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From crisis to cure: The journey of symmetrical peripheral gangrene in a female patient

Abhishek Kumar[1], Eram Nahid[2*], Fahim Ahmad[3], Priyanka Gupta[4], Vikram Singh[5]
[1] Department of General Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[2] Department of Endocrinology and Metabolism, All India Institute of Medical Sciences Jodhpur, Rajasthan, India
[3] Department of Pediatric Surgery, Maulana Azad Medical College, New Delhi, India
[4] Department of Pathology, Uttar Pradesh Institute of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India
[5] Department of Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract
Despite its typically benign nature, *Plasmodium vivax* can occasionally present as severe malaria. Symmetrical peripheral gangrene (SPG), characterized by distal ischemic changes without significant vascular obstruction, is an infrequent complication linked to various infections, medications, or underlying conditions. While SPG in malaria cases is rare, it commonly associates with *Plasmodium falciparum* or mixed infections, often accompanied by disseminated intravascular coagulation (DIC). This report presents a distinctive case of isolated *Plasmodium vivax* malaria with DIC and SPG, an exceedingly uncommon scenario. A 75-year-old female presented in emergency with history of fever and severely painful blackening of her toes, accompanied by feeble peripheral pulses. A diagnosis of SPG was made. During the etiological evaluation, *Plasmodium vivax* malaria was identified as the underlying cause, leading to DIC and subsequent development of this complication. Treatment was initiated with antimalarials and other conservative measures. Remarkably, the patient experienced a complete recovery without the necessity of limb amputation. This case highlights the necessity of maintaining a high index of suspicion for SPG in malaria patients to differentiate it from other conditions. Early recognition and intervention are crucial in halting gangrene progression and averting limb loss.

Keywords: Disseminated intravascular coagulation, symmetrical peripheral Gangrene, *P. Vivax,* Malaria

Introduction
Symmetrical peripheral gangrene (SPG) is a rare but severe complication characterized by bilateral distal ischemic changes affecting two or more sites, typically without evidence of vasculitis or significant large-vessel obstruction [1]. While SPG can arise from a range of bacterial and viral infections, medications, or underlying conditions like coagulopathies, connective tissue diseases and low cardiac output states; its link with malaria is particularly uncommon [2]. Most reported cases are associated with *P. falciparum* infection or mixed *P. falciparum/P. vivax* malaria, often accompanied by disseminated intravascular coagulation (DIC) [3–5]. Specifically, the association of SPG with *P.vivax* malaria is rare.
We presented a unique case of 75 year female diagnosed with *P.vivax* malaria, presenting with DIC and SPG. This case is noteworthy as the occurrence of DIC and SPG in association with isolated *P. vivax* malaria is exceedingly rare in the literature [6–8]. While amputation is often deemed necessary in such cases, yet in our instance, the patient was effectively managed with antimalarials and conservative measures, leading to full recovery. This underscores the criticality of early diagnosis and prompt initiation of treatment in mitigating severe complication.

Case presentation
75 year old female from North India without any known comorbidities presented in emergency with high grade fever associated with chills 12 days back, responded to antipyretics and she became afebrile for last 5 days. She also complained of rashes over bilateral upper limb and lower limb for last 7 days. For last three days these rashes were associated with severe pain, tingling, itching and coldness of bilateral foot along with blister formation and blackening of bilateral toes. There was decreased urine output 1 week back (<500ml/day) for which she had received one session of hemodialysis from outside, after which urine output improved.
On clinical examination patient was concious, oriented with heart rate of 80 beats per minute and blood pressure of 106/58mm Hg. Bilateral radial and dorsalis pedis arteries were feeble, however other pulses (carotid, brachial, femoral) were palpable and normal in volume. There was severe pallor, bilateral pitting type pedal edema was present, no organomegaly and chest was clear bilaterally with functional murmur in apical area. On limb examination there was reddish-purplish rashes present over both lower limbs till knee joint and both upper limb extending above elbow joint along with some vesicles. Lower limb was cold upto ankle joint and dry gangrene was present in all toes. (Fig. 1)
Laboratory investigations are mentioned in Table 1. There was pancytopenia, abnormal liver and renal functions and coagulation profile were deranged with APTT of >180 sec (normal: 25-35sec), pt/INR of 22.4 sec/ 1.75 (normal: 11-14 sec/<1.4) and d-dimer was >4 (normal <0.5 mg/L fibrinogen equivalent units). Serum LDH was 681 U/L (normal: 132-228U/L), complement levels were low with C3 of 76 mg/dL (normal; 90-180) and C4 of 11 mg/dL (normal: 16-40). Tests for antinuclear antibodies and anti-neutrophil cytoplasmic antibodies were negative.
Malarial antigen Rapid diagnostic test detected *P.vivax* Lactate Dehydrogenase (LDH) thus ruled out mixed infection with *P.falciparum*. On peripheral blood smear (Geimsa stain) schizont of plasmodium vivax was seen. NS1 antigen and dengue serology were negative. Arterial

Doppler of both upper and lower limbs was normal and did not reveal any thrombus in any of the arteries. Chest radiography was normal.

She was managed with intravenous artesunate 120 mg and doxycycline 100 mg twice a day for 7 days followed by lumefantrine 480mg and artemether 80 mg two times per day for 3 days, antipyretics and other conservative treatment. She also received 2 unit of packed red blood cells (PRBC), 8 units of fresh frozen plasma (FFP) and 1 unit of single donor platelet (SDP). The response to this line of treatment was remarkable and satisfying. She became asymptomatic after 7 days and was discharged in stable condition. After 3 months of followup she is doing better and gangrene has completely resolved.

Table 1: Baseline investigations of the patient

Parameter	Result	Reference range
Hemoglobin, g/dL	6.70	12-16
Total Leukocyte Count, cells/microliter	2.92 x 10^3	4-11 x 10^3
Neutrophil/Lymphocytes (%)	93/4	40-70/25-45
Platelets, cells/microliter	16 x 10^3	150-450 x 10^3
Urea, mg/dL	111	17 - 43
Creatinine, mg/dL	1.83	0.66 – 1.09
Serum alkaline phosphatase, IU/L	76	30 - 120
Serum glutamic oxaloacetic transaminase/Serum glutamic pyruvic transaminase, IU/L	63/ 68	<50 / <50
Albumin, g/L	2.99	3.5 – 5.3
Total Bilirubin/direct bilirubin, mg/L	1.1/0.35	0.1-1.2/ 0-0.2
Lactate Dehydrogenase, U/L	681	132-228
PT (seconds) / INR	22.4/1.75	11-14/<1.41
aPTT, seconds	>180	25-35
C3, mg/dL	76	90-180
C4, mg/dL	11	16-40
d-Dimer, mg/L fibrinogen equivalent units	>4	<0.5

Figure Legends

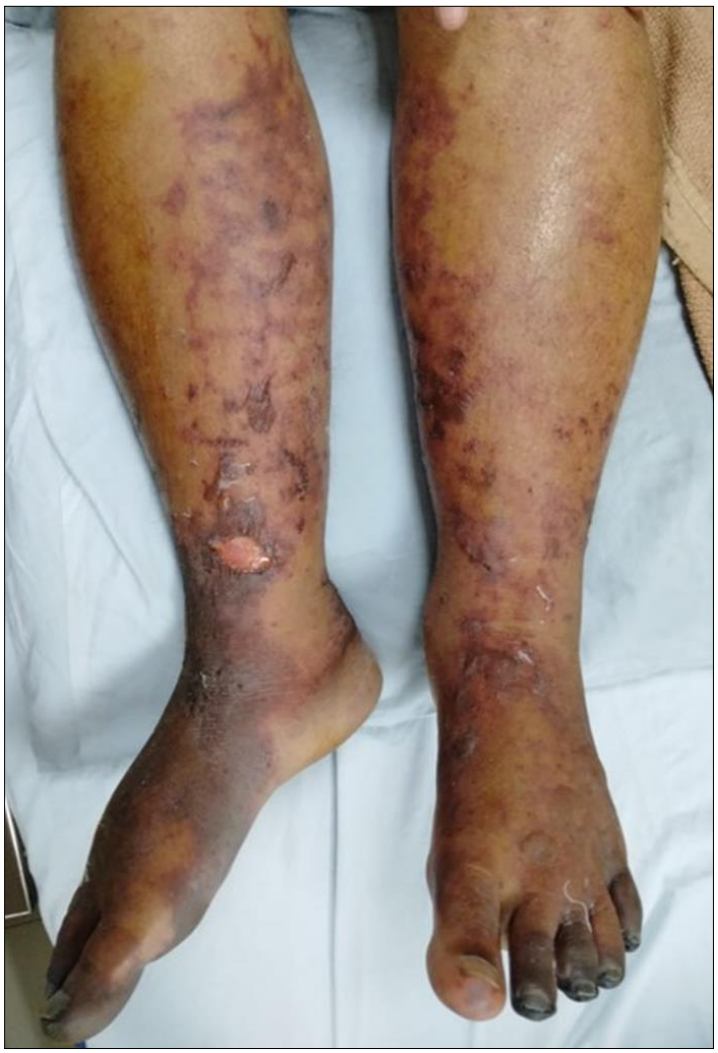

Fig 1: Reddish purplish rashes over both lower limbs along with blackening of toes

Discussion

While *P. vivax* typically exhibits lower pathogenicity compared to *P. falciparum* in otherwise healthy individuals, it still has the potential to induce complex and severe disease outcomes. Severe malaria complications can be broadly categorized into sequestration-related, such as cerebral malaria, renal dysfunction, hepatic dysfunction, and acute respiratory distress syndrome (ARDS), and non-sequestration-related, including anemia and thrombocytopenia [9].

Irrespective of the etiology, DIC is the final common pathway for pathogenesis of SPG [10]. DIC is linked to various clinical conditions, typically characterized by systemic inflammation activation. These include sepsis, trauma, malignancies, transfusion reactions, acute pancreatitis, obstetric complications, and severe toxic reactions.

The SPG in malaria is postulated to be due to heavy parasitemia that triggers activation of the complement and coagulation pathways, ultimately leading to microvascular thrombosis. Infected erythrocytes interact with various endothelial receptors, including intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, thrombospondin, and histidine-rich protein, resulting in microcirculatory obstruction. DIC also contributes to malaria-related SPG, albeit rarely associated with significant bleeding [11].

SPG occurs rarely with malaria and most of the cases are associated with falciparum malaria [3, 5]. The emergence of severe *P. vivax* malaria with SPG is indeed a concerning development [6, 7]. Amputation may be necessary to salvage the limb in SPG, but in our scenario, the timely diagnosis and initiation of treatment spared the limb from such drastic measures. The fact that all reported cases are from India suggests that there may be regional factors contributing to this phenomenon [6–8]. It is possible that genetic variations in the *P. vivax* parasite, environmental factors, host immune responses, or healthcare infrastructure play a role.

In the meantime, healthcare professionals in regions where *P. vivax* malaria is prevalent should be vigilant for signs of severe malaria, including SPG, and ensure timely diagnosis and appropriate management to prevent complications and to save limb.

Conclusion

The current case underscores SPG as a rare complication of *P.vivax* malaria and highlights high index of suspicion for this clinical entity to differentiate it from other conditions which present with SPG like collagen vascular diseases. Early recognition and initiation of treatment are crucial in halting the advancement of gangrene and saving the limb from amputation.

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