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Case Report

Dengue fever in Lebanon: First confirmed case since 1945 and review from the region

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Abstract

Lebanon yearly witnesses a high flux of expatriates and workers from Dengue virus (DENV) endemic regions. Multiple cases of Dengue fever have been documented at the American University of Beirut Medical Center (AUBMC) in travellers to endemic regions. Given the presence of the *Aedes aegypti* mosquito in Lebanon, introduction of DENV to the country is highly likely. We report a case of DENV infection in Lebanon diagnosed in April 2012 in a patient with no prior travel history. The patient presented with fever (39°C) and lower urinary tract symptoms and was initially diagnosed with culture negative prostatitis. He was started on empiric antibiotics but continued to have severe headache, diffuse myalgias, bone pain, and fatigue. He later developed a faint rash with leukopenia and thrombocytopenia. Extensive work-up was unrevealing. DENV IgM and IgG were positive suggesting acute infection. This is the first reported case since 1945 from Lebanon in a patient with no prior travel history.

Key words: Dengue; Lebanon; DENV; MENA.

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Introduction

DENV is a member of the family Flaviviridae. The Dengue complex comprises four distinct serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) and infection with one serotype confers long term immunity to that serotype only as cross resistance is partial and temporary [1]. Dengue fever is a public health concern and gained particular interest from the World Health Organization (WHO) which issued the latest guidelines in 2009 [2]. DENV is transmitted to humans through the bites of infected *Aedes* mosquitoes, principally *Ae. aegypti* and *Ae. Albopicus* [3]. Most patients recover following a self-limiting non-severe clinical course while a small proportion progress to severe disease, mostly characterized by plasma leakage with or without haemorrhage, so-called severe dengue [4].

This report focuses on the clinical presentation of DENV in a Lebanese patient with no prior travel history and serves to raise awareness among healthcare providers about the presence of DENV and its vector in Lebanon. To the best of our knowledge, this is the first case of Dengue fever reported from Lebanon since 1945 in a patient with no travel history.

Case Report

The patient is a 47 years-old Lebanese man, previously healthy, living in Aley, Mount Lebanon governorate, and presented to the American University of Beirut Medical Center in April 2012 for lower urinary tract symptoms with fever (39°C) and chills. He had severe fatigue with myalgias. The patient had no prior history of urinary infections. He denied flank pain and penile discharge. The patient took ciprofloxacin before presentation. He was started empirically on intravenous ciprofloxacin after collecting urine and two sets of blood cultures. Urinary symptoms improved, however, fever persisted. The patient was previously healthy. He had never travelled before. His physical examination was unremarkable. Laboratory exams (Table 1) showed a normal complete blood count (CBC) with a white blood cells count (WBC) of 7,800/mm^3 and 90% neutrophils. Alkaline phosphatase 90 IU/L, Aspartate Aminotransferase (AST) 53 IU/L, Alanine Transaminase (ALT) 75 IU/L, Gamma-Glutamyltransferase (GGT) 218 IU/L, bilirubin total/direct 1.1/0.5 mg/dL, urine analysis showed numerous white blood cells. Chest X-ray was negative. He continued to have chills and was switched to ceftriaxone the following day to cover for possible quinolone resistant Enterobacteriacae. Urine and blood cultures were negative. Ultrasound of kidneys and pelvis showed a slightly enlarged prostate with a non-significant post-void residue. Anaemia work-up showed normal iron studies and no evidence of

Table 1. Patient's laboratory data during hospitalization.

	April 9	April 10	April 12	April 13	April 14	April 15	April 16
WBC (cells/mm^3)	7800	4300	3500	4900	4100	5000	4800
Neutrophils (%)	90%	81%	66%	78%	65%	54%	52%
Lymphocytes (%)	5%	10%	20%	13%	22%	30%	30%
Monocytes (%)	5%	8%	14%	9%	13%	15%	14%
Hemoglobin (g/dL)	14	14	13.8	14	13.9	13.9	13
Hematocrit (%)	41	42	41	41	40	41	38
Platelets (10^3/mm^3)	167	141	125	130	138	193	253
Alkaline Phosphatase (IU/L)	90		168	175	206		182
GGT (IU/L)	218		385	383	464		437
AST (IU/L)	53		94	139	286		142
ALT (IU/L)	75		99	134	236		202

WBC: White Blood Cells; GGT: Gamma-Glutamyltransferase; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; IU/L: International Units Per Liter.

haemolysis. Ceruloplasmin, LDH, and alpha-1 antitrypsin levels were normal and antinuclear antibody test (ANA) was negative. Abdominal ultrasound and Magnetic resonance cholangiopancreatography were negative. Four days later, his urinary symptoms improved but he complained of severe headaches radiating to the orbital area, myalgias, bone pain and night sweats. Brucella antibodies (direct and indirect) and urine for TB Polymerase Chain Reaction (PCR) and acid-fast stain were negative. Repeat CBC showed a WBC of 3,500/mm^3 and a platelet count of 125,000 /mm^3. Two days later, the patient developed a non-pruritic faint rash over his chest. At this point, other diagnoses were considered. Hepatitis B and C serology, HIV antibodies, malaria smear, Weil Felix serology, EBV IgM and CMV IgM all returned negative. The patient was still complaining of diffuse myalgias, bone pain and severe headache with orbital pain with normal neurologic exam. In view of the persistent fever, severe headache, rash, leukopenia and thrombocytopenia, a serum sample was obtained on the eighth day of illness for DENV serology testing. DENV laboratory tests are not available in Lebanon. The serum was sent to Bioscientia labs in Germany. Fever subsided after a total of 10 days. The patient was discharged home on an empiric course of meropenem and vibramycin for 10 days. Later on, after discharge home, DENV serology (using NovaLisa Dengue IgG/IgM ELISA) came back positive with IgM of 4.1 (negative < 0.9) (sensitivity 90% and specificity 97.6%) and IgG 2.9 (negative < 0.9) (sensitivity of > 90%, specificity 93%) establishing a presumptive diagnosis of DENV infection. The Lebanese Ministry of Public Health (MOPH) was informed about the case and vector control measures were taken. Upon later follow-up, no family members or neighbours were reported to have undefined fever before or after the diagnosis of DENV fever in our patient. DENV IgG testing was not performed on family members or neighbours due to the unavailability of the test in Lebanon and the expenses associated with sending the test abroad. Since 2012, no cases of DENV were diagnosed in Lebanese non-travellers. This could be related to a multitude of causes including the vague clinical presentation coupled with the lack of awareness of healthcare providers about the presence of this disease among non-travellers and the unavailability of DENV diagnostic tests in Lebanon.

Discussion

Our patient had on presentation lower urinary symptoms and was diagnosed and treated as having culture negative prostatitis. However, he had complaints of severe headache, retro-orbital pain, sweating, severe myalgia and bone pain that suggested an alternative diagnosis. The leukopenia and thrombocytopenia suggested the possible diagnosis of dengue fever. This man had not travelled outside Lebanon. The diagnosis of DENV infection can be confirmed either by detecting viral nucleic acid in the serum by real-time PCR (RT-PCR), typically during the first five days of illness or by detecting the viral soluble non-structural protein 1 (NS1) typically during the first seven days of illness with the highest sensitivity during the first four days of illness [5,6]. Detection of IgM seroconversion by enzyme-linked immunosorbent assay (ELISA) on paired samples taken in the acute (as early as four days from the onset of symptoms) and convalescent phases confirms the acute DENV infection, whereas detection of IgM on a single specimen in a patient with compatible signs and

symptoms of DENV infection would establish a presumptive diagnosis [7]. Our patient was not vaccinated or suspected of having an infection with a related flavivirus (e.g. Yellow Fever virus, Zika virus) which, if present, could have produced false positive serologic results [5,7]. Given that DENV laboratory tests are not available in Lebanon and given the expenses, only a single serum specimen was sent for IgM and IgG ELISA on the eighth day of illness and returned positive, establishing a presumptive diagnosis of DENV infection.

Climate conditions in the Middle East and North Africa (MENA) (extremely dry weather) were historically not favourable for the disease vector, however, Pakistan and the Red Sea countries are currently known to harbour the DENV [8]. Climate change may promote the spread of the *Aedes* mosquitoes into geographical areas previously thought to be unfavourable for the vector [9]. War and conflict in the Middle East represent perfect conditions for arthropod-borne diseases outbreaks. Most recently, leishmaniasis outbreaks have been reported in Syrian refugee camps from multiple countries such as Lebanon [10] and Turkey [11]. Immigration and refugee displacement from endemic areas, urbanization, poor sanitary measures, use of open water storage containers and lack of vector control methods are all risk factors for the emergence of DENV and other arthropod-borne diseases in the Middle East [12,13]. Following the second conference of the Eastern Mediterranean Public Health Network (EMPHNET), Al Nsour *et al.* summarized the reported cases of dengue fever infection in the Eastern Mediterranean (EM) Region [14].

In Lebanon, located in the Eastern Mediterranean coast, DENV was considered endemic, causing extensive epidemics (years 1861, 1889, 1913 and 1921). The last reported epidemic occurred in the fall of 1945 and affected more than a third of the 300,000 persons living in Beirut. In 1948, Saad B. wrote about dengue in Lebanon and described four particularities of this viral infection: it occurs more commonly in the summer and much less in the cold season, it has a trend to affect more than one family member at the same time, it is commonly seen following a flu illness, and it seems that the epidemic has a periodic rhythm where it comes after the immunity to a previous infection has waned [15]. It was estimated to affect more than 25% of the people living on the Lebanese coast in Beirut, Tripoli, Tyre and Sidon. Rarely, it was seen at high altitudes. The diagnosis was historically made clinically based on the presence of severe backache, diffuse arthralgias, mainly in the knees, high grade fever reaching 40°C, low appetite, generalized weakness, eyelids oedema, heavy sweats and severe asthenia. It was known as "danac", vulgarly named "aboul-rekab" in view of the marked severe pain in the knees [16]. However, no serological tests were available to confirm the diagnosis. Since these initial reports and for more than 60 years, dengue fever was not reported again in Lebanon despite the fact that evidence of arbovirus infection was established in Lebanese residents in a serologic survey using hemagglutination inhibition (HAI) tests carried out in 1962-65 [17]. The results showed antibodies to DEN- 1 in 49.1% and DEN- 2 in 61.9% of the tested subjects. At that time, the attempt to isolate the virus from the mosquitoes was unsuccessful. *Ae. aegypti* is thought to have been eliminated from the country during malaria control program and mosquito elimination efforts that occurred between 1945-1975 [18]. These control programs completely ceased after the start of the civil war in 1975 [18] and since then, there was always a concern that mosquitoes with their potential to transmit diseases (dengue fever, West Nile and malaria) live among us [19]. The first time a mosquito with the potential to transmit DENV was recorded in Lebanon and Syria by N. Haddad *et al.* in 2003 and 2005 who published their findings in 2007 [20]. Numerous larvae of the *Ae. albopictus* mosquito were collected from four locations in Lebanon: Sarba (Mt. Lebanon), Chibtine and Batroun (North) and Hermel (Bekaa). One female was collected from one location in Syria: Kotryeh (Latakia) [21]. Interestingly, our patient lived in the Mt. Lebanon governorate where larvae of the *Ae. albopictus* have been collected, however, the patient lived and worked in good sanitary conditions and reported no presence of open water storage containers around. The mosquito called "black-and-white striated mosquito" is recognized as an aggressive biter but no one has linked any clinical picture with its bite. More recently, *Ae. albopictus* Lebanese specimens were sampled by Haddad *et al.* in 2009 and 2010 and a phylogenetic analysis was done [20]. Results showed an efficient transmission of the three arboviruses, CHIKV (Chikungunya virus), DENV and WNV (West-Nile virus) by the mosquito and a marked preference for human blood (46.8% fed on humans). *Aedes*-borne diseases should thus be regarded as a potential threat in Lebanon. The introduction of DENV, WNV and CHIKV to Lebanon is highly likely given the flux of workers and the return of Lebanese expatriates from endemic areas in Latin American, MENA and South-East Asia [18].

Conclusion

Dengue fever has become a global problem which now includes the MENA region. There is no doubt that we do have DENV and its vector in Lebanon. The infection could be underdiagnosed in this region. Early diagnosis might prevent the unnecessary use of empiric antibiotics and the excessive unnecessary and expansive laboratory work-up of persistent fever.

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