Successful resolution of symmetrical digital gangrene associated with vasopressor administration

Symmetrical peripheral gangrene, also known as *purpura fulminans*, is a rare clinical syndrome characterized by bilateral distal vascular impairment leading to gangrene, in the absence of major vascular occlusive disease. The etiology of the condition is multifactorial but symmetrical gangrene of two or more extremities has been associated with the use of vasopressors. We report a case of symmetrical digital gangrene presenting in a female patient after perioperative administration of norepinephrine. This condition is a medical emergency requiring rapid diagnosis and treatment. Our aim is to draw attention to this rare condition and to raise the level of clinical suspicion and improve its management.

Symmetrical peripheral gangrene (SPG) is characterized by symmetric necrosis of the skin and distal extremities, in the absence of large artery occlusion. Fingers and toes are most commonly affected; the nose, earlobes and scrotum are less often involved. In some cases the initial lesions are hemorrhagic, and there may be a gradual progression of gangrene, known as *purpura fulminans*.

The mechanism of vascular occlusion is poorly understood, but disseminated intravascular coagulation (DIC) has been implicated as the final common pathway in its pathogenesis. Peripheral pulses are usually palpable, as a result of the sparing of larger vessels. SPG carries a mortality rate as high as 35–40% and a high morbidity rate, with a documented amputation rate upwards of 70%.

SPG should be suspected at the first sign of marked coldness, pallor, cyanosis, purpura fulminans, or pain in an extremity, since the condition can progress rapidly to acrocyanosis and, if not reversed, frank gangrene. These signs and symptoms may be mistaken for other disorders such as simple purpura, vasculitis, or other causes of gangrene. The onset of purpura fulminans is a medical emergency requiring rapid diagnosis and treatment of the underlying cause, and initiation of aggressive supportive management in a multidisciplinary intensive care unit (ICU).

Although SPG presents in patients with a wide range of underlying medical conditions, it has also been associated
with the use of vasopressors. Our aim is to draw attention to this rare condition, in order to raise the level of clinical suspicion and improve its management. The case is described here of symmetrical peripheral gangrene occurring after perioperative administration of norepinephrine (NE).

CASE PRESENTATION

A 66-year-old female underwent total abdominal hysterectomy, bilateral salpingo-ovariectomy, omentectomy, appendectomy and systematic pelvic and para-aortic lymphadenectomy for ovarian carcinoma. She had not undergone any prior surgical procedures and had no history of smoking, diabetes mellitus (DM), peripheral vascular disease, hypercoagulation, vasculitis or connective tissue disease. Perioperatively, the patient developed profound shock with a poor response to fluid resuscitation and she was transferred intubated to the ICU, receiving vasopressors, specifically NE, at an infusion rate of 3 μg/kg/min through the central venous line.

The patient was extubated the following day and continued receiving NE, with the dose being tapered off gradually. Two days later her fingers developed blue discoloration, then became dusky, but no skin necrosis developed in other areas. Symmetrical peripheral ischemia of the digital extremities was observed (fig. 1). She was hemodynamically stable with steady vital signs, the peripheral pulses were palpable in both the upper and lower extremities and sonography of the upper extremity vessels was unremarkable. An arterial line inserted in her left arm was immediately discharged. There were no marks of endocarditis, DIC or purpura fulminans, which involves extensive multicentric skin necrosis. She had been taking low-molecular weight heparin 0.4 mL/day, and because of the suspected diagnosis of SPG, she was also given oral aspirin 75 mg/day and oral pentoxifylline 400 mg twice a day, and progressed well clinically over the next few days. Starting on the 10th postoperative day, desquamation of the skin of her fingers started, followed by shedding of gangrenous scabs from the tips of her fingers, with complete resolution after 3 months. The patient continued chemotherapy for the ovarian carcinoma, but finally succumbed to peritoneal carcinomatosis 16 months post-operatively.

DISCUSSION

SPG is a relatively rare syndrome characterized by the sudden onset of symmetrical gangrenous lesions of the extremities, which initially appear in the form of acrocyanotic and dusky discoloration of the skin, resembling lesions associated with erythematous cold extremity exposure. This clinical presentation was first described in 1891 as the sudden onset of acral gangrene occurring in a symmetrical distribution associated with purpura fulminans. In 1938 it was suggested that this condition was a result of impaired peripheral perfusion caused by a reduction in cardiac output exacerbated by intense reflex vasoconstriction.

The link between DIC and SPG, primarily driven by a disordered clotting pathway, was first described in 1970. This theory has been supported to the present time as the etiology of SPG, given that DIC is diagnosed in over 85% of patients suffering from SPG. Although this association has been well defined in previously published series, it may not be recognized by clinicians as it is relatively rare. DIC may lead to inappropriate thrombin activation resulting in increased fibrin breakdown products and intravascular microthromboses. Histopathological examination of amputated specimens often reveals thrombi concentrated in the small vessels.

A wide array of infective and non-infective etiological factors has been linked with the development of DIC and consequently SDG, which has been described in conditions such as Shwartzman reaction, bacterial endotoxin release, sepsis, shock, myeloproliferative disorders, low-flow states and following treatment with vasoactive agents, such as vasopressin, dopamine and NE. Septicemia is commonly associated with clinical DIC and occurs in approximately 30–50% of patients with SPG.

NE is a powerful vasopressor with predominant alpha-adrenergic activity, producing vasospastic effects in the peripheral vascular beds rather than in large systemic vessels, a phenomenon exacerbated in the context of DIC. NE is commonly recommended as a first-line vasopressor treatment for critically ill patients with acute circulatory failure, but it can be associated with a poor outcome due to excessive vasoconstriction and progress to SDG. SDG caused by NE usually affects the toes, bilaterally, but asymmetrical presentation and finger gangrene have also been described. Pre-existing peripheral vascular disease, concomitant use of other vasopressors, especially...
dopamine, and prolonged hypotension can all increase the risk of NE-induced digital necrosis.\textsuperscript{6,15} As a result, peripheral gangrene is not unexpected following high doses of dopamine or NE.\textsuperscript{16}

Early recognition of the disease and its underlying conditions can have a decisive impact on the management of the condition and its final outcome. First-line measures when SPG is identified early include discontinuation of vasopressors, reversal of DIC by cautious anticoagulation, and aggressive treatment of shock and sepsis. Adjuvant therapy with tissue plasminogen activator, plasmapheresis, sympathetic blockade and aspirin has been recognized to contribute to a favorable outcome. Amputation remains the final treatment option available for the patient with established gangrene. The level of amputation is determined by the line of demarcation of necrosis, in combination with consideration of the biomechanics of stump stability, weight bearing, and ambulation.\textsuperscript{15}

In conclusion, although the etiology of SPG is multifactorial, the disease can also occur following the administration of vasopressors such as dopamine and NE in therapeutic doses. It is crucial that physicians are able to recognize the causative factors of SPG and then select and rapidly apply the appropriate treatment. Early recognition and treatment are of paramount importance in preventing an untoward outcome such as amputation.

### References

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