Symmetrical Peripheral Gangrene after Using High-Dose Inotropes

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Abstract

Symmetrical peripheral gangrene (SPG) is an uncommon but devastating complication in critically ill patients with a high mortality. It is seen in a wide variety of medical conditions, presenting as symmetrical gangrene of two or more extremities without large vessel obstruction. We hereby report a 65-year-old woman diagnosed of having *E. coli* bacteremia with urosepsis, who presented with acute abdomen, consciousness disturbance and multiple organ failure. Owing to low blood pressure and unstable hemodynamic status, inotropic agents with maximum dose of dopamine at 12.7 µg/kg/min and levophed of 2.6 µg/min were used. On the 4th day of admission, patient developed cyanosis and gangrene of fingers and toes. However, even with the dose of inotropic agents tapered, the cyanosis and gangrene did not resolve. Autoamputation developed and the patient underwent multiple surgical amputations of her fingers and toes. Patient also developed acute kidney injury with anuria and pulmonary edema, thus necessitating hemodialysis treatment.

KEY WORDS: symmetrical peripheral gangrene (SPG), inotropes, urosepsis

Introduction

Symmetrical peripheral gangrene (SPG), sometimes termed purpura fulminans is uncommon but not rare in critically ill patients. It is characterized by distal ischemic change of two or more extremities without large vessel occlusion or vasculitis. It is often associated with various diseases leading to hypotension and impaired peripheral perfusion and the potential effect of vasoactive drugs including dopamine was documented in many reports.

Dopamine, because of its positive inotropic effects, is frequently used in the management of critically ill patients with cardiogenic or septic shock. However, ischemic changes in extremities may be observed with prolonged administration especially in high infusion rates (1). Progression of this ischemia resulting in gangrene is rare, but may lead to a catastrophic complication with high mortality rate and high frequency of multiple limb amputations in surviving patients.

Case Report

A 65-year-old woman presented with acute abdomen, consciousness disturbance and multiple organ failure (hepatic, respiratory and renal failure). Pertinent laboratory data on admission revealed white blood cells, 24,300/µL; C reactive protein, 7.1 mg/dL; hemoglobin, 8.9 g/dL; hematocrit, 25.8%; platelet count, 21 × 10^9/mL; AST, 2923 IU/L; ALT, 1886 IU/L; lactic dehydrogenase, 439 U/L; albumin, 2.0 g/d; BUN, 54 mg/dL; creatinine, 5.6 mg/dL; amylase, 148 U/L; and lipase, 66 U/L; Except for hepatitis C and hypertension, she had no past history of diabetes mellitus or chronic kidney disease. Plain abdomen revealed no free air collection at bilateral subphrenic levels. Abdominal computed tomography
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(CT) scan showed a hyperdense and contracted gall bladder with poor details of its wall, swelling of pancreas and increased soft tissue density over the peripancreatic head, paraaortic space and bilateral renal hila, mild left hydronephrosis, and bilateral pararenal fascia thickening with minimal ascites. Urinalysis was positive for protein, occult blood, and leukocyte esterase, with 50-100 red blood cells, numerous white blood cells and bacteruria. Blood and urine culture grew *E. coli*, favoring urinary tract infection with septic shock. Owing to her unstable hemodynamic status with initial blood pressure of 70/40 mmHg, severe metabolic acidosis and hypoxemia, she was intubated and put on mechanical ventilatory support. Broad spectrum antibiotics and inotropic agents with maximum dose of dopamine at 12.7 µg/kg/min and levophed at 2.6 µg/min were used. During admission, she had passage of massive tarry stools for a week. She had a prolonged protrombin time of 20.70 seconds, international normalized ratio (INR) of 2.04, activated partial thromboplastin time of 59.2 seconds, and thrombocytopenia with platelet count of $21 \times 10^{9}/\text{mL}$. Disseminated intravascular coagulation (DIC) was highly suspected. Upper gastrointestinal endoscopy was performed and showed duodenal ulcer with active bleeding near the posterior wall and a lower third esophageal ulcer. Patient was put on nothing per orum (NPO) and intravenous proton pump inhibitor. Multiple and repeated packed red blood cell, platelet, fresh frozen plasma and cryoprecipitate transfusions were given. Patient developed pulmonary edema and anuria with urine output of 0 to 2 mL per day for the first three days. Follow-up BUN and creatinine were 67 mg/dL and 7.4 mg/dL respectively; hence, initial non-heparin hemodialysis for 2 hours was arranged, with ultrafiltration of 2 kilograms. Patient had no episode of hypotension during hemodialysis. Blood pressure was around 130/60 mmHg and dopamine infusion was tapered to a dose of 3.65 µg/kg/min. On the 4th day of hospitalization, progressive cyanosis and gangrene of fingers and toes were noted. However, even with the dose of inotropic agents tapered, the cyanosis and gangrene did not resolve (Figs. 1, 2). Autoamputation developed and the patient underwent multiple surgical amputation of her fingers and toes (Figs. 3, 4). Her condition gradually stabilized and improved; and she was discharged on the 84th day of hospitalization. However, her renal function remained impaired and she continues to receive long term regular hemodialysis.

**Discussion**

SPG is a relatively rare syndrome characterized by sudden onset of symmetrical gangrene of both hands and feet. Ischemia producing gangrene of extremity was first reported in 1973 as a complication of using dopamine (Intropin) (2). Although SPG is uncommon, it may occur as a complication of low

![Fig. 1. Dry gangrene of bilateral toes.](image1)

![Fig. 2. Dry gangrene of bilateral fingers.](image2)

![Fig. 3. Amputation of bilateral toes.](image3)

![Fig. 4. Amputation of bilateral fingers.](image4)
cardiac output state, atherosclerosis, diabetic microangiopathy, arterial emboli/thrombosis, other medical conditions like DIC (3-5), sepsis (6), frostbite and administration of vasoactive agents, such as vasopressin (7), dopamine (8, 9) and noradrenaline (10), as well as following ergot administration (11, 12). This has been attributed to the vasospastic effects of the drugs, which may be more intense in digital vascular beds than in large systemic vessels.

Dopamine has three distinct actions depending on dosage. When administered in low doses (1-2 µg/kg/min), it causes dilatation in the renal and mesenteric vascular beds. In moderate doses (2-10 µg/kg/min), dopamine enhances cardiac contractility due to beta adrenergic action. Higher dosage above 10 µg/kg/min has a potent alpha adrenergic vasoconstriction effect. The development of SPG leading to gangrene in our patient occurred at a dosage of 12.7 µg/kg/min, which was a relatively high dose. However, gangrene complicating dopamine therapy as reported in the literature occurs at dosages of 5.1 to 10.2 µg/kg/min (3, 4). Gangrene has also been reported after a dose of only 1.5 µg/kg/min (13). Reports on low-dose dopamine causing SPG are associated with superimposed vascular disease (14, 15), or a hypercoagulable state of DIC (3, 4) that can cause peripheral vessels to narrow below a critical diameter. Underlying atherosclerosis, peripheral vascular disease, diabetic microangiopathy and hypotension might also contribute to the pathogenesis of the gangrene.

Treatment of established SPG is generally unsatisfactory. Numerous therapeutic manoeuvres have been advocated including intravenous administration of phenolamine, trimetaphan, nitroprusside and heparin, as well as sympathetic blockade. Although this treatment is rarely successful, there is a reported case of upper limb ischemia associated with pneumococcal sepsis, wherein ischemia was reversed by sympathetic blockade (6). A report claimed that the combination of epoprostenol and tissue plasminogen activator may minimize tissue loss in SPG (16), while another report stated that early acrocyanosis appeared to be reversed by administration of epoprostenol (10). In our patient with severe sepsis, unstable hemodynamic status and active duodenal ulcer bleeding, these drugs could further increase the risk of hypotension and hemorrhagic complications.

There was a reported case of SPG in a patient on periodic hemodialysis (17) and another report of successful management of critical limb ischemia with intravenous sodium thiosulfate in a chronic hemodialysis patient (18). Our patient had no episode of hypotension during her initial hemodialysis and at that time dopamine infusion was already tapered to a dose of 3.65 µg/kg/min. Critically ill patients with acute kidney injury and sepsis may benefit from sustained low-efficiency dialysis (SLED), which is efficacious, cost effective and easy to perform (19). Published reports indicated that SLED can be administered in either 6 or 12 hours per day, usually 5 or 6 days a week with dialysate flow rates of 200-400 mL/min, blood flow rates of 50-200 mL/min and the dialysate temperature maintained at 36.6°C. Owing to increased risk of bleeding, anticoagulation is unsafe. Regional citrate increases the risk of citrate accumulation with its toxicity, hypocalcemia, alkalosis and hypotension. There are reports that heparin free SLED using citrate dialysate is safe and effective (20). In patients with SPG attributed to acute kidney injury, it is better to perform SLED to minimize and avoid hypotension during renal replacement therapy.

**Conclusion**

SPG is a cutaneous marker of serious underlying medical disease. The rarity of this complication suggests that it is produced only by specific combination of predisposing events. However, once ischemia developed, it is difficult to prevent its relentless course to gangrene. Hence, we need to have a high index of suspicion, provide early treatment of underlying consumptive coagulopathy, correct hypovolemia, and control septicemia in patients using dopamine. Our report hopefully could call attention to a more judicious use of dopamine in critically ill patients.

**References**