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Case Report

Symmetrical peripheral gangrene in sepsis after treatment with inotropes

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Abstract

Symmetrical peripheral gangrene (SPG) is characterized by sudden onset of peripheral, frequently symmetrical, gangrene in the absence of major vascular occlusive disease. We report a case of four limb SPG caused by septic shock with disseminated intravascular coagulation (DIC) that had been treated with inotropes. This case shows that SPG may be present as a complication of sepsis due to systematic derangement that affects a wide range of organ systems, including coagulation and microcirculation. Early recognition and prompt management of sepsis and optimization of the process of weaning off the inotropes at the earliest opportunity are necessary to avoid SPG.

Keywords: *Inotropes, Sepsis, Symmetrical peripheral gangrene*

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Introduction

Symmetrical peripheral gangrene (SPG) is a rare but severe complication of disseminated intravascular coagulation (DIC) that frequently accompanies sepsis [1-4]. It can also occur as a complication of measles [5], chickenpox [6], malignancy, and ergotism [7]. Aggravating factors include increased sympathetic tone, diabetes mellitus (DM) [8], immunosuppression [4], cold injury to the extremities, and the use of vasopressors [9-13]. It is characterized by distal ischemic changes to two or more extremities without large vessel occlusion or vasculitis [11]. SPG should be suspected at the first sign of marked coldness, pallor, cyanosis, or pain in an extremity as the condition can progress rapidly to acrocyanosis and if not reversed, frank gangrene [3]. These changes are not ordinarily preceded by demonstrable peripheral vascular occlusive disease and may be associated in the early stages with an intact distal pulse; this is because the large vessels are often spared. SPG results in a high rate of mortality (up to 40%). About half of the patients who survive require amputation of the affected limb [4]. Thus, early recognition of SPG and its underlying conditions can have profound impact on the management of the condition and its final outcome. The following case presentation involved bilateral limb necrosis during septic shock and DIC that involved the use of norepinephrine and dopamine.

Case report

A 76-year woman was admitted to the emergency department after several days of vomiting, diarrhea, and fever. Examination revealed a blood pressure of 39/28 mmHg, a pulse rate of 120–140 beats/min, and a temperature of 36.2°C. The results of a chest X-ray were unremarkable. A cardiac examination revealed rapid atrial fibrillation but no murmur. An increased number of white blood cells and bacteria were seen after urinalysis. An abdominal bedside ultrasonography revealed right renal hydronephrosis and a computerized tomography scan of abdomen showed the right kidney pyelonephritis. The patient had a history of DM, hypertension, and cardiac disease. There was no antecedent record of peripheral ischemia or smoking. She had metabolic acidosis that was characterized by a lactate level of 16 mmol/L, an arterial blood pH of 7.056, and a bicarbonate level of 8.6 mmol/L. Routine laboratory investigations revealed a white blood cell count of 12,120/μL, a platelet count of 99,000/μL, a blood glucose level of 298 mg/dL, a potassium level of 6.2 mmol/L, a fibrinogen level of 376.8 mg/dL, and a D-dimer level of 1557551 ng/mL. The patient had impaired renal function with a blood urea nitrogen of 59 mg/dL and a creatinine level of 4.1 mg/dL. Impaired liver function with an alanine transaminase level of 123 U/L was also noted. The patient was treated with fluid resuscitation, antibiotics, vasopressor therapy, and a ventilator. A low central venous pressure value (<0 cmH_2O) was detected. Due to her hemodynamic state and an initial diagnosis of urosepsis, septic shock and DIC secondary to pyelonephritis, the patient was transferred to the intensive care unit. Urine and blood culture results indicated *Escherichia coli* and a sputum culture reported the presence of carbapenem-resistant *Acinetobacter baumannii*. Despite fluid resuscitation, she needed high doses of dopamine (20 ug/kg/min) and norepinephrine (0.41–1.03 ug/kg/min) to maintain her mean arterial pressure >65 mmHg for the 1st week after being hospitalized. Two days after admission, peripheral ischemia appeared on her fingers and toes. The ischemia became progressed worse leading to erythematous cold extremities over the next days [Figure 1a-d], which gradually developed into gangrene

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after 2 weeks [Figure 2a-c]. Radial pulses, dorsalis pedis, and posterior tibial pulses were palpable. On her 15th hospital day, after respiratory support and antibiotic therapy, her medical condition improved, but the acral necrosis and dry gangrene with mummification remained. The affected extremities were protected from further trauma, cold, and secondary infection. Examination by peripheral Doppler ultrasound showed sparing of the large peripheral arteries. On her 35th of hospital stay, the patient was discharged from the hospital after having been given medical and plastic surgery outpatient department appointments.

Discussion

SPG is a relatively rare phenomenon characterized by symmetrical distal ischemic damage that leads to gangrene at two or more sites in the absence of large blood vessel obstruction with vasoconstriction rather than thrombosis being implicated as the underlying pathophysiology [14]. With SPG, autopsy has often revealed thrombi concentrated in the small vessels and not in the large vessels [3]. The important clinical features that give rise to a suspicion of SPG include fever followed by marked coldness, pallor, cyanosis, pain, and restricted mobility of extremity [15]. The gangrenous lesions initially appear in the form of acrocyanotic and dusky discolorations of the skin starting from the distal extremity within 24–48 h and resemble lesions that are normally associated erythematous cold extremity exposure [16].

While a wide array of infective and noninfective etiological factors have been linked to the development of SPG [17], nevertheless, DIC is involved in up to 85% of cases of SPG [4]. In our case, where septic shock and DIC were present, coagulation activation that was not balanced by the physiological anticoagulant systems was likely to have occurred due to multiple factors, including endothelial injury, consumption of fibrinogen, down-regulation of circulating impaired fibrinolysis, and enhanced platelet-vessel wall interactions. Hypercoagulability may also have occurred and this would also have led to a prothrombotic state and vascular occlusion [1,18]. During infection, elevated levels of cytokines and lipopolysaccharides induce enhanced tissue factor production by monocytes and the vascular endothelium, which results in an inhibition of natural anticoagulant proteins, including thrombomodulin, together with the overexpression of plasminogen activator inhibitor. The overall result of the above is a suppression of fibrinolysis [19]. In addition, in response to infection, neutrophils are induced to release neutrophil extracellular traps (NETs) at the site of infection. It has been proposed that NETs promote the formation of microthrombin in intact blood vessels to trap and prevent the spread of invading pathogens. DIC arising from a severe infection may result from the aberrant or uncontrolled activation of the NET pathway [20].

DM is an established risk factor in the development of lower extremity peripheral arterial disease (PAD) [21]. The mechanism of PAD in patients with DM includes derangements in the vessel wall through promotion of vascular inflammation and endothelial cell dysfunction; abnormalities in blood cells, smooth muscle cells, and platelets; and changes in factors that affect hemostasis [22]. Underlying diabetic microangiopathy in this case might also contribute to the progress in the pathogenesis to gangrene.

Furthermore, the use of vasopressors simultaneously involves the creation of spasms that affect the vessels and these aggravate microcirculation problems [23]. Evidence has shown that norepinephrine should be regarded as the first-line vasopressor when treating septic shock [24]. Norepinephrine stimulates β1-adrenergic receptors and α-adrenergic receptors and causes increased contractility and an improved heart rate, in addition to vasoconstriction. Ischemic changes in extremities can be observed in some cases when there is prolonged administration of dopamine and norepinephrine; in our case, a high infusion rate for both drugs was necessary. While we found the risk factors in this case to be different, they still followed the same development pattern normally associated with SPG. The patient's coagulation system is disrupted as a result of the DIC. The DIC results in intravascular thrombosis and infarction of

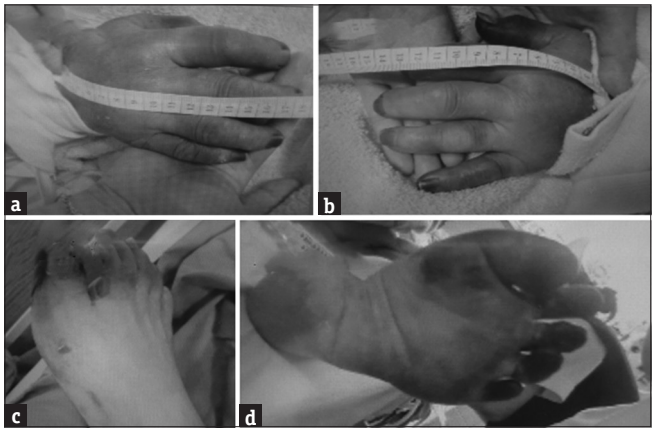

Figure 1: (a-d) Ischemic change in the upper and lower limbs

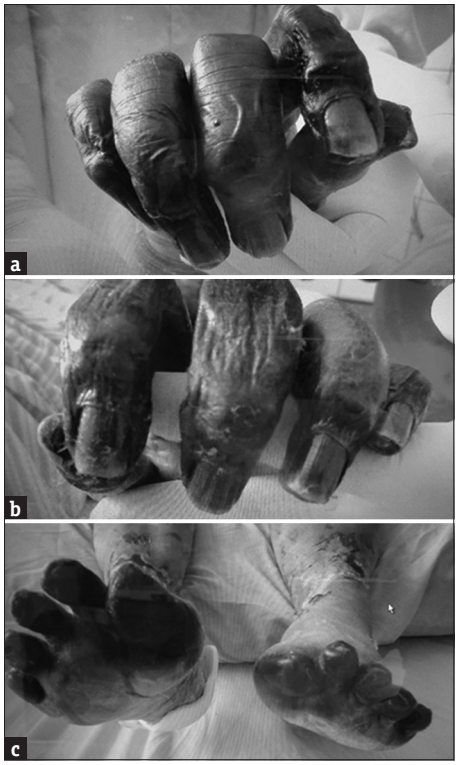

Figure 2: (a-c) Bilateral gangrene of distal limbs

the distal extremities follows. In such circumstances, the condition can be aggravated by hypothermia, DM, cardiovascular disease, and inotrope infusion, all of which can contribute to low blood flow and vascular disturbances.

Thromboangiitis obliterans, atherosclerosis, thromboembolic gangrene, secondary Raynaud's phenomenon, diabetes, neuropathy, chemical/toxic agents, calciphylaxis, and vasculitic gangrene are close mimickers of the condition among others diseases. The sparing of the major arteries, a history that is suggestive of SPG, the disease's natural course, and the absence of the features of vasculitis on histopathological examination should differentiate SPG from these other conditions [17]. Gangrene most commonly occurs in the distal extremities, such as the fingers, toes, tips of the nose, and ear lobules, while the lips or genitalia may be affected in severe cases [25]. The gangrenous aspects of SPG are frequently symmetric and are associated with intact distal pulses. Infection is usually absent in the lesional skin [17]. Necrosis of the fingers and toes in this case was symmetrical as expected and involved both extremities, which is different to necrosis when it is associated with an embolic event; in such circumstances, necrosis is usually asymmetric. Moreover, the symptoms progressed to dry gangrene and advanced proximally along a line of demarcation as they developed [26].

No specific treatment has been shown to consistently prevent the progression of SPG or to reverse SPG [17]. The management priority is usually the underlying condition and DIC; therefore, SPG is typically not treated immediately. The management of the DIC should be guided by basic tests that assess coagulation [14]. If bleeding is the predominant feature, depleted coagulation factors need to be replaced. On the other hand, in cases where thrombosis is predominant, several anticoagulants have been tried. Randomized trials have failed to show any encouraging result regarding the use of antithrombin [14,17]. However, heparin was not considered for use during our case because there had been a vomitus of coffee ground material noted on admission. Septic shock is a systemic derangement affecting all organ systems, including coagulation and microcirculation, and results in hypoperfusion of the peripheries. Awareness, early recognition, and prompt management of SPG are necessary to avoid its dreadful consequences, namely, SPG and amputation.

Other treatment that might be helpful include sympathetic blockade in the form of a ganglion block or intravenous trimethaphan therapy [3], intravenous nitroprusside therapy [23], topical nitroglycerine ointment [27], the local or intravenous infusion of an α-blocker (for example, phentolamine or chlorpromazine), and intravenous infusion of prostaglandin (epoprostenol) [28]. Diuretics (for example, furosemide or hydrochlorothiazide), medicines for high blood pressure, or other vasodilators (for example, minoxidil) may interact with epoprostenol and as a result the risk of low blood pressure may be increased. We did not use epoprostenol because it was not available in our hospital and did not use the other therapeutic medication due to their possible side effects. Interdigital padding and protection from trauma may also decrease tissue injury [29]. Amputation of the gangrenous areas may be inevitable, but initially, a nonsurgical approach to the disease's management is preferred to allow time for the patient's condition to stabilize and to allow the gangrene to become demarcated [27,30,31]. Thus, in patients with septic shock and DIC complicated by SPG, fluid resuscitation should be administered first, vasopressors and inotropes should be withdrawn as early as possible, especially in the presence of any coldness and discoloration in an extremity. It is crucial that physicians are able to recognize the causative factors of SPG and then select appropriate approaches to treatment. Further investigations, preferably involving collaborative interdisciplinary studies, are needed to create appropriate treatment guidelines for SPG.

Declaration of patient consent

The authors certify that the patient has obtained appropriate patient consent form. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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