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Case report

A case report of discordant Chikungunya manifestations in a married couple: From acute undifferentiated fever to fatal sepsis with purpura fulminans

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ABSTRACT

Chikungunya virus, an alphavirus transmitted by mosquitoes, causes chikungunya fever, a non-fatal febrile illness characterized by severe arthralgia and rash. We are reporting on two Chikungunya cases who recently returned from the Thailand-Cambodia border. The first case involved a man who presented with atypical manifestations, including purpura fulminans and multi-organ failure, ultimately leading to death. Conversely, the subsequent case pertains to the spouse of the deceased, who exhibited typical symptoms.

Introduction

Chikungunya is an arthropod-borne disease, mainly transmitted by the Aedes mosquito [1]. It is caused by the Arbovirus named Chikungunya virus (CHIKV), a single-stranded RNA virus in the *Togaviridae* family [2]. Chikungunya has been reported across various regions worldwide but it is endemic in tropical areas such as Southeast Asia, Africa, and South America [3–5]. Classic manifestations of Chikungunya include acute fever, myalgia, headache, asymmetrical polyarthralgia, and generalized maculopapular rashes [2,3,6]. Although Chikungunya is generally not a life-threatening condition, it may lead to severe manifestations such as multi-organ failure, sepsis, septic shock, or death [7–9]. Severe manifestations are more likely to occur in the elderly or those who have underlying diseases such as ischemic heart disease, cerebrovascular disease, or diabetes mellitus [8–10]. The pathogenesis of severe chikungunya cases remains unclear. A recent study found an association between elevated cardiac biomarkers and fatal chikungunya cases [11]. An animal study demonstrated that CHIKV infection directly impairs redox-related mechanisms within vascular cells, leading to arterial dysfunction [12]. Furthermore, Y-box binding protein 1 (YBX1) was identified as a virulence factor that promotes high levels of virus replication and production in multiple alphaviruses, including Chikungunya virus [13].

In this paper, we reported two cases of Chikungunya in a married couple. Both cases developed symptoms at the same time but with extremely discordant manifestations. The husband presented with acute fever, septic shock, purpura fulminans, and multi-organ failure, while the wife presented with typical symptoms of acute fever, myalgia, and generalized maculopapular rashes. Two weeks before experiencing symptoms, they had just returned from a one-month trip in Sakaew province, Thailand, and Poi Pet City, Cambodia (Thailand-Cambodia border).

Case report-1 (The husband)

A 69-year-old man with no known underlying disease was admitted on Day-6 of symptoms with acute fever, septic shock and purpura fulminans. On the first day of illness (Day-1), he had generalized myalgia and right knee pain. On the second day of illness (Day-2), he subsequently developed pain and swelling in both knees, both wrists, and all finger joints. His symptoms did not improve after taking paracetamol and muscle relaxants. On Day-4, he experienced a low-grade fever, a runny nose, and non-pruritic, non-blanchable erythematous rashes on both legs. One day before admission (Day-5), he developed a high-grade fever with chills, debilitating polyarthralgia that made walking difficult, and previous rashes progressed to large purplish lesions. He denied taking any medications or herbal remedies other than those previously mentioned.

Upon arrival at the emergency department, the patient appeared drowsy. His vital signs showed a body temperature of 36.6 C, a blood

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pressure of 111/69 mmHg, a heart rate of 122 beats per minute, and a respiratory rate of 44 breaths per minute. Physical examination revealed well-defined erythematous purplish plaques on both upper and lower extremities, and multiple large hemorrhagic blebs on the upper and lower limbs as shown in Fig. 1A, and B. Musculoskeletal system examination showed swollen, warm, and limited range of motion of both knees, proximal interphalangeal joints (PIP), distal interphalangeal joints (DIP), and metacarpal (MCP) joints of both hands. Additionally, swollen and tender muscles in both thighs and calves were observed. Bilateral lung auscultation revealed fine crackles. Tachycardia was present, and no heart murmur was detected.

Laboratory investigation revealed hemoconcentration (Hb 19.7 g/dl), marked leukocytosis with neutrophil predominance (white blood cell count 20,690 cell/mm3, neutrophils 90.0 %), thrombocytopenia (platelet count 71,000 cell/mm3), prolonged prothrombin time and partial thromboplastin time (PT 15.4 seconds and PTT 46.1 seconds). The blood chemistry showed severe lactic acidosis (lactate 10.6 mg/dl), elevated serum creatinine (Cr 2.7 mg/dl), elevated total bilirubin (TB 2.31 mg/dl), elevated alkaline phosphatase (ALP 200 mg/dl) and elevated aspartate aminotransferase (AST 198 mg/dl).

Based on the findings, the differential diagnoses were severe sepsis from meningococcemia, gram-negative bacteremia, and leptospirosis. He was immediately transferred to an isolation room in the intensive care unit. Treatment commenced promptly with aggressive fluid resuscitation and empirical antibiotics (intravenous ceftriaxone and azithromycin). Sixteen hours later, he subsequently required vasopressors, hydrocortisone, mechanical ventilation, continuous renal replacement therapy, and hemoperfusion to treat excessive release of inflammatory cytokines associated with septic shock (cytokine storm). Despite these aggressive interventions, the patient's clinical status rapidly deteriorated, and he finally passed away within 40 hours after admission.

Microbiology investigations revealed negative blood cultures, negative serology tests for leptospirosis and rickettsiosis, and a positive dengue IgG test but negative NS-1 Ag, dengue IgM, and dengue real-time PCR (RT-PCR) tests. The acute fever panel showed only a positive result for Chikungunya virus, with all other tests negative. The Chikungunya single plex RT-PCR test was positive with a cycle threshold value of 22. A respiratory pathogen 23 panel test of an endotracheal suction specimen revealed adenovirus. All other tested pathogens, including COVID-19 by rapid PCR, were negative. Therefore, the final diagnosis of this patient was Chikungunya infection, which ultimately led to his death.

Case report-2 (The wife)

A 71-year-old woman with underlying hypertension and dyslipidemia. On the first day of symptoms (Day-1), she experienced generalized myalgia, and pain in both ankles which can be relieved by taking paracetamol. On Day-4, she developed a low-grade fever and a runny nose without any rash or joint pain. Generalized non-pruritic rashes were noticed on Day-6. After her husband was admitted due to severe sepsis with suspicion of meningococcemia, she was simultaneously admitted to an isolation room.

Upon admission, her vital signs showed a body temperature of 37.3 C, a blood pressure of 161/81 mmHg, a heart rate of 64 beats per minute, and a respiratory rate of 16 breaths per minute. Physical examination revealed generalized non-pruritic maculopapular rashes predominantly at both arms and legs as shown in Fig. 1d. There were no signs of joint inflammation.

Laboratory investigations showed normal complete blood count, normal liver function test, and mildly elevated serum creatinine (Cr 1.55 mg/dl). She received only supportive treatment including intravenous fluid and paracetamol. She was admitted to observe the clinical progression while waiting for all investigations. Treatment included supportive measures such as analgesic drugs and intravenous fluid hydration. Her clinical symptoms rapidly improved, and she was discharged two days after admission.

Similar to her husband's microbiology results, her blood culture, serology test of leptospirosis, rickettsiosis, and dengue and dengue RT-PCR were all negative. The acute fever panel showed only a positive result for Chikungunya virus, with all other tests negative. The Chikungunya single plex RT-PCR test was positive with a cycle threshold value of 39.

The timeline of symptoms of both cases is depicted in Fig. 2, and the results of all laboratory investigations are summarized in Table 1.

Discussion

Severe manifestations of chikungunya are remarkably uncommon.

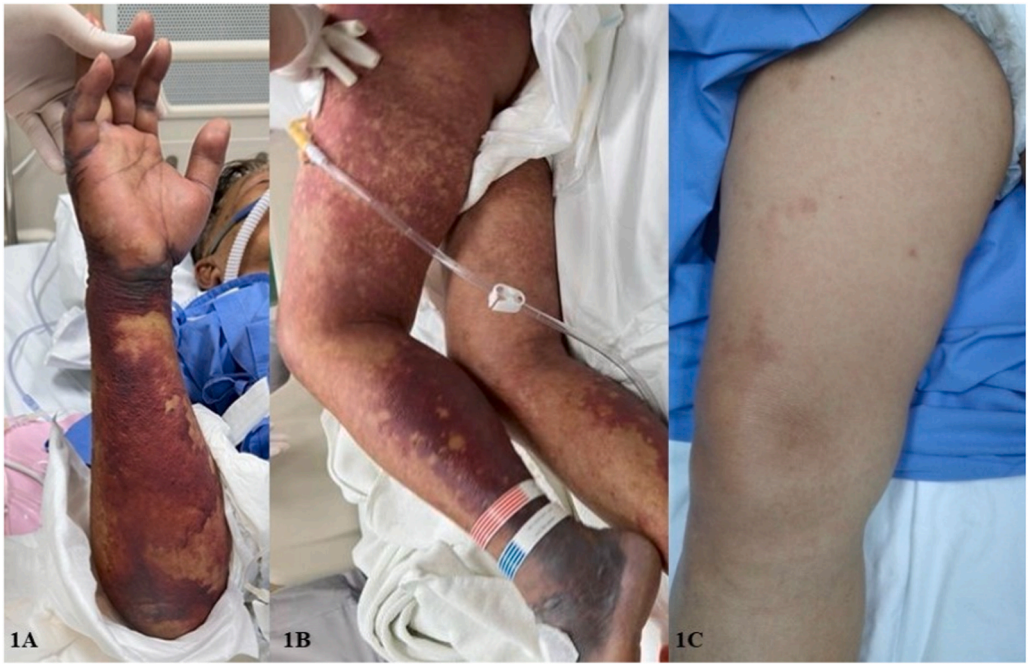

Fig. 1. Skin manifestations of the case-1 (1 A and 1B) and the case-2 (1 C).

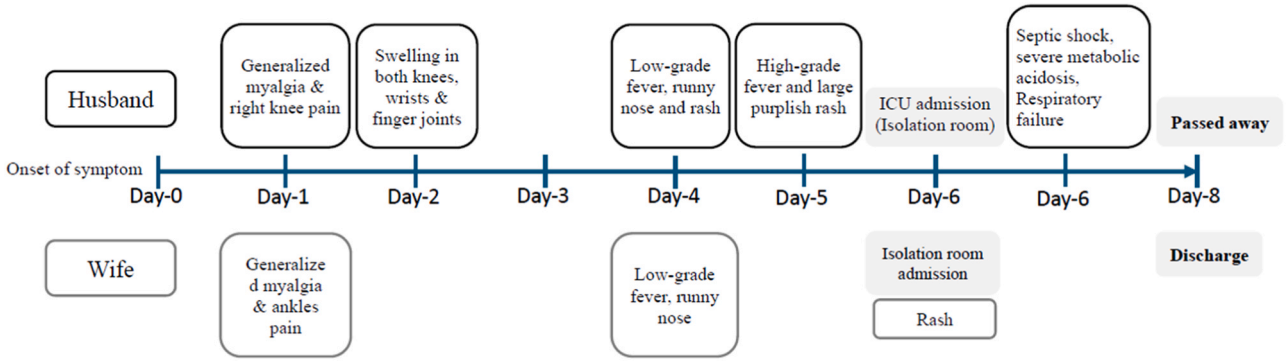

Fig. 2. The timeline of symptoms for the case-1 (husband) and the case-2 (wife).

Table 1
Laboratory results of the case-1 and the case-2 on Day-6 of symptoms.

Parameters	CASE-1 (Husband)	CASE-2 (Wife)
Complete blood count		
Hemoglobin (g/dl)	19.7	12.6
Hematocrit (%)	59.3	39.7
WBC count (/mm^3)	20,690	5240
Neutrophil (%)	90.0	66.6
Lymphocyte (%)	3.0	23.3
Platelet (mm^3)	71,000	255,000
Blood chemistry		
Blood urea nitrogen (mg/dl)	42.6	36
Creatinine (mg/dl)	2.7	1.55
Sodium (mmol/L)	127	140
Potassium (mmol/L)	4.2	4.4
Bicarbonate (mmol/L)	11	16
Total bilirubin (mg/dl)	2.31	0.4
Direct bilirubin (mg/dl)	1.75	0.15
AST (U/L)	198	16
ALT (U/L)	45	17
ALP (U/L)	200	81
Globulin (g/dl)	4.2	3.8
Albumin (g/dl)	3.1	3.9
Lactate (mmol/L)	10.6	NA
Creatinine phosphokinase (U/L)	363	NA
Coagulogram		
Prothrombin time (second)	15.4	NA
Partial thromboplastin time (second)	46.1	NA

The 2005 Reunion Island chikungunya outbreak was notable for its high incidence of unusual symptoms and fatalities, revealing new and severe forms of the disease [10]. During the outbreak, approximately one-third of inhabitants were infected with Chikungunya virus, with only 0.2 % developing atypical presentations. Chikungunya can cause a variety of atypical complications, such as encephalitis, myocarditis, pneumonia, nephritis, and hemorrhagic manifestations [10]. The overall case-fatality rate was low at 0.02 %, but the case-fatality among those with atypical presentations was up to 10.7 % due to multi-organ failure [10]. The severity and prognosis of the disease appear to be significantly associated with older age, having pre-existing underlying diseases, and atypical presentations [8–10]. While our first case was an elderly individual without other medical conditions, this suggests the disease itself can cause fatal complications.

Another factor contributing to the patient's severity may be viral mutation. A study of 22 chikungunya virus strains from the 2018–2019 Thailand outbreak found all East/Central/South African (ECSA) genotype sequences contained E1:K211E and E2:V264A mutations, previously linked to increased infectivity, dissemination, and transmission in *Aedes aegypti* [14]. However, genome sequencing was not performed to identify viral mutations in our patient's sample.

Dermatological manifestations can be observed in 40–75 % of chikungunya cases, with a maculopapular rash being the most common presentation [15]. Hemorrhagic skin lesions, including petechiae and purpura occur in approximately 11 % of dermatological manifestations [15]. These lesions are often associated with thrombocytopenia or direct vascular damage from viral replication within the capillary endothelium or arterial dysfunction by directly affecting redox mechanisms in vascular cells. [12,16]. Previous studies suggest that chikungunya virus can disrupt vascular signaling and potentially contribute to

While severe hemorrhagic manifestations such as hemorrhagic bullae and purpura fulminans are rare [17], they should be considered in differential diagnoses along with meningococcemia and severe disseminated intravascular coagulation (DIC) from other serious infections. Notably, in our case 1, purpura fulminans developed before the onset of septic shock. This suggests a direct endothelial cell involvement rather than DIC.

Hemoconcentration and thrombocytopenia are significantly less frequent in chikungunya compared to dengue infection [18]. Although viral infections can cause leukocytosis, it usually occurs during the early stage of infection. Furthermore, such an extremely high white blood cell count (20,690 cells/mm2) as the first case report is more likely to be associated with bacterial infections. However, several studies have demonstrated a correlation between elevated WBC count and the presence of severe disease or multiorgan failure in chikungunya cases [19, 20].

We hypothesized that the severe and atypical manifestations in the first case were due to a high burden of chikungunya virus (chikungunya PCR cycle threshold of 22) and possibly bacterial or dengue co-infection. A case series from Thailand suggests that peak viral load, as measured by PCR, is sustained until approximately day 5 of illness [21]. Without knowing the definitive onset of infection in both cases, it is difficult to conclude that the first case had a higher viral load. Blood cultures were negative for bacterial pathogens. Co-infection with chikungunya and dengue, although reported in some studies [22], was not observed in this case. However, without a paired serum sample, we cannot exclude the possibility of other co-infections.

In conclusion, we reported two cases of chikungunya infection, one with typical and one with atypical presentations. The atypical case exhibited rare complications like purpura fulminans, septic shock, severe hemoconcentration, thrombocytopenia, and leukocytosis. Recent evidence suggests that the incidence of atypical and severe manifestations of chikungunya infection may be higher than previously anticipated. This emphasizes the need for clinicians to be aware of these less common but serious forms of chikungunya to improve diagnosis and treatment outcomes.

Ethical approval statement

The authors confirm that they have read and complied with the policy on ethical consent. Written informed consent was obtained from the patient (case-2) and the legal representative (case-1) for the publication of this case report. All identifying information has been removed

to ensure patient privacy.

Consent

Written informed consent was obtained from the patient (case-2) and the legal representative (case-1) for the publication of this case report.

Authors' statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship.

Authors contribution

Patient treatment: DP, NH, PR. Drafting the manuscript: DP, PR. All authors have read and approved the final version of the manuscript.

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CRediT authorship contribution statement

Pathomchareansukchai Ditthawat: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Rattanaumpawan Pinyo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Horthongkham Navin:** Writing – review & editing, Investigation, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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