Co-infection of Dengue Virus and Chikungunya Virus in Two Patients with Acute Febrile Illness

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SUMMARY

During an outbreak of chikungunya in a dengue hyper-endemic area within the Kinta district of Perak, two patients with acute febrile illness were laboratory confirmed to have co-infection of both dengue and chikungunya viruses in their blood. The concomitant presence of two types of viruses transmitted by the same vector in a susceptible population contributed to the resultant event. A good understanding of virus vector ecology in association with population dynamics and wider application of improved laboratory techniques by using different cell-lines suited for optimal replication of each type of virus and the correct utilization of powerful molecular techniques will enhance accurate diagnosis of these infectious diseases.

KEY WORDS:
Co-infection, Chikungunya virus, Dengue virus

INTRODUCTION

The phenomenon of co-infection of two or more infectious pathogens in a patient is not uncommon in clinical medicine. The situations are most commonly seen in immunocompromised patients whether the cause of immunosuppression is congenital, iatrogenic (organs transplantation and chemotherapy) or in acquired immunodeficiency syndrome (AIDS) due to human immunodeficiency (HIV) 1 or 2. In AIDS patients, co-infection of HIV 1 or 2 with reactivated or re-infected human herpesviruses (especially human herpesvirus 1,2, 4, 5 and 6) were well documented and similarly with hepatitis viruses and other viruses, bacteria or fungi causing acute infections[1]. Likewise, co-infection of two hepatitis viruses, especially those viruses that have the tendency to cause persistent or chronic infections (hepatitis B, C, D, and G), in patients with history of intravenous drug abuse and frequent receipt of blood or blood products was well described. Unlike situations described above, co-infection of two viruses in which both cause only acute non-persistent infections in the human hosts is uncommon. Normally, it may happen in situations that provide both viruses the opportunity to enter the susceptible host at about the same time period. We report two patients who stayed in a dengue hyper-endemic area, developed acute febrile illness that had the co-infection of dengue virus and chikungunya virus during an outbreak of chikungunya in the same locality.

CASE REPORT

Case 1: A 28-year old female Malay teacher from Butterworth, Penang visited her sick father-in-law in Manjoi, the suburb of Ipoh city within the Kinta district, on 25th November 2006. Almost two weeks later, she developed an abrupt onset of high fever associated with headache, chills, rigor, severe myalgia, bone pain and lethargy. There was no associated vomiting, abdominal pain, rash nor arthralgia. She was bedridden for two days and consulted a doctor at a nearby health clinic on Day 3 of her illness. Physical examination confirmed she was febrile but there was no other significant finding. A provisional clinical diagnosis of acute dengue was made and a venous blood sample was taken to confirm her diagnosis.

The following day, her condition deteriorated and she was admitted to Ipoh General Hospital for dengue haemorrhagic fever. While in hospital, she presented with mild intermittent episodes of gum and intermenstrual per vaginal bleeding on Day 6 and 7 of the illness. Her fever subsided on Day 8 and she was discharged on Day 11 of the illness. Her serial blood profiles during hospitalization are shown in Table I. Besides the minor elevation of serum glutamyl-aspartate transaminase (155 U/L) and glutamyl-alanine transaminase (232 U/L) enzymes, her liver function test, renal function test and serum electrolytes were essentially within the normal limits.

Chikungunya virus of Central/East African genotype was isolated in Vero cells and dengue virus type 1 was isolated in C6/36 cells from her acute serum sample. Chikungunya virus specific RNA was detected by RT-PCR based on the technique by Hasebe *et al.*[1] and dengue virus specific RNA was detected by RT-PCR based on the method by Lanciotti *et al.*[2]. Dengue specific nonstructural protein 1 (NS1) was also detected by a commercial NS1 antigen-capture ELISA on the same serum sample (Bio-Rad, France). Her anti-dengue IgM was weakly positive as assayed by a commercial IgM-capture ELISA (Panbio, Australia).

Case 2: A 22-year old lady from the same Kinta district had visited the same sick relative (father-in-law of Case 1) from 25 of November 2006 to 5 December 2006. On 7 December 2006 (Day 1), she developed sudden high fever, associated with periorbital pain, myalgia, backache, asthenia and lethargy. She was on self-medication to control her fever. On Day 4 of her illness, she developed mild gum and intermenstrual per

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Table I: The serial blood profiles of a 28-year old Malay lady (Case 1) who developed acute febrile illness due to co-infection of dengue virus and chikungunya virus.

Parameter	Date in December 2006						
	11th	12th	13th	14th	15th	16th	17th
Haemoglobin (gm%)	11.6	13.4	11.0	12.4	12.2	12.5	11.6
Total white cells (103/µl)	1.5	1.9	1.4	1.4	1.5	2.1	3.1
Packed cell volume (%)	34.5	41.9	32.7	36.2	36.3	36.5	34.4
Platelets (103/µl)	85	115	75	74	54	53	79

vaginal bleeding and was admitted to Ipoh General Hospital the following day. A provisional clinical diagnosis of acute dengue was made and a venous blood sample was taken to confirm her diagnosis.

At admission, she was still febrile and a maculopapular pruritic rash was noted especially over her extremities. Other systemic examination was unremarkable. She was afebrile by Day 7 and was subsequently discharged well on Day 9 of the illness (15th December 2006).

Chikungunya virus of Central/East African genotype was isolated in Vero cells from her acute serum sample. Though no dengue virus was isolated, dengue specific nonstructural protein 1 (NS1) was detected by a commercial NS1 antigen-capture ELISA (Bio-Rad, France) and anti-dengue IgM was tested positive by a commercial IgM-capture ELISA (Panbio, Australia).

DISCUSSION

Chikungunya (CHIK) virus is a mosquito-borne virus belonging to the genus *Alphavirus* under the family *Togaviridae* and dengue virus is also a mosquito-borne virus but belonging to the genus *Flavivirus* under the family *Flaviviridae*. However, both types of viruses have the same mosquito vector, the *Aedes* genus (especially *Aedes aegypti*)[4] With the introduction of CHIK virus in an area that is dengue hyperendemic, such as Kinta District, it is indeed possible for individuals to get infected with both types of viruses at the same time. Since both types of viruses have fairly similar incubation periods, the infected patients will have both viruses circulating in their blood.

CHIK virus and dengue virus co-infection has been reported previously in Thailand[3]. In that study, although both dengue and CHIK viruses were separately isolated from a number of patients, nine patients were reported to have concurrent infection of both types of viruses based on simultaneous fourfold or greater rise in CHIK and dengue haemagglutination inhibition (HI) antibodies between acute- and convalescent-phase specimens. The failure to isolate both types of viruses from the same acute serum specimen of each patient was probably due to the use of a single virus isolation system in that study. In this study, the use of different cell-lines to provide optimal replication of each type of virus probably account for the success in the isolation of two different types of viruses in the same blood specimen.

It will be of interest to investigate whether both types of viruses replicate in the same cell types in the human hosts or of preferential differences in optimal replication in different cell types. This information will give a better understanding of the nature and extent of interactions between the two types of viruses during co-infection which may in turn shed light on the clinical manifestations of disease in patients with co-infection. Similarly, work needs to be done to study whether both types of viruses can co-replicate efficiently in the same mosquito which will provide a better understanding on the co-transmission of the virus in the community.

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