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Original Article

Cutaneous Findings of Crimean-Congo Hemorrhagic Fever: a Study of 269 Cases

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SUMMARY: Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic viral disease. We aimed to investigate the cutaneous manifestations of CCHF and reveal their associations with fatality. Two hundred and sixty-nine patients diagnosed with CCHF were assessed. Skin findings were observed in 170 (63.2%) patients. A facial rash was the most common cutaneous finding (n = 82, 30.5%). In severe cases, hemorrhagic cutaneous manifestations (petechiae and ecchymoses) were recognized. A statistically significant correlation was obtained between cutaneous manifestations and fatality, and it was determined that there was a strong positive correlation between fatality and ecchymosis (r = 567, $p < 0.001$). In addition, a logistic regression analysis was performed, and death occurred 4.69 times more in those with skin signs than in those without. We hypothesize that CCHF patients with ecchymosis are at the highest risk and that cutaneous findings can contribute to the prognosis of CCHF.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is an acute zoonotic infection with a 5–10% fatality rate. The CCHF virus (CCHFV) is a single-stranded RNA virus in the *Nairovirus* genus of the Bunyaviridae family (1). The first case in Turkey was identified in the Tokat province in the Kelkit River Valley in 2002, and the Turkish fatality rate ranges from 4 to 5% (2,3). This disease can be mild or mortal (4), and the early signs typically include fever, tachypnoea, hypotension, relative bradycardia, pharyngitis, and occasionally conjunctivitis. The early stage of this disease is called the prehemorrhagic phase, which is characterized by elevated liver enzyme levels, increased bleeding duration, and thrombocytopenia. Hyperemia can be seen in the area where the tick was attached. A petechial rash is the first symptom, followed by petechiae and ecchymoses on the skin and petechiae on the internal mucosal surfaces (4–7). After several days, it is followed by the hemorrhagic phase, in which epistaxis, hematemesis, hematuria, melena, hemoptysis, and bleeding from venipuncture sites are common. Moreover, bleeding can occur in other organs, including the brain (8). Given that the symptoms of CCHF are non-specific and may mimic a broad spectrum of infectious diseases, it is crucial to correctly identify this disease, particularly in regions where it frequently occurs, to ensure the necessary precautions are taken and treatment is initiated without delay.

The aim of this study was to investigate the cutaneous manifestations of CCHF and reveal their associations with fatality. This is one of the studies that evaluate a large number of CCHF cases based on skin findings.

MATERIALS AND METHODS

Two hundred and 69 patients who were admitted to the Infectious Diseases and Dermatology Clinics of Tokat State Hospital between April 1 and September 1 of 2011 were hospitalized with clinical and laboratory findings compatible with CCHF and confirmed as a CCHF according to the diagnostic criteria, were enrolled in this prospective cohort study. The patients' demographic data, dermatological and epidemiological findings, and disease courses were analyzed. Dermatological findings were examined and recorded by a dermatology specialist. Dermatological findings were defined as follows; a macule was a flat blemish or discoloration measuring less than 1 cm. A papule was an elevated lesion measuring less than 1 cm. Combining these 2 terms, a maculopapular rash was a smooth skin rash or redness covered by elevated bumps. Petechiae/purpura were pink-colored lesions caused by extravasation of blood. When these lesions were smaller than 5 mm, they were called petechiae, and when larger than 5 mm, purpura. Ecchymosis is commonly characterized by reddish or bluish skin discolorations that measure more than 1 cm.

In patients prediagnosed with CCHF, the diagnostic criteria were as follows.

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Clinical findings: At least 2 symptoms (fever, headache, myalgia, nausea/vomiting, arthralgia, weakness, or bleeding), leukopenia (< 4,000/μL)/thrombocytopenia (< 150,000/μL), and elevation of serum aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) levels.

Supportive findings: Hemorrhagic-purpuric rash and other hemorrhagic symptoms.

Epidemiological history of one or more of the following exposures within 3 weeks before the onset of symptoms: Living in or travel to an endemic area, a history of tick exposure, contact with blood or other body fluids of an animal, contact with blood or other body fluids of a confirmed CCHF patient, and/or work in a laboratory that handles CCHF specimens.

Suspected case definition: Case meets the clinical and epidemiologic linkage criteria.

Probable case: Case meets the clinical and epidemiologic linkage criteria and meets 2 supportive findings or meets the clinical and epidemiologic linkage criteria in areas endemic for CCHF.

Confirmed case: Case meets the clinical demonstration of viral RNA in blood and tissue samples, specific immunoglobulin (Ig)M positivity, a 4-fold increase in specific IgG titer, and an epidemiological association with a confirmed CCHF patient.

For all participants, the case definition forms and serum samples were submitted to the National Reference Laboratory by the Public Health Institution of Turkey.

The specimens were tested for anti-CCHF IgM and IgG antibodies using an enzyme-linked immunosorbent assay, while a reverse transcription polymerase chain reaction (RT-PCR) and direct sequence analysis were carried out for the detection of CCHFV RNA. RT-PCR and/or anti-CCHF IgM positivity were suggestive of CCHF in those patients. A total of 269 patients who were CCHF PCR- and/or IgM antibody-positive and who were diagnosed and hospitalized with CCHF were included in the study. We did not use ribavirin in our treatments. All patients were treated with supportive care.

The exclusion criteria were other dermatological problems and systemic collagen tissue diseases. The patients were allowed to take their own photographs. All enrolled patients provided written informed consent prior to study inclusion. The study population has been described previously. The study was performed in accordance with the 1975 Declaration of Helsinki for prospective biomarker studies and was approved by the relevant ethics committee.

Statistical Analyses: Statistical analyses were conducted using the Statistical Package for the Social Sciences version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). If the continuous variables were normal, they were described as mean ± standard deviation (SD) ($p > 0.05$ in the Kolmogorov-Smirnov or Shapiro-Wilk's test [$n < 30$]). An independent sample t-test (t-test in the independent groups) was performed on the quantitative data showing a normal distribution. However, since the variables did not have a normal distribution, a Mann-Whitney U test was applied. The qualitative data comparison was performed using a chi-square test, and a p-value of < 0.05 was considered statistically significant. The correlation between 2 continuous variables was analyzed using Spearman's bivariate correlation, and the correlation was significant at 0.01 (2-tailed). The factors affecting fatality were evaluated using logistic regression analysis, and Pearson's chi-square test was used to compare categorical variables between groups.

RESULTS

A total of 269 CCHF cases and 17 deaths (6.3%) were identified during the study period. Of the included cases, 159 (59.1%) were men and 110 (40.9%) were women. The mean age of the patients was 36.28 years (SD 10.21, min-max 15–73). Skin findings were observed in 170 patients. The epidemiological findings were similar, with or without cutaneous findings, and a statistically significant difference was not found. The evaluation of other viral infections and drug histories was negative in our patients.

A facial rash was the most common cutaneous finding, and it was observed in 82 (30.5%) of CCHF patients. Twenty-one (7.8%) patients had petechiae, 23 (8.6%) had maculopapular rashes, and 8 (3.0%) had purpura. The cutaneous findings of the patients are summarized in Table 1. In the severe cases, hemorrhagic cutaneous manifestations were recognized, which included petechiae (Fig. 1) and ecchymoses (Figs. 2 and 3).

A statistically significant correlation was obtained between the cutaneous manifestations and fatality, and it was determined that there was a strong positive correlation between fatality and ecchymosis ($r = 0.567$, $p < 0.001$). In addition, a logistic regression analysis was performed, and death occurred 4.69 times more in those with skin signs than in those without.

Based on the correlation analysis, there was a significant positive correlation between fatality and skin findings ($p < 0.001$, $r = 0.381$). The correlations between fatality and the laboratory findings were as follows:ALT, $p < 0.001$ and $r = 0.704$; AST, $p < 0.001$ and $r = 0.787$; CPK, $p < 0.001$ and $r = 0.458$; LDH, $p < 0.001$ and $r = 0.719$; white blood cell (WBC) count, $p = 0.004$ and $r = 0.176$; platelet (Plt) count, $p = 0.009$ and $r = -0.158$; prothrombin time (PT), $p = 0.044$ and $r = 0.123$; partial thromboplastin time, $p < 0.001$ and $r = 0.277$; and international normalized ratio (INR), $p < 0.001$ and $r = 0.366$.

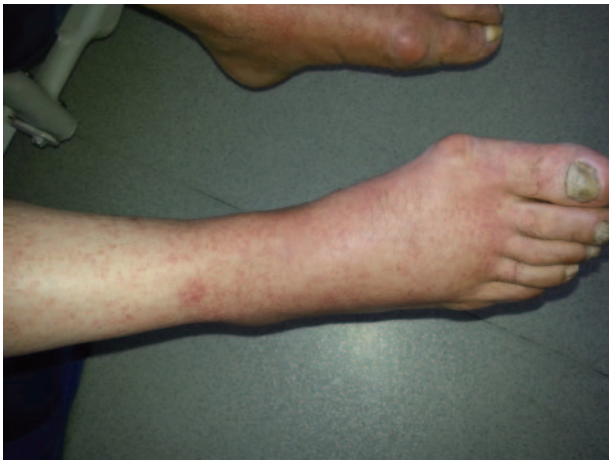

Fig. 1. (Color online) Petechiae of CCHF patient on the dorsalis pedis and anterior tibia.

Table 1. The cutaneous and laboratory findings of the patients

	Total case $N = 269$ (%)	Fatality ($N = 17$) (%)	Recovery ($N = 252$) (%)	P
Age mean ± SD	36.28 ± 10.21	56.70 ± 10.45	49.18 ± 17.82	> 0.05
Male	159 (59.1)	9 (52.9)	150 (59.5)	> 0.05
Living in rural area	259 (96.3)	16 (94.1)	243 (96.4)	> 0.05
Skin findings	170 (63.2)	15 (88.2)	155 (61.5)	0.002
Facial rash	82 (30.5)	2 (11.8)	80 (31.7)	
Maculopapuler rash	23 (8.6)	0	23 (9.1)	
Petechia	21 (7.8)	0	21 (8.3)	
Purpura	8 (3.0)	0	8 (3.2)	
Ecchymoses	22 (8.2)	13 (76.5)	9 (3.6)	
Facial rash and petechia	22 (8.2)	11 (64.7)	11 (4.4)	
Facial rash and purpura	3 (1.1)	0	3 (1.2)	
Ecchymoses and petechia	2 (0.7)	2 (11.8)	0	
Facial rash and ecchymoses	11 (4.1)	11 (64.7)	0	
Multiple skin findings	60 (22.3)	13 (76.5)	47 (18.7)	
ALT* (U/L) median (IQR)	159 (84–297)	1,335 (872–3,151)	146.5 (81.2–256)	< 0.001
AST* (U/L) median (IQR)	295 (144–640.5)	7,087 (2,329–10,672)	267.5 (138.2–544.7)	< 0.001
CPK* (mg/dL) median (IQR)	353 (168.5–794)	2,560 (1,389.2–4,414.2)	306 (142.2–657.8)	< 0.001
LDH* (U/L) median (IQR)	605 (428–1,087)	4,818 (3,429–7,430)	574 (416–912)	< 0.001
WBC (10^9/L) median (IQR)	1,650 (1,270–2,200)	1,300 (1,170–2,820)	1,600 (1,292.5–2,177.5)	> 0.05
Plt (10^9/L) median (IQR)	32.7 (16.9–60.2)	12.9 (10.2–16.5)	34 (18–63.9)	< 0.001
PT median (IQR)	11.9 (10–14.3)	15.4 (14.3–18.8)	11.7 (10–13.8)	< 0.001
aPTT median (IQR)	41.1 (35–52)	81.1 (51.4–95.7)	40.95 (34.5–49.9)	< 0.001
PT INR median (IQR)	1 (0.9–1.2)	1.39 (1.2–1.7)	1 (0.9–1.2)	< 0.001

WBC, white blood cell count; Plt, platelet value; PT, prothrombine time; aPTT, active tromboplastine time; INR, the international normalized ratio; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.
*: Normal values: ALT 30–65 mg/dL, AST 15–37 mg/dL, CPK 21–232 mg/dL, LDH 110–240 IU/L.

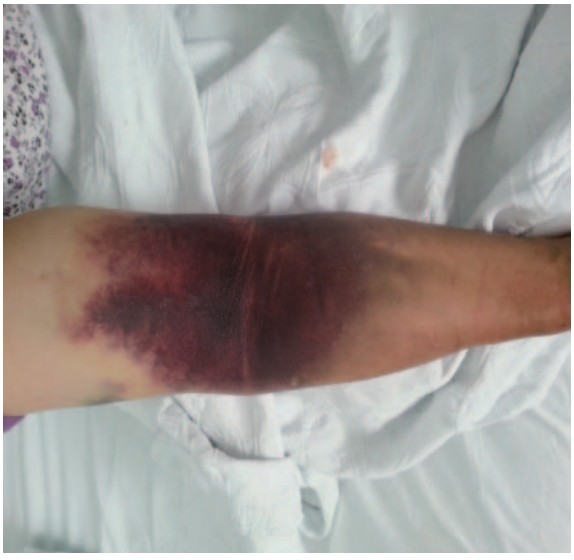

Fig. 2. (Color online) Ecchymosis of CCHF patient on the upper extremity on flexor surface.

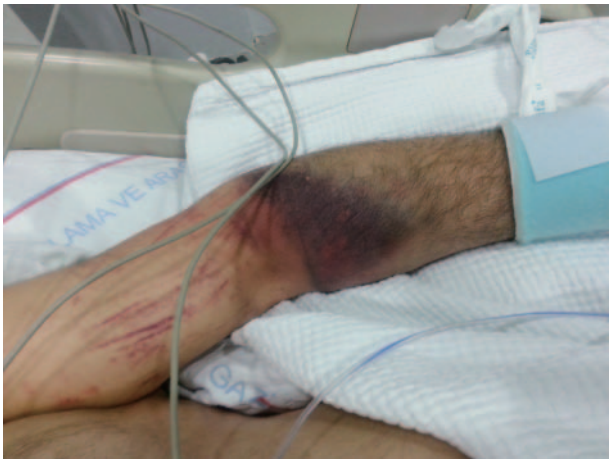

Fig. 3. (Color online) Ecchymosis of CCHF patient on the upper extremity on flexor surface.

DISCUSSION

A distinctive rash, fever, and influenza-like symptoms may indicate a tick-borne disease (9–11). The diseases caused by tick-borne pathogens in Turkey include babesiosis, anaplasmosis, Lyme borreliosis, tularemia, CCHF, and Mediterranean spotted fever. Mediterranean spotted fever is characterized by a maculopapular rash (involving the palms or soles) and/or a black mark at the site of the tick bite. In CCHF patients, maculopapular rashes not involving palms and soles and the absence of an eschar (tache noir) can help to differentiate CCHF from Mediterranean spotted fever. Nonspecific skin rashes have been reported in babesiosis and anaplasmosis cases (9–11). In addition, in the literature, cases of erythema figuratum due to septic babesiosis have been reported (12–15). The 3 characteristic cutaneous manifestations of Lyme disease are erythema migrans, borrelial lymphocytoma, and acrodermatitis chronica atrophicans (16). Erythema multiforme, ulcers, urticaria, erythema nodosum, and cellulitis can be seen in

tularemia cases (17).

The dermatological signs of CCHF are morbilliform eruptions, petechial lesions, purpura, ecchymosis, and oral erythema-petechiae (7,11). However, there have been few studies describing the cutaneous manifestations and their relationships with fatality in CCHF patients. In recent years, Akyol et al. (18) investigated the cutaneous manifestations (31.4% morbilliform eruptions) of CCHF and found a correlation between the morbilliform eruptions and a reduced platelet number. In another study conducted at a different hospital over a different period in 2011, 176 CCHF patients were examined, and a significant relationship was found between skin findings and fatality ($p < 0.01$, r = 0.435) (19).

In a previous study, 281 patients prediagnosed with CCHF were evaluated, and 10 patients (3 CCHF +) had bruises on the body, 20 (8 CCHF +) had skin eruptions, 8 (3 CCHF +) had petechiae, and 4 (2 CCHF +) had ecchymosis. However, there was no significant difference between CCHF-positive and -negative patients with regard to skin findings (20). In another study, the clinical findings of 99 patients with CCHF were reviewed, and a total of 36 patients had maculopapular rashes (7 patients exitus). However, no significant difference was found in terms of the cutaneous findings when the exitus patients were compared with the others (4).

Humans can also develop inflammatory responses to tick bites in the dermis, including infiltrates of neutrophils, eosinophils, histiocytes, and lymphocytes, as well as vascular thrombi, erythrocyte extravasation, and neutrophil damage to the blood vessels consistent with vasculitis. Despite these data, it remains unclear how tick-induced changes at the tick-dermal interface may enhance pathogen transmission and how the host's responses to repeated tick bites might inhibit such transmission, especially as a result of CCHF. Repeated tick exposure is associated with the interruption of tick feeding, early tick detachment, and the prevention of tick-borne pathogen transmission (12–15).

The main contributors to the pathogenesis of CCHFV are endothelial cells and immune cells. Following the entry of the CCHFV into the host, it encounters the innate immune cells, including monocytes and dendritic cells (21). The infected cells produce various types of cytokines, chemokines, and inflammatory factors. An exaggerated proinflammatory cytokine response or a "cytokine storm" can cause endothelial cell activation and increase vascular permeability, resulting in hypotension, shock, multiple organ failure, and death (22–25). The proinflammatory cytokines may be the reason for the CCHF dermatological signs (morbilliform eruptions, petechial lesions, purpura, ecchymosis, and oral erythema-petechiae), and they are secreted after endothelial injury. One case of CCHF with erythema nodosum has been reported in the literature (26,27). In the study conducted by Kilinc et al. (20), CCHF-positive and -negative patients were compared, and 40% of the CCHF-positive patients had skin eruptions, 36.3% had petechiae, and 36.1% had ecchymoses. However, no significant difference was found between the CCHF-positive and -negative patients. A previous study of 220 CCHF patients conducted in 2016 found petechiae in 21.4% of the patients, ecchymoses in 15.9%, and maculopapular rashes in 11.4%. The petechiae and ecchymoses were reported to be significantly higher in the exitus patients ($p = 0.018$ and $p < 0.001$, respectively) (28).

The limitations in this research are that we did not investigate the site of the tick bite in our records of examinations, or the possible dermatological effects of drugs such as paracetamol, anti-emetics, blood, and blood products which were used in supportive care.

CCHF is a public health problem that is especially important in certain regions of Turkey. The distribution of the disease may not be limited to the reported areas and may be underdiagnosed in many regions. CCHFVs cause variable skin lesions, and these lesions play an important role in the clinical diagnosis of CCHF. Similar skin lesions occur in other endemic zoonotic diseases in Turkey; therefore, we confirmed the diagnosis using PCR. A proper diagnosis is essential to facilitate early treatment to decrease morbidity and fatality, even though treatment should often be initiated before a definitive diagnosis is made. Dermatological findings should be examined carefully as they can provide insight into the patient's prognosis and fatality risk. We hypothesize that CCHF patients with ecchymosis are at the highest risk of death and that cutaneous findings can contribute to the prognosis of CCHF; however, future studies are needed.

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Conflict of interest None to declare.

REFERENCES

1. Swanepoel R, Gill DE, Shepherd AJ, et al. The clinical pathology of Crimean-Congo hemorrhagic fever. Rev Infect Dis. 1989;11:S794-800.
2. Duygu F, Kaya T, Baysan P. Re-evaluation of 400 Crimean-Congo hemorrhagic fever cases in an endemic area: is ribavirin treatment suitable? Vector Borne Zoonotic Dis. 2012;12:812-6.
3. Akinci E, Bodur H, Sunbul M, et al. Prognostic factors, pathophysiology and novel biomarkers in Crimean-Congo hemorrhagic fever. Antiviral Res. 2016;132:233-43.
4. Bakir M, Ugurlu M, Dokuzoguz B, et al. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures. J Med Microbiol. 2005;54: 385-9.
5. Ozkurt Z, Kiki I, Erol S, et al. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. J Infect. 2006;52:207-15.
6. Ergönül O, Celikbaş A, Dokuzoguz B, et al. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. Clin Infect Dis. 2004; 39:284-7.
7. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol. 1979;15: 307-417.
8. Whitehouse CA. Crimean-Congo hemorrhagic fever. Antiviral Res. 2004;64:145-60.
9. Elston DM. Tick bites and skin rashes. Curr Opin Infect Dis. 2010;23:132-8.
10. Bakken JS, Dumler JS. Clinical diagnosis and treatment of human granulocytotropic anaplasmosis. Ann N Y Acad Sci. 2006;1078:236-47.
11. Bratton RL, Corey R. Tick-borne disease. Am Fam Physician. 2005;71:2323-30.
12. Patterson JW, Fitzwater JE, Connell J. Localized tick bite reaction. Cutis. 1979;24:168-9,172.
13. Beaudouin E, Kanny G, Guerin B, et al. Unusual manifestations of hypersensitivity after a tick bite: report of two cases. Ann Allergy Asthma Immunol. 1997;79:43-6.
14. Stefanato CM, Phelps RG, Goldberg LJ, et al. Type-I cryoglobulinemia-like histopathologic changes in tick bites: a useful

clue for tissue diagnosis in the absence of tick parts. J Cutan Pathol. 2002;29:101-6.
15. Pajvani U, Zeikus PS, Basile O, et al. Thrombogenic vasculopathy with diffuse neutrophilic inflammation: a histologic manifestation of a tick bite. Cutis. 2006;78:321-4.
16. Müllegger RR, Glatz M. Skin manifestations of lyme borreliosis: diagnosis and management. Am J Clin Dermatol. 2008;9:355-68.
17. Şenel E, Satılmış Ö, Acar B. Dermatologic manifestations of tularemia: a study of 151 cases in the mid-Anatolian region of Turkey. Int J Dermatol. 2015;54:e33-7.
18. Akyol M, Ozçelik S, Engin A, et al. Cutaneous manifestations of Crimean-Congo haemorrhagic fever: morbilliform eruptions may reflect a favorable outcome and not low platelet levels. Eur J Dermatol. 2010;20:523-4.
19. Pancar GS, Duygu F, Kalkan G. The prognostic role of the new entity butterfly-like facial rash and cutaneous findings in patients with crimean congo haemorrhagic fever. J Eur Acad Dermatol Venereol. 2014;28:604-8.
20. Kilinc C, Gückan R, Capraz M, et al. Examination of the specific clinical symptoms and laboratory findings of Crimean-Congo hemorrhagic fever. J Vector Borne Dis. 2016;53:162-7.
21. Xiao X, Feng Y, Zhu Z, et al. Identification of a putative Crimean-Congo hemorrhagic fever virus entry factor. Biochem Biophys Res Commun. 2011;411:253-8.
22. Akinci E, Bodur H, Leblebicioglu H. Pathogenesis of Crimean-Congo hemorrhagic fever. Vector Borne Zoonotic Dis. 2013;13:429-37.
23. Bodur H, Akinci E, Ongürü P, et al. Evidence of vascular endothelial damage in Crimean-Congo hemorrhagic fever. Int J Infect Dis. 2010; 14:e704-7.
24. Bente DA, Forrester NL, Watts DM, et al. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res. 2013;100:159-89.
25. Chen JP, Cosgriff TM. Hemorrhagic fever virus-induced changes in hemostasis and vascular biology. Blood Coagul Fibrinolysis. 2000; 11:461-83.
26. Appannanavar SB, Mishra B. An update on crimean congo hemorrhagic fever. J Glob Infect Dis. 2011;3:285-92.
27. Bijani B, Mardani M, Toosi P. Erythema nodosum in the course of Crimean-Congo haemorrhagic fever. Trop Doct. 2010;40:123-4.
28. Bastug A, Kayaaslan B, Kazancioglu S, et al. Crimean-Congo hemorrhagic fever: prognostic factors and the association of leukocyte counts with mortality. Jpn J Infect Dis. 2016;69:51-5.