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Four limb amputations due to peripheral gangrene from inotrope use – Case report and review of the literature

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ABSTRACT

INTRODUCTION: We present a rare case of 4 limb amputations due to peripheral gangrene which resulted from the use of inotropes for septic shock.
PRESENTATION OF CASE: A 72-year-old woman with no past medical history presented with fever and pain in bilateral big toes. She was diagnosed with *Streptococcal pneumoniae* septicaemia and was started on broad spectrum antibiotics, dopamine and noradrenaline in the medical intensive care unit. She developed peripheral gangrene of all 4 extremities due to microvascular spasm from inotrope use and 4 limb amputations were performed electively in a single stage.
DISCUSSION: The gangrene was contributed by the presence of disseminated intravascular coagulation and septic shock. There was no evidence of an autoimmune disorder or vasculitis on laboratory investigations and tissue histology.
CONCLUSION: Microvascular spasm is a rare complication of inotrope use which may lead to extensive peripheral gangrene. Anecdotal reports of reversal agents have been discussed. Four limb amputations are a reasonable option especially if done in an elective setting after the gangrene has demarcated itself. Rehabilitation with prosthesis after 4 limb amputations can result in good functional outcome.

1. Introduction

Multiple limb amputations are uncommon and can be caused by metabolic disorders such as crygoglobulinemia [1], burns [2–4], purpura fulminans [5–7], and drug use such as cocaine [8]. Inotropes such as dopamine have been frequently used in the treatment of hypotension, and its effectiveness in treating cardiogenic, septic, and traumatic shock is firmly established. It can cause peripheral gangrene with prolonged administration at high doses and was first reported as a complication in 1973 by Holzer et al. [9], but it rarely leads to 4 limb amputations [10–14]. In this case report, we describe the eventual result of elective 4 limb amputations for peripheral dry gangrene from the use of inotropes in a 72-year-old woman for septic shock. This report brings to light an uncommon but devastating complication of inotrope use which will continue to exist due to its prevalent usage. Elective single-stage 4 limb amputations is a reasonable surgical option in the setting of peripheral dry gangrene.

2. Presentation of case

A 72-year-old woman was admitted for fever of one day duration associated with pain in bilateral big toes. There was no history of trauma and any insect bites recently. These episodes happen twice a year and resolves spontaneously. She used to take Traditional Chinese Medicine in the past for these episodes but drug toxicology screen was negative. There was no diagnosis of any joint problem such as gout, or any autoimmune problem such as Lupus or Raynaud's syndrome in the past. Vasculitis screen was negative except for a borderline positive anti-nuclear antibody. There were also no risk factors for peripheral vascular disease. Upon physical examination, there was pain on bilateral big toes likely due to bilateral podagra but there was minimal swelling with full range of motion, and her pulses were well felt. She was admitted to Medical Intensive Care Unit due to diagnosis of streptococcal septicaemia with growth of *Streptococcus pneumoniae* in her blood culture. Broad spectrum antibiotics were started, but her hypotension of 60/40 mmHg and urine output of <20 ml/h did not respond to fluid replacement. Dopamine was used up to 18 mcg/kg/min on the day of admission to increase the blood pressure for adequate organ perfusion. Noradrenaline was also used in view of septic shock up to 0.5 mcg/kg/min on the second and fifth day of admission. Her

Abbreviations: DIVC, disseminated intravascular coagulation; SPG, symmetrical peripheral gangrene.

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Fig. 1. Severity of dry gangrene on her left upper limb.

Fig. 2. Extent of dry gangrene on her right lower limb with a sharp demarcation.

vital signs normalized with the use of inotropes, but her extremities were noted to be dusky. On the second day of admission, marked livedo reticularis was noted on her peripheries. Subsequently, patches of ecchymosis and mottled skin started appearing on her extremities and nose. On the fifth to seventh day, her terminal digits and tip of nose started looking necrotic and signs of dry gangrene were appearing. In the second week, ecchymotic bullae appeared over her bilateral lower limbs with plantar gangrene and her dorsalis pedis and posterior tibial pulses were not palpable. There were also ecchymotic bullae over her bilateral hands and forearms and her radial pulses were not palpable. By then, the dry gangrene had involved all her digits. A referral to the vascular surgeon revealed a diagnosis of microvascular spasm due to inotropes resulting in peripheral gangrene. Toe pressure could not detect any pulsations in view of gangrenous extremities. Nevertheless, an arterial occlusion test revealed moderate calcification of bilateral lower limb arteries. A referral was made to plastic surgery and the plan was to await the dry gangrene to demarcate before attempting any further procedures. Her dry gangrene had progressed to her bilateral ankles and wrists by the first month. It eventually demarcated itself up to her upper forearms (Fig. 1), up to her mid-shin on her left lower limb and up to her upper shin on her right lower limb (Fig. 2).

The patient was re-admitted electively two months later for 4 limb amputations. This was considered in view of the dry gangrene causing quadruple non-functional limbs, the inconvenience of wound nursing and the risk of the limbs being a septic focus. She underwent bilateral below knee amputations and bilateral above elbow amputations. Recovery was smooth post-operatively and rehabilitation was started. Five years from her operation, the patient is now ambulatory with bilateral lower limb prosthesis which was installed half a year from the operation, and also utilizes bilateral upper limb prosthesis.

3. Discussion

Dopamine and noradrenaline [14] are frequently used in septic shock because of their positive inotropic effects. When dopamine is administered in low doses of 2–5 mcg/kg/min, it causes vasodilatation of the coronary, renal and mesenteric vessels. In moderate doses of 5–20 mcg/kg/min, it brings about a desired outcome of enhancing cardiac contractility caused by a direct action on beta-adrenergic receptors and by the release of phenylpropanolamine from tissue storage sites [10]. However in higher doses of up to 20–50 mcg/kg/min, vasoconstriction may occur due to alpha-receptor stimulation [13]. The use of noradrenaline, an alpha-receptor stimulator is used frequently in patients with septic shock but their vasospastic effects may be more intense in the digital vascular beds. As a result, peripheral gangrene is not unexpected following high doses of dopamine or noradrenaline.

The patient in our report lacked risk factors for peripheral vascular disease and diabetes mellitus, and treatment with inotropes was not prolonged and was not used in high doses. Therefore, the development of gangrene in our patient may have suggested an idiosyncratic response to inotropes or a multifactorial cause. This includes the presence of disseminated intravascular coagulation (DIVC) with concurrent septic shock [11]. Acute DIVC is defined as laboratory studies demonstrating thrombocytopenia, prolonged partial thromboplastin time, decreased fibrinogen and increased fibrinolysis (e.g. elevated D-dimer and fibrin-degradation products) [5]. Our patient had a low platelet count of $<50 \times 10^9$/L, prolonged partial thromboplastin time of 62.9 s, decreased fibrinogen of 1.25 g/L and elevated D-dimer of >32 mg/L on admission, suggesting an element of DIVC. DIVC is the clinical manifestation of inappropriate thrombin activation and concurrent septic shock may block the reticuloendothelial system and prevent clearing of platelet and

fibrin microemboli that form in DIVC [11]. Symmetrical peripheral gangrene (SPG) [12] in purpura fulminans may be a differential diagnosis in another patient with a similar presentation. This may require the expert opinion of a dermatologist especially during the early presentation. SPG occurs as a result of impaired peripheral perfusion caused by a reduction in cardiac output and exacerbated by intense reflex peripheral vasoconstriction [15]. It presents as the sudden onset of acral gangrene occurring in a symmetrical distribution [5] and is associated with purpura fulminans. Park also concluded that DIVC is a risk factor that increase the likelihood of SPG induction by dopamine [12]. Streptococcal pneumoniae was the underlying culprit in some case series [6,7] of peripheral gangrene. Johansen et al. [7] discussed the possibility that the pathogenesis of peripheral gangrene associated with pneumococcal sepsis may not be iatrogenic as only 2 out of his 10 patients with pneumococcal sepsis-associated peripheral ischemic received vasopressor therapy. However, sepsis-associated peripheral vasoconstriction remains poorly understood. Some authors [16] have suggested that the phenomenon is related to the development of DIVC, while others have suggested a vasospastic phenomenon [7].

We recommend close monitoring of the extremities for ischemic changes whenever dopamine is initiated in patients with DIVC. Beneficial use of chlorpromazine hydrochloride (alpha-adrenergic antagonist) by intravenous drip [17], phentolamine hydrochloride (alpha-adrenergic antagonist) infiltration of the ischemic area [18], local application of nitroglycerine ointment [19], early use of epoprostenol [14] and even the use of sympathetic blockade [20] have been reported. If there is a concurrent DIVC, the underlying source of coagulopathy should be treated and heparinisation can be initiated [11]. In the event of peripheral dry gangrene, vasopressors should be minimized, and early surgical intervention should be deferred until gangrene has demarcated as suppuration rarely complicates this condition [7].

4. Conclusion

In conclusion, we report this rare case of 4 limb amputations due to inotrope use for septic shock in the absence of overt predisposing vasculopathic conditions. Microvascular spasm is a rare complication of inotrope use which must be considered especially in patients with pre-existing peripheral vascular disease. As dopamine remains the vasopressor of choice due to its effectiveness in managing vascular instability, its use may sometimes be necessary in severe cases of shock. Suggested treatments for peripheral gangrene in this setting are mainly from anecdotal reports. As we have demonstrated, rehabilitation with prosthesis after 4 limb amputations can result in good functional outcome.

Conflicts of interest

None.

Funding

None.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Ang Chuan Han and Koo Oon Thien: data collection, data analysis and interpretation, writing the paper; Howe Tet Sen: study concept and design, writing the paper.

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