

CASE REPORT

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# Acrocyanosis as a rare presentation of drug-induced cutaneous vasculitis: a case report

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## Abstract

**Background** Acrocyanosis is characterised by persistent bluish discolouration of the extremities, resulting from reduced peripheral blood flow leading to increased oxygen extraction. The aetiology can be divided into primary and secondary causes. While primary acrocyanosis is generally painless and has a benign course, secondary causes may lead to complications. This case reported acrocyanosis secondary to cutaneous vasculitis which progressed to digital gangrene, which is a rare complication of cutaneous vasculitis.

**Case presentation** A 68-year-old man presented with a four-day history of bluish discolouration involving bilateral toes associated with pain and started to become gangrenous. Investigations for critical limb ischemia did not show evidence of critical arterial stenosis. Further history revealed history of recent administration of intramuscular injections with diclofenac, a non-steroidal anti-inflammatory agent for renal colic pain a few days prior to the onset of the. Thorough skin search showed multiple purpuric rash of his thighs, buttocks and abdomen. Skin biopsy confirmed the diagnosis of cutaneous (lymphocytic) vasculitis, which was likely to be drug-induced. The acrocyanosis initially responded to methylprednisolone, however unfortunately it progressed further to digital gangrene which required bilateral transmetatarsal amputations.

**Conclusion** Knowledge on clinical features, aetiology and investigations of secondary acrocyanosis is crucial for early recognition and treatment of the underlying cause to prevent irreversible complications.

**Keywords** Peripheral cyanosis, Bluish discolouration, Gangrene, NSAID-induced, Skin biopsy

## Introduction

Acrocyanosis is characterised by persistent bluish discolouration of the extremities, resulting from reduced peripheral blood flow leading to increased oxygen extraction. While it can stem from various aetiologies, drug-induced acrocyanosis is a rare yet significant concern. Among the pharmacological agents implicated, diclofenac, a widely prescribed nonsteroidal anti-inflammatory drug (NSAID), has yet to be associated with this adverse effect. This case report describes a rare presentation of diclofenac-induced acrocyanosis, underscoring the importance of early recognition and prompt management.

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**Fig. 1** Maculopapular and petechial eruption on the trunk

### Case Report

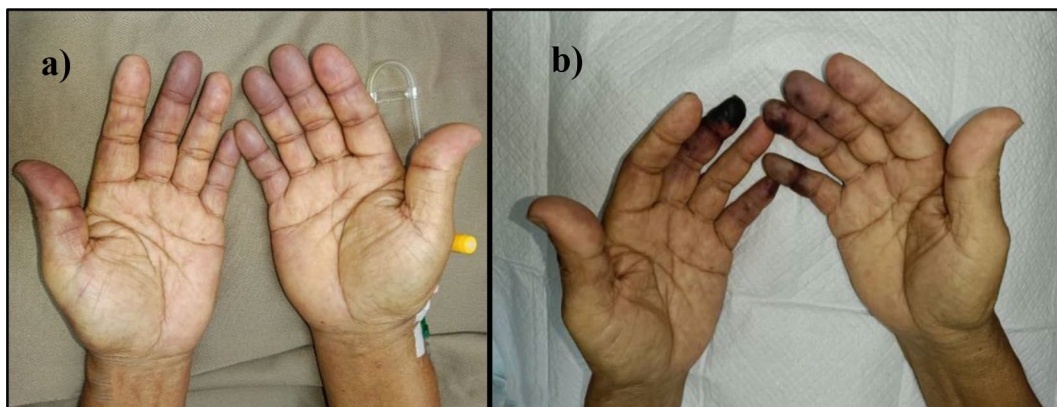
A 68-year-old gentleman with background history of hypertension and hyperlipidaemia was referred to our hospital from another centre following a four-day history of sudden onset bilateral forefoot numbness, pain, and discolouration, extending to the fingers, with the suspicion of peripheral arterial disease. He is a non-smoker and lives in a tropical region that is not affected by temperature fluctuations. On initial review by the surgical team, he had dusky appearance of all fingers and toes, however the peripheral pulses namely the bilateral radial, posterior tibialis, and dorsalis pedis pulses were palpable. Arterial ultrasound Doppler scan showed biphasic and

triphasic signals from all the arteries including ulnar arteries. Arterial CT angiogram of the lower limbs also confirmed the patency of major arteries. He was then referred to the rheumatology team for possible Raynaud's phenomenon in view of cyanosis involving all digits.

Further history revealed episodes of colicky loin-to-groin pain a few days prior to the symptom onset where he had sought treatment from a general practitioner. He was diagnosed with renal colic and administered a few intramuscular injections of diclofenac.

Upon clinical examination at our centre, he was afebrile, HR 88 bpm, RR 16 breaths per minute, BP 155/80mmHg and SpO<sub>2</sub> 97% on room air. The digits were of dusky appearance, with continuous tingling sensation, without the classical triad of Raynaud's phenomenon; the cyanosis-pallor-erythema triphasic reaction. The peripheral pulses and sensation in both hands and feet were intact. Full skin examination revealed presence of petechial and pruritic morbilliform rash on trunks, buttocks and thighs.(Fig. 1) Limb examination showed purpuric patches on his digits bilaterally (Fig. 2a), with few areas of pinpoint necrotic ulcers over tip of toes (Fig. 3a), and bullae formation over purpuric patch on left anterior shin. Differential diagnoses at the time included thromboembolism, arterial dissection, and vasculitis.

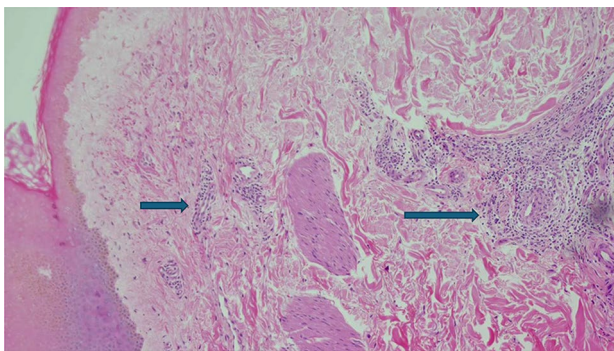
Investigations including viral screening, blood cultures, anti-nuclear antibodies, extractable nuclear antibodies, complements level, antineutrophilic cytoplasmic and antiphospholipid antibodies were negative. Echocardiogram showed structurally normal heart without evidence of clot or vegetation. Computed tomography angiography of the aorta, bilateral upper and lower limbs revealed no evidence of arterial dissection, thrombosis, or stenosis. 72-hour Holter monitoring was unremarkable. Histopathological examination of skin biopsies revealed mild perivascular lymphocytic infiltration of the superficial small vessels at the papillary dermis and within the vascular wall, with predominantly lymphocytes with some



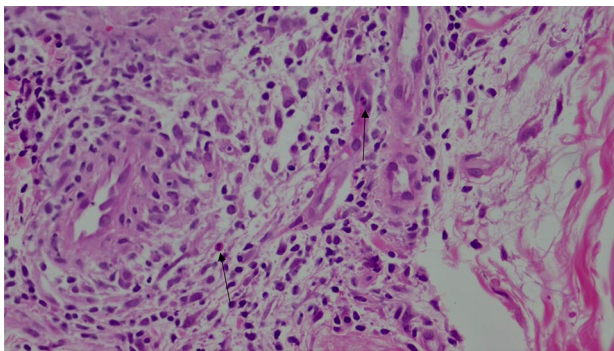
**Fig. 2** (a) Purpuric patches on fingers at initial presentation, (b) 2 weeks later: Progression to black necrotic tissue consistent with dry gangrene



**Fig. 3** (a) Purpuric patches on toes and distal feet at initial presentation, (b) 2 weeks later: Progression to black necrotic tissue consistent with dry gangrene, (c) Post-transmetatarsal amputation



**Fig. 4** Histologically at 10x ocular magnification highlights the presence of perivascular inflammatory response predominantly by lymphocytes and occasional plasma cells.(the arrows)



**Fig. 5** At 40x ocular magnification, occasional eosinophils (arrows) are also seen among the lymphocytes

plasma cells and occasional eosinophils. No granuloma was seen and the direct immunofluorescence studies were negative. Overall this was consistent with lymphocytic vasculitis. (Figures 4 and 5) The diagnosis of drug-induced cutaneous vasculitis was made.

He was initially treated with anticoagulants, pentoxifylline, and calcium channel blocker. Subsequently, he received intravenous methylprednisolone 500 mg daily for 3 days followed by oral prednisolone 20 mg daily. There were no further worsening of the cyanosis of his digits and the truncal eruption cleared. However, he had

severe bouts of pain requiring oral gabapentin, patient-controlled analgesia (PCA) morphine and bilateral stellate ganglion block.

Unfortunately, 2 weeks later he represented with worsening cyanosis of his toes which has progressed to gangrene.(Fig. 2b) and 3b)) He underwent transmetatarsal amputation of both feet (Fig. 3c) and conservative treatment was decided for his left middle fingertip gangrene. He was discharged well with tapering doses of prednisolone.

## Discussion

Acrocyanosis is originated from Greek word which literally means bluish (*kyanos*) discoloration of the extremities (*akron*). First coined by Crocq in 1986, acrocyanosis is a part of acrosyndromes together with Raynaud's phenomenon and erythromelalgia. It refers to persistent abnormal deep blue or cyanotic discoloration of skin over the extremities (hand and feet most commonly) due to decreased oxyhemoglobin secondary to vasospasm. Acrocyanosis usually presents with coolness and violaceous dusky discolorations of hands and less frequently the feet [1]. Other peripheral parts like ear, nose, lips, and nipple can also be affected. It is marked by symmetry and aggravated by exposure to cold, and frequently associated with local hyperhidrosis of hands and feet [2]. Its prevalence remains unknown due to scarcity of reported cases [1].

Acrocyanosis can be divided into primary and secondary acrocyanosis according to the absence or presence of causative factors. Primary acrocyanosis is not associated with an identifiable cause and is usually benign with a good prognosis in which ulceration and tissue loss are extremely rare. In primary acrocyanosis, there is no associated pain and patients are normally asymptomatic aside from discoloration. Trophic skin changes and ulceration are not seen except in remittent necrotising acrocyanosis. It is also associated with enhanced susceptibility to cooling and pain, as well as ulceration and gangrene of the fingers [1]. Secondary acrocyanosis is associated with

other conditions and may lead to ulceration and necrosis. This includes hypoxaemia, cardiovascular disease, thromboembolism, vasculitis, hematological diseases, toxic exposures, and drug induced [3].

Investigations for acrocyanosis include meticulous history taking and clinical examinations to determine the possible aetiology. Capillary oximetry that shows normal oxygen saturation rules out vaso-occlusive disease. Other laboratory investigations and imaging studies are needed to identify the aetiology of secondary acrocyanosis depending on the clinical signs and symptoms of underlying disease in individual cases. Complete haemogram is essential for lymphoproliferative disease and essential thrombocythemia. Screening for connective tissue disease and antiphospholipid antibody syndrome is compulsory. Metabolic screening may be required for fucosidosis in suspected cases. In addition, CT scan, MRI, and nerve conduction study may be required to rule out any underlying neoplastic disease, spinal cord injuries, thromboembolism, and nerving plexus neuropathy [1]. When cutaneous vasculitis is suspected, skin biopsy is the gold standard investigation to confirm the diagnosis [4]. Drug-induced acrocyanosis have been observed with certain drugs such as selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine, clonidine, interferon, alphaprodine, amphotericin B, and intra-arterial injection of propoxyphene. Intravenous chemotherapy with gemcitabine, cisplatin or oxaliplatin have also been reported to cause acrocyanosis [1]. Other drugs known to induce acrocyanosis are metoclopramide, imipramine, desipramin, and fluoxetine [5]. To the best of our knowledge, this is the first reported case of diclofenac-induced acrocyanosis.

In this case, our patient presented with acrocyanosis secondary to drug-induced cutaneous vasculitis, which was confirmed on skin biopsy showing lymphocytic vasculitis. Lymphocytic vasculitis is more common in connective tissue diseases, viral infections and drug eruptions [4]. Unfortunately, our patient's condition progressed to develop digital gangrene. The pathophysiology of inflammation-induced thrombosis is complex. Thrombosis is a well-known association with systemic vasculitis, however thrombosis in small vessel vasculitis is comparatively rare [6]. Hyperactivation of the coagulation system along with the impaired activation of the fibrinolytic system may explain the thrombosis formation [6]. Damage to the endothelial cells, induced oxidative stress along with hypercoagulability states will further lead to gangrene and amputations of the limbs in the majority of the cases [3]. Symptoms of toe gangrene in our patient improved initially with steroids and anticoagulation. However, the progression to toe necrosis were unsalvageable. Transmetatarsal amputations were

performed as the final resolution to resolve the persistent toes infection.

Treatment for secondary acrocyanosis involves mainly by treating the underlying cause [1]. In severe cases, drugs like calcium channel blocker (CCB) and alpha-adrenergic blocking agents (prazosin) can be used in view of vasodilatory action of these drugs. Trial of combination of pentoxifylline and diltiazem in remittent necrotising variety also had been shown to have good results in primary acrocyanosis [1]. In cases of cutaneous vasculitis, in some instances, it may require only symptomatic management as the process may be self-limited after removing the potential trigger. However, at present, the evidence-based guide to treat cutaneous vasculitis is limited due to the varying types of vasculitis affecting the skin and is mainly based on case series and experts opinion [7]. The choice of treatment will depend on the severity of the vasculitis. Systemic corticosteroids (0.5-1 mg/kg) has been used in IgA/IgM immune complex vasculitis to achieve rapid resolution and can safely be tapered slowly over 3–6 weeks. However, due to high risk of relapse with rapid tapering, those with chronic or recurrent disease or flare while tapering down steroids, other steroid-sparing agents had been used including colchicine, dapsone and azathioprine [7].

## Conclusion

This case highlights the significance of vigilance regarding adverse drug reactions, even with commonly prescribed medication such as diclofenac. Thorough clinical history of medication use with extensive skin search for other cutaneous lesions are of utmost importance in searching for the diagnosis. Acrocyanosis, although rare, should prompt clinicians to consider both primary and secondary causes especially drug-induced aetiology. Prompt recognition and discontinuation of the offending agent remain paramount and prompt management of the complications is crucial. Further research into the pathophysiological mechanisms underlying NSAID-induced acrocyanosis and vasculitis is warranted to elucidate preventive strategies and optimise patient care.

## Abbreviations

CCB	Calcium channel blocker
CT	Computed tomography
MRI	Magnetic resonant imaging
NSAID	non-steroidal anti-inflammatory drug

## Acknowledgements

None.

## Author contributions

S.N.M.N and W.S.W.G were responsible for concept of the manuscript, clinical case and discussion. E.R.Z wrote the clinical presentation, findings, and discussion. H.S performed the skin biopsy and wrote the clinical findings section. N.S.S was involved in the management of the case and reviewed the manuscript substantively. S.M.S was responsible for the histopathological

examination and images. All authors reviewed and contributed to each section of the manuscript.

#### Funding

No funding.

#### Data availability

No datasets were generated or analysed during the current study.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

The patient reported in the case has given his verbal and written consent for the publication of the details and images related to the case.

##### Competing interests

The authors declare no competing interests.

Received: 1 July 2024 / Accepted: 2 September 2024

Published online: 10 September 2024

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