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CASE REPORT

Atypical skin manifestation of purpura fulminans in Chikungunya infection on elderly patients: A case report

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ABSTRACT:

Background: Chikungunya is a vector-borne infectious disease that is usually characterized by fever, joint pain, muscle ache, headache, rash, or fatigue. Severe life-threatening complications such as septic shock, acute respiratory distress syndrome, and multiple organ dysfunction can develop during the acute phase of the disease. Purpura fulminans were rarely reported.

Case presentation: A previously healthy 69-year-old male patient with no known medical history presented with a 3-day history of fever, malaise, and arthralgia at both knees. He developed dyspnea, purpura, and hemorrhagic blebs at the right leg for 1 day. He was initially diagnosed with sepsis and oliguric renal failure with severe lactic acidosis. After fluid therapy was given to maintain stable hemodynamics, his lactate level increased rapidly. Continuous renal replacement therapy and hemoperfusion with cytokine adsorbent were then initiated simultaneously. On the second day of admission, the skin and soft tissue lesions progressed rapidly, and the patient experienced refractory shock and multiple organ dysfunction. Finally, he was diagnosed with a Chikungunya infection. Three days following the onset of edema in his extremities, he expired.

Conclusions: Purpuric skin manifestations and shock are rare but serious in Chikungunya infections. Clinicians should be aware of the potential for life-threatening complications. Aggressive management and adjunctive therapy such as hemoperfusion and intravenous immunoglobulins should be further studied.

Keywords: Chikungunya infection; Hemorrhagic bleb; Atypical manifestations

INTRODUCTION

Chikungunya is a vector-borne infectious disease caused by the chikungunya virus (family Togaviridae, genus Alphavirus), which can be transmitted to humans by Aedes aegypti and Aedes albopictus mosquitoes. Chikungunya infection was first discovered in 1952 in a febrile patient in Tanzania, Africa.[1] The first Chikungunya outbreak in Thailand was reported in Bangkok in 1958, caused by Asian genotype.[2] The disease is usually characterized by fever, joint pain, muscle ache, headache, rash, or fatigue, which are not fatal conditions. Severe life-threatening complications such as septic shock, acute respiratory distress syndrome, and multiple organ dysfunction can develop during the acute phase of the disease, which are more common in infants, the elderly, the immunocompromised, and pregnant patients. [3,4.] Purpura fulminans were rarely reported. [5.]

CASE PRESENTATION

A previously healthy 69-year-old male patient with no known medical history presented with a 3-day history of fever, malaise, and arthralgia at both knees. He developed dyspnea, purpura, and hemorrhagic blebs at his right hand and right leg, accompanied by edema of both hands and feet for 1 day. He denied a history of smoking and drinking alcohol. His wife also experienced a low-grade fever, muscle pain, and fatigue for 5 days (2 days before the patient). He and his wife just returned from Cambodia the prior week.

In the emergency room, his vital signs were as follows: body temperature of 37.7°C, blood pressure of 111/69 mmHg, pulse rate of 122 beats per minute, respiratory rate of 24 breaths per minute, and oxygen saturation of 95% on room air.

Upon examination at admission, the patient was mildly irritable, cold, and had a delayed capillary refill time in all extremities. His heart, lung, gastrointestinal, and nervous system examinations were unremarkable. His extremities showed arthritis of the right knee. The physical examination was most remarkable for revealing pain and swelling of all extremities with multiple hemorrhagic bulges over his right forearm and right leg (Figure 1 A-D). Cervical and superficial lymph nodes were not palpable. He also had oliguria.

Laboratory investigations revealed a hemoglobin count of 19.7 g/dL, hematocrit of 59.3%, white blood cell count of 20690 cells/mm^3 (neutrophils, 90%, band 3%, lymphocyte 3%, eosinophils 1%, monocytes 2%, basophils 0%), and platelet count of 71,000/mm^3. Coagulation showed PT 15.4 sec (normal range 10.7-12.6 sec), INR 1.37, aPTT 46.1 sec (normal range 22-30 sec), fibrinogen 695 mg/dl, and D-dimer > 35.2 mg/L.

Other blood chemistry showed blood urea nitrogen was 42.6 mg/dL, creatinine was 2.7 mg/dL (baseline creatinine was 0.98 mg/dL), sodium was 127 mmol/L, potassium was 4.2 mmol/L, chloride was 88 mmol/L, bicarbonate was 11 mmol/L, lactate was 10.6 mmol/L, and creatinine phosphokinase was 363 U/L consecutively. Liver testing: albumin of 3.1 g/dL, globulin of 4.2 g/dL, total bilirubin of 2.31 mg/dL, and direct bilirubin of 1.75 mg/dL. Levels of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were 198 U/L, 45 U/L, and 200 U/L, respectively. Arterial blood gas had a pH of 7.36, a $PaCO_2$ of 26.3 mmHg, and PaO_2: FiO_2 ratio of 313 mmHg. Inflammatory markers revealed C-reactive protein of 203.28 mg/L, procalcitonin of 23.5 ng/mL, and interleukin-6 of 2906 pg/mL. The chest X-ray was unremarkable. The arthrocentesis was postponed due to thrombocytopenia and coagulopathy.

In the emergency department, he was treated with ceftriaxone and azithromycin intravenously, accompanied by fluid resuscitation with isotonic crystalloid. A surgical consultation was done to exclude surgical conditions such as necrotizing fasciitis. He was initially diagnosed

KEY MESSAGES:

- Severe life-threatening complications can develop during the acute phase of the Chikungunya infection, especially in high-risk or predisposing patients.
- Purpuric skin manifestations are atypical but serious in Chikungunya infections. Clinicians should be aware and consider Chikungunya infection in the differential diagnosis. However, there is no specific treatment for the Chikungunya infection.

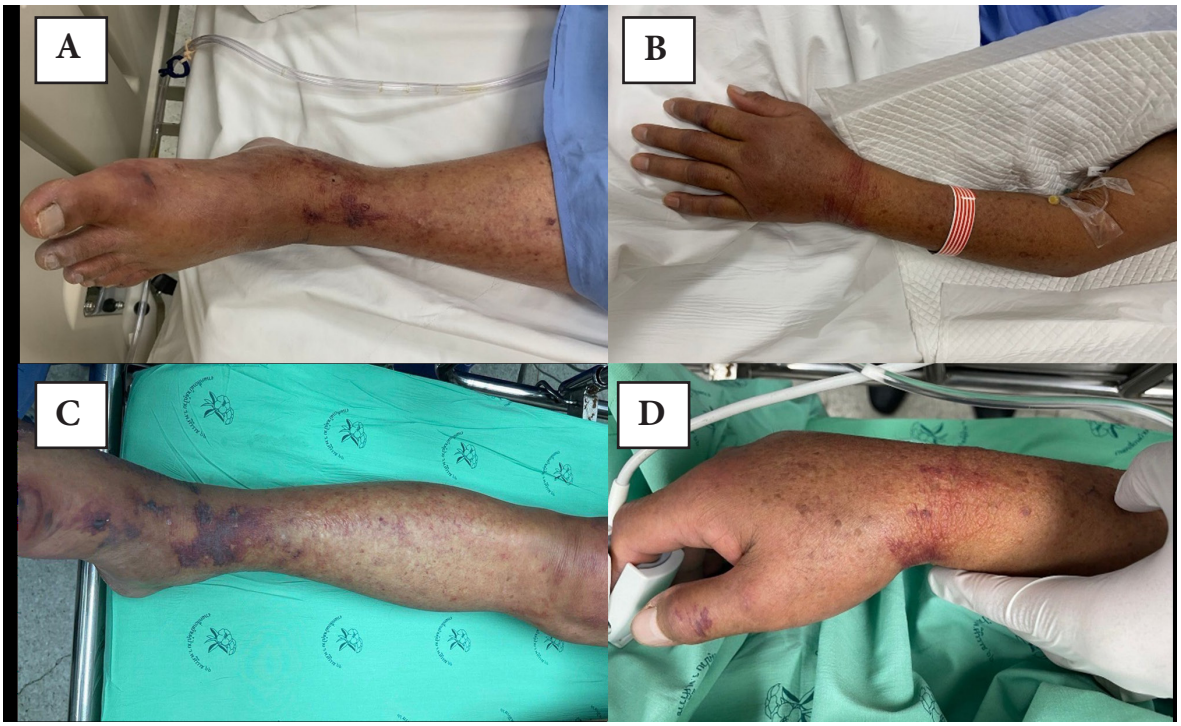

Figure 1. A-D: Pictures of extremities at presentation.

with sepsis, disseminated intravascular coagulopathy, and oliguric renal failure with severe lactic acidosis. On the first day of intensive care unit admission, he developed hypotension, edema, and progressive extensive hemorrhagic bullousness and purpura at all extremities. (Figure 2 A-D). Bedside echocardiography showed the inferior vena cava was 1.3 cm in diameter with inspiratory collapse > 50%, a left ventricular ejection fraction (LVEF) of 70% (Teichholz's formula), no regional wall motion abnormality, and no pericardial effusion. Fluid therapy with 5% human albumin, fresh frozen plasma, and cryoprecipitated plasma was initiated to maintain stable hemodynamics. However, his lactate level was increasing rapidly, although his mean arterial pressure was 65- 75 mmHg. On the second day, he was intubated due to respiratory failure type 4. Continuous renal replacement therapy and hemoperfusion with cytokine adsorbent were then initiated simultaneously, aimed at correcting acidosis and removing inflammation cytokines. The skin and soft tissue lesions progressed rapidly (Figure 2.), and purpura fulminans were diagnosed. Clindamycin, ciprofloxacin, and oseltamivir were added to cover all possible organisms that caused purpura fulminant. The patient experienced refractory shock and multiple organ dysfunction within 48 hours of admission, despite fluid resuscitation, a high-dose vasopressor infusion, acidosis, and hypocalcemia. Corrections were promptly given. Three days following the onset of edema in his extremities, he expired.

Blood culture, urine culture, and sputum culture were negative for bacterial pathogens. Respiratory panels detected rhinovirus, but they did not fully explain his clinical symptoms. Dengue NS-1 antigen is negative, Dengue IgG is positive, Dengue IgM is negative, and Dengue RNA is negative. A PCR for the acute undifferentiated febrile illness panel, which includes bacterial, viral, and parasitic infections, was performed to confirm the diagnosis, and it was positive only for Chikungunya RNA.

His wife was also diagnosed with the Chikungunya infection, which is characterized by fever, muscle ache, arthralgia, and maculopapular rash. The laboratory also confirmed the diagnosis by PCR positive for Chikungunya RNA.

DISCUSSION

This case report was a rare presentation of chikungunya infection. According to the Reunion Island outbreak in 2005–2006, overall mortality was 1 in 1000 populations, while the fatality rate of those who required intensive care units was 48%.[3,4,6] Similar to the Guadeloupe outbreak in 2014, which showed 48% mortality in severe sepsis or septic shock associated with the Chikungunya infection. [8] Chikungunya virus infection may be responsible for a very severe clinical presentation, including in young patients with unremarkable medical histories.[3-8]

Purpura fulminans is a syndrome of skin hemorrhagic necrosis that is caused by microvascular thrombosis. Acute infectious purpura fulminans is the most common type, which is usually caused by bacterial pathogens. [12.] In this case, purpura fulminans, meningococcemia, and necrotizing fasciitis were the initial differential diagnoses. After excluding other conditions, Purpura fulminans was diagnosed despite a fibrinogen level elevation because fibrinogen is also an acute phase protein, which can increase from sepsis or inflammation. This syndrome is a severe and rapidly fatal form of acute disseminated intravascular coagulation. In addition to proper antibiotics, anticoagulants also play a role in purpura fulminans, but in this patient, the anticoagulant was deferred due to progressive thrombocytopenia. Protein C concentration was also reported as an adjunctive treatment in acute infectious purpura fulminans, but there are strong recommendations only for congenital protein C deficiency patients. [16] Table 1 demonstrates the clinical data of our patient

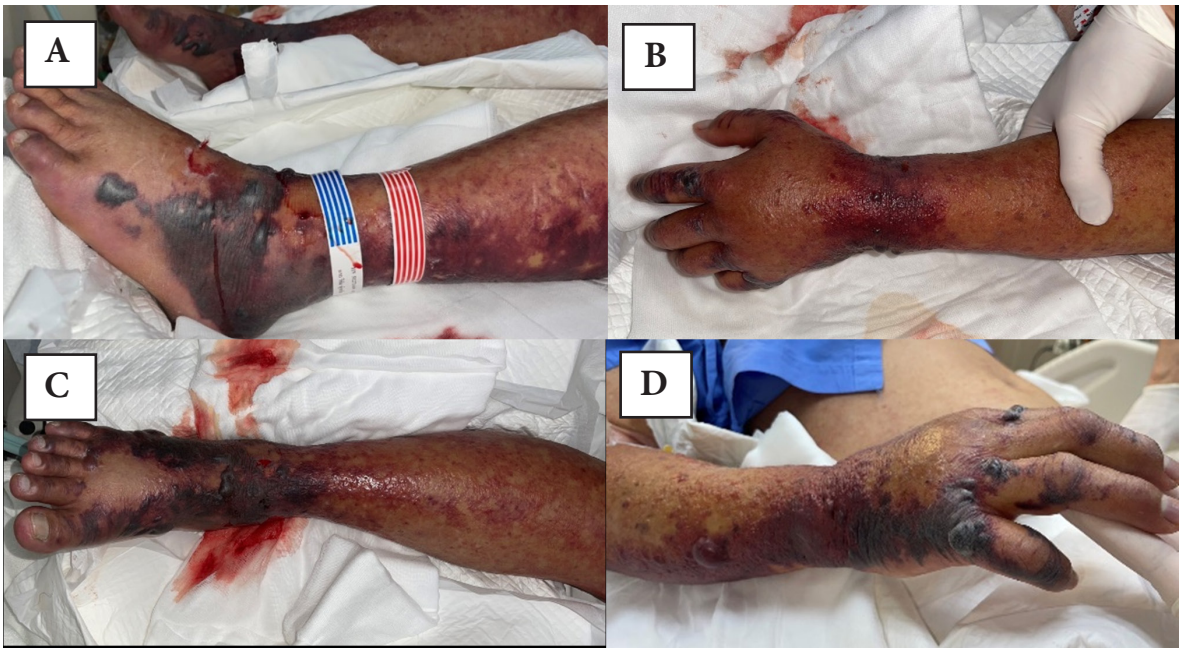

Figure 2. A-D: Pictures of extremities on the second day of admission.

Table 1. Case report of severe Chikungunya infection with atypical skin manifestations.

	Case	Skin manifestations	Complication	Treatment and outcome
Torres J., et al. [13]	1. A 75-year-old man with no known underlying disease presented with fever with chill, arthralgia, and bilateral swelling in the hands and feet interphalangeal joints, ankles, and knees for 3 days	- Generalized erythematous macular rash at feet. - Bullae - Facial and palpebral edema	- Shock - AF with RVR - Multiorgan failure: renal, liver	- Non-specific treatment - Dead
	2. A 53-year-old female with iron deficiency anemia presented with a fever with chill, arthralgia, rigor, and facial edema for 3 days	- Erythematous maculopapular rash and petechiae at all extremities - Anasarca-like appearance - Sharply delineated necrotic lesion at nasal region	- Acute respiratory distress - Disseminated intravascular coagulation - Shock	- Non-specific treatment - Dead
	3. A 75-year-old man with hypertension presented with fever, malaise, and arthritis for 4 days	- Violaceous erythematous rash at both hands and foot - Generalized ecchymosis - Livedo reticularis	- Acute respiratory distress - Disseminated intravascular coagulation - Renal failure	- Non-specific treatment - Dead
	4. A 32-year-old female wit history of Hodgkin's lymphoma and post splenectomy presented with fever, malaise, myalgia, and arthralgia for 1 day	- Purpura at face, limbs, and oropharynx. - Acrocyanosis with necrosis at fingertip at all limbs - Hemorrhagic bullae at limbs	- Acute respiratory distress - Disseminated intravascular coagulation - Cardiomyopathy	- Non-specific treatment - Survived
Benjamanukul S., et al. [14]	18-years-old female at 31-week gestations presented with fever, malaise, myalgia, and arthralgia for 6 hours.	- Maculopapular rashes at cheeks, nose, forehead, and abdominal wall - Non hemorrhagic vesicular rash on the lateral side of both thighs	- Shock - Acute respiratory distress syndrome	- Non-specific treatment - Survived
Fernandes A., et al. [15]	56-years-old male presented with fever, headaches, paresthesia, and pain in the right arm for 10 days	- Extensive hemorrhagic bullous lesions at upper and lower extremities	- Hypotension - Transient ischemic attack 10 days after IVIg administration	-IVIg 400mg/kg/d for 5 days - Survived

compared with previous cases reporting a severe Chikungunya infection with atypical skin manifestations.

This case is also presented with sepsis, according to the definition of sepsis-3. [9] Investigational tests suggested that these symptoms resulted from a Chikungunya infection. Bacterial, influenza, and common tropical diseases such as dengue, leptospirosis, and murine typhus were excluded. The pathogenesis of viral sepsis is dysregulated immune response, loss of endothelial barrier function, functional immunosuppression, and cytopathic effects, resulting in increased vascular permeability and immune cell migration into tissues.[10] Moreover, this patient was elderly and predisposed to severe disease due to an abnormal immune response. [3-4.] The immune response of older patients decreases their ability to eradicate viral infection through a mechanism called inflammaging, which is a loss of control over systemic inflammation and an increase in the baseline of inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor alpha.[11] The influence of a preceding dengue infection on chikungunya disease might be another aggravating factor in this patient. However, previous reports showed that Chikungunya patients with previous dengue infection had a similar acute disease presentation but suffered more frequently from long-term musculoskeletal and neuropsychological symptoms.[17]

In this case, we encountered an intravascular fluid deficit due to vasodilation and capillary leakage from viral sepsis. On the first day, we achieve hemodynamics with colloids and blood components, but lactate levels are still increasing, which might be from persistent microvascular alteration. Due to clinical manifestations and laboratories indicating cytokine storms, we then initiated continuous renal replacement therapy simultaneously with hemoperfusion with cytokine adsorbent to correct acidosis and remove inflammatory cytokines. However, the patient experienced severe leaky processes and developed hypotension, becoming unresponsive to fluid resuscitations and vasopressors. The utilization of hemoperfusion to remove inflammatory cytokines in chikungunya infection with viral sepsis and shock needs further research.

CONCLUSION

Purpuric skin manifestations and shock are rare but serious in Chikungunya infections. Clinicians should be aware of the potential for life-threatening complications. Aggressive management and adjunctive therapy such as hemoperfusion and intravenous immunoglobulins should be further studied.

ETHICS

The patient clinical and demographic data were collected in accordance with the guidelines set forth by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The patient profiled in this report gave written informed consent to be studied and reported upon in this case report.

CONSENT FOR PUBLICATION

Informed consent to publish identifying data was obtained from the study participant and that this consent was informed.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the patient profiled in this report for formally permitting us to report details relating to his case.

ABBREVIATIONS

ng/mL: nanograms/milliliter; ng/dL: nanograms/deciliter; pg/mL: picogram/milliliter; U/L: unit/liter; g/dL: grams/deciliter; mg/dL: milligrams/deciliter; mg/L: milligrams/liter; mmol/L: millimoles/liter; cells/mm^3: cells/cubic millimeter; mmHg: millimeter of mercury; RNA: ribonucleic acid; NS1: nonstructural protein 1; IgG: immunoglobulin G; IgM: immunoglobulin M; PCR: polymerase chain reaction.

AUTHORS' CONTRIBUTIONS

P.D. and R.R. contributed to data acquisition, data interpretation, and drafting and revision of the manuscript. All authors have read and approved the final version of the manuscript to be submitted for journal publication.

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