Case Report

Symmetrical Peripheral Gangrene and Falciparum Malaria: A Case Report and Review of all Cases

Veerabhadra Radhakrishna[1*], Rajshekhar Patil[2], Nitin D. Tengli[2]

[1]Department of Paediatric Surgery, Indira Gandhi Institute of Child Health, Bangalore; [2]Department of General Surgery, Basaveshwar Hospital, M.R. Medical College, Gulbarga, India.*

Abstract | Introduction: Symmetrical Peripheral Gangrene (SPG) is defined as a symmetrical distal ischemic injury at two or more locations without any large vessels blockade. Malaria has been reported as one of the causes of SPG, although only 36 cases have been complicated with Symmetrical peripheral gangrene till date. Case Report: A 30-year male presented to us 15 days after the onset of malaria with gangrene of all four limbs with superadded infection. His wounds were debrided and amputated. Once the infection was controlled and gangrenous parts demarcated, amputations were done again for the lower limbs. Discussion: In *P. falciparum* infections, the processes of cytoadherence, rosetting, and agglutination are the factors responsible for the pathogenesis of SPG. It's vital to identify this rare, quickly developing complication. Heparin is being tried; blood transfusion has also been explored in the management of some of the patients but not found to be effective. If allowed to advance, surgical intervention is unavoidable.

Keywords | Symmetrical peripheral gangrene; Severe falciparum malaria; Amputation; Anticoagulant therapy

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***Correspondence** | Veerabhadra Radhakrishna, Department of Paediatric Surgery, Indira Gandhi Institute of Child Health, Bangalore; **Email:** vbrps2016@gmail.com
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INTRODUCTION

Symmetrical Peripheral Gangrene (SPG) is defined as a symmetrical distal ischemic injury at two or more locations without any large vessels blockade (Molos and Hall, 1985). Its pathogenesis is not well known, and it has been related to an extensive variety of infective and non-infective causative factors (Ghosh and Bandyopadhyay, 2011).

Malaria is one of the major parasitic infections occurring in humans, affecting 108 countries comprising more than three billion populations and causes approximately one million demises annually (White and Breman, 2012). It has been reported as one of the causes of SPG (Ghosh and Bandyopadhyay, 2011), although only 36 cases have been complicated with SPG till date. Here we report a case of Symmetrical Peripheral Gangrene in a patient with severe falciparum malaria presented to our institution. We have also reviewed all 37 cases, which hasn't been done till date.

A 30-year male presented to emergency room with high-grade fever with chills and rigors for two days. Later he developed vomiting and became drowsy. A day later, he developed blackish discoloration of all four limbs (Figure 1 and 2). He was not a smoker, alcoholic or drug abuse; and had no history of diabetes, hypertension or any angiopathies. His cardiovascular, respiratory and abdominal examination was normal. He was diagnosed with severe falciparum malaria based on peripheral smear and treated with Artesunate as per CDC guideline (CDC guidelines 2013). As patient improved from severe illness, he got discharged against medical advice.

Fifteen days later the patient returned with gangrene of all four limbs with superadded infection. Vital and systemic examinations were found to be normal. His haemoglobin was 6.2g/dL, Total Count of 4600/mcL, platelet count of 428000/mcL; HIV, HBV, HCV, and VDRL on ELISA were negative. Blood sugar, Renal function tests, and

clotting profile were normal. His wounds were debrided and amputated. After the infection was controlled, revision amputations were done for the lower limbs. He was referred to rehabilitation. Currently, he is performing his daily activities with minimal help from his family.

Figure 1: Gangrenous upper limbs

Figure 2: Gangrenous lower limbs

DISCUSSION

Symmetrical peripheral gangrene (SPG) was initially described in 1981 by Hutchinson. SPG commonly occurs with bacterial infections like *Staphylococcal, Pneumococcal, Meningococcal, Streptococcal, E.coli, Pseudomonal septicemia, Viruses* or *Rickettsial* infections (Ghosh nd Bandyopadhyay, 2011). Less commonly it follows after usage of drugs like ergot, vasopressin, noradrenaline, thiopentone or inadvertent intramuscular injection gone intra-arterially. Conditions like Polymyalgia rheumatica, Sickle cell disease, Raynaud's phenomenon, diabetes mellitus, cryoglobulinemia and inherited coagulopathies like protein-C, S and Antithrombin-3 deficiency can also cause SPG (Ghosh and Bandyopadhyay, 2011).

World Health Organization defines complicated malaria as those accompanied by one or more of the following clinical or laboratory findings i.e. severe anemia, an impaired level of consciousness (Glasgow Coma Scale score 7), acidosis, hypoglycemia, hyperlactatemia, pulmonary edema, hyperparasitemia (of more than 5%), bleeding and renal impairment (White and Breman, 2012). This type of malaria has a mortality of more than 10% (White and Breman, 2012).

In *P. falciparum* infections, the erythrocytes develop membrane protuberanceson their surfaces 12–15 hours after the cell's invasion by the parasite. These "knobs" produce a high-molecular-weight, strain-specific, antigenically variant erythrocyte membrane adhesive protein (PfEMP1) that facilitates attachment to receptors on the endothelium of venules and capillaries. This event is termed ***cytoadherence***. The most important among these vascular receptors is intercellular adhesion molecule-1 (ICAM-1); others include thrombospondin (TSP), chondroitin sulfate B,endothelial leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), his tidine rich protein (HRP) and CD36. Thus, the infected erythrocytes stick to the endothelium and eventually block capillaries and venules. Simultaneously, the *P. falciparum*–infected RBCs may also adhere to uninfected RBCs (to form rosettes) and to other parasitized erythrocytes (agglutination). The processes of cytoadherence, rosetting, and agglutination are the factors responsible for the pathogenesis of SPG (White 1996; White and Breman, 2012).

There are a total of 37 cases (including our patient) found to have malaria-induced symmetrical peripheral gangrene till date. Mean age of this population was 28.6 years. The smallest patient affected was eleven months old, and the eldest patient was 65 years. Males were most commonly affected (20 patients; 54%) than females probably because males are at more risk of getting exposed to the mosquito bite. Except for one patient (Sharma, 1987), all were found to have anemia. Fifteen patients were found to have thrombocytopenia.

The management of severe malaria is well standardized. But, the management of microvascular induced by malaria is not established. This includes the use of anti malarial therapy and occasional use of anticoagulants in the presence of ischaemic symptoms (Losert et al., 2000). Quinine was the most commonly used anti malarial in severe malaria. There was a suspicion of quinine as the reason for the development and progression of malaria-induced gangrene as in some cases; quinine was started before the onset of gangrene. But there's no support in the literature.

The dreaded complication of malaria, Symmetrical peripheral gangrene, necessitates the eradication of the parasite with simultaneous treatment of the gangrene. It's a challenge to identify this rare, hastily developing complication,

Table 1: Review of all Falciparum Malaria cases with SPG

No	Author	Country	Age/ sex	Hb (g/ dL)	Plt (lakh / cu.mm)	Parasite count (%)	Clinical features	Antimalarial therapy	Anti-clotting therapy	Result
1	Edwards et al.	Zimbabwe	11/M	11.6	0.21	NA	DIC	Quinine	Heparin	Resolved
2	Edwards et al.	Zimbabwe	9/M	12.9	0.1	NA	DIC, Cerebral malaria	Quinine	Heparin, Streptokinase	Resolved
3	Chittichai et al.	Thailand	13/F	7.6	0.52	75	Cerebral Malaria	Quinine	None	Resolved
4	Chittichai et al.	Thailand	10/F	10.7	0.5	88	DIC, Cerebral malaria, jaundice	Quinine	None	Resolved
5	Kochar et al.	India	46/F	5	1.6	6	Prolonged Q-Tc, Atrial & Ventricular fibrillation	Quinine, Chloroquine	None	Amptuated
6	Anuradha S. et al	India	21/M	6.8	2.1	NA	DIC, dry gangrene of fingers and toes	Artesunate	None	Amptuated
7	Anuradha S. et al	India	59/M	5.5	1	NA	DIC, dry gangrene of fingers and toes	Quinine	None	Resolved
8	Anuradha S. et al	India	35/F	7.1	1.1	NA	DIC, dry gangrene of both feet	Quinine	None	Resolved
9	Jain D. et al.	India	26/F	10	NA	NA	Dry gangrene of fingers and toes	Quinine	None	Amptuated
10	Sharma SN et al.	India	22/M	13	1.9	NA	Dry gangrene of fingers and toes	Quinine	None	Amptuated
11	Liechti et al.	Switzerland	56/F	10.9	0.13	10.3	DIC, Cerebral Malaria	Quinine	Heparin	Amptuated
12	Sharma BD et al.	India	65/F	3.2	1.56	14	DIC, Cerebral malaria	Quinine	None	Amptuated
13	Tamhankar P. et al	India	3/F	6	0.8	90	Dry gangrene of fingers, toes, earlobes, patches on arms and legs	Quinine	None	Resolved
14	Agarwal et al.	India	10/F	4.4	0.92	>5	Dry gangrene of toes	Quinine	Heparin, Warfarin	Amptuated
15	Pramod S. et al.	India	1/F	4	70	5	Dry gangrene of thigh, lower left abdominal wall and gluteal region	Quinine	None	Resolved
16	Vipa et al.	Thailand	40/M	9.7	3.95	21	Dry gangrene over lower limbs	Artesunate	None	Resolved
17	Vipa et al.	Thailand	45/M	12.3	2.3	20	Dry gangrene of toes	Artesunate, Mefloquine	None	Amptuated
18	Vipa et al.	Thailand	59/M	10	3.4	11	Dry gangrene of toes	Artesunate, Mefloquine	None	Resolved
19	Kakati et al.	India	26/F	9.75	2.3	NA	Dry gangrene of toes	Artesunate, Ceftriaxone	None	Not stated

20	Raimund S. et al.	Uganda	61/M	NA	NA	NA	DIC, Dry gangrene of toes	Quinine, Mefloquine	None	Amptuated
21	Ghafoor SZ et al.	Nigeria	44/F	11.8	0.48	24	DIC, dry gangrene of fingers and toes	Artesunate, Doxycycline	Heparin	Resolved
22	Rajoo T. et al	India	6/F	5.6	0.84	>90	Dry gangrene of toes	Artesunate, Mefloquine, Primaquine	Heparin, Warfarin	Amptuated
23	Bhattacharya et	India	12/M	7	1.66	21	Dry gangrene of lower limbs	Quinine	None	Refused Amputation
24	Alkizim et al	Uganda	54/M	9.03	4.5	NA	Dry gangrene of hands and feet	Quinine	Clopidogrel	Amptuated
25	Ibrahim et al	Sudan	36/F	9.2	2.34	22	Cerebral Malaria, Renal failure	Quinine	None	Resolved
26	Ibrahim et al	Sudan	44/F	8.2	2	17	Cerebral malaria, Dry gangrene of toes	Quinine	None	Resolved
27	Masse et al	Belgium	63/F	NA	0.21	1	All four limbs digits gangrene, Bacteraemia, Candidemia	Quinine	None	Amputated
28	Martins DB et al	USA	11m /M	NA	NA	NA	All four limbs digits gangrene	NA	NA	Auto amputation
29	Martins DB et al	USA	3/M	NA	NA	NA	Bilateral foot gangrene	NA	NA	Lost follow up
30	Martins DB et al	USA	6/M	NA	NA	NA	Bilateral foot gangrene	NA	NA	Amputated
31	Martins DB et al	USA	7/F	NA	NA	NA	Gangrene of left upper limb digits up to wrist, cerebral malaria	NA	NA	Amputated
32	Arora N et al	India	22/M	8	0.22	NA	Gangrene of hands & feet, DIC.	Artesunate	Heparin	Amputated
33	Raghunandan J	India	1.5/ M	7	1.5	NA	Gangrene of both hands	Artesunate	NA	Resolved
34	Abdali N et al	India	45/M	NA	NA	NA	Gangrene of all four limb digits	Artemisinin	Heparin	NA
35	Gupta A et al	India	50/M	NA	NA	NA	Gangrene of toes of both lower limbs	Quinine	None	Amputated
36	Rana A et al	India	17/M	1.1	0.1	NA	Gangrene of feet	Quinine	None	Resolved
37	**Current Case**	**India**	**30/M**	**6.2**	**4.28**	**NA**	**Cerebral malaria, Gangrene of all 4 limbs**	**Artesunate**	**None**	**Amptuated**

before ischemia sets in, as anticoagulants are not conventionally included in the management regime of common malaria. Heparin was tried in a few cases to combat thrombosis and gangrene formation, but no absolute protection has been found. Moreover, the high risk of haemorrhage in severe thrombocytopenia contraindicates the use of heparin.

As per the Table 1, anti-clotting therapy was given in nine cases; pre-gangrenous changes got resolved in three of them while five underwent amputation, result unknown for a patient. Anti-clotting therapy was not used in 28 cases and 11 of them got their pre-gangrenous changes resolved. It concludes that anti-clotting therapy has got no advantage in the treatment of SPG (Fischer's exact test, p= 0.7).

Blood transfusion has also been tried in the management of some of the patients. But its advantage is still controversial (Riddle et al., 2002).

The extremely short period of Malaria-induced SPG from onset to rapid progression of tissue necrosis practically gives no time to intervene. But with the correct and timely intervention, the ischemia may resolve before developing into gangrene. If the disease progresses, surgical techniques would be unavoidable, which depend on the extent and severity of gangrene ranging from debridement to amputation (Table 1). Our patient presented with gangrene with superadded infection, requiring amputation.

CONCLUSION

Falciparum Malaria is one of the commonest diseases worldwide. One should anticipate SPG as a complication of severe falciparum malaria. Timely and prompt management of the disease is a must. SPG, when occurs, rapidly progresses to irreversible gangrene, thereby demanding amputation. Concerned doctors should, therefore, be attentive and on the look-out for SPG to intervene quickly and halt its progression.

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHORS CONTRIBUTION

Dr Veerabhadra Radhakrishna conceptualized and designed the study, conducted the analyses, drafted the initial manuscript, and made final revisions based on critical feedback received from Drs Rajshekhar Patil and Nitin Tengli. Dr Rajshekhar and Nitin conceptualized the study in collaboration with Dr Veerabhadra, reviewed the results, and provided critical feedback for the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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