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Case Report

Zika virus infections imported from Brazil to Portugal, 2015

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ABSTRACT

Zika virus is an emerging arbovirus transmitted by *Aedes* sp. mosquitoes like the Dengue and Chikungunya viruses. Zika virus was until recently considered a mild pathogenic mosquito-borne flavivirus with very few reported benign human infections. In 2007, an epidemic in Micronesia initiated the turnover in the epidemiological history of Zika virus and more recently, the potential association with congenital microcephaly cases in Brazil 2015, still under investigation, led the World Health Organization (WHO) to declare a Public Health Emergency of International Concern on February 1, 2016.

Here, we present the clinical and laboratory aspects related to the first four imported human cases of Zika virus in Portugal from Brazil, and alert, regarding the high level of traveling between Portugal and Brazil, and the ongoing expansion of this virus in the Americas, for the threat for Zika virus introduction in Europe and the possible introduction to Madeira Island where *Aedes aegypti* is present.

Introduction

Zika virus (ZIKV) is a member of the Spondweni serocomplex within the genus *Flavivirus* firstly isolated in 1947 from a sentinel rhesus monkey in Zika Forest, Uganda [1]. There are two main lineages of ZIKV, the African and the Asian lineages [2,3].

ZIKV was until recently considered a mildly pathogenic mosquito-borne flavivirus with very few reported human cases of self-limiting acute febrile illnesses most often with maculo-papular rash, headache, arthralgia, myalgia and conjunctivitis [4–6]. In 2007, after an epidemic in Micronesia [7,8] the geographic range of ZIKV expanded dramatically. In 2013–2014, through an outbreak in French Polynesia a link relating ZIKV infections with the increased incidence of Guillan–Barré syndrome and other neurological complications was assumed mainly in regions with previous dengue epidemics [9,10]. The potential association with congenital microcephaly cases in Brazil 2015 [11,12], still under investigation, raise several questions, that undoubtedly increase public health awareness to ZIKV, and led the WHO declaration, considering "the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia" a Public Health Emergency of International Concern on February 1, 2016 [13]. As most pathogenic flavivirus, only a small percentage of ZIKV cases (estimated to be about 25%) are symptomatic [8], and transmission via transfusion of infected blood or organs donations, or sexual transmission, remains a risk.

Here we report four cases of patients with Zika infection, diagnosed in Portugal, shortly after returning from Brazil. In June 2015, Zika virus infection was serologically detected for the first time in a couple returning from Ceará state and in the end of 2015, Zika virus was detected in the urine samples of two patients after visiting Rio de Janeiro and Espírito Santo states.

Case presentation

Cases 1 and 2

In June 2015, a Portuguese couple in their sixties with no past medical history, traveled to northeast Brazil (Ceará State) on holidays for two weeks. At midstay (day 1 of illness) both developed fever (38.3 °C) and arthralgias. The fever lasted for three days, responding to acetaminophen and ibuprofen. Arthralgias were located in the hands, wrists and ankles, lasting till admission. At day 4, they complained of macular rash with no pruritus,

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predominantly on the lower limbs in the woman, and on the trunk in the man. Both reported anorexia with weight loss and the man felt asthenic.

Upon admission in Portugal, on day 11 of illness, they both appeared sick and tired with dry mucosae and lower extremity rashes below the knee. The laboratory findings in the hospital were within normal limits, except for C-reactive protein 10.6 mg/L (norm: <5 mg/L) and slightly elevated aminotransferase, ALT 58 U/L for the man and 52 U/L for the woman (norm: 4–50 U/L). Specific diagnostic was requested for Dengue, Zika and Chikungunya viruses. Serology was IgM positive for Zika virus in both patients. The patients recovered without complications.

Case 3

A 62 year old Brazilian woman, with a past medical history of systemic lupus erythematosus, fibromyalgia, cardiomyopathy and hyperuricemia who had lived in Portugal for the last 15 years, developed fever, myalgias and arthralgias on November 22 2015 after a month trip to Rio de Janeiro and Espírito Santo states (southeast Brazil). The next day, she developed a maculopapular rash, more prominent on the forearms and thighs with mild conjunctival hyperemia. In the ER, on the fourth day of illness, she was afebrile and hemodynamically stable. Basic laboratory workup did not revealed leukopenia, thrombocytopenia or abnormal liver enzymology. The fever continued for eight days in total, with bi-daily peaks. The rash remained from the second to the sixth day of illness, as well as myalgias. Differential serological diagnosis was requested for *Trypanosoma* sp., Chikungunya, Dengue and Zika viruses. The serology (ELISA) for *Trypanosoma* sp. was negative. Real-time PCR in urine and IgG serology were positive for Zika virus.

The patient had only symptomatic treatment with paracetamol and full recovery without sequel. She kept her long term medication with chloroquine sulphate, digoxin, candesartan, carvedilol, furosemide, trazodone, duloxetine and alopurinol.

Case 4

A 57 year old Portuguese man, with no past medical history, presented on December 7 2015 complaining of chills, generalized asthenia and myalgia and rash, one day after returning from Rio de Janeiro after a 10 day stay. The study in the hospital revealed

Table 1
Characteristics of the four imported cases of Zika virus infections based on epidemiological, clinical and virological data.

		Case 1	Case 2	Case 3	Case 4
Epidemiological data					
Gender		Male	Female	Female	Male
Age		61 years	59 years	62 years	57 years
Date of return		26 Jun. 2015	26 Jun. 2015	22 Nov. 2015	6 Dec. 2015
Onset of symptoms		19 Jun. 2015	19 Jun. 2015	22 Nov. 2015	7 Dec. 2015
Clinical data					
Fever		3 days	3 days	8 days	5 days
Arthralgia		Hands, wrists and ankles	Hands, wrists and ankles	Discrete	–
Myalgias		No	No	Yes	Generalized
Skin rash		Maculopapular: trunk	Maculopapular: lower limbs	Maculopapular: forearms and thighs	Maculopapular: generalized
Anorexia		Yes	Yes	No	No
Asthenia		Yes	No	No	Yes
Conjunctivitis		No	No	Yes	No
Leucopenia		No	No	No	No
Thrombocytopenia		No	No	No	126 000/μL
Elevated liver enzymes		ALT 58 U/L	ALT 52 U/L	No	No
Viral investigation					
1st sample (days post onset)		13	13	8	9
Zika virus	RT-PCR blood	–	–	NS	–
	RT-PCR urine	NS	NS	+(Ct = 34.76)	+(Ct = 34.57)
	IgM[a]	+128	+64	–	–
	IgG[b]	+512	+512	+262,144	–
Dengue virus	RT-PCR blood	–	–	NS	–
	RT-PCR urine	NS	NS	–	–
	IgM	–	–	–	–
	IgG	+64	+256	+131,072	–
Chikungunya virus	RT-PCR blood	–	–	–	–
	RT-PCR urine	NS	NS	NS	ND
	IgM	–	–	–	–
	IgG	–	–	–	–
2nd sample (days post onset)		25 days	25 days		11 days
Zika virus	IgM	+64	+32	NS	+32
	IgG	+1024	+512	NS	–
Dengue virus	IgM	–	–	NS	+16
	IgG	+64	+128	NS	–
3rd sample (days post onset)	–	–	–		
Zika virus	IgM	NS	NS	NS	+32
	IgG	NS	NS	NS	+64
Dengue virus	IgM	NS	NS	NS	–
	IgG	NS	NS	NS	–

(+) positive; (–) negative; Ct: cycles threshold; ND: not determined; NS: not sampled.
[a] IgM cut-off value 16.
[b] IgG cut-off value 32.