Symmetrical peripheral gangrene in a patient with septic shock and a multi-drug resistant *Klebsiella pneumoniae* infection

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Abstract

Symmetrical peripheral gangrene (SPG) can sometimes occur without definite disseminated intravascular coagulation. The differential diagnosis comprises the exclusion of many non-infectious diseases and the effort to isolate the microbic agent in the case of septic shock. Between bacterial causes, *Klebsiella pneumoniae* is one of the bacteria that can trigger SPG through hypervirulence and hypercoagulopathy mechanisms. We report a case of SPG associated with septic shock and a multi-drug resistant *K. pneumoniae* infection.

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Introduction

Symmetrical peripheral gangrene (SPG) can occasionally develop without clear disseminated intravascular coagulation. We detail a rare SPG case with normal blood flow in both arterial and venous districts associated with septic shock and evidence of *Klebsiella pneumoniae*.

Case report

A 74-year-old woman presented to the Emergency Department (ED) with severe hypotension and anuria. Her daughter reported that the patient had experienced epigastric pain in the past five days with nausea, water, and food rejection. Profuse diarrhea not responding to symptomatic treatment appeared, associated with diuresis contraction, cyanosis of the lips and peripheral extremities, and a 50/40 mmHg blood pressure.

Clinical history included dyslipidemia in statin and omega-3 supplementation, major depression treated with selective serotonin reuptake inhibitors and benzodiazepines, and a cholecystectomy three years before. Intravenous dopamine 200 mg in 250 mL NaCl 0.9% was administered during ambulance transportation to the ED; at admission, noradrenaline at 0.05 mcg/kg/min was started (patient weight 70 kg). Empiric antibiotic therapy was initiated with piperacillin/tazobactam 2.5 g/500 mg and metronidazole 500 mg thrice daily.

A computed tomography (CT) scan of the chest and abdomen showed tardive contrast washout of the kidneys and a modest amount of free abdominal fluid; bilateral consolidations and ground glass areas were displayed at chest level. Due to the persistence of anuria, the patient was moved to the nephrology ward and started continuous renal replacement therapy. Blood and urine cultures, a nose tampon for methicillin-resistant *Staphylococcus aureus* (MRSA), and a rectal tampon for carbapenemase-producing *Enterobacteriaceae* (CPE) were all done, but no pathogen agent was found. The patient's condition worsened despite noradrenaline intravenous infusion at 0.3 mcg/kg/min: mean arterial pressure was 30 mmHg, and lactates reached 9.0, with cold extremities and cyanosis. Emergency intubation was performed, and she was moved to the intensive care unit (ICU), where the clinical

conditions began to improve and the noradrenaline infusion was stopped. Markers of inflammation started to drop too. After two days in the ICU, a dark coloring in her fingers and toes was observed (Figure 1). The evolution of hematomas resulting from disseminated intravasal coagulation evolution was suspected (Figure 1), and a vascular consult with duplex ultrasound was made, showing normal blood flow in both the arterial and venous districts; a valid flow was observed at the digital extremities of the hands and feet, where cutaneous lesions like septic emboli were observed.

Cultures on blood samples recurred, but no pathogen entity emerged again. Cyanosis of the extremities with dark finger coloring persisted despite good peripheral blood oxygenation (pO2: 129) in invasive mechanical ventilation at fraction of inspired O2 50% and oxygen saturation 99%; a mean arterial pressure of 80 mmHg was observed in the absence of hemodynamic support; hemoglobin was 10.5 g/dL; platelet count (PLT) was 41,000, so another vascular consult was required. The second duplex ultrasound confirmed normal blood flow with hot hands and feet and distal ischemia, addressing a precedent episode of vasoconstriction or septical microembolism. The hands' phalanxes showed dry necrosis, while the feet had wet necrosis.

A second CT scan of the chest and abdomen showed a markedly hypodense stenotic segment in the medium ascendant colon without evidence of fat stranding in the perivisceral loose tissue or regional lymphatic adenopathies. At the chest level, bilateral consolidations worsened compared to the first CT exam. After 8 days in the ICU, the patient was finally extubated and transferred to the Geriatric Ward. She started a washout from antibiotic therapy, and tests for drug-resistant germs were immediately performed: MRSA resulted negative, while the CPE tampon demonstrated positivity.

Urine cultures reported negative results again, while blood sample cultures showed a multi-drug resistant *K. pneumoniae*. Therefore, intravenous therapy with ceftazidime/avibactam 2.5 g tid was established after an infectious diseases consultation for stewardship. Transthoracic echocardiography and a positron emission tomography (PET) study with fluorine-18 fluorodeoxyglucose (18F-FDG) were requested to rule out endocarditis and aortitis that may have caused micro septic embolism in the first place, but both resulted negative; plus, PET imaging demonstrated no 18F-FDH capture, ruling out the possibility of an unacknowledged oncologic disease determining peripheral thrombosis (although the site and distribution of ischemia were not typical).

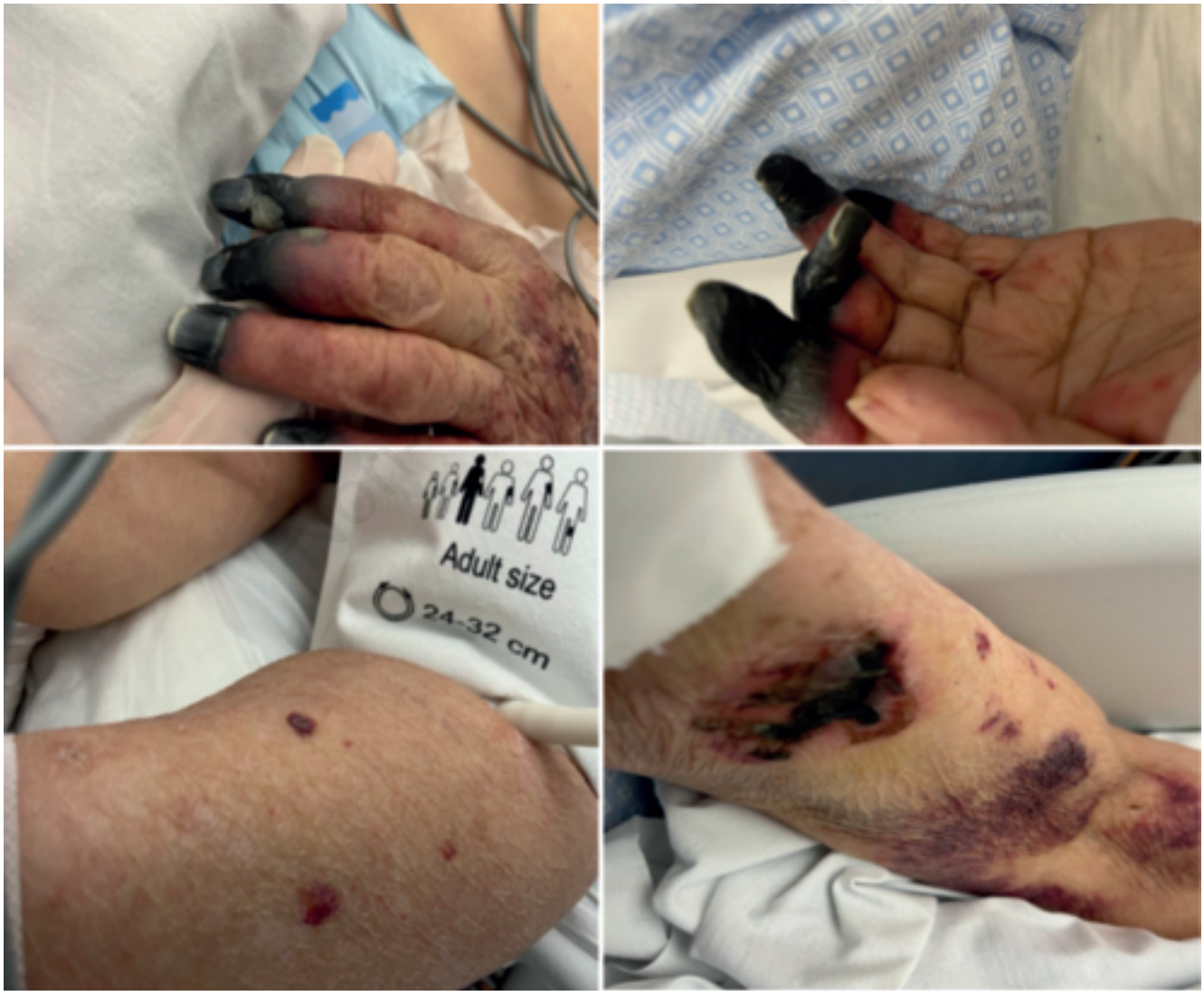

Figure 1. Gangrene in the fingers and suspected intravascular coagulation dissemination.

Anticardiolipin antibodies, antithrombin III, protein C and protein S, and autoimmunity were requested, showing a negative result. The peripheral gangrene extension began to subside after administering a higher dose of low molecular weight heparin, circumscribing the injury at the distal phalanxes, as shown in Figure 1. Hence, a final vascular consultation indicated prolonged medical treatment, rejecting the amputation option. The patient progressively improved; over the days, she had better differentiation of finger necrosis. After sepsis regression and functional reactivation, the individual rehabilitation plan suggested integrated home care.

Discussion

SPG usually occurs in critically ill cardiogenic or septic shock patients. In these cases, the term purpura fulminans is applicable. The pathophysiological feature is microthrombosis associated with a disturbed procoagulant-anticoagulant balance.[1] Although the laboratory studies performed at the time of admission did not strongly support a diagnosis of decompensated disseminated intravascular coagulation [06/01/2023: international normalized ratio (INR) 1.35, activated partial thromboplastin time (APTT) 27.6 sec, fibrinogen 350 mg/dL, D-dimer 8.96 mg/dL, PLT 88×103/mL; 07/02/2023: INR 1.03, APTT 27.7 sec, fibrinogen 176 mg/dL, D-dimer 1 mg/dL, PLT 133×103/mL; 16/02/2023: INR 1.05, APTT 27.1 sec, fibrinogen 285 mg/dL, D-dimer 0.8 mg/dL, PLT 150×103/mL], hypercoagulability is the more frequent aspect related to SPG.

However, the SPG in the intensive care unit is a rare complication. SPG may be symmetrical ischemic damage, which occurs at the distal part of the limbs or genitalia without a major vascular occlusive disease. It has a high risk of mortality and a high frequency of multiple limb amputations in those who survive. The etiology of SPG is multifactorial; however, in general, it has been divided into two main categories: infective and noninfective factors (Table 1).[2]

Since the unique microbic isolation was of multi-drug resistant *K. pneumoniae*, we concluded that hypercoagulability complicating *K. pneumoniae* sepsis was the main cause of the SPG in our clinical case. *K. pneumoniae* can cause pneumonia, urinary tract infections, and bacteremia in immunocompromised or frequently healthcare-exposed patients. In the *Enterobacteriaceae* family, *K. pneumoniae* isolates have, over time, acquired resistance to carbapenems belonging to the carbapenem-resistant *Enterobacteriaceae* worldwide.[3]

In the literature, a case report of multifactorial SPG was reported to be triggered by viral gastroenteritis and shock, as in our patient.[4] Another case report described SPG due to *K. pneumoniae* and anticardiolipin antibodies.[5] The authors recognized anticardiolipin and b2-glycoprotein antibodies, suggesting that a catastrophic antiphospholipid syndrome rather than an infection might have played a role. They found an immunoglobulin G anticardiolipin antibody that was still positive after six weeks. In our case report, the anticardiolipin antibodies were negative. *K. pneumoniae* is a gram-negative organism that can cause a pyogenic liver abscess without hepatobiliary disease.[6] In our case, PET imaging and other instrumental exams excluded liver abscesses.

Conclusions

K. pneumoniae is an important gram-negative opportunistic pathogen that causes various infectious diseases, including urinary tract infections, bacteremia, pneumonia, and liver abscesses. *K. pneumoniae* infection can trigger a hypercoagulability state

Table 1. Etiology of symmetrical peripheral gangrene. Reproduced from: Foead *et al.* (2018).

Infective	Noninfective
Bacterial	Cardiovascular
Neisseria meningitidis	Myocardial infarction
Streptococcus pneumoniae	Cardiac failure
Staphylococcus aureus	Hypovolemic shock
Streptococcus pyogenes	Hypertension
Klebsiella pneumoniae	Pulmonary embolism
Salmonella paratyphi	Supraventricular tachycardia
Proteus vulgaris	Drugs
Proteus mirabilis	Adrenaline
Pasteurella multocida	Noradrenaline
Enterococcus faecalis	Dopamine
Escherichia coli	Warfarin
Mycobacterium tuberculosis	Propylthiouracil
Capnocytophaga	Malignancy
Parasitic	Hodgkin's lymphoma
Plasmodium falciparum	Lung adenocarcinoma
Viral	Adenocarcinoma associated thrombotic endocarditis
Viral gastroenteritis	Connective tissue disorders
Rubeola	Systemic lupus erythematosus
Varicella zoster	Polymyalgia rheumatic
Dengue	Antiphospholipid syndrome
HIV	Miscellaneous
	Deficiency of Protein C and S
	Sickle cell disease
	Cryoglobulinemia
	Suprapubic prostatectomy
	Emergency neurosurgery
	Idiopathic

HIV, human immunodeficiency virus.

associated with SPG in septic shock. Many aspects should be investigated to clarify the link between *K. pneumoniae* and SPG.

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