



Sandfly Fever-Related Acute Hepatitis Outbreak After Kahramanmaraş Earthquake

Kahramanmaraş Depremi Sonrası Tatarcık Ateşi İlişkili Akut Hepatit Salgını

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ABSTRACT

Introduction: Sandfly fever virus, a member of the Phlebovirus (Bunyaviridae family), can cause sandfly fever, also known as “Pappataci fever”. This vector-related disease occurs primarily in endemic regions during the summer months. Epidemics may develop in different regions if favorable environmental conditions and vector transport are present. Laboratory changes, such as elevated transaminases and creatine kinase levels, leukopenia, and thrombocytopenia, may be observed in sandfly fever. In this study, we aimed to evaluate the laboratory results and progression of sandfly fever cases, which were concentrated in the conditions developing in the earthquake-affected region.

Materials and Methods: Seventeen sandfly fever cases who were followed up in our clinic between August and October 2023 were included in the study. These cases were patients who presented with non-specific complaints related to infection in the earthquake-affected area after the February 6 Kahramanmaraş earthquake and had acute hepatitis with elevated transaminases, creatine kinase, and C-reactive protein (CRP). The study retrospectively evaluated the laboratory results and findings of cases positive for the sandfly fever virus.

Results: Of the cases, 58.8% were male (n= 10), 41.2% were female (n= 7), with a mean age of 40.88 ± 19.59. The mean aspartate aminotransferase (AST) was calculated as 325.53 U/L, alanine aminotransferase (ALT) as 311.88 ± 282.36 U/L, alkaline phosphatase (ALP) as 109.64 ± 49.59 U/L, gamma-glutamyl transferase (GGT) as 80.82 ± 71.05 U/L, lactate dehydrogenase (LDH) as 564.47 ± 404.57 IU/L and creatine kinase (CK) as 872.38 U/L. Of the 17 cases, nine had leukopenia (53%), nine had neutropenia (53%), and five had lymphopenia (29.4%). Thrombocytopenia was observed in seven cases (41.1%). The mean CRP level was high at 3.78 mg/dL. Acute renal failure was also present in three cases. The cases were discharged after supportive treatment and observation, with improvements in both clinical and laboratory findings.

Conclusion: Our study showed that sandfly virus-related epidemics may occur, particularly during warm months, when suitable conditions develop, such as after an earthquake. Additionally, it was determined that an acute hepatitis presentation, characterized by a significant increase in transaminases and creatine kinase, can be observed in sandfly virus infection. Our study also indicates that caution should be exercised regarding the potential for larger and more serious epidemics that may affect the region, especially during the summer months, if current conditions persist.

Key Words: Acute hepatitis; Sandfly fever; Creatine kinase; Leukopenia; Thrombocytopenia

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ÖZ

Kahramanmaraş Depremi Sonrası Tatarcık Ateşi İlişkili Akut Hepatit Salgını

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Giriş: Phlebovirüsler (Bunyaviridae familyası) üyesi olan sandfly fever virüsü vektör ilişkili olarak özellikle yaz aylarında endemik bölgelerde “Pappataci ateşi” olarak da bilinen tatarcık ateşine neden olabilmektedir. Uygun çevre koşullarının gerçekleşmesi ve vektör taşıyıcının olması durumunda, farklı bölgelerde salgınlar görülebileceği belirtilmektedir. Tatarcık ateşinde transaminazlar ve kreatin kinazda yükselme, lökopeni, trombositopeni gibi laboratuvar değişiklikleri görülebilmektedir. Bu çalışmada deprem bölgesinde gelişen koşullara birlikte yoğunlaşmış olan tatarcık ateşi vakalarının sonuçları ve seyrinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metod: Ağustos-Ekim 2023 tarihleri arasında 6 Şubat Kahramanmaraş depremi sonrasında depremten etkilenen bölgede enfeksiyonla ilişkili non-spesifik şikayetlerle başvuran; transaminazlar, kreatin kinaz, C-reaktif protein (CRP) yüksekliğiyle birlikte akut hepatit tablosu mevcut olan 17 vaka çalışmaya dahil edildi. Vakaların etiyolojik değerlendirmesinde diğer transaminaz yüksekliği ve akut hepatit tablosu oluşturan sebeplerin dışlanması sonrasında sandfly fever virüsü pozitif saptananların laboratuvar sonuçlarının ve bulgularının retrospektif değerlendirilmesi çalışma gerçekleştirildi.

Bulgular: Vakaların %58.8’i erkek (n= 10), %41.2’si kadındı (n= 7); yaş ortalaması 40.88 ± 19.59 olarak bulundu. Ortalama aspartat aminotransferaz (AST) 325.53 U/L, alanin aminotransferaz (ALT) 311.88 ± 282.36 U/L, alkalen fosfataz (ALP) 109.64 ± 49.59 U/L, gama-glutamil transferaz (GGT) 80.82 ± 71.05 U/L, laktat dehidrogenaz (LDH) 564.47 ± 404.57 IU/L ve kreatin kinaz (CK) 872.38 U/L olarak ölçüldü. On yedi vakanın dokuzunda lökopeni (%53), dokuzunda nötropeni (%53) ve beşinde lenfopeni (%29.4) mevcuttu. Yedi vakada (%41.1) trombositopeni vardı. Ortalama CRP 3.78 mg/dL olarak bulundu. Üç vakada akut böbrek yetmezliği tablosu da mevcuttu. Vakalar destekleyici tedavi ve gözlem sonrası klinik ve laboratuvar bulgularında düzelme ile taburcu edildi.

Sonuç: Bu çalışma, deprem sonrası gibi uygun koşulların olduğu senaryolarda -özellikle sıcak aylarda- sandfly virüsüyle ilişkili salgınlar gelişebileceğini göstermiştir. Yine sandfly virüsü enfeksiyonunda özellikle transaminazlar ve kreatin kinazın baskın yükselmesiyle seyreden akut hepatit tablosunun görülebildiği saptanmıştır. Mevcut koşulların devam etmesi halinde özellikle yaz dönemlerinde bölgeyi etkileyebilecek daha geniş çaplı ve ciddi salgınlar açısından da dikkatli olunması gerekmektedir.

Anahtar Kelimeler: Akut hepatit; Tatarcık ateşi; Kreatin kinaz; Lökopeni; Trombositopeni

INTRODUCTION

Many hepatotropic viral agents increase transaminase levels and cause hepatitis epidemics, including hepatitis A, B, and C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), respiratory syncytial virus (RSV), measles, SARS-CoV-2, and phlebovirus^[1-4]. It has been reported that the transmission and frequency of vector-related diseases to different regions around the world have increased in recent years due to climate change, changes in environmental conditions, and increased global mobility^[5].

Phleboviruses (family *Bunyaviridae*) are geographically located in Europe, Africa, Central Asia, and America. Four serotypes have been identified, namely Sandfly Sicilian virus, Sandfly Cyprus virus, Sandfly Naples virus, and Toscana virus, which are widely circulating, especially in the Mediterranean region. These viruses cause sandfly fever, also known as “three-day fever”

or “Pappataci fever”^[6,7]. In endemic areas, infections occur during the summer months and peak in August, coinciding with the maximum activity of sandfly vectors^[6,7]. After an incubation period of 3-6 days, a high fever (39-40 °C) develops, lasting between six and 72 hours, hence the name “three-day fever”. The most common symptoms include headache, anorexia, myalgia, photophobia, back pain, retro-orbital pain, and weakness^[4,6,8]. Leukopenia characterized by lymphopenia followed by prolonged neutropenia and thrombocytopenia may also occur^[6,8]. Along with abdominal discomfort, temporary diarrhea or constipation may also develop. Sandfly fever viruses may also cause neurological disorders such as meningitis, encephalitis, and meningoencephalitis^[4,6]. One of the most important findings in sandfly fever is the elevation of transaminases accompanied by hepatic cytolysis^[4,8].

The diagnosis of phlebovirus infections is based on the dynamics of viremia and the host's immune response. For diagnosis, viral antigens or nucleic acids, as well as IgM and IgG antibodies, which are elements of the immune response, can be used as detection targets. Various methods can be used for the detection of phlebovirus antibodies, including hemagglutination inhibition assay, immunofluorescence assay (IFA), enzyme-linked immunosorbent assay, immunoblot (IB), and neutralization-based assays^[7].

In this study, we aimed to highlight the outbreak of sandfly fever viral acute hepatitis, which we identified after the etiological evaluation of patients hospitalized in our clinic following the earthquake that occurred on February 6, 2023, centered in Kahramanmaraş.

MATERIALS and METHODS

The study was conducted at the Internal Medicine and Infectious Diseases Clinic of Malatya Turgut Özal University Training and Research Hospital. Seventeen cases hospitalized in our clinic with acute hepatitis between August and October 2023 were included in the study. In all cases, sandfly fever diagnoses were confirmed by serological tests using the immunofluorescent antibody (IFA) method. Ethics committee approval for the study was received from Malatya Turgut Özal University's Non-Invasive Clinical Research Ethics Committee with the number 27.12.2023/37. Written informed consent forms were obtained from the patients.

The results of the cases were evaluated retrospectively. The clinical findings of the patients admitted to our clinic were retrieved from their files. Patients were interviewed face-to-face, their complaints were documented, and examination findings were assessed. The acute and chronic medications they used were recorded, and risk factors such as the use of herbal agents or mushroom consumption were investigated. The results of hemograms, liver function test, viral hepatitis markers, *Brucella* Rose-Bengal and Wright standard tube agglutination, Gruber-Widal test, venereal disease research laboratory, viral serology, thyroid function tests, abdominal ultrasonography (USG), and, if available, abdominal tomography of the

cases were recorded and evaluated.

Patients over the age of 18, who presented with acute hepatitis and were diagnosed with sandfly fever were included in the study. Cases with acute cholecystitis, pancreatitis, and cholangitis, as well as those involving the use of herbal products, mushrooms, or non-routine medications, were not included in the study. Individuals with other viral factors, bacterial infections, toxic or ischemic-hypoxic causes, and thyroid dysfunction as etiological factors for transaminase elevation were excluded.

The complete blood count of the patients was measured automatically on the Sysmex Corporation (XN-10, Kobe, Japan) device in the Hematology Laboratory of Malatya Turgut Özal University Training and Research Hospital, using 2 cc of blood collected in standard ethylene diamine tetraacetic acid tubes.

For biochemical examinations, blood samples were collected without anticoagulant, incubated at 37 °C for 20 minutes, and then centrifuged at 1800 rpm for 10 minutes to obtain serum samples. Serum levels of C-reactive protein (CRP), creatinine (CRE), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total and direct bilirubin, lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase-MB (CK-MB) were automatically measured using the Abbott Architect c16000 autoanalyzer (Illinois, United States) with Abbott brand commercial kits (Sentinel Diagnostic, Illinois, United States). The units used were mg/dL for CRE, total bilirubin, direct and indirect bilirubin, and CRP; U/L for AST, ALT, ALP, GGT, CK, and CK-MB; and IU/L for LDH.

To evaluate viral serology, the following tests were conducted: hepatitis A IgM, HBsAg, anti-HBs, anti-HBc IgM, anti-HBc total, anti-HCV, anti-HIV, CMV IgM, EBV IgM, parvovirus IgM, rubella IgM, toxoplasma IgM, leptospira IgM and IgG, bartonella virus IgM and IgG, Crimean-Congo hemorrhagic fever and West Nile fever PCR, measles IgM, and sandfly virus IgM and IgG.

Blood samples taken from cases to detect sandfly virus were transferred under appropriate

conditions in accordance with recommendations and confirmed using the immune fluorescent antibody IgM and IgG method at the Ministry of Health's Ankara National Rash and Central Nervous System Viral Infections Reference Laboratory.

Statistical Analysis

The data analysis for this research was conducted using SPSS (Statistical Program for Social Sciences) version 25. Descriptive statistics for the variables were presented as mean, standard deviation, median, minimum, and maximum values.

RESULTS

With admissions increasing between August and October 2023, it was determined that 17 sandfly fever cases received inpatient treatment in our clinic and were included in the study. Of these cases, 58.8% were men (n= 10) and 41.2% were women (n= 7). The mean age of the cases was 40.88 ± 19.59 years, with an

age range of 18-85 years.

Patients presented with fever and sweating in 100% of cases, headache, myalgia, and joint pain in 88.2%, weakness in 88.2%, anorexia and nausea in 70.5%, vomiting and diarrhea in 53%, and redness in the body and eyes in 35.3%. Sandfly bite marks could be detected in 53% of the cases. Upon abdominal examination, mild tenderness and guarding were detected in 41.2% of the cases. Organomegaly and lymphadenopathy were not detected. Erythematous rashes on the body were observed in 23.5% of the cases, and conjunctivitis was noted in 35.3% of the cases.

Laboratory results were as follows: the mean AST level: 325.53 U/L, ALT 311.88 ± 282.36 U/L, ALP 109.64 ± 49.59 U/L, GGT 80.82 ± 71.05 U/L, LDH 564.47 ± 404.57 IU/L, CK 872.38 U/L, and CK MB 46.96 ± 34.11 U/L. Notably, there was a significant increase in AST (highest level= 1476 U/L), ALT (highest level= 1068 U/L), LDH (highest level= 1947 IU/L),

Table 1. Descriptive values of the measurements

Variable	Mean $\pm$ *SD	[†] M ([§] Min- [§] Max)
CRE (mg/dL)	1.13 $\pm$ 0.55	0.95 (0.49-2.60)
AST (U/L)	325.53	213 (21-1476)
ALT (U/L)	311.88 $\pm$ 282.36	217 (22-1068)
ALP (U/L)	109.64 $\pm$ 49.59	100 (56-254)
GGT (U/L)	80.82 $\pm$ 71.05	46 (12-223)
LDH (IU/L)	564.47 $\pm$ 404.57	390 (171-1947)
Total bilirubin (mg/dL)	0.8 $\pm$ 0.53	0.59 (0.31-2.23)
Indirect bilirubin (mg/dL)	0.52 $\pm$ 0.36	0.42 (0.17-1.41)
Direct bilirubin (mg/dL)	0.28 $\pm$ 0.18	0.23 (0.11-0.82)
CK (U/L)	872.38	104.61 (28.45-3913)
CK-MB (U/L)	46.96 $\pm$ 34.11	34 (10.1-119.5)
Leukocyte (N, thousand)	5.3 $\pm$ 3.06	5.44 (1.61-13.55)
Thrombocyte (N, thousand)	184.70 $\pm$ 83.95	220 (80-406)
Neutrophil (N, thousand)	3.34 $\pm$ 2.73	3.42 (0.72-10.77)
Lymphocyte (N, thousand)	1.40 $\pm$ 0.59	1.46 (0.41-2.08)
Eosinophil (N, thousand)	0.06 $\pm$ 0.07	0.02 (0-0.25)
CRP (mg/dL)	3.78	(0.2-29.9)

*SD: Standard deviation, [†]M: Median, [§]Min: Minimum value, [§]Max: Maximum value, ^{||}N: Number, CRE: Creatinine, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, CK: Creatine kinase, CK-MB: Creatine kinase-MB, CRP: C-reactive protein. Bold values are used to demonstrate the abnormal levels.

and CK (highest level= 3913 U/L) levels. The mean CRE level was measured at 1.13 ± 0.55 mg/dL (Table 1). However, the CRE level was 2.60 mg/dL in an 85-year-old patient, 1.76 mg/dL in a 56-year-old patient, and 1.65 mg/dL in a 46-year-old patient.

Although the mean leukocyte, neutrophil, and lymphocyte counts were normal, 9 of 17 cases had leukopenia (53%, lowest count= 1.61), nine had neutropenia (53%) and five had lymphopenia (29.4%). Despite the mean platelet count being normal, moderate thrombocytopenia was detected in seven cases (41.1%) with platelet counts ranging between 80.000 and 150.000 (Table 2). There was also a moderate elevation in CRP levels among the cases, with the mean CRP being 3.78 mg/dL (Table 1).

Patients were discharged after 7-10 days of supportive and symptomatic treatment and observation, with improvements in both clinical and laboratory findings. No additional complications developed in the patients. Among the cases, two had chronic diseases including diabetes mellitus, one had hypothyroidism, two had asthma, two had hypertension and coronary artery disease, and one patient had chronic atrial fibrillation.

DISCUSSION

Our results showed a concentration of sandfly fever cases in the earthquake-affected region. It was observed that the cases that presented to our clinic exhibited acute hepatitis, characterized by a significant increase in transaminases. Additionally, some of the most important findings were the increases in CK and LDH levels. There were also cases presenting with leukopenia and thrombocytopenia. Furthermore, in our study, clinical deterioration and multiple organ dysfunction were noted, particularly in middle-aged and elderly patients with impaired oral intake, delayed access to supportive treatment, and comorbidities.

Sandfly fever outbreaks have been reported in Türkiye, especially after 2010^[6,8,9]. Data from Türkiye indicate that sandfly fever cases are predominantly endemic along the Mediterranean and Aegean coasts, particularly in the regions of Adana, Mersin, İzmir, and Antalya^[7,9-11]. Kocak Tufan et al. and Carhan et al. also reported an outbreak of sandfly fever in the Ankara region^[8,9]. Kayabaş et al. reported a sandfly fever outbreak of 25 cases in 2014 at a construction site in the Malatya region where cleanliness and environmental conditions

Table 2. Numerical and percentage representation of abnormal results

Variable	*n= 17 (Total)	(%)
AST (>40 U/L)	17	100
ALT (>40 U/L)	17	100
LDH (>250 IU/L)	15	88.23
CK-MB (>25 U/L)	11	64.70
CK (>200 U/L)	8	47.05
GGT (>65 U/L)	7	41.17
ALP (>150 U/L)	3	17.65
CRE (>1.3 mg/dL)	3	17.65
CRP (>0.5 mg/dL)	13	76.47
Leukopenia (<4500)	9	52.94
Neutropenia (<2000)	9	52.94
Thrombocytopenia (<150000)	7	41.17
Lymphopenia (<1000)	5	29.41

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK-MB: Creatine kinase-MB, CK: Creatine kinase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, CRE: Creatinine, CRP: C-reactive protein.

were inadequate^[12]. It has been stated that global epidemiological changes, expansions in trade and transport networks, and demographic and climate changes contribute to the spread of vector-associated infections^[13,14]. Hendrickx et al. reported that vector-related infections, particularly sandfly fever, which is endemic to the Mediterranean region, have begun to be seen more frequently in Europe in recent years due to social mobility and the increased transportation of food and beverages^[15]. The sandfly fever outbreak we reported occurred in the summer months following the February 6 Kahramanmaraş earthquake, during a period of significant destruction. During this time, communities were living in tents and containers, environmental cleanliness and hygiene conditions were poor, and there was intense transportation into the region for support. In our literature review, no articles related to a sandfly fever epidemic in our region in recent years were found, except for our study. For these reasons, the increase in cases during this period was thought to be related to the prevailing conditions. Given the known increase in epidemics following disasters, our findings suggest that sandfly fever epidemics may occur in Türkiye when suitable conditions develop. This highlights the need for necessary precautions to be taken in this regard.

Although publications are reporting that acute hepatitis may develop in the clinical course of sandfly virus fever (Papatacci fever), comprehensive studies on this subject are limited in the literature^[8,11,16,17]. There are publications reporting that the elevation of CK is also a finding in the course of sandfly fever^[6,11,18]. All of the patients in our case series presented to our clinic primarily with symptoms of acute hepatitis. A significant 8-9 fold increase in the average transaminase levels of the cases was detected, and they were subsequently followed up and treated as inpatients in the clinic. Additionally, in our series, CK elevation was found to be a significant finding, with an average elevation of five times the upper limit of normal observed. These findings are valuable as they show that moderate to severe elevations in transaminases and creatine kinase may occur in sandfly fever. The development of

leukopenia and thrombocytopenia in laboratory findings of sandfly virus infection has also been reported^[6,19,20]. Although the cases presented to the clinic with non-specific complaints, the most important clinical finding in our study was the development of acute viral hepatitis. Mild leukopenia and thrombocytopenia were observed in approximately half of our cases. We observed that renal dysfunction developed along with fever, poor oral intake, and dehydration, particularly in a group of elderly patients with chronic diseases. None of our cases developed signs of meningoencephalitis, and all patients responded well to treatment and were discharged in good condition.

The limitations of our study include its single-center design, the small number of cases, and its retrospective nature. It is thought that a larger case series could be provided if data from other clinics in the region were included in the study. Although the number of cases decreased with the arrival of winter, the possibility of a more intense epidemic next summer is foreseeable if the post-earthquake period is prolonged, environmental conditions are not improved, cleaning and hygiene conditions remain poor, building demolitions continue intensively, and population mobility remains high due to ongoing external aid.

As a result, our study showed that vector-related (sandfly, mosquito) epidemics may develop in our region, especially during the warm months, when suitable conditions develop, such as after an earthquake. It emphasizes that sandfly fever should be considered along with other hepatotropic viral infections in patients presenting with increased transaminase and creatine kinase levels and signs of infection. It also highlights the need for caution regarding the potential for larger and more serious epidemics in the region during future summers if current conditions continue.

ETHICS COMMITTEE APPROVAL

This study was approved by the Malatya Turgut Özal University Non-Invasive Clinical Research Ethics Committee (Decision no: 37, Date: 27.12.2023).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: DK, ŞED

Analysis/Interpretation: All of authors

Data Collection or Processing: NGY, HMC

Writing: NGY, HMC, DK

Review and Correction: DK, ŞED

Final Approval: All of authors

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