceal pathology [22]. In severe cases with massive hemorrhage, DIC, intracranial bleeding, massive liver necrosis, and irreversible shock may develop, ultimately leading to death. The reported frequencies of hemorrhagic symptoms in fatal cases were 85% and 81.8% in the studies by Mardani et al. and Cevik et al., respectively [18,23]. Particularly, bleeding in the gastrointestinal and central

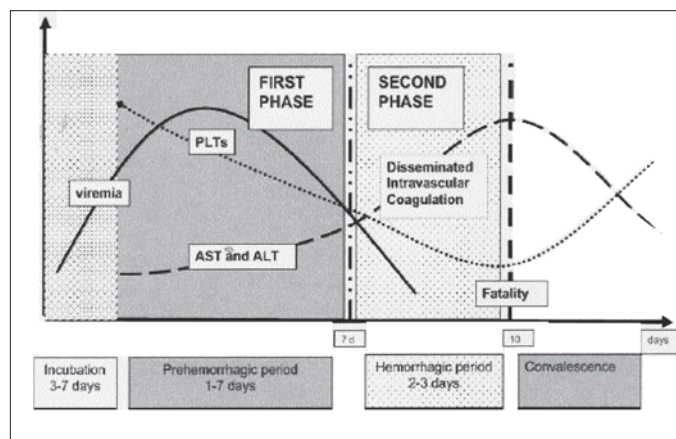


Figure 1. Clinical Stages of CCHF (Ergönül et al.)

Table 1. Clinical and laboratory findings of CCHF (1,5,6,12,14,18-25,28-30,37)

Clinical Findings	Laboratory Findings
Cardiovascular System	Biochemical
Bradycardia	Elevated AST, ALT
Low blood pressure	Elevated lactate dehydrogenase
Heart murmur	Elevated creatine kinase
Myocardial infarction	Hyperferritinemia
Cardiorespiratory arrest	Hypertriglyceridemia
Respiratory System	Hematological
Cough, rales, tachypnea	Anemia
Pleural effusion	Leukopenia, leukocytosis
Acute respiratory distress syndrome	Thrombocytopenia
Diffuse alveolar hemorrhage	Prolonged PT, aPTT
	Decreased fibrinogen
	Elevated D-dimer
Skin	Immunological
Jaundice, hair loss	Increased levels of cytokines (TNF α , IL-1, IL-6, IL-10)
	Increased serum neopterin
	Increased absolute number of peripheral blood natural killer cells
Gastrointestinal System	
Hepatomegaly, splenomegaly	
Abdominal tenderness	
Central Nervous System	
Polyneuritis, headache	
Somnolence, lethargy	
Loss of hearing, poor vision	
Loss of memory	
Hematological Findings and Bleeding Symptoms:	
Petechia, ecchymoses	
Hematemesis, melena	
Gingival bleeding, epistaxis	
Bloody otorrhea	
Subconjunctival and/or retinal hemorrhage	
Hematuria	
Vaginal bleeding	
Hemoptysis	
Diffuse alveolar hemorrhage	
Intracerebral hemorrhage	
Hemophagocytosis	

nervous system is associated with a poor prognosis [23,24]. Hepatosplenomegaly was detected in approximately one-third of the patients with CCHF [2,3,5]. Hemophagocytosis was first reported in the study by Karti et al. [12] from Turkey, where half of the patients had this condition. Subsequently, other investigators also reported this important finding in CCHF [25,26], which is now considered to be associated with the development of cytopenia and poor prognosis [12,25]. In our view, routine use of bone marrow aspiration might yield a higher frequency of hemophagocytosis than the one reported in patients with CCHF. Cevik et al. [23] reported melena and hematemesis as the most common bleeding symptoms among fatal cases, with a particular emphasis on prolonged PTT (>60 sec) and low platelet count (<20000/mm³) as the most important risk factors for mortality. In addition, profound thrombocytopenia has been recognized as a poor prognostic sign by other investigators [2,5,23,24,27,28], and Tasdelen Fisgin et al. [27] found that 42% of patients with CCHF required transfusion of platelet suspensions. In a recent study by Ergonul et al. [24], hematemesis, melena, somnolence, low platelet count, prolonged PT and aPTT, and higher AST, ALT and fibrinogen levels were significantly more common among fatal cases compared to survivors. Similarly, Joubert et al. [16] found higher DIC scores in fatal cases. Decreased activity of thrombin-activatable fibrinolysis inhibitor (TAFI) was present in patients with CCHF and was attributed to the imbalance in fibrinolysis and DIC [29]. In another study from Turkey, increased natural killer (NK) cell counts were observed in CCHF patients, and this finding was correlated with abnormalities in AST/ALT and aPTT [30]. In another study, cytotoxic T lymphocyte (CD8) counts were increased [31].

Pathogenesis

The basic pathogenesis of CCHF at the molecular level is complex and not well defined. Endothelial cells, immune response, viral load, and coagulation cascade play important roles in the disease pathogenesis. Blood and endothelium appear to be the target tissues of the disease. Marked viral replication results in severe viremia during the first two phases of the disease. On the other hand, inappropriately activated T helper 1 (CD4 Th1) lymphocytes produce tumor necrosis factor- α (TNF- α) and interferon gamma (IFN γ), which promote macrophage co-activation and oversecretion of interleukin-1 (IL-1) and IL-6. The endothelium is directly infected by the virus and/or damaged by secreted cytokines that stimulate the production of some vasodilator substances, platelet aggregation, and activation of coagulant proteins. Activation of coagulation may contribute to the development of DIC and multiorgan failure [1,5,6,12,15,18,23,24,28]. Following macrophage activation and profound cytokine secretion, hemophagocytosis may occur in various infectious diseases including CCHF. Hemophagocytosis is an important clinical entity, which is presumed to be associated with cytopenia and increased risk of mortality [12,25,27,28,32-34]. Papa et al. [35] and Ergonul et al. [36] reported increased levels of TNF- α , IL-1, and IL-6 in patients with CCHF. They also found significantly higher TNF- α and IL-6 levels in fatal cases as compared to mild cases, emphasizing the pivotal role of the cytokine storm in the pathogenesis of CCHF

[35-38]. Ongoru et al. [39] showed high serum neopterin levels in CCHF and its increment correlated with mortality from the disease. Since neopterin is produced by activated macrophages upon secretion of IFN γ , their findings may be considered as a further piece of evidence supporting the important role of cytokine secretion and macrophage activation in the pathogenesis of CCHF. Oversecretion of IL-18-induced Fas ligand expression on lymphocytes may contribute to the cytotoxicity of Fas-expressing hepatocytes, which might be responsible for hepatic failure and bleeding in secondary hemophagocytosis [40,41]. A similar mechanism might also be relevant in patients with CCHF. Extremely increased ferritin levels were reported in patients with CCHF virus infection [27,28], and this has been accepted among the diagnostic criteria for primary hemophagocytic lymphohistiocytosis (HLH) [42].

Our Experience

The facilities of our university are located in the Black Sea region of Turkey, which is close to the area endemic for CCHF. To date, 164 cases, most of whom were adults, have been diagnosed and followed in our hospital [14,25,27,47]. Between 2004 and 2006, we diagnosed and followed nine children with CCHF. The age range was between 2 and 16 years, and their initial clinical and laboratory findings were as follows: fever and fatigue were present in all nine patients; nausea, vomiting, and petechial rash were present in eight, hematemesis and melena in five, and epistaxis in two. One patient presented with hemoptysis, somnolence and convulsions. Two patients had hepatomegaly and one had splenomegaly. Laboratory findings included anemia (Hb: 4.5-10 g/dl) and leukopenia (WBC counts: 1400-3900/mm³) in five and thrombocytopenia (platelet count: 5000-36000/mm³) in seven children. Elevated levels of AST (105-2852 U/L), ALT (372-3100 U/L), LDH (912-5100 U/L) and CPK (297-2900 U/L) were present in eight, seven, eight, and six patients, respectively. Prolonged PT (16-32 sec) and aPTT (54-140 sec) were detected in four and seven cases, respectively. Increased D-dimer (609-1430 U/L) was found in seven children. Bone marrow aspiration was performed in three children and significant hemophagocytosis was determined in all of these cases. With a presumptive diagnosis of CCHF, ribavirin therapy and supportive measures including the administration of fresh frozen plasma (FFP) and/or packed red cells and/or platelet suspensions were initiated until the diagnosis was confirmed with ELISA or PCR. Full recovery was obtained in all children without any complication [25,43].

Diagnosis and Treatment

Early diagnosis is very important with regard to the outcome in CCHF. Patients with clinical and laboratory findings of CCHF and history of tick bite or exposure to infection should be tested for CCHF. Laboratory methods include virus isolation and serologic and molecular assays with reverse transcription PCR or real time PCR. Antibodies are detectable in the serum by ELISA or immunofluorescence assay (IFA) about seven days after the onset of disease. Antibodies are not detectable in fatal cases who die within the first days of illness. Molecular studies are necessary for confirmation of the disease in such cases [1,2,5,44,45].

There are three principal and equally important objectives in the treatment of CCHF: close monitoring of all coagulation parameters, supportive treatment with FFP, erythrocyte and platelet suspension, and early antiviral treatment [1,5,6,46].

Continuous evaluation of clinical status, including vital organ functions and observation of bleeding, are mandatory for patients with CCHF. Supportive treatment should be provided with FFP and erythrocyte and platelet suspensions. Close monitoring of platelet count, fibrinogen and D-dimer levels is important for early detection of DIC, which also allows early correction of coagulation parameters. Ergonul et al. [1] reported a higher requirement for platelet suspensions in cases with a fatal outcome. If available, apheresis of platelet suspensions that provide a large amount of platelet content (3×10^{11} /per apheresis platelet suspension) should be preferred. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit blood clotting and cause an increased risk of bleeding; therefore, they should not be used in CCHF. FFP transfusion is indicated for the correction of coagulopathy in bleeding or for the prevention of bleeding in CCHF. When PT and aPTT are at least 1.5 times greater than the upper limit of the normal range or international normalized ratio (INR) is >1.6 , FFP (15-20 ml/kg) should be given, and this treatment should be repeated every 8-12 hours, if necessary. In addition to these supportive measures, unfractionated or low molecular weight heparin, recombinant human activated protein C, recombinant activated factor VII, and antifibrinolytic agents should also be considered in CCHF patients with uncontrolled bleeding and DIC [1,5,6,12,14,18,46].

Although the effect of ribavirin treatment in CCHF virus infection has not been proven in randomized prospective clinical trials, and there are some conflicting results in the clinical reports, however majority of them indicate its beneficial effects [11,15,46-49]. Based on these reports, ribavirin seems to be widely accepted in the treatment of CCHF and its use is recommended especially in the early phase of the disease [11,15,46-48].

Secondary hemophagocytosis may resolve upon the treatment of underlying disease, although it may be as fatal as primary HLH [32,33]. A genetic mutation is responsible for the impaired antiviral defense, dysregulated immune response and insufficient lymphocytic apoptosis in primary HLH [32,33,42,50]. A protocol consisting of dexamethasone, cyclosporine A and etoposide has been widely accepted in the treatment of patients with primary HLH [42]. This was also shown to be beneficial in the treatment of Epstein-Barr virus-associated HLH [51,52]. Although a genetically transmitted dysregulated immune response occurs in the above-mentioned HLHs, which are completely distinct from secondary hemophagocytoses including CCHF, these entities share some common clinical and laboratory features, most of which are mediated via the same mechanisms. Uncontrolled CD4 Th1 activation and overproduction of proinflammatory cytokines with macrophage coactivation-induced hemophagocytosis are well established in all types of HLH [32,33,42,50-52]. Pathogen-directed therapy might not always be sufficient to control cytokine storm in secondary hemophagocytoses including the one associated with CCHF. Although immunosuppression is known to exacerbate the spread of infections, use of immunosuppressive

therapy along with ribavirin might be considered in the treatment of the patients with CCHF who have uncontrolled hemophagocytosis and severe bleeding symptoms. Jabbari et al. [53] reported a complete recovery in six patients with CCHF who received corticosteroids combined with ribavirin in the early phase of the disease. Similarly, cyclosporin and/or etoposide with or without steroids successfully controlled excessive activation of lymphocytes/monocytes and oversecretion of cytokines in various infection-associated HLHs [52-59].

New treatment strategies such as IFN or antibodies against TNF or IL-6 could prove to be valuable in CCHF [38], but the experience is limited, and further studies are warranted. Obviously, the timing of these therapeutic approaches should also carry a significant importance.

It is our hope that an effective immunization strategy with a safe vaccine and/or specific serum against CCHF virus will soon be in use in order to overcome this frequently fatal disease.

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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