

An investigation of pulmonary findings of Crimean–Congo haemorrhagic fever patients

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Aim: Crimean–Congo haemorrhagic fever (CCHF) generally affects many organs. In this study a retrospective evaluation of the pulmonary findings of CCHF patients was made.

Materials and methods: The records of patients were retrospectively analysed. For each patient an evaluation was made of age, sex, occupation, place of residence, contact with ticks, smoking history, and pulmonary radiological and laboratory findings. A confirmed diagnosis of CCHF was made on determination by enzyme-linked immunosorbent assay or polymerase chain reaction.

Results: Of the 128 patients, 48.4% were female. Symptoms of coughing were determined in 18% of patients, sputum in 4.7%, chest pain in 3.9%, dyspnoea in 3.1%, and haemoptysis in 0.8%. The mortality rate was 7%. In terms of sex, place of residence, contact with ticks, smoking, findings of the respiratory system, and physical examination findings, no statistically significant difference was seen between the survivor and nonsurvivor groups ($P > 0.05$). The white blood cell count values of the survivors were determined to be significantly lower compared to those of the nonsurvivors and the alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, and C-reactive protein values of the nonsurvivors were significantly higher compared to those of the survivors ($P < 0.05$).

Conclusion: CCHF can be fatal for the respiratory system. An early diagnosis of CCHF and referral to a specialised centre is therefore important.

Key words: Crimean–Congo haemorrhagic fever, lung, pulmonary radiograph

1. Introduction

Crimean–Congo haemorrhagic fever (CCHF) is a viral disease that generally shows an aggressive, acute course and affects many organs. The agent is a nairovirus, which is an RNA-type virus of the family *Bunyaviridae* (1,2). The disease is spread to people from infected tick bites or through contact with the blood or body fluids of infected people (3). CCHF is characterised by high temperature, myalgia, widespread haemorrhage, ecchymosis, and impaired liver function. Mortality rates vary between 3% and 80% depending on the virus strain and epidemiological characteristics (4,5). It initially affected more than 200 people in 1944 in Crimea and was confirmed in the Congo in 1956, and so it was named CCHF in 1969 (5). This virus has been isolated or the disease has been identified in more than 30 countries in Asia, Africa, Southeast Europe, and the Middle East (2,6).

The first case in Turkey was reported in 2002 (7–9). The cases reported in Turkey have been in central and northern areas such as Tokat, Sivas, Yozgat, Çorum, and Erzurum

(10,11). The number of cases and mortality have increased since 2002 (2002: 17/0; 2003: 133/6; 2004: 249/13; 2005: 266/13; 2006: 438/27; 2007: 713/33; 2008: 1315/63; 2009: 1300/62) (12). Knowledge of the pathogenesis of CCHF is still limited (6). Causes of death are refractory shock, severe coagulopathy, and multifocal necrosis of the liver and other organs (8,13). Public health education and prevention of the disease are also very important in addition to treatment (14). Although there are several studies on CCHF, few studies on respiratory system involvement are available. In this study, we retrospectively examined the respiratory system findings, diagnosis and treatment, clinical and laboratory results, and demographics of patients with CCHF who were monitored at the Infectious Diseases and Clinical Microbiology Clinic of our hospital.

2. Materials and methods

The records of 128 patients diagnosed with CCHF and admitted to the Infectious Diseases and Clinical Microbiology Clinic of Ankara Training and Research

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Hospital between April 2008 and September 2011 were retrospectively analysed. This study was approved by the ethics committee of our hospital. An evaluation was conducted for age, sex, occupation, place of residence, history of tick bites, smoking, pulmonary radiological results, and laboratory findings for each patient.

During the acute and convalescent period, serum was collected from the patients and sent to the Refik Saydam Hıfzısıhha Central Virology Laboratory for serological and virological testing. CCHF was confirmed by enzyme-linked immunosorbent assay (ELISA), using virus-specific immunoglobulin M (IgM) antibodies or polymerase chain reaction (PCR) with segments belonging to the virus genome when typical clinical and epidemiological findings were present.

2.1. Statistical analysis

The data were analysed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The frequencies and percentage distributions are reported. The Mann-Whitney U test was used for paired groups and independence between variables was analysed using chi-square independence analysis. $P < 0.05$ was considered significant.

3. Results

The study comprised 128 patients [62 females (48.4%) and 66 males (51.6%); mean age, 51.4 ± 17.7 years; range, 15–83 years]. Most patients (47.7%) were 55 years old or older. The patients presented between April and September and

were most frequently (47.7%) from Çorum. The most common occupation was farming [71 (55.5%)] and most patients resided in rural areas [116 (90.6%)]. There had been direct contact with ticks in 74 (57.8%) patients and the contact occurred 5–14 days previously.

The demographic characteristics of the patients are given in Table 1. Symptoms and physical examination findings of the patients are given in Table 2, while those related to the respiratory system are given in Table 3.

Eighteen (14.1%) of the patients were cigarette smokers (2 females, 16 males). Four (3.1%) patients had a history of asthma and 2 (1.6%) had a history of chronic obstructive pulmonary disease (in total 4.7%).

The pulmonary radiographs were normal in 96 (75%) patients; radiological findings in pulmonary radiographs were infiltration, hilar pathology, interstitial pathology, pleural thickening, and pleural effusion in a total of 32 patients (25%). Both lobes were affected by lesions in 9.4% of all the patients. None of the patients had acute respiratory distress syndrome (ARDS) findings. The pulmonary radiograph findings of the patients are shown in Table 4.

Anaemia was identified in 18 (14.1%) patients, thrombocytopenia in 125 (97.7%), leukopenia in 105 (82.0%), increased aspartate aminotransferase (AST) levels in 123 (96.1%), increased alanine aminotransferase (ALT) in 107 (83.6%), increased alkaline phosphatase (ALP) in 16 (12.5%), increased gamma-glutamyl transpeptidase (GGT)

Table 1. Demographic characteristics of the patients.

		Survivors (n = 119), %	Nonsurvivors (n = 9), %	Total (n = 128), %	P-value
Sex	Female	52.9	33.3	48.4	0.314
	Male	47.1	66.7	51.6	
Age	15–24	10.1	11.1	10.2	0.975
	25–34	9.2	11.1	9.4	
	35–44	10.9	11.1	10.9	
	45–54	22.7	11.1	21.9	
	55 and over	47.1	55.6	47.7	
Occupation	Farmer Livestock	56.3	44.4	55.5	0.366
	Health worker	29.4	33.3	29.7	
	Housewife Retired	0.8	0	0.8	
	Others	1.7	0	1.6	
Place of residence	Urban	0.8	0	0.8	0.319
	Rural	10.9	22.2	11.7	
Contact with ticks		10.1	0	9.4	0.166
Smoking		89.9	100	90.6	0.467
Asthma - COPD*		59.7	33.3	57.8	0.346
		13.4	22.2	14.1	
		4.2	11.1	4.7	

*: COPD: Chronic obstructive pulmonary disease.

Table 2. Symptoms and physical examination of the patients.

	Survivors (n = 119), %	Nonsurvivors (n = 9), %	Total (n = 128), %	P-value
Fever	87.4	100	88.3	0.597
Headache	53.8	77.8	55.5	0.297
Nausea	53.8	77.8	55.5	0.297
Vomiting	37.8	44.4	38.3	0.731
Fatigue	89.1	100	89.8	0.597
Myalgia	68.1	77.8	68.8	0.719
Abdominal pain	22.7	11.1	21.9	0.683
Haemorrhage	16.0	33.3	17.2	0.184
Hepatomegaly	0.8	0	0.8	1.0
Splenomegaly	0.8	0	0.8	1.0

Table 3. Symptoms and physical examination findings related to the respiratory system.

	Survivors (n = 119), %	Nonsurvivors (n = 9), %	Total (n = 128), %	P-value
Cough	17.6	22.2	18.0	0.664
Sputum	5.0	0	4.7	0.492
Dyspnea	3.4	0	3.1	0.578
Chest pain	4.2	0	3.9	0.532
Haemoptysis	0.8	0	0.8	0.783
Rales	5.9	22.2	7.0	0.122
Rhonchi	3.4	11.1	3.9	0.310

Table 4. The pulmonary radiography findings of the patients.

		Survivors (n = 119), %	Nonsurvivors (n = 9), %	Total (n = 128), %	P-value
Pulmonary radiography	Normal findings	75.6	66.7	75	0.690
	Abnormal findings*	24.4	33.3	25	
Involvement in lung	Unilateral	65.5	33.3	15.6**	0.647
	Bilateral	34.5	66.6	9.4	

*: Abnormal findings: Infiltration, hilar pathology, interstitial pathology, pleural thickening, and pleural effusion

** : Comparisons were made between patients with abnormal findings in pulmonary radiographs.

in 84 (65.6%), increased lactate dehydrogenase (LDH) in 117 (91.4%), and increased creatine phosphokinase (CPK) in 97 (75.8%). The mean values of the laboratory tests are given in Table 5.

In PCR for CCHF, 90 (70.3%) patients were positive. IgM positivity by ELISA was identified in 41 (32%) patients. Ribavirin was prescribed for the treatment of 19 (14.8%) patients.

The mortality rate was 7% (9 patients), and 93% (119 patients) survived.

When comparisons were made between the survivors and nonsurvivors in terms of sex, place of residence, contact with ticks, and smoking, no statistically significant difference was seen ($P > 0.05$) (Table 1).

No significant difference was observed for the symptoms and physical examination findings and findings

Table 5. The mean values of the laboratory tests.

	Survivors (n = 119), mean	Nonsurvivors, (n = 9), mean	Total (n = 128), mean	P-value
Hb	13.4	14.5	13.8	0.099
Plt	53,873.9	30,333.3	50,796.9	0.053
WBC	2512.1	4233.3	2563.6	0.002
AST	348.6	496.3	373.6	0.528
ALT	133.43	299.5	155.2	0.004
ALP	82.5	135.3	89.5	0.013
GGT	91.9	156.0	97.1	0.097
LDH	775.0	1567.0	801.2	0.004
CPK	620.9	928.3	642.3	0.045
ESR	15.5	13.2	15.3	0.467
CRP	1.6	5.6	2.0	0.000

Hb: haemoglobin, Plt: platelet count, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

related to the respiratory system between the survivors and nonsurvivors ($P > 0.05$) (Tables 2 and 3).

No significant difference was observed for the pulmonary radiography findings and unilateral or bilateral involvement between the survivors and nonsurvivors ($P > 0.05$).

No difference was observed between the 2 groups in terms of haemoglobin, platelet, AST, and GGT levels or erythrocyte sedimentation rate, but white blood cell (WBC) counts of the survivors were significantly lower than those of the nonsurvivors, and ALT, ALP, LDH, CPK, and C-reactive protein (CRP) levels of the nonsurvivors were significantly higher than those of the survivors ($P < 0.05$) (Table 5).

No difference was observed between the survivors and nonsurvivors in terms of ribavirin therapy ($P > 0.05$).

4. Discussion

CCHF is a viral and zoonotic disease with accompanying haemorrhagic fever and a high mortality rate. The incubation period varies from 2 to 7 days (15–17).

Patients present with complaints of fever, headache, gastrointestinal system dysfunction, muscular pain, and haemorrhage. Petechiae on the face and chest and redness of the conjunctivae are noticeable during the first few days. Epistaxis, haematemesis, melena, or haematuria are common. Sudden onset of haemorrhage with fever is seen in severe cases. The clinical course of the disease can be characterised by laboratory findings of thrombocytopenia,

leukopenia, and increased liver and muscle enzymes. Thrombocytopenia is the most typical laboratory finding in CCHF cases (8,15,18,19). In addition, impairments may be seen in prothrombin time, partial thromboplastin time, and other coagulation tests, and these impairments indicate a poor prognosis (1,3,20). The most frequently determined findings of patients in the current study were fatigue, fever, myalgia, headache, and nausea (89.8%, 88.3%, 68.8%, 55.5%, and 55.5%, respectively). Findings of haemorrhage were identified in 22 (17.2%) patients.

Tick bites are more often seen in adult males (7,10,21). In a study by Sümer et al. (7) of CCHF patients, 51.8% were males and 48.2% were females. In the present study, 51.6% of the patients were males and 48.4% were females.

Agricultural workers, those involved with animal care, veterinary surgeons, butchers, abattoir workers, healthcare workers, soldiers, and housewives have been identified as risk groups (10,22). In this study, the most affected group was farmers (55.5%).

Taşkesen et al. (20) reported that 53% of tick bites are seen in rural areas. We determined that 90.6% of our patients came from rural areas.

Transfer of the disease to humans is the result of a bite from an infected tick or contact with the blood or tissue of infected animals (6). In the current study, 57.8% of the patients had contact with ticks.

Thrombocytopenia is a sign of infection that does not change (13,18,19). In patients with leukopenia, there are increased AST, ALT, LDH, and CPK levels. All laboratory

tests for surviving patients returned to normal within 5–9 days (15). A total of 14.1% of the patients in this study developed anaemia, 97.7% thrombocytopenia, 82% leukopenia, 96.1% increased AST levels, 83.6% increased ALT levels, 12.5% increased ALP levels, 65.6% increased GGT levels, 91.4% increased LDH levels, and 75.8% increased CPK levels.

Mortality criteria were defined by Swanepoel et al. (13). According to these criteria, leukocyte count of $>10,000/\text{mm}^3$, thrombocyte count of $<20,000/\text{mm}^3$, AST levels of >200 U/L, ALT levels of >150 U/L, active partial thromboplastin time of >60 s, and fibrinogen of <110 mg/dL in the first 5 days of the disease are indicators of a severe course. AST, ALT, and LDH levels are higher in patients with a severe course (15,18). In the current study, the WBC counts of the survivors were significantly lower than those of the nonsurvivors. ALT, ALP, LDH, CPK, and CRP levels of the nonsurvivors were significantly higher than those of the survivors.

Pneumonia, haemoptysis, pleural effusion, and pulmonary haemorrhage have been reported as symptoms of other viral diseases (17,23,24). However, direct invasion of the pulmonary system by the CCHF virus has not yet been sufficiently reported (25). In the current study, 23 (18.0%) patients had a cough and 4 (3.1%) had dyspnoea. Haemoptysis was only seen in 1 (0.8%) patient. There were 6 (4.7%) patients with a history of sputum and 5 (3.9%) patients had a history of chest pain. On physical examination, rales were heard in 9 (7%) patients and 5 (3.9%) had rhonchi.

Dyspnoea, chest pain, and haemoptysis are indicative of a worse prognosis and are symptoms more often seen in those who will die from CCHF (13,17). In the current study, no difference was identified between the survivors and nonsurvivors in terms of respiratory symptoms.

Pleural effusion has been reported during the clinical course of CCHF but the reason for this effusion is unclear (26). Pleural effusion was seen in 1 patient in the present study.

Abadoğlu and Engin (27) determined the relationship between CCHF and allergic rhinitis and allergic pulmonary diseases such as asthma. In the current study, 4 (3.1%) patients had asthma.

Patients with CCHF may haemorrhage in the pulmonary parenchyma. This haemorrhaging event, along with symptoms of dyspnoea, chest pain, and haemoptysis and infiltration on pulmonary radiographs, may indicate mortality. In a study by Dilber et al. (28) of 21 patients, pulmonary haemorrhage developed in 2 and ventilator support was required. Doganci et al. (29) reported a case of bilateral alveolar haemorrhage caused by the CCHF

virus. In a study from Russia of 283 patients with CCHF, a relationship was determined between the severity of CCHF and ARDS, resulting in a high level of inflammatory cytokines. Haemoptysis was also observed in these patients (30). In the current study, haemoptysis was identified in 1 (0.8%) patient, but mortality did not occur.

Although pulmonary radiographs are insufficient for a detailed evaluation, infiltration can be observed on radiographs in conditions such as pulmonary haemorrhage. Thoracic computed tomography is useful for detecting pulmonary haemorrhage in patients (31). In the present study, the pulmonary radiographs were normal in 96 (75%) of the patients. On pulmonary radiography and thorax computed tomography of a patient with haemoptysis, unilateral infiltration was present, but no haemorrhage was detected.

Although recovery may be achieved in 9–10 days, it can sometimes take 4 weeks or longer. Mortality is mostly seen in the second week (5–14 days) at rates of 8%–80% (10). In a study by Bakir et al. (9), a CCHF mortality rate in Turkey of 30%–62% was found to be lower than that reported in the literature. Public education through written and visual media, particularly in rural areas, is important to reduce the mortality rate of CCHF (15). In the current study, the mortality rate was 7%. This low mortality rate was believed to be associated with good patient care and the ability to provide appropriate supportive treatment.

The fundamental route seems to be protection against and prevention of tick bites (2). Treatment is based on supportive therapy (replacement of blood and blood products, respiratory support, parenteral nutrition). The antiviral agent ribavirin is administered orally or parenterally as medicinal treatment (2). Although there are no randomised clinical studies showing the efficacy of ribavirin for treating CCHF, its efficacy has been demonstrated in several clinical observational studies. Using ribavirin during the early stage of the disease had a beneficial effect in several studies (1,9). In the present study, ribavirin was administered to 19 (14.8%) patients, but no difference was identified between those patients who received ribavirin and those who did not.

The incidence of deaths resulting from tick bites in recent years in Turkey has engendered greater attention to this topic and various studies have been initiated to prevent this disease (7). CCHF must be suspected when patients present from areas where CCHF is endemic, particularly in the summer months, with a high temperature, haemorrhagic findings, increased liver function test results, and thrombocytopenia and leukopenia. Further studies are required with larger numbers of patients with CCHF regarding the respiratory system and other systems.

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