

Case Report

Sandfly Fever with Skin Lesions: A Case Series from Turkey

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(Received 13 Apr 2015; accepted 17 Feb 2016)

Abstract

Sand fly fever (SF) is an arthropod-borne viral disease, also known as “Phlebotomus fever”, “mosquito fever”, three-day fever or “Papatacci fever”. It is transmitted by *Phlebotomus papatasi*, starts with acute onset of high fever, and lasts for three days. We present first cases in a different district of Turkey with the clinical findings of fever, myalgia-arthralgia, headache, gastrointestinal symptoms such as diarrhoea and nausea-vomiting and skin lesions (in two of them). All the patients were treated symptomatically and discharged with complete cure. These cases are indicating that sand fly fever is more common than we thought. It should be considered in the differential diagnosis in patients presenting with fever, arthralgia-myalgia and skin lesions, especially it is important to be aware of this disease in travellers returning from endemic areas.

Keywords: Sandfly fever, *Phlebotomus* fever, Skin lesions

Introduction

Sand fly fever (SF), also known as *Phlebotomus* fever, three-day fever or pappataci fever, is an arthropod-borne disease caused by different types of *Phlebovirus* belonging to family Bunyaviridae and transmitted by phlebotomine sand flies (Dionisio et al. 2003). Sand fly fever occurs in subtropical countries, particularly in the countries around the Mediterranean Sea, and cases have been reported from the Balkans, Russia, Iraq, Iran, Pakistan, India and some parts of South America (Eitrem et al. 1991, Saidi et al. 1977, Tavana 2007). In the Mediterranean area, the common serotypes of phleboviruses are Sand fly fever Sicilian virus (SFSV), Sand fly fever Naples virus (SFNV) and Toscana virus (TOSV) (Izri et al. 2008).

In endemic areas, infections occur during the summer due to the activity of the Sand fly vectors (Dionisio et al. 2003, Konstantinou

et al. 2007). Furthermore, the disease may occur among travellers and troops going to endemic countries and among immigrants from endemic regions (Eitrem et al. 1990, 1991, Imirzalioglu et al. 2006, Ellis et al. 2008, Nissen et al. 2011).

Infections with sand fly fever are generally mild, but acute encephalitis may present with Toscana virus. The incubation period is between three and six days, and then high fever (39–40 °C) develops afterwards (three-day fever) (Dionisio et al. 2003, Konstantinou et al. 2007). Patients present with influenza-like symptoms, including headache, myalgia, photophobia, retro-orbital pain, arthralgia, fatigue, chills and abdominal discomfort, and they usually recover within a few days to weeks. Significant leukopenia, thrombocytopenia and elevation of serum aspartate-aminotransferase (AST) and alanine-aminotrans-

ferase (ALT) levels are characteristic laboratory findings (Dionisio et al. 2003, Konstantinou et al. 2007). Given that the symptoms of sand fly fever are non-specific and may mimic a broad spectrum of infectious diseases and haematological malignancies, difficulty in differential diagnosis and misdiagnosis is frequent. Recently, sand fly fever and Crimean-Congo haemorrhagic fever (CCHF) have become important public health problems in some regions in Turkey although their vectors are different. These two diseases are characterised by fever, arthralgia-myalgia headache, gastrointestinal symptoms such as diarrhoea, nausea and vomiting, and abnormalities in liver enzymes and haematological test results (McGraw Hill 2007). Distinguishing one disease from the other has become important because of the different transmission, prognosis and management of the diseases.

Although hives on skin due to insect bites may occur in cases with sand fly fever, primary skin lesions have not been described previously. In this paper, we present the first cases of sand fly fever infection with skin lesions misdiagnosed as CCHF in Yozgat Province, Turkey. We aim to increase awareness about sand fly fever and its unusual findings. Yozgat is a province in Central Anatolia located in an endemic area for CCHF. The city has not been reported as the endemic areas for sand fly fever, and thus the other purpose is to emphasise that sand fly fever may be more common than we thought.

Case report

Four patients from Yozgat Province in 2015 were admitted to the Infectious Disease Unit of Yozgat State Hospital, Yozgat Province, Turkey, with clinical findings of fever, myalgia-arthralgia, headache, gastrointestinal symptoms such as diarrhoea, nausea and vomiting, and skin lesions (superficial erythematous lesion in two patients). The patients dealt with livestock, lived in a rural endemic

area for CCHF, but had no history of tick bites. In the physical examination, all patients had fever >38.3 °C, and their system evaluations revealed normal findings except for the dermatologic lesions (Fig. 1).

Laboratory findings revealed leukopenia (2100 cell/ μ L–4500 cell/ μ L), thrombocytopenia (80000 cell/ μ L–110000 cell/ μ L), elevated AST (65 IU/L–218 IU/L), elevated ALT (72 IU/L–305 IU/L), elevated creatinine phosphokinase (268 U/L–1441 U/L) and elevated C-reactive protein (35 mg/L–50 mg/L) in all patients. The patients were hospitalised with presumptive diagnosis of CCHF because of haematological findings accompanying high fever. During hospitalisation, additional microbiological analyses were performed for differential diagnosis. Stool samples were obtained from three patients suffering from diarrhoea. Direct microscopic examination and culture of the stool samples did not reveal any features. Gruber–Widal agglutination tests for *Salmonella* and tube agglutination tests for *Brucella* were negative. The clinical and laboratory findings of the patients are presented in Table 1.

The patients were tested for possible CCHF, *Borrelia burgdorferi* and sand fly fever. Although the same vector is involved in cutaneous leishmaniasis, we did not perform any test for cutaneous leishmaniasis but preferred to follow-up on the lesions of the patients when we considered the clinical findings and abnormal laboratory values. Serum samples were sent to the Virology Reference Laboratory of Public Health Institution of Turkey in Ankara. All serum samples were negative for CCHF real-time polymerase chain reaction (RT-PCR) and CCHF IgM. *Borrelia burgdorferi* and also tested by a commercial mosaic immunofluorescence test (IFT) (Euroimmun, Germany) for the detection of specific IgM and IgG antibodies against SFSV, SFNV, and TOSV. SFV-IgG antibodies were positive for the SFSV serotype in two patients, and SFV-

IgM antibodies were positive for the SFSV serotype in all patients. SFSV by RT-PCR was positive in all patients.

All patients were treated symptomatically

and discharged following complete recovery, including that of skin lesions. The diagnosis of Lyme disease and cutaneous leishmaniasis was excluded clinically.

Table 1. Symptoms, clinical and laboratory findings of patients

Patient number	1	2	3	4
Gender/age (yr)	Female/24	Male/26	Male/27	Male/28
Fever	38.3	39.7	38.8	39.1
Headache	Yes	Yes	No	No
Myalgia/arthralgia	Yes	Yes	Yes	yes
Diarrhoea	No	Yes	Yes	no
Nausea/vomiting	No	Yes	Yes	No
Skin lesion	Yes	Yes	No	No
WBC count ($10^9/L$)	2100	2700	3200	4500
Platelets ($10^9/L$)	80000	82000	98000	110000
CRP (mg/dL)*	38	35	42	50
AST/ALT (I.U)*	65/86	92/72	218/305	124/99
CK (mg/dL)*	743	1441	268	648
SFV-IgM	+	+	+	+
SFV-IgG	+	-	+	-
PCR result	+	+	+	+

WBC, white blood cell, CRP, C-reactive protein, AST, aspartate aminotransferase; ALT, alanine aminotransferase, CK, creatine kinase, SFV, sand fly virus,

*: Normal values: CK 21–232 mg/dl, CRP <5 mg/dl, AST 15–37 mg/dl, ALT 30–65 mg/dl.



Fig. 1. Superficial erythematous lesions of patients

Discussion

Although sand fly fever has been known for a long time, it remains a significant public health problem in some parts of world (Tesh et al. 1976, Dionisio et al. 2003). The prevalence of sand fly fever is related to the distribution of its vector. After World War II, human cases and outbreaks were reported

from many countries, mainly around the Mediterranean area, the Middle East and Central Asia (Saidi et al. 1977, Darwish et al. 1987, Tavana 2001, Konstantinou et al. 2007). Infected phlebotomine sand flies remain infected through their lifetime, and the virus may be transmitted transovarially, which leads to the further spread of the disease. The distribution of the disease may not be limited to the reported areas and may be underdiagnosed in many regions, even in endemic regions (Depaquit et al. 2010).

Sand fly fever viruses cause a variable clinical picture involving asymptomatic diseases, mild and self-limited diseases and central nervous system complications (Dionisio et al. 2003 and Imirzalioglu et al. 2006). None of the clinical and laboratory findings is distinctive. Therefore, most infectious diseases, such as influenza, viral haemorrhagic

fever, brucellosis and salmonellosis, are determined in differential diagnosis depending on the regional endemic diseases. Conversely, sand fly fever is a neglected disease. As it is usually not suspected, diagnosis is difficult and may lead to unnecessary and expensive laboratory tests especially in travel-related conditions.

Recently, sand fly fever outbreaks and cases have been reported in Turkey, especially in the Mediterranean region and in Central Anatolia. All three serotypes (SFSV, SFNV and sand fly Turkey virus) have been identified (Ergunay et al. 2011). In this report, the first cases of sand fly fever in a distinct city were described. Fever, myalgia–arthralgia, headache and gastrointestinal symptoms such as diarrhoea, nausea and vomiting were the most common symptoms in our cases as previously reported. Laboratory findings included leukopenia, thrombocytopenia, elevation of ALT and AST levels and elevation of creatinine phosphokinase (Konstantinou et al. 2007, Ergunay et al. 2011). As Yozgat is an endemic region for CCHF, we had to consider presumptive diagnosis. Moreover, we had to distinguish it from Lyme disease because of the appearance of lesions on the leg of the first patient. Similar findings have also been presented in previous studies, but skin lesions have not been reported (Eitrem et al. 1990, Simsek et al. 2007, Konstantinou et al. 2007, Semenza and Menne 2009, Torun et al. 2010, Carhan et al. 2010, Ergunay et al. 2011). Cutaneous leishmaniasis is another disease to distinguish.

The detection of IgM antibody is a reliable method for the diagnosis of an acute sand fly fever infection, but cross-reactions can occur among SFV serotypes (Dionisio et al. 2003). We confirmed the diagnosis by PCR.

Some recommendations to be considered for sand fly fever prevention. These recommendations include conduct public awareness and education campaigns, avoid contact with animals and apply repellents in endemic

areas, in addition to being awareness of sand fly fever signs and symptoms (Tavana 2015).

Conclusion

Sand fly fever may be common in all subtropical countries and may present with unusual symptoms, as shown in this case report. Physicians should keep it in mind during differential diagnosis of cases with compatible clinical manifestations, even in the presence of dermatological lesions in travellers returning from endemic areas.

Acknowledgements

We acknowledge the contributions of all research team members who have played crucial role in data acquisition. Each author has contributed important intellectual content during manuscript drafting or revision. The authors declare that there is no conflict of interests.

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