Chikungunya Fever Presenting as Life Threatening Thrombotic Thrombocytopenic Purpura

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Abstract
It is well known for Chikungunya fever to present as myriad of skin rash along with usual joint pain and fever, but probably this is the first case report of Chikungunya fever presenting as severe life threatening thrombotic microangiopathy, thrombotic thrombocytopenic purpura leading to multiple areas of skin necrosis, peripheral digital gangrene, haemolytic anemia, renal failure and severe thrombocytopenia with bleeding. This complication was most likely due to inhibitor autoantibody formation against ADAMTS13 triggered by chikungunya virus leading to thrombotic thrombocytopenic purpura. Patient was treated with plasmapheresis and other supportive care which she responded. Her symptoms subsided, and she is symptom free and leading normal life in her follow up visits.

Introduction
Chikungunya fever is caused by Chikungunya virus, vector being Aedes mosquito. This disease usually presents with fever, joint pain and various types of skin rash. We describe in this case, a very unusual presentation of Chikungunya fever presenting as thrombotic thrombocytopenic purpura which to our best knowledge has not been reported so far in a patient of Chikungunya.

Case Report
A 24-year old married female, hailing from North-west Delhi, who was an employee in a motorcycle showroom, with no prior illness or any known medical condition presented with illness of 5 days. Her illness started with fever which was high grade (103°F) and associated with chills but no rigors, followed by multiple episodes of vomiting and profuse watery diarrhea, along with severe joint pain involving both large and small joints of the body. Although her fever and abdominal symptoms subsided after two days of illness, she continued to have severe joint pain, and on the 4th day of illness, she developed dark purple-reddish rash involving bilateral hand and feet, bridge of the nose. She also noted similar skin rash on genital area and lower back. She also noticed dark crusted lesions on lips and vulva. She also had complaints of dysphagia after the appearance of these rashes, some degree of headache and a history of decreased urine output for two days.

There was no history of syncope, altered sensorium, seizures, blurring of vision or weakness of any part or any sensory loss at presentation. There was no history of bleeding from any site during presentation, no history of cough, expectoration or shortness of breath. There was no history of travel outside the town in last 6 months or exposure to pets or other animals in the recent past. Patient gave no history of substance abuse. She was a divorcee and had one child of two-year age born of normal vaginal delivery. There was no significant medical history in any close family member.

At presentation, she was vitally stable, although tachycardia was present. She didn’t require any respiratory or hemodynamic support. General physical examination revealed pallor, cyanosis of all digital tips, purpuric rash all over bilateral hand and feet and bridge of the nose, petechial rashes all over bilateral upper and lower limb, necrotic black rash on natal cleft, right shin and right groin area (Figure 1). Generalized erythema was present all over the body but more pronounced over the trunk. Hemorrhagic rash with crusting was seen over mucocutaneous junction of lips and vagina. Paresthesia was present all over both hand and feet and with severe tenderness in large and small
joints of hands and feet. At the time of presentation, her central nervous system examination and other systemic examination were within normal limits.

Her initial work up revealed anemia, thrombocytopenia, deranged renal profile and slightly prolonged coagulation profile (Table 1).

All workup for common causes of acute febrile illness (dengue, peripheral smear for malaria, leptospirosis, scrub typhus, including chikungunya) were negative on day 6 of the illness (Table 2). With high degree of clinical suspicion of chikungunya in this patient, the test for chikungunya was repeated and the result came out to be positive on day 9 signifying acute infection. Her coagulation profile normalized on its own in two days and DIC (Disseminated intravascular coagulation) was ruled out by further testing.

During hospital stay, her thrombocytopenia further worsened and platelets fell further to 6000/µL and she started having epistaxis and melena, for which she required platelet and packed RBC transfusion.

Her peripheral smear showed schistocytes, LDH was raised. Unconjugated hyperbilirubinemia was present and her direct/indirect coomb’s test was negative signifying non-immune haemolytic anemia.

She started developing progressive gangrene of the digital tips of left hand and of the tip of lower limb digits (Figure 2). Urgent arterial doppler ultrasound of all limbs was performed which showed no occlusion of any large arteries. Her sensorium started dipping in the form of confusion and she also complained of severe headache, a CT head was done to rule out intracranial bleed secondary to thrombocytopenia, it came out to be normal study. Hemolytic-uremic syndrome (HUS), was ruled out although there was history of diarrhea, but the renal involvement was only transient (for 24-48 hours) and not a prominent feature, the microvascular thrombosis was more prominent and rapidly progressive. A clinical diagnosis of Chikungunya induced thrombotic thrombocytopenic purpura (TTP) was made based on clinical and lab features of non-immune haemolytic anemia with thrombocytopenia with evidence of microvascular thrombosis, immediate testing for ADAMTS13 activity was not possible due to unavailability of test in the hospital and because of financial constraints of the patient. A recently developed clinical tool PLASMIC score[1,2] which predicts the ADAMTS13 activity <10% and studies have shown better prediction of TTP as compared to clinical assessment when applied in appropriate clinical setting when ADAMTS13 activity turn-around time is more or unavailable in resource limited settings, was calculated after day 4 of admission which came out to be 7, categorizing the patient in high risk group.

Other conditions mimicking
TTP were ruled out subsequently. Vasculitis panel was negative, DIC was ruled out and all viral markers (HIV/HBsAg/Anti-HCV) were negative. In a young female with thrombotic complications, though rarely microvascular, very lower down a possibility of APLA (Anti-phospholipid antibody) syndrome was kept and was ruled out by testing. Workup for other hypercoagulable state like homocysteinemia, Factor VLeiden mutation and Factor IV levels, all came out to be negative (Table 3). Skin biopsy done on the first day of admission showed microvascular occlusion and no evidence of vasculitis (Figure 3).

Urgent plasmapheresis was planned in view of serious complication of thrombosis with progressive gangrene, severe thrombocytopenia causing bleeding and altered sensorium. She received total of 5 sessions of plasmapheresis over a period of one week. She did not receive any steroids. The condition of the patient improved with each session of plasmapheresis. There was improvement in the platelet count, decrease in LDH, unconjugated bilirubin and percentage of schistocytes. Her digital gangrene didn’t progress further.

She was discharged in stable condition with platelets more than 1.5 lacs/µL and schistocytes of less than 1%. LDH levels also had become normal (Table 4 and 5). She was regularly followed up in the outpatient department (OPD). Her skin lesions completed resolved. After formation of complete line of demarcation in digital gangrene (Figure 4) she was referred to surgical team for amputation and disability rehabilitation. The patient is doing fine when she was followed last in the OPD.

**Discussion**

Chikungunya fever is caused by chikungunya virus (CHIKV) of genus alpha virus of family Togaviridae, transmitted by mosquito Aedes aegypti and Aedes Albopictus largely. The virus was first isolated after an epidemic in present-day Tanzania in the year 1952-1953. The disease is endemic in many parts of Africa, India and South-east Asia region and a seasonal trend in incidence is seen. The disease usually presents as acute febrile illness with asthenia, arthralgia, myalgia and rash, unlike dengue fever the infection is usually symptomatic with less than 15% having asymptomatic infection with seroconversion.

Usually the disease is self-limiting and non-life threatening in majority of patients, and the complications tend to occur in extremes of age group and patients with co-morbidities like diabetes mellitus, hypertension, cardiovascular or renal disease, immunosuppressed individuals. The complications include encephalitis, myocarditis, hepatitis, multi-organ failure and bleeding although rare with chikungunya but can occur and more likely to occur with patients with co-infection with dengue virus.

It is not uncommon for the disease to present with unusual complications. Some of the major unusual complications described in literature areguilian-barre syndrome, transverse myelitis, disseminated intravascular coagulation. The mechanism postulated for such complication might be molecular mimicry of some viral elements with the host elements, but it is not fully understood as of now.

Thrombotic thrombocytopenic purpura (TTP) is severe life-threatening disease with mortality rate of around 90% without timely treatment with plasma exchange therapy. It is described as a classic pentad of thrombocytopenia, microangiopathic haemolytic
Fig. 2: Images of left hand both feet on 4th day of admission

Fig. 3: Skin biopsy from right shin revealed Ischemic epidermal necrosis (Arrow; A), No definitive evidence of leucocytoclasia/fibrinoid necrosis identified. (B) Microvascular thrombi completely occluding the lumen (Arrow)

Fig. 4: Images of both hands and feet at the time of discharge

anemia, neurological symptoms, kidney failure and fever, although classic pentad of symptoms is rarely seen together. Differential diagnosis of TTP is wide and mainly includes ruling out other thrombotic microangiopathies and conditions like DIC, rheumatic diseases, malignancy or pregnancy related complications (Table 6). It is caused by acquired or inherited deficiency of ADAMTS13 (A disintegrin and metalloprotease with a thrombospondin type I motif, member13) leading to its reduced activity (<10%). ADAMTS13 is a plasma protease which cleaves ultra large molecules of von Willebrand factor (VWF) synthesized by endothelial cells. This normal cleavage to smaller fractions prevents these large molecules to accumulate. When the activity of this protease is reduced, ultra large VWF molecules accumulate on endothelial surface where platelets attach and accumulate leading to thrombosis of vessels.

Majority of TTP cases (95%) are acquired due to formation of an inhibitory autoantibody to

Table 3: Work up for hypercoagulable states

<table>
<thead>
<tr>
<th>Vasculitis workup</th>
<th>Viral markers</th>
<th>APLA workup</th>
<th>Hypercoagulability workup</th>
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<tr>
<td>ANA</td>
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<td>Negative β2 GP</td>
<td>S. Homocysteine Normal levels</td>
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<td>RF</td>
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2D-Echo EF- 61.8%, No vegetation/clot seen, no pericardial effusion, all valve morphology and opening normal; Normal study
Arterial Doppler all limbs All major vessels show normal flow, no occlusion or decreased flow.
Peripheral smear Day 4
Microcytic hypochromic cells with target cells, acanthocytes,(MCV-72fL)
2% schistiocytes, retic-0.3%, few activated lymphocytes
Platelets<10,000
Day 10
Normocytic normochromic cells with occasional schistiocytes(<1%), corrected retic-3.06%
Platelets-1.5 lac, few clumps seen
Day 10
Normocytic normochromic cells with occasional schistiocytes(<1%), corrected retic-3.06%
Platelets-1.5 lac, few clumps seen

At discharge
ADAMTS13 activity of <10% in the setting of microangiopathic haemolytic anaemia and thrombocytopenia confirms the diagnosis of TTP, activity levels of 10-50% is non-diagnostic and can be seen in many hospitalized patients in inflammatory, septic conditions or malignancy, it can also be seen in TTP patients who receive transfusion prior to testing. Levels of ≥50% is considered normal. Many a times this testing in not available in emergency setting and resource limited setup and if available also, turn-around time for test is much, and usually these patients require urgent plasma exchange. So the diagnosis remains clinical most of the times and tools like PLASMIC score has certain added advantage to increase sensitivity to early recognize this condition and institute timely therapy.

**References**


