CASE REPORT

# Symmetrical peripheral gangrene complicating recurrent cholangiocarcinoma: a case report

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## Abstract

Symmetrical peripheral gangrene (SPG) is a rare, life-threatening complication often linked to severe illnesses. This case report describes the case of a 28-year-old male with recurrent cholangiocarcinoma who developed SPG after being admitted to the intensive care unit (ICU) for septic shock. Despite initial survival with antibiotics, vasopressors, and supportive care, he refused amputation, leading to secondary infection and death. Early management of septic shock and disseminated intravascular coagulation (DIC), with cautious vasopressor use, is crucial to prevent SPG.

**Keywords:** Cholangiocarcinoma, Symmetrical peripheral gangrene, Sepsis, Diffuse intravascular coagulation.

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## Introduction

Symmetrical peripheral gangrene (SPG) is a rare, severe condition marked by vascular occlusion in areas of low peripheral blood flow. It affects individuals of any age or gender. SPG is characterised by symmetrical ischaemia and necrosis in distal parts of the body, occurring without notable occlusion of major arteries.[1] Several factors contribute to SPG, including infectious diseases from various pathogens, cardiovascular diseases, malignancies, connective tissue disorders, and additional factors like animal bites.[2,3]

Cholangiocarcinoma (CCA) constitutes a rare and markedly heterogeneous malignancy, representing about 3% of all gastrointestinal cancers. It ranks as the second most prevalent primary liver cancer, following hepatocellular carcinoma (HCC). Often asymptomatic in its initial stages, CCA's aggressive behaviour and chemoresistance lead to a notably high mortality rate. Typically diagnosed in advanced stages, the five-year survival rate for CCA patients varies between 7% and 20%.[4]

In this report, we present a case involving a patient who experienced recurrent CCA after surgery and subsequently developed SPG following septic shock. To the best of our knowledge, this is the first account of such a case in published literature.

Patient's consent was taken prior to the writing of the manuscript.

## Case Report

On October 25, 2022, a 28-year-old male with unexplained jaundice was admitted to West China Hospital of Sichuan University, Sichuan, China. Upon hospital admission, an abdominal magnetic resonance imaging (MRI) was done which indicated a constriction of the common bile duct at the pancreatic segment, raising suspicions of cholangiocarcinoma. The patient underwent a pancreaticoduodenectomy on November 1, 2022. Subsequent histopathological analysis revealed moderately differentiated adenocarcinoma involving the common bile duct, pancreatic parenchyma, and the surrounding fibroadipose tissue, with evidence of neural invasion and intravascular tumour emboli. Six months after the surgery, the patient developed recurrent jaundice. Further diagnostic assessments showed markedly elevated tumour markers (CEA and CA199), and an abdominal contrast-enhanced computed tomography (CT) scan identified multiple enlarged lymph nodes along the hepatoduodenal ligament and the para-aortic region, indicative of metastasis.

Due to suspicions of tumour recurrence and metastasis, the patient was admitted to the hospital for chemotherapy on June 9, 2023. During the second night of hospitalisation, the patient experienced chills, high fever, nausea, and vomiting, which rapidly progressed to shock and altered consciousness within 24 hours. The respiratory rate increased to 33 breaths per minute, blood pressure dropped to 66/34 mmHg, and pulse rate escalated to 145 beats per minute. Additionally, the patient exhibited facial ecchymosis and cold extremities. Treatment interventions included administration of

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**Table-1:** Laboratory Test Results and Normal Values.

| Laboratory Test | Test Result | Normal Range |
|---|---|---|
| Leukocytes (10^9/L) | 42.25 ↑ | 3.5-9.5 |
| Neutrophil percentage % | 95.2 ↑ | 40-75 |
| Lymphocyte percentage % | 1.7 ↓ | 20-50 |
| Haemoglobin (g/dl) | 128 | 130-175 |
| Platelets (10^9/L) | 28 ↓ | 100-300 |
| C-reactive protein (mg/L) | 171 ↑ | <5 |
| Interleukin 6 (IL-6) (pg/ml) | >5000 ↑ | 0-7 |
| Procalcitonin (pg/ml) | >100 ↑ | <0.046 |
| liver function | | |
| Total bilirubin (mg/dl ) | 4.15 ↑ | 0.29-1.6 |
| Direct bilirubin (mg/dll) | 3.46 ↑ | <0.5 |
| AST (U/L) | 530 ↑ | <40 |
| ALT (U/L) | 154 ↑ | <50 |
| Albumin (g/L) | 26.3 ↓ | 40-55 |
| Coagulation Profile | | |
| PT (seconds) | 44 ↑ | 9.6-12.8 |
| APTT(seconds) | >180 ↑ | 24.8-33.8 |
| INR | 3.71 ↑ | 0.88-1.15 |
| D-dimer (ng/dl) | >38 ↑ | <0.55 |
| FDP (mg/L) | >80 ↑ | <5 |
| Fibrinogen (g/L) | 0.39 ↓ | 2-4 |
| Antithrombin III per cent | 30.4 ↓ | 75-125 |
| Thrombomodulin (TU/ml) | 41.5 ↑ | 3.8-13.3 |
| Basic Metabolism Test | | |
| Creatinine (mg/dl) | 2.5 ↑ | 0.76-1.2 |
| Urea nitrogen (mg/dl) | 31,64 ↑ | 8.68-22.4 |
| Lactate (mmol/L) | 15.3 ↑ | <2 |
| Blood glucose ( mg/dl ) | 5.97 | 97-106 |
| Cardiac Enzymes | | |
| Myoglobin (ng/ml) | >3000 ↑ | <72 |
| Troponin-T (ng/L) | 4951 ↑ | 0-14 |
| Creatine kinase isoenzymes MB mass (ng/ml) | >300 ↑ | <4.94 |
| B-type natriuretic peptide precursor (ng/L) | >35000 ↑ | 0-88 |

AST=aspartate aminotransferase ALT= alanine aminotransferase PT= Prothrombin Time APTT-Activated partial thromboplastin time INR=International Normalized Ratio.

broad-spectrum antibiotics, Norepinephrine for vasopressor support, and fluid resuscitation. Despite these measures, the patient's condition continued to worsen, marked by persistently low blood pressure and poor oxygenation. On the early morning of the fourth day, the patient required endotracheal intubation and was subsequently transferred to the ICU for advanced care.

Following admission to the ICU, laboratory data indicated elevated inflammatory markers, increased lactate levels, thrombocytopenia, coagulation abnormalities, anticoagulation irregularities, and raised B-type natriuretic peptide precursor and cardiac enzymes (Table 1).

Blood cultures conducted prior to the administration of antibiotics indicated positive results for Burkholderia citrate. CT scans revealed multifocal infectious lesions in both the lungs. Furthermore, sputum cultures confirmed the presence of Klebsiella pneumoniae.

In the ICU, the patient received both respiratory and circulatory support. This included a regimen of Tigecycline and Vancomycin for antimicrobial therapy. Additionally, vasopressor agents such as Norepinephrine, Vasopressin, and Methylene blue were administered to maintain a mean arterial pressure (MAP) above 65 mmHg. Norepinephrine was given at a rate up to 3μg/kg/min, and Vasopressin at 0.04 units/min. The patient also received fresh frozen plasma transfusions, platelets, and cryoprecipitate. Furthermore, treatments including bedside blood purification and intra-aortic balloon counter pulsation were conducted.

Upon admission to the ICU, the patient exhibited progressive, extensive cyanosis of the extremities, accompanied by ecchymosis and petechiae on the facial skin, and a dark purple discolouration in the nasal area (Figure 1). Despite these symptoms, a Doppler ultrasound examination revealed normal flow in the ulnar, radial, femoral, and posterior tibial arteries.

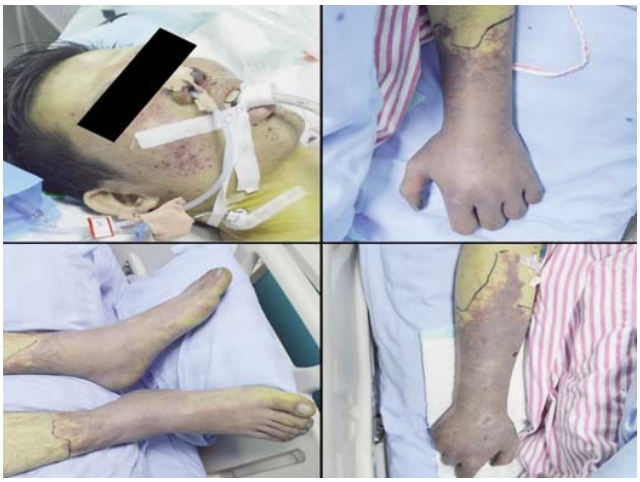

**Figure-1:** Petechial skin lesions appeared on the patient's face, hands and feet.

With appropriate treatment, the patient's infection was managed effectively, leading to gradual haemodynamic stability and improvement in consciousness. Consequently, the patient was successfully weaned off vasoactive drugs and the ventilator. However, ischaemic necrosis of the limbs continued to progress, manifested by the formation of blisters, ulceration, and scabs on various skin areas, which distinctly delineated the ischaemic regions from the normal tissues (Figure 2).

Although amputation was deemed necessary, the patient declined the surgical procedure and did not consent to

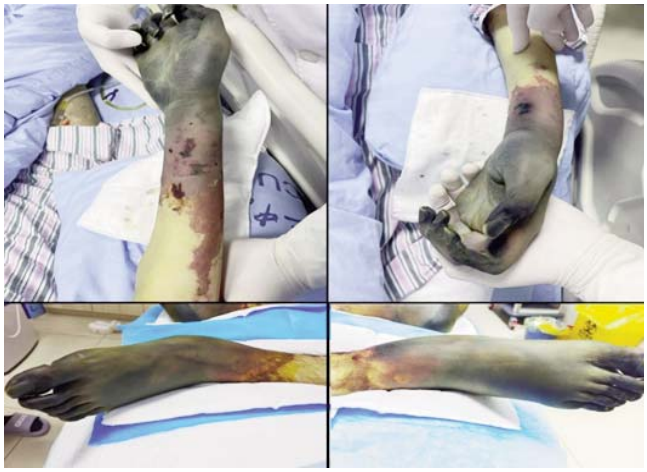

**Figure-2:** Symmetrical peripheral gangrene of his hands and feet.

limb removal. Necrotic skin areas developed partial purulent discharge with an offensive odour; a culture of the discharge identified Pseudomonas fluorescens. The treatment involved frequent cleansing and change of dressings. By the 44th day of hospitalisation (July 22, 2023), the patient experienced a recurrent high fever, accompanied by elevated inflammatory markers. On the 58th day (August 6, 2023), the patient's condition deteriorated, leading to shock, respiratory failure, and multiple organ dysfunction. Subsequently, the family opted to cease all invasive interventions, and the patient eventually succumbed.

## Discussion

Prior research has pinpointed risk factors for SPG development, including shock induced by vasoactive drugs (either septic or cardiogenic), DIC, and deficiency in natural anticoagulant factors.

The patient's primary diagnosis was cancer, presenting with septic shock at admission. Infections were detected in multiple sites, including the lungs and bloodstream, as confirmed by blood and sputum cultures. The clinical presentation also included shock, heart failure, liver damage, and DIC. To maintain blood pressure, high doses of vasoactive drugs were necessary, reflecting the presence of numerous high-risk factors associated with an increased risk of SPG.

This patient received continuous treatment with vasoactive drugs for over one week. Specifically, Norepinephrine was administered at a rate of 3μg/kg-min for more than 24 hours, coinciding with the onset of ischaemic changes in the skin of the face and extremities. It is well-documented that gangrene of the extremities can occur with the use of Dopamine, Epinephrine, and Norepinephrine at recommended or therapeutic doses in patients experiencing DIC and hypovolaemia. A recent multicentre epidemiologic study observed that two out of every 1,000 patients, who were dependent on vasoactive drugs during sepsis (with administration lasting more than one hour within the 48 hours prior to and 24 hours following the onset of sepsis), required surgical amputation due to acute limb ischaemia.[5] Thus, vasoactive drugs are recognised as significant contributors to the risk of SPG.[6]

Furthermore, the patient exhibited severe dysfunction in both coagulation and anticoagulation during the treatment. Theoretically, any factor that enhances coagulation or diminishes anticoagulation may increase the risk of inducing or exacerbating SPG in vulnerable patients. DIC is a critical complication stemming from various causes. It affects approximately 80% of sepsis patients and is characterised by endothelial dysfunction, coagulation pathway activation, and microcirculatory thrombi formation. Endothelial damage leads to increased capillary permeability, plasma extravasation, capillary collapse, and platelet dysfunction, all contributing to thrombus formation.[7] Conversely, DIC results in the depletion of natural anticoagulants, such as protein C and antithrombin, and reduced production of anticoagulants due to ischaemic liver injury, thereby accelerating thrombus formation.

Furthermore, cancer patients are more susceptible to high-risk factors for the development of SPG, such as infection and sepsis, coupled with an enhanced procoagulant state and a deficiency in natural anticoagulants. Initially, cancer independently increases the risk of sepsis, making infections or sepsis more prevalent among cancer patients compared to those without cancer. Additionally, cancer also independently heightens the risk of DIC, with substantial evidence indicating that nearly all patients with advanced malignancies are in a procoagulant condition,[8] and approximately 10-15% of these patients are likely to develop DIC.[9] Moreover, cancer-induced obstructive jaundice in this patient presents another pathological mechanism contributing to coagulation dysfunction.

It should be emphasised that the predominant clinical symptoms of DIC include extensive skin congestion, haematomas, and bleeding from wounds or puncture sites, typically involving the entire body rather than only the distal limbs. In the case under discussion, the necrotic lesions predominantly affected the peripheral limbs, indicating a heightened susceptibility of the peripheral blood vessels to endogenous and exogenous catecholamines.

Currently, there is no established and fully effective treatment for SPG. When it develops, the progression of the condition is generally irreversible. The mortality rate associated with SPG ranges from 18 to 40%, and most survivors necessitate amputation.[10] While secondary infections are rare, there is an elevated risk of infection in the necrotic regions for patients with SPG.

## Conclusion

Regarding this patient, it is hypothesised that microcirculatory thrombosis may have developed due to DIC and deficits in natural anticoagulant factors. The presence of shock and administration of high doses of vasoactive drugs likely enhanced the propensity for thrombus formation in peripheral vessels. Furthermore, an underlying malignant tumour could exacerbate the development of SPG. SPG could thus be attributed to a confluence of these factors. Consequently, early detection and proactive treatment of sepsis and DIC, coupled with judicious use of vasoactive drugs to preserve blood circulation, are imperative to prevent SPG.

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**Conflict of Interest:** None to declare

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**CY, JH & XH:** Drafting, final approval and agreement to be accountable for all aspects of the work.
**XF:** Concept, design, final approval and agreement to be accountable for all aspects of the work.