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Cabozantinib-associated microthrombi causing necrotizing fasciitis-like findings

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cabozantinib, microthrombi, necrotizing cellulitis, necrotizing fasciitis, vascular endothelial growth factor inhibitor

Dear Editors,

Necrotizing fasciitis is a rapidly progressive, life-threatening soft tissue infection requiring urgent intervention. Although necrotizing fasciitis has been reported in association with vascular endothelial growth factor (VEGF) inhibitors [1, 2], necrotizing cellulitis presenting with necrotizing fasciitis–like cutaneous necrosis has not been previously described in patients treated with VEGF inhibitors, including multi-kinase inhibitors (MKIs). We present a rare case of necrotizing cellulitis mimicking necrotizing fasciitis in a patient treated with cabozantinib.

A 70-year-old Japanese man was treated with cabozantinib for renal cell carcinoma, with the dose initially set at 40 mg/day and subsequently reduced to 20 mg/day because of adverse effects, including hand–foot syndrome; 18 months after treatment initiation, he developed complete lower limb paralysis due to spinal metastasis, prompting a new increase in the dose to 40 mg/day. Three months later, the patient developed ulcers and edema in his lower legs, and another month later, he developed a fever and decreased consciousness.

At presentation, the left lower leg was swollen with purpura, petechiae, erosions, and bullae, without fluctuance (Figure 1A). Paralysis precluded pain assessment. Laboratory findings included thrombocytopenia ($9.5 \times 10^3/\mu L$), elevated creatinine (2.93 mg/dL), CK (1723 U/L), CRP (37.64 mg/dL), and procalcitonin (139.84 ng/mL), with a Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score of 9. Plain CT showed inflammation predominantly involving the subcutaneous tissue, with no evidence of gas formation or deep fascial involvement in the left lower extremity (Figure 1B). An exploratory incision revealed full-thickness skin necrosis without purulent discharge or fat necrosis; the fascia appeared viable with normal coloration, and the finger test was negative, indicating that the findings were not consistent with necrotizing fasciitis (Figures 1C,D). A skin biopsy showed dermal fibrin thrombi without vasculitis (Figure 1E). Blood and tissue cultures grew *Streptococcus dysgalactiae*.

Necrotizing fasciitis was initially suspected based on the presence of bullae and purpura, a high LRINEC score, disseminated intravascular coagulation (DIC), and the patient's underlying diabetes with chemotherapy-induced immunosuppression. However, based on the surgical and histopathological findings, together with the clinical course, the diagnosis was revised to necrotizing cellulitis with *Streptococcus dysgalactiae* sepsis and DIC. Cabozantinib was discontinued, and the patient was treated with systemic antibiotics and anticoagulants, resulting in gradual clinical improvement. Despite extensive epidermal necrosis and ulceration (Figure 1F), conservative management led to the formation of granulation tissue by day 42 (Figure 1G).

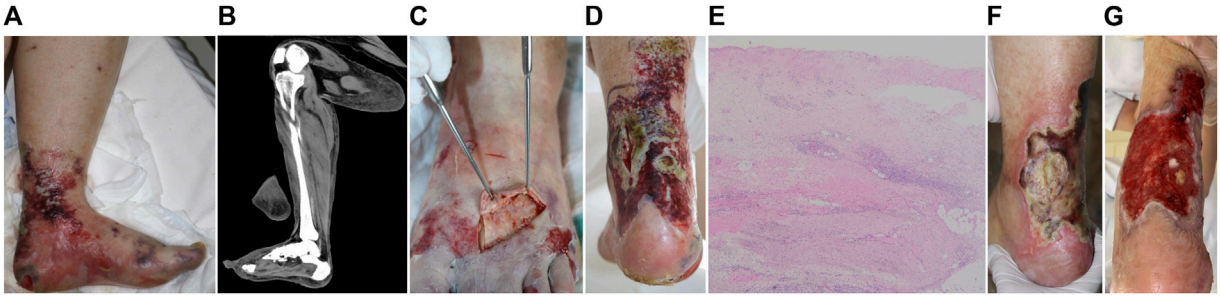

FIGURE 1
(A) Day 1: hemorrhagic petechiae with flaccid bullae were observed on the left lower leg. **(B)** Day 1: a non-contrast CT scan showing no evidence of gas formation or deep fascial involvement in the left lower extremity. **(C,D)** Day 2: an exploratory incision revealed no friable tissue and "dishwater" discharge. The finger test was negative. **(E)** Day 2: histopathological findings. A biopsy of the purpura on the dorsum of the left foot revealed fibrin thrombi in the superficial to mid dermis (hematoxylin-eosin stain, ×40). **(F)** Day 10: the lower leg developed ulcers with epidermal necrosis. **(G)** Day 42: the ulcer was completely covered with red granulation tissue.

Necrotizing soft tissue infections (NSTIs) can be classified based on the depth of tissue involvement into necrotizing cellulitis, which affects the epidermis and subcutaneous tissue, and necrotizing fasciitis, which extends to the fascial planes [3]. Accurate distinction between these entities is crucial, as surgical debridement is mandatory for necrotizing fasciitis but may not be required for necrotizing cellulitis.

Although the LRINEC score was high (score of 9) in this case, this scoring system has limited specificity and may be elevated in severe infections and inflammatory conditions, such as sepsis and DIC. The clinical course was not rapidly progressive, which is atypical for necrotizing fasciitis.

Cabozantinib, an MKI targeting the VEGF receptor 2, the MET proto-oncogene-encoded receptor tyrosine kinase (MET), and the AXL receptor tyrosine kinase (AXL), suppresses angiogenesis and increases the risk of thromboembolism [4, 5]. While necrotizing fasciitis has been reported with other VEGF-inhibitory agents, NSTIs associated with cabozantinib have not.

A Streptococcus dysgalactiae infection likely triggered systemic inflammation and DIC. However, the severity of microvascular thrombosis and tissue necrosis appeared disproportionate to the degree of infection and could not be fully explained by the infection alone. We therefore speculate that endothelial injury induced by cabozantinib further exacerbated the prothrombotic state, resulting in extensive tissue damage.

To our knowledge, this is the first reported case of necrotizing cellulitis mimicking necrotizing fasciitis in a patient receiving a VEGF inhibitor. Clinicians should be aware that VEGF-inhibitory therapies may cause severe cellulitis with thrombotic features that closely resemble necrotizing fasciitis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

IK, YM, TS, MK, and TN were involved in the diagnosis and treatment of the patient. IK and YM drafted the manuscript. TS, MK, TN, TK, and AT critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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