

# EVALUATION OF RESPIRATORY FINDINGS IN CRIMEAN-CONGO HEMORRHAGIC FEVER

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**Abstract.** Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease with a high mortality rate causing viral hemorrhagic fever. We studied the respiratory system findings, demographics, clinical and laboratory findings of patients with CCHF admitted to our hospital. In this retrospective study we evaluated 108 patients with CCHF confirmed by laboratory findings. The charts of all hospitalized patients were reviewed, and the age, sex, occupation, city of residence, history of tick bite or of removing a tick, smoking history, chest X-ray results, outcome and clinical and laboratory findings were recorded for each patient. Sixty of the chest radiographs were read as normal, 33 were read as showing unilateral pathology and 15 showed bilateral pathology. Seven of the 108 patients died due to severe pulmonary infection and hemorrhage. The frequency of pathological chest radiographs was higher among the CCHF patients who died than among the survivors, but the difference was not significant. Pulmonary parenchyma hemorrhage can occur in CCHF patients with hemoptysis, dyspnea, chest pain and infiltration on chest radiographs and may lead to mortality.

**Keywords:** chest X-ray, Crimean-Congo hemorrhagic fever, lung

## INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease with a high mortality rate causing viral hemorrhagic fever. It is caused by the CCHF virus, genus *Nairovirus*, family Bunyaviridae. The disease results in a 30% fatality rate (Whitehouse, 2004). CCHF came to the attention of modern medical science and was first described as a clinical entity in 1944-1945. The disease is now present in

about 30 countries in Africa, Asia, and Europe. In Turkey, patients infected with CCHF virus were first encountered at Tokat, Amasya and Sivas Provinces in 2002 (Bakir *et al*, 2005). Since 2002, CCHF has been endemic in Turkey and large outbreaks have been seen in the service area of our training hospital during spring and summer seasons. Until 2009, 4,453 confirmed CCHF cases were reported in Turkey (MoH, 2008). Humans become infected through tick bites, by crushing infected ticks, through contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock.

In patients with viral hemorrhagic

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fever, refractory shock, severe coagulopathy and multifocal necrosis of the liver and other viscera are the cause of death (Bray, 2005). Despite an increasing knowledge about hemorrhagic fever viruses, there is little known about the pathogenesis of CCHF (Whitehouse, 2004).

There are some studies reporting the effects of Crimean-Congo hemorrhagic fever (CCHF) on different organs (Sannikova *et al*, 2007; Doganci *et al*, 2008; Engin *et al*, 2009). However, the number of publications reporting the effects of this disease on the respiratory system is small. In the present study, we aimed to present respiratory system findings as well as demographic, clinic and laboratory findings of patients with CCHF who have been admitted and followed in our department.

## MATERIALS AND METHODS

We carried out a retrospective study of 108 patients having CCHF confirmed by laboratory findings between July 1 and August 31, 2009 at Cumhuriyet University Hospital, Sivas, a city located in the central Anatolia, Turkey. All the patients were treated at Infectious Diseases and Clinical Microbiology Department, Cumhuriyet University Hospital. The study protocol was approved by the Human Ethics Committee of Cumhuriyet University School of Medicine.

Blood was obtained from all patients and the serum specimens were stored at -70°C until testing. Acute and convalescent phase serum samples were sent to the Virology Laboratory of Refik Saydam Hygiene Center in Ankara, Turkey for serological and virological analyses. A definitive diagnosis of CCHF infection was based on the typical clinical and epidemiological findings and detection of

CCHF virus-specific IgM by ELISA or of the genomic segments of the CCHF virus by reverse transcription-polymerase chain reaction (RT-PCR) either in the acute or convalescent phase of the disease.

Charts of all hospitalized patients were reviewed; age, sex, occupation, city of residence, history of tick bite or history of removing a tick, smoking history, chest X-ray results, outcome and clinical and laboratory findings were recorded for each patient.

## Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 14.0 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Results were expressed as mean  $\pm$  SD and categorical data as percentages. Data were analyzed with the chi-square test and the Mann-Whitney *U* test. In all comparisons a *p*-value <0.05 was considered statistically significant.

## RESULTS

One hundred eight patients with CCHF were included in the present study. Of these patients, 67 (62%) were male with a mean age of 51.3 $\pm$ 17.5 years and 41 (38%) were female with a mean age of 54.2 $\pm$ 14.4 years. The sex and occupational distributions of patients are shown in Table 1.

Of the cases, 32 (29.6%) and 36 (33.3%) were from Tokat and Sivas, respectively, while 40 cases were from other neighboring cities. Twenty-eight patients (25.9%) were smokers with a mean smoking duration of 5.9 years. Smoking history and respiratory system and other organ system complaints are shown in Table 2. The mean time to onset of clinical symptoms was 3.8 $\pm$ 1.7 days. Eighty-three patients had no co-morbid disease. Four patients (3.7%) had diabetes mellitus, 4 (3.7%) had

Table 1

Gender and occupational distribution of the patients with CCHF.

| Gender | Occupation          | <i>n</i> | %     |
|--------|---------------------|----------|-------|
| Male   | Farmer              | 46       | 68.7  |
|        | Officer             | 4        | 6.0   |
|        | Tradesman           | 11       | 16.4  |
|        | Healthcare provider | 6        | 9.0   |
|        | Total               | 67       | 100.0 |
| Female | Farmer              | 7        | 17.1  |
|        | Housewife           | 34       | 82.9  |
|        | Total               | 41       | 100.0 |

CCHF, Crimean-Congo hemorrhagic fever

Table 2

History of smoking, respiratory findings, and other findings among patients with CCHF.

| Symptom         | Positive (%) | Negative (%) |
|-----------------|--------------|--------------|
| Cough           | 19.4         | 80.6         |
| Sputum          | 15.7         | 84.3         |
| Dyspnea         | 8.3          | 91.7         |
| Chest pain      | 5.6          | 94.4         |
| Hemoptysis      | 5.6          | 94.4         |
| Fatigue         | 53.7         | 46.3         |
| Nausea-vomiting | 35.2         | 64.8         |
| Headache        | 25.0         | 75.0         |
| Myalgia         | 19.4         | 80.6         |
| Abdominal pain  | 6.5          | 93.5         |

congestive cardiac failure, 1 (0.9%) had chronic obstructive pulmonary disease and 16 (14.8%) had hypertension. There was a history of tick exposure in 71 patients (65.7%), but no history of exposure was identified in 37 patients (34.3%). Of the patients with a history of tick exposure, 54 had a history of attached ticks (bite-embed), 17 patients had a history of finding a tick on their body. Of the 71 patients with a tick exposure history, 64

Table 3

Some clinical features of CCHF patients.

| Clinical features     | No. (%)   |
|-----------------------|-----------|
| Respiration rate      |           |
| <18                   | 30 (27.8) |
| 18-30                 | 78 (72.2) |
| Fever                 |           |
| No                    | 85 (78.7) |
| Yes                   | 23 (21.3) |
| Chest radiography     |           |
| No abnormal findings  | 72 (66.7) |
| Unilateral pathology  | 27 (25.0) |
| Bilateral pathology   | 9 (8.3)   |
| Auscultation findings |           |
| Normal                | 72 (66.7) |
| Crackles              | 34 (31.5) |
| Rhonchi               | 2 (1.9)   |

removed the tick themselves and 7 had the tick removed by a hospital. Eighty-four patients (77.8%) worked in the animal husbandry business and 24 worked in butchering. Some clinical features of the patients are presented in Table 3. Of the abnormal radiographs, 27 had unilateral pathology and 9 had bilateral pathology. The findings of the chest radiographs are shown in Table 4. When chest radiographs of the patients were evaluated, 60 were considered normal. Table 5 shows the laboratory data of the patients with CCHF at the time of diagnosis. Seven of the 108 patients died due to severe pulmonary infection and hemorrhage, whereas 101 patients survived. Five of the patients who died had patchy infiltrations on chest X-ray.

There were statistically significant differences in dyspnea, chest pain, hemoptysis, platelet count, PT, INR, PTT, AST, LDH and CPK levels between cases who died and those who survived ( $p < 0.05$ ).

Table 4  
Findings of chest radiographs among  
CCHF patients.

| Findings               | n (%)     |
|------------------------|-----------|
| Normal                 | 60 (55.6) |
| Infiltration           | 19 (17.6) |
| Pleural thickening     | 7 (6.5)   |
| Hilar pathology        | 15 (13.9) |
| Interstitial pathology | 6 (5.6)   |
| Mediastinal pathology  | 1 (0.9)   |

Table 5  
Some laboratory data at diagnosis of the  
patients with CCHF.

|                             | Mean±Standard deviation |
|-----------------------------|-------------------------|
| Hematocrit                  | 41.4 ± 6.3              |
| WBC                         | 4,050.4 ± 4,453.2       |
| Platelets(mm <sup>3</sup> ) | 68,295.7 ± 50,692.9     |
| PT                          | 14.4 ± 9.7              |
| INR                         | 1.1 ± 0.2               |
| PTT                         | 50.5 ± 21.9             |
| AST                         | 277.5 ± 422.3           |
| ALT                         | 128.8 ± 203.7           |
| LDH                         | 648.3 ± 620.9           |
| CPK                         | 612.6 ± 738.2           |
| d-dimer                     | 2,897.5 ± 3,663.8       |

PT, Prothrombin time; INR, International normalized ratio; PTT, Partial thromboplastin time; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; CPK, Creatine phosphokinase.

Comparisons between patients who died and survived regarding tick exposure and clinical and laboratory findings are shown in Table 6.

## DISCUSSION

CCHF is an acute disease which affects several organs and is characterized

by diffuse ecchymosis, internal bleeding and deterioration in liver function with a fatal potential (Whitehouse, 2004).

The disease appears after a short incubation period of two to seven days with spread of the virus to all parts of the body (Ergonul, 2006; WHO, 2006). In severe cases of CCHF, illness begins abruptly with bleeding and high fever. Thrombocytopenia and other clotting abnormalities may occur. During the clinical course of the disease, laboratory abnormalities, include leukopenia, thrombocytopenia, elevated muscle and liver enzymes may be present. A direct invasion of pulmonary interstitial tissue by the CCHF virus has not yet been reported (Doganci, 2007).

Pleural effusion, pneumonia, hemoptysis and pulmonary hemorrhage, seen with other viral hemorrhagic fevers, are also reported (Schnittler and Feldman, 2003). However, pulmonary involvement and the pulmonary course of patients with CCHF are poorly established. In a Russian study of 283 patients with CCHF, acute respiratory distress syndrome (ARDS) was detected as pulmonary pathology and high levels of inflammatory cytokines were found in relation to disease severity; hemoptysis was observed in these patients (Sannikova *et al*, 2007). In the present study, cough and dyspnea were more common symptoms. Hemoptysis occurred in only 6 cases. In a study by Dilber *et al* (2009), pulmonary hemorrhage requiring ventilator support was present in 2 of 21 children. Doganci *et al* (2008) reported a single case which had bilateral alveolar hemorrhage caused by CCHF virus. We detected abnormal chest radiography in 33 of 108 cases. Among these, 19 had parenchymal infiltration. Although standard chest radiography did not allow detailed evaluation, some of the pathology could include pulmonary

Table 6  
Comparison of tick exposure, clinical and laboratory findings of Crimean-Congo hemorrhagic fever patients who survived versus those who died.

|            |         | Died              |     | Survived        |     | p-value |
|------------|---------|-------------------|-----|-----------------|-----|---------|
|            |         | n                 | (%) | n               | (%) |         |
| Dyspnea    | Yes     | 3                 | 43  | 6               | 6   | 0.001   |
|            | No      | 4                 | 57  | 95              | 94  |         |
| Chest pain | Yes     | 2                 | 29  | 4               |     | 0.006   |
|            | No      | 5                 | 71  | 97              |     |         |
| Hemoptysis | Yes     | 2                 | 29  | 4               | 6   | 0.006   |
|            | No      | 5                 | 71  | 97              | 94  |         |
| Platelet   | Mean±SD | 29,000 ± 15,588   |     | 71,019 ± 51,181 |     | 0.023   |
| PT         | Mean±SD | 15.4 ± 3.2        |     | 14.3 ± 10.0     |     | 0.041   |
| INR        | Mean±SD | 1.3 ± 0.2         |     | 1.1 ± 0.2       |     | 0.038   |
| PTT        | Mean±SD | 81.8 ± 36.3       |     | 48.3 ± 18.9     |     | 0.017   |
| AST        | Mean±SD | 592.0 ± 662.3     |     | 255.7 ± 396.4   |     | 0.010   |
| LDH        | Mean±SD | 1,461.4 ± 1,017.8 |     | 591.9 ± 548.5   |     | 0.018   |
| CPK        | Mean±SD | 1,089.0 ± 1,161.7 |     | 579.5 ± 696.5   |     | 0.029   |

PT, Prothrombin time; INR, International normalized ratio; PTT, Partial thromboplastin time; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; CPK, Creatine phosphokinase

hemorrhage. Infiltration was present in 4 of 6 patients with hemoptysis. Computed tomography of the chest would be useful in suspected patients, if the clinical condition allows. It has been reported pleural effusion may develop during the clinical course of CCHF; however the cause of the effusion is not clear (Tanir *et al*, 2009). No pleural effusions were seen in the present series.

In patients with abnormal chest radiography, no difference were seen between patients who died and those who survived. This may be due to the small sample size of patients who died. Of the 7 patients who died, 5 had infiltrations on chest radiography.

Cough (19.4%), sputum (15.7%), dyspnea (8.3%), hemoptysis (5.6%) and chest pain (5.6%) were present as respi-

ratory findings. Dyspnea, chest pain and hemoptysis were more common among patients who died than survivors. Cough and sputum may infrequently occur in patients with CCHF. If these symptoms occur, they are associated with a poor prognosis.

In a study among 114 patients with CCHF, Abadoglu and Engin (2009) reported no relationship between CCHF and allergic respiratory disease, such as allergic rhinitis and asthma. In the present study, we also found no such association with allergic disease.

CCHF is a serious disease in our country. The pathogenesis is not well understood. Evaluating the effect of the disease on different organ systems should contribute to our knowledge about the clinical course and pathogenesis of the

disease. We believe it would be beneficial to the respiratory system and other systems of patients with CCHF in larger series. Pulmonary parenchymal hemorrhage can be present in patients with CCHF, causing hemoptysis, dyspnea, chest pain and infiltration on chest radiographs and may lead to mortality.

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