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Research Note

Chikungunya virus-associated death in Malaysia

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Abstract. Chikungunya virus (CHIKV) is a mosquito-borne alphavirus which causes fever, rash, and arthralgia. In the past, life-threatening complications were very rarely reported. However, during the recent worldwide outbreaks, there have been several reports of unusually severe complications and deaths. Malaysia is experiencing a nationwide outbreak of CHIKV, with over 10 000 patients affected since April 2008. We report the first case of culture-confirmed CHIKV-associated death in Malaysia, in a patient with fever, rash, acute exacerbation of pre-existing heart failure, rhabdomyolysis, and multiple organ failure. CHIKV infections may cause atypical, severe or fatal presentations.

INTRODUCTION

Chikungunya virus (CHIKV), an *Aedes* mosquito-borne alphavirus of the *Togaviridae* family, causes outbreaks of fever, rash, and arthralgia (Sam & AbuBakar, 2006). The disease is usually self-limiting, although arthralgia occasionally persists for months. Since 2005, CHIKV has caused unparalleled worldwide outbreaks, centering on the Indian Ocean and India (Josseran *et al.*, 2006; Mavalankar *et al.*, 2007; Beesoon *et al.*, 2008).

In past outbreaks, severe complications and deaths were rarely reported. However, an excess in crude deaths was noted during the recent CHIKV outbreaks in Réunion (Josseran *et al.*, 2006), India (Mavalankar *et al.*, 2007), and Mauritius (Beesoon *et al.*, 2008). In most cases, the lack of critical clinical data, virological confirmation, and exclusion of other infectious causes make it difficult to attribute the increased mortality directly to CHIKV (Farnon *et al.*, 2008).

From April 2008 to the time of writing (March 2010), Malaysia has been experiencing a nationwide CHIKV outbreak involving over 10 000 cases, with no reported fatalities (Ministry of Health, Malaysia, 2010). We describe the first case of CHIKV-associated death in Malaysia seen at our hospital in Kuala Lumpur.

CASE REPORT

A 53-year-old male presented in December 2008 with a 2-day history of fever, rash, and acutely worsening shortness of breath. He had a history of cardiac failure and hypertension, and had not left Kuala Lumpur in the previous 2 months. On examination, he was confused, with a temperature of 39.6°C, and had a

generalised maculopapular rash. He was tachypnoeic and had bilateral coarse crackles on auscultation. A chest X-ray showed cardiomegaly and pulmonary congestion. An ECG showed no acute ischaemic changes. Ceftriaxone and azithromycin were commenced to treat the possible community-acquired pneumonia. As his conscious level and blood pressure deteriorated rapidly, he was transferred to the intensive care unit for ventilatory and inotropic support.

Blood tests showed lymphopenia (0.38 $\times 10^9$/L), raised C-reactive protein (122 mg/L), metabolic acidosis, disseminated intravascular coagulation (platelets 34 $\times 10^9$/L, deranged clotting, and positive D-dimers), and acute renal failure (peak urea 25.4 mmol/L, creatinine 490 µmol/L). A peak creatine kinase of 13,596 IU/L, with a low myocardial fraction (CK-MB) of 3%, and normal cardiac troponin T, indicated rhabdomyolysis rather than myocardial damage. There was no significant growth from blood, urine, stool, or tracheal aspirate. Initial serology tests for dengue, leptospirosis, *Mycoplasma*, typhoid and typhus were negative.

On day 2, echocardiography showed dilated chambers and a poor ejection fraction of 10%. The patient continued to deteriorate, and died on day 3, despite the initiation of haemodialysis and maximum doses of inotropes. No post-mortem was performed, and the death certificate recorded death caused by septic shock with multi-organ failure.

At the time, few CHIKV infections had been reported in Kuala Lumpur. However, the patient's son reported symptoms of fever and arthralgia in household members, although the patient himself did not have arthralgia. Two serum samples from the patient, taken on the day of death and the day before death, tested positive by PCR for CHIKV E1 and nsP1 genes (Hasebe *et al.*, 2002). PCR for dengue was negative. CHIKV was subsequently isolated from Vero cell culture of serum obtained on the day of the patient's death.

Phylogenetic analysis of CHIKV *E1* gene sequences of 1320 bp from this patient and 2 other patients from the current outbreak was performed. Sequences were aligned with Geneious 4.0.4 (Biomatters Ltd., Auckland, New Zealand). The best-fitting substitution model was estimated with jModeltest 0.1.1 (Posada, 2008), and found to be the general time reversible model with proportion of invariant sites and gamma-distributed rates among sites (GTR+I+G). The phylogenetic tree was obtained using the Bayesian Markov Chain Monte Carlo method in BEAST 1.5.4 (Drummond & Rambaut, 2007), run for 30 million generations with a 10% burn-in. The exponential model of population growth and uncorrelated lognormal clock were applied. The maximum clade credibility tree (Figure 1) was viewed using FigTree 1.3.1 (http://tree.bio.ed.ac.uk/software/figtree/). CHIKV isolates from the current Malaysian outbreak, including the deceased patient's isolate, grouped with isolates from the recent worldwide outbreaks in the Central/East African genotype, as previously reported (Sam *et al.*, 2009). There were no unique *E1* gene substitutions in the dead patient's isolate when compared to isolates from 11 other Malaysian patients with uncomplicated CHIKV infection.

DISCUSSION

Despite the involvement of many countries during the recent CHIKV outbreaks, there are few published studies on fatal cases. These are reported only from the Réunion Island and India. Linking CHIKV with deaths may be hampered by poor reporting of causes of death and lack of diagnostic facilities, especially in less-developed countries where the mosquito vectors are endemic. Deaths following unusual manifestations such as encephalitis and myocarditis have been reported in previously healthy patients infected with CHIKV (Lemant *et al.*, 2008; Tandale *et al.*, 2009). In the Réunion outbreak, most patients with severe CHIKV infection had underlying cardiac and respiratory conditions, and often presented with

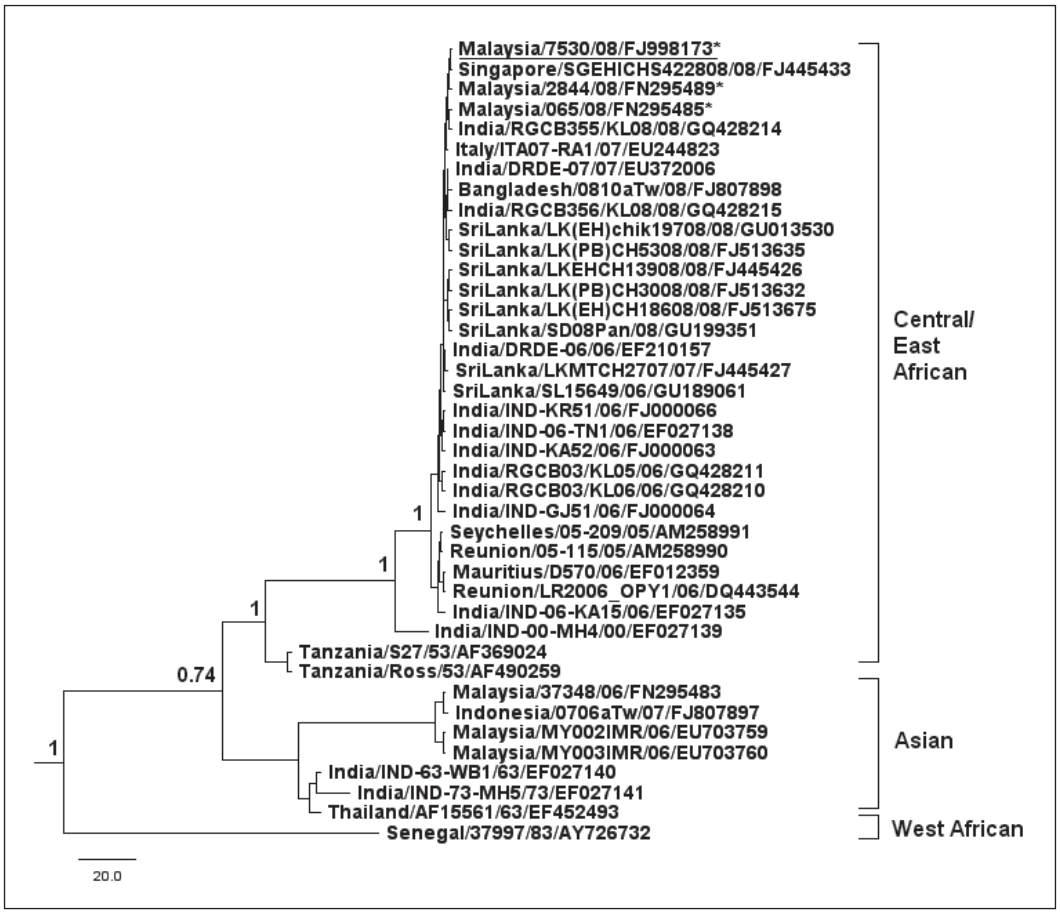

Figure 1. Maximum clade credibility tree of *E1* gene nucleotide sequences (1320 bp) of CHIKV isolated from the patient in this report (FJ998173, underlined), and other CHIKV strains available in GenBank. Isolates are named as country of origin/strain name/year of isolation/accession number. The three genotypes, West African, Central/East African, and Asian, are shown. * indicates the three CHIKV isolates from the current Malaysian outbreak. CHIKV MY/06/37348, from an earlier Malaysian outbreak in Bagan Panchor in 2006, was caused by the Asian genotype. Posterior probability values are shown at the key nodes. CHIKV virus strain 37997 of the West African genotype was used as the outgroup

exacerbations of those conditions (Economopoulou *et al.*, 2009).

In the absence of a post-mortem, the cardiac pathology underlying our patient's death is not known. There are several possibilities. Decompensation of heart failure could result from the physiological stress induced by any infection. Alternatively, acute worsening of heart failure during a CHIKV infection may be due to myocarditis, as CHIKV has been detected in the myocardium of a fatal case (Lemant *et al.*, 2008). However, the low serum levels of myocardial enzymes in our patient count against myocarditis. Another possibility is the CHIKV-induced release of inflammatory cytokines such as IL-1β and IL-6 (Ng *et al.*, 2009), which can increase oxygen demand and have negative inotropic effects on the human myocardium (Mann, 2002; Hoffman *et al.*, 2007). However, cytokines were not measured in our patient. Rhabdomyolysis and renal impairment, present in our patient, were also frequently seen in CHIKV patients requiring intensive care (Lemant *et al.*, 2008). CHIKV infects skeletal muscle precursor cells, and can be detected in

muscle biopsies of patients with myalgia, a common symptom of the infection (Ozden *et al*., 2007).

We report a patient with underlying cardiac disease, who died of multi-organ failure likely to have precipitated by a confirmed, acute CHIKV infection. CHIKV was not suspected as the etiological agent initially due to the severe presentation and lack of typical arthralgia. The pathophysiology of severe CHIKV disease is not known. More clinical and laboratory studies of severe and fatal cases are required, preferably with direct virological confirmation and histopathological analysis. Factors which may contribute to the increased disease severity include a more virulent CHIKV strain and increased host susceptibility. In the meantime, clinicians should be alert to the possibility of CHIKV infection with severe or atypical presentations.

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