CASE REPORT

ZIKA VIRUS INFECTION IN AUSTRALIA FOLLOWING A MONKEY BITE IN INDONESIA

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Abstract. A traveller returning to Australia developed Zika virus infection, with fever, rash and conjunctivitis, with onset five days after a monkey bite in Bali, Indonesia. Flavivirus RNA detected on PCR from a nasopharyngeal swab was sequenced and identified as Zika virus. Although mosquito-borne transmission is also possible, we propose the bite as a plausible route of transmission. The literature for non-vector transmissions of Zika virus and other flaviviruses is reviewed.

Keywords: Zika virus, monkey bite, traveller

INTRODUCTION

Zika virus is a member of the family Flaviviridae, genus *Flavivirus*, first discovered in sentinel rhesus monkeys in Uganda in 1947 (Dick *et al*, 1952). In humans, it can produce a self-limited febrile illness similar to dengue fever, and has widespread distribution, including Africa, Southeast Asia (Olson *et al*, 1981), a well-described outbreak on Yap Island, Micronesia in 2007 (Duffy *et al*, 2009) and in the south Pacific (Roth *et al*, 2014) in 2012-2014. Genomic sequencing for the virus was completed in 2006 (Kuno and Chang, 2005) and polymerase chain reaction (PCR) assays have been developed for viral detection (Faye *et al*, 2008).

The virus is primarily thought to be transmitted via *Aedes* mosquito vectors, including *Ae. aegypti* (Boorman and Porterfield, 1956). However, a non-vector-borne transmission was recently described, probable via sexual contact (Foy *et al*, 2001). Here we report the case of an acute Zika virus infection in a returned traveller following a monkey bite in Bali, Indonesia.

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CASE REPORT

A 27-year-old Australian man presented to Royal Darwin Hospital, Australia with fever and rash following a macaque monkey bite seven days earlier at the Ubud Monkey Forest in Bali, Indonesia. He travelled to Bali on vacation ten days before his presentation, and stayed for six days before his return to Darwin. The monkey bite occurred on his right torso through his clothing, drawing blood and leaving several puncture marks (Fig 1). The wound was irrigated with water immediately after-

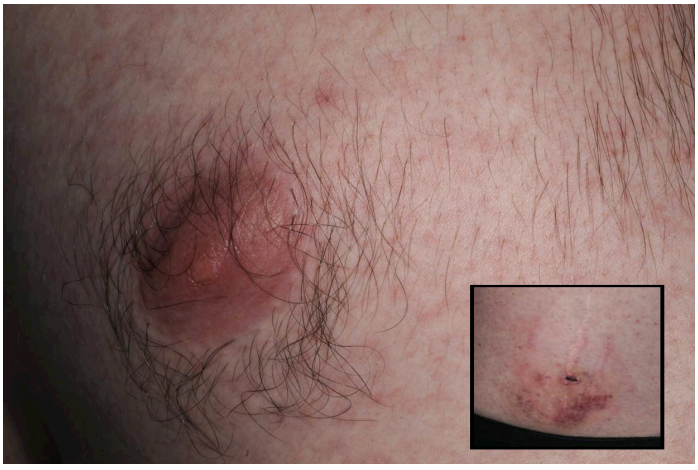

Fig 1–Generalized maculopapular rash seen on the torso and arms, with a monkey bite mark on the right inferolateral torso.

wards. He sought local medical attention the following day, and was administered two doses of rabies vaccine.

He developed fevers and myalgia two days after his return, five days following the bite. The next day he developed a generalized maculopapular blanching rash over his face, arms, legs and torso, and on the morning of hospital presentation, developed bilateral conjunctivitis. He denied headache, meningeal, respiratory or urinary symptoms.

He recalled mosquito bites whilst in Bali. There was no history of recent sexual contacts, intravenous drug use, water exposure or tick bites. There had been no other overseas travel in the previous twelve months.

On examination his temperature was 37.9°C, with normal vital signs. He had a generalised, blanching maculopapular rash (Fig 1). There were no eschars, petechiae or genital ulcers. Conjunctival injection was noted bilaterally. There was no lymphadenopathy. Throat, chest, joint, abdominal and neurological examinations were normal.

Initial investigations revealed a normal white cell count (6.1 $x10^9$/l) with mild lymphopenia (1.0 $x10^9$/l), a normal hemoglobin level (15.1g/dl) and platelet count (191 $x10^9$/l), and normal blood electrolytes, urea, creatinine, bilirubin and liver enzymes. Malaria antigens and a blood film examination for malaria parasites were negative. Dengue NS1 antigen and IgM were negative.

Although atypical, the initial concern was for possible herpesvirus B infection following the monkey bite, with one of the three initial clinical presentations of herpesvirus B infection being influenza-like illness with fever, myalgia and conjunctivitis [although rash is not a feature (Cohen *et al*, 2002)]. Serum and swabs of the bite site, conjunctivae and nasopharynx were sent to the national reference laboratory for viral PCR. He was treated with empirical intravenous acyclovir (12.5 mg/kg three times daily) pending herpesvirus B PCR. He was also given rabies immunoglobulin and rabies vaccine. His acyclovir was stopped on day 4 when his herpesvirus B PCR was reported negative, and with symptomatic improvement he was discharged. Flavivirus RNA was detected on PCR of a nasopharyngeal swab. This was sequenced and identified as Zika virus (Fig 2). Flavivirus PCR was negative in the serum and a swab sample taken from the bite site. All symptoms had resolved within two weeks. Dengue IgM and IgG serology were negative on both the initial and convalescent samples taken two weeks later. Serological tests for HIV, syphilis, rickettsiae, leptospirosis, Ross

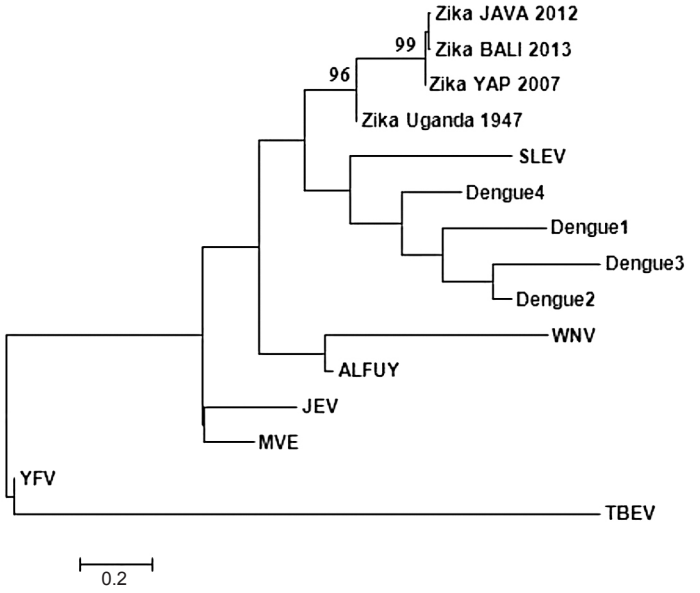

Fig 2–An unrooted phylogenetic tree of Flavivirus species generated from the sequences of the NS5 gene including Zika virus BALI 2013. Sequences from representative viruses were obtained from GenBank. Phylogenetic reconstruction used the neighbor-joining method. The Zika virus reference strains and GenBank accession numbers are Zika virus JAVA 2012 (KF258813), Zika virus Uganda 1947 (EU074027), Zika virus YAP 2007 (EU545988), Alfuy virus (EUO73972), dengue 1 (HG316481), dengue 2 (KM204118), dengue 3 (HG316484) and dengue 4 (JQ513342). The virus names abbreviated are Murray Valley encephalitis virus (MVE)(JX123032), Japanese encephalitis virus (JEV)(KF667313), West Nile virus (WNV)JX1123031), St Louis encephalitis virus (SLEV)(EU099354), yellow fever virus (YFV)(JX898880) and tick borne encephalitis virus (TBEV)(JQ825162). Bootstrap values >90% are shown. Bootstrap support was based on analysis of 1,000 replicates of the data set.

River and Barmah Forest virus were all negative on paired sera.

DISCUSSION

Zika virus is generally accepted to be transmitted by mosquitoes. The virus has been isolated from *Aedes africanus* (Dick, 1952), *Ae. aegypti* (Boorman and Porterfield, 1956; Marchette *et al*, 1969) and most recently from *Ae. albopictus* (Grard *et al*, 2014). In an early experimental model by Boorman and Porterfield (1956), a rhesus monkey became asymptomatically infected from an *Aedes aegypti* mosquito, as evidenced by seroconversion. In non-epidemic settings, Zika virus is thought to circulate in a sylvatic cycle involving mosquitoes and a predominantly non-human primate reservoir (Haddow *et al*, 2012), with humans thought to serve as primary amplification hosts during epidemics (Haddow *et al*, 2012), such as those reported from Yap island in 2007 (Duffy *et al*, 2009) and French Polynesia in 2012-14 (Roth *et al*, 2014)

Acute symptomatic Zika virus infection in the case reported here followed a monkey bite and we propose this as a potential route of transmission. Whilst mosquito-borne transmission is possible in this case, non-vector-borne transmission of Zika virus has been previously described: the source patient had returned to Colorado where the virus has never been described, the known vectors for Zika virus were absent, and the patient had not travelled to any countries known to harbour Zika virus (Foy *et al*, 2011). Exposure to bodily fluids through sexual intercourse was postulat-

ed as the probable mode of transmission (Foy *et al*, 2011). Perinatal transmission of Zika virus has also been described (Besnard *et al*, 2014). This case demonstrates the presence of Zika virus in the human pharynx and Zika virus RNA has been identified in saliva from humans with symptomatic and asymptomatic infection (Besnard *et al*, 2014), consistent with the potential for transmission from primate bites. Other flaviviruses have also been demonstrated in saliva, including dengue virus (Mizuno *et al*, 2007; Poloni *et al*, 2010). Non-vector transmission of other mosquito-borne flaviviruses has also been documented (Kuno, 2001), including several cases of dengue transmission following needlestick injuries, and a case of transmission through mucocutaneous exposure (Chen and Wilson, 2004). West Nile virus, another flavivirus, has also been demonstrated to infect humans without a mosquito vector, via direct contact with infected fluids, including blood transfusions and organ transplantation (Gould and Solomon, 2008).

Zika virus is not endemic to Australia. Two other cases of imported Zika virus have been reported in Australia, acquired during travel to Indonesia (Kwong *et al*, 2013) and the Cook Islands (Pyke *et al*, 2014), respectively. In Australia, *Aedes aegypti* exist only in northern Queensland, but the importation of one of these cases to this region highlights the potential risk for introduction to Australia (Pyke *et al*, 2014).

With millions of travellers visiting Southeast Asia each year, including areas where Zika virus is thought to be distributed, there is likely a significant underdiagnosis of Zika virus, given its self-limited nature, overlap of clinical manifestations with other viral syndromes, such as dengue fever, and only limited availability of the test to detect Zika virus by PCR. Returned travellers with a similar viral syndrome may be misdiagnosed as having dengue fever, without being tested for other flaviviruses, although the maculopapular rash and conjunctivitis (Fig 1) differ from the blanching diffuse erythema without conjunctivitis more commonly seen in dengue infection. The absence of thrombocytopenia in this and other reports of Zika infection is also unusual in dengue infection.

Tens of thousands of travellers from non-endemic areas visit Ubud and Sangeh Monkey Forests in Bali each year, and macaque bites are common (Wheatley, 1999). Transmission of Zika virus by monkey bite or other non-vector borne routes and attribution of illness to dengue or other infections may be more frequent than the absence of prior reports suggests. The implementation of molecular diagnostics for flaviviruses will allow for greater detection of this under-reported disease.

ACKNOWLEDGEMENTS

We thank Amy Crowe and Kevin Freeman for their assistance. NA is supported by a NHMRC Practitioner Fellowship.

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