



## Case report

## Necrotizing fasciitis associated with sorafenib treatment

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## ABSTRACT

We present here a case of extensive necrotizing fasciitis during sorafenib treatment in a patient with HBV-related hepatocellular carcinoma. Despite emergent extensive surgical debridement, the patient's clinical status progressive worsened until interruption of sorafenib therapy. The patient was successfully treated with temporal interruption of sorafenib therapy. To our knowledge, this is the first case report of sorafenib-associated necrotizing fasciitis. Given the life-threatening nature of the infection and the necessity for urgent intervention, clinicians should be aware of this possible adverse effect of tyrosine kinase inhibitors.

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## Introduction

Sorafenib, an oral tyrosine kinase inhibitor (TKI), inhibits vascular endothelial growth factor (VEGF) receptors and prevents tumor proliferation and angiogenesis [1]. Hypertension, hand-foot skin reactions, hepatotoxicity, fatigue, diarrhea and stomatitis were the most frequently observed adverse effect of treatment with VEGF-inhibitors. Impaired wound healing have been reported during TKI therapy [1,2]. Temporary interruption of TKIs therapy is recommended for precautionary reasons in patients undergoing major surgical procedures [3]. In 2013, manufacturer of bevacizumab, a monoclonal antibody to the VEGF-A ligand, alerted healthcare professionals to rare cases of necrotizing fasciitis (NF) in patients treated with bevacizumab [4–6]. Recently, NF during sunitinib treatment has been reported in medical literature [7]. This serious adverse drug reaction has not previously been reported in patients who has taken sorafenib. To our knowledge, this is the first case report of sorafenib-associated NF.

## Case report

A 57-year-old male presented to the emergency department complaining of painful right inguinal swelling for 2 days. The patient denied any history of trauma, insect bites or allergies. His medical history revealed that a history of chronic hepatitis B virus (HBV) infection and liver cirrhosis (Child-Pugh A). He was

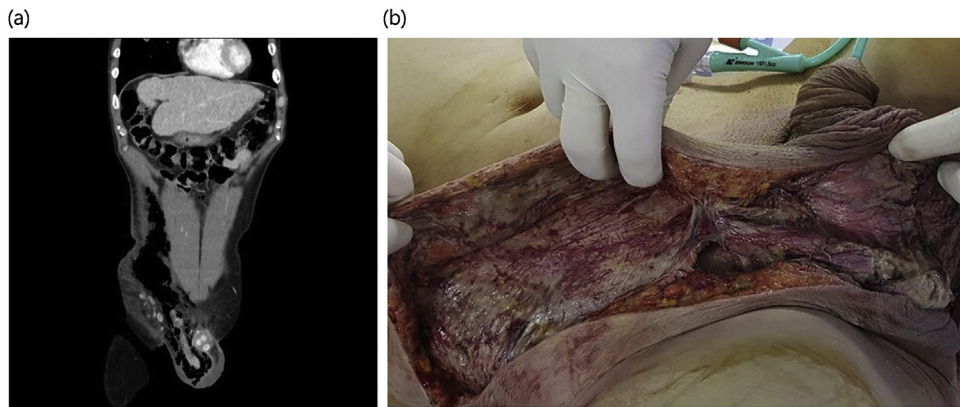
diagnosed with HBV-related hepatocellular carcinoma. The patient was felt to be unfit for curative approach and he underwent seven sessions of transcatheter arterial chemoembolization and intensity modulated radiation therapy. He was being treated with tenofovir disoproxil fumarate 300 mg/day, and sorafenib 800 mg daily, which began 3 months before the admission. His general health of the patient was not poor, with body mass index 23.9 kg/m<sup>2</sup> and his Eastern Cooperative Oncology Group performance status score was 0.

On admission to the emergency department, the patient had a temperature of 36.5 °C, a blood pressure 92/52 mmHg, heart rate 109/min, respiratory rate 22/min, and oxygen saturation 99% on room air and was alert and oriented. After fluid hydration with 1 L normal saline, his follow-up vital signs were stable, with blood pressure 114/61 mmHg, and heart rate 95/min. Physical examination revealed marked erythema over his right lower abdomen, right inguinal area and the scrotum. The overlying skin was warm, mildly edematous, and extremely tender when palpated. No sign of crepitus was identified. Laboratory studies included a white blood cell count  $11.84 \times 10^9/L$ , absolute neutrophil  $10.96 \times 10^9/L$ , hemoglobin 14.7 gm/L, platelets  $41 \times 10^9/L$ . Coagulation study showed abnormal prothrombin time 18.2 s, international normalized ratio 1.56 and an activated partial thromboplastin time of 44.7 s. Inflammatory markers were elevated with a C-reactive protein of 15.96 mg/dL and a procalcitonin 7.94 ng/mL. Initial urine and blood cultures failed to reveal any organisms. Computed tomography of the lower abdomen and pelvis revealed extensive emphysema around the testicles, perineal subcutaneous tissue, and around the right lower abdomen wall (Fig. 1a).

Based on the clinical features, diagnosis of NF was made and the patient started on empirical intravenous broad-spectrum antimicrobials combinations (ampicillin-sulbactam plus clindamycin)

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**Fig. 1.** (a) Computed tomography showing extensive emphysema around the lower abdominal wall, inguinal area, and scrotum. (b) Intraoperative image of the immediate surgical debridement demonstrating the extensive necrosis of the lower abdominal wall, inguinal area, and scrotum.

and later adjusted to the culture sensitivity of the microbial isolates. He underwent emergent surgical debridement under general anesthesia and all the necrotic and dead tissue was removed, leaving behind a margin of healthy looking tissue (Fig. 1b). Pus and necrotic tissue were sent for culture and sensitivity testing and showed the growth of *Staphylococcus lugdunensis* and susceptibility to the previously started antimicrobials. Local wound care was performed with moist gauze dressings changed daily until healthy granulation tissue was observed. Despite emergent extensive surgical debridement, the patient's clinical status progressively worsened until the interruption of sorafenib therapy. The infection gradually subsided, the Fournier's gangrene resolved completely, and good granulation was present one week after interruption of sorafenib therapy. Secondary closure of the wound was performed on hospital day 14. The subcutaneous air completely disappeared on abdominal CT and the patient was finally discharged on the 23rd postoperative day.

## Discussion

NF is a life-threatening infection, with reported mortality rates ranging from 8.7% to 73% (mean 32.2%) [8]. There are several risk factors for this condition, the most recognizable being immunodeficiency, diabetes, obesity, and alcohol abuse [9]. Rarely, NF can develop related to all-trans-retinoic acid, bisphosphonates, and radiotherapy [8]. In addition, several reports have shown that liver cirrhosis is a common underlying disease in patients with NF [10]. Liver cirrhosis can weaken the intestinal-portal route barrier, which facilitates the entry of bacteria into the systemic circulation and renders patients prone to various infectious diseases [10]. This patient had a several predisposing comorbidity factors which can be a predispose causes of NF, such as liver cirrhosis, malignancy and history of radiation. Therefore, sorafenib was determined to be the "possible cause", not "probable cause" of the necrotizing fasciitis according to the Naranjo Adverse Drug Reaction Probability Scale (+4), and WHO-UMC causality categories [11,12].

There are only few case reports available on necrotizing fasciitis resulting from molecular targeted therapy. NF has been reported in patients receiving bevacizumab in both clinical trials and in the post-marketing setting [5,6,13,14]. A case report by Piszczek et al. described a case of sunitinib-related NF [7]. This serious adverse drug reaction had not previously been reported in patients who were taken sorafenib. Given the common pathophysiologic mechanism of skin toxicity in patients who treated with molecular targeted therapy is subcutaneous artery thrombosis leading to tissue hypoxia, necrosis, and increased susceptibility to invasion by

pathogenic and opportunistic bacteria, sorafenib also might be a risk factor for this rare but fatal complication [7,14].

Hung et al. described the first case of necrotizing fasciitis jointly associated with the microbes Group B *Streptococcus* and *S. lugdunensis* [15]. *S. lugdunensis* is a coagulase-negative *Staphylococcus* with a pathogenicity and virulence more similar to *Staphylococcus aureus* than to other coagulase-negative *Staphylococcus* spp. [15,16]. These organisms are frequently misidentified as *S. aureus* because of their morphologic appearance with yellow pigmentation and complete hemolysis when cultured on blood agar [15,17,18]. Even so, appropriate identification of *S. lugdunensis* is imperative as misidentification may result in inadequately treated, prolonged, and persistent infection [15,18].

Besides initial administration of broad-spectrum antimicrobials, urgent and aggressive surgical intervention, often comprising multiple debridement procedures before eventual definitive reconstruction, is required [4,19]. Auxiliary measures can also be implemented, such as negative pressure wound therapy (NPWT) or hyperbaric oxygenation [19]. We did not use NPWT or hyperbaric oxygenation therapy in this patient. We performed only daily saline irrigation and povidone soaked gauze application by being sealed with a waterproof film to protect local wound infection and fecal contamination. Secondary closure of the wound was also performed without skin graft or flaps. Nevertheless, the late recognition of sorafenib taking resulted in more requirement of additional debridement and prolongation of hospital stay.

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## Ethics statement

The protocol of the present study was reviewed and approved by the Institutional Review Board (IRB) of our hospital (IRB No. 2019-03-011). The patient provided written informed consent.

## Authorship contribution

Ho Won Kang: Conception and design of study, acquisition of data, drafting the manuscript.

Seok-Joong Yun: Conception and design of study, revising the manuscript critically for important intellectual content.

Wun-Jae Kim: revising the manuscript critically for important intellectual content.

## Declaration of Competing Interest

None of the authors has a conflict of interest.

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