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(CASE REPORT)

CABOZANTINIB-INDUCED SCROTAL ULCERATION IN A PATIENT WITH ADVANCED HEPATOCELLULAR CARCINOMA: A CASE REPORT

Kripa Mariyam John [1,*], Surabhi Soman [2] and Harikrishnan [2]

[1] Nazareth college of pharmacy, Othera, Thiruvalla.
[2] Believers Church Medical College Hospital, Thiruvalla.

* Corresponding Author

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ABSTRACT

Cabozantinib is an oral multikinase inhibitor widely used for the treatment of advanced Hepatocellular Carcinoma (HCC).A rare but possibly dangerous adverse drug reaction linked to cabozantinib's anti-angiogenic properties is scrotal ulceration. Reduced blood flow and poor tissue repair may contribute to the development of ulcers. About six weeks after starting cabozantinib therapy, a 66-year-old man with advanced hepatocellular carcinoma experienced painful scrotal ulcerations. Clinical examination showed mild erythema and superficial ulcerative lesions with polycyclic boundaries around the scrotum, but no signs of necrotising fasciitis or infection. The lesions completely healed once cabozantinib was stopped, and the patient was treated conservatively with supportive therapy and local wound care. This case report highlights early recognition of cabozantinib-induced genital ulceration and the role of prompt drug withdrawal in management.

Keywords: Cabozantinib; Hepatocellular carcinoma; Scrotal ulceration; Tyrosine kinase inhibitor; Adverse drug reaction; Cutaneous toxicity

1 INTRODUCTION

Cabozantinib is an orally administered, multitargeted tyrosine kinase inhibitor used in the management of various malignancies, including renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer. It exerts its antitumor effects primarily by inhibiting multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR), MET, and AXL, which play important roles in tumour angiogenesis, growth, invasion, and metastasis.

Although cabozantinib has demonstrated significant clinical benefits, its anti-angiogenic activity can also lead to adverse effects involving the skin and mucous membranes. Commonly reported adverse effects include palmar–plantar erythrodysesthesia, rash, diarrhoea, fatigue, hypertension, and impaired wound healing. However, genital skin complications, including scrotal ulceration, are extremely rare and may be under recognized.

Scrotal ulceration associated with cabozantinib may result from impaired angiogenesis, reduced tissue perfusion, and delayed wound healing due to inhibition of the VEGF signalling pathway. The presence of an ulcer in the scrotal region also requires careful evaluation to exclude infectious, vascular, inflammatory, and malignant causes. Severe cases may progress to secondary infection, tissue necrosis, or potentially life-threatening conditions such as Fournier's gangrene.[1]

Therefore, early recognition of cabozantinib-induced scrotal ulceration is essential for prompt intervention. Appropriate management may include evaluation for alternative causes, wound care, treatment of secondary infection when present, and consideration of temporary interruption or discontinuation of cabozantinib depending on the severity of the reaction. This rare adverse drug reaction highlights the importance of continuous pharmacovigilance and close monitoring of patients receiving anti-angiogenic anticancer therapy. To date, 40,908 adverse drug reactions (ADRs) induced by cabozantinib have been reported to Uppsala Monitoring Centre (UMC), of which scrotal ulceration accounts for only 16 ADRs.

We describe a rare case of cabozantinib-induced scrotal ulceration in a patient with advanced hepatocellular carcinoma.

2 CASE PRESENTATION

A 66-year-old male with advanced Hepatocellular Carcinoma associated with paraneoplastic erythrocytosis presented with painful erosive lesions over the scrotum. He was a known case of chronic liver disease, type 2 diabetes mellitus, and hypertension.

Contrast-enhanced computed tomography (CECT) of the abdomen demonstrated chronic parenchymal liver disease consistent with hepatocellular carcinoma. Baseline serum alpha-fetoprotein (AFP) level was elevated at 625.78 IU/mL, while CA 19-9 was <0.8 U/mL.

The patient was initially started on Lenvatinib therapy. Upper gastrointestinal endoscopy subsequently revealed a Forrest grade III duodenal ulcer. During follow-up, AFP levels increased to 1299.19 IU/mL, suggestive of progressive disease, following which the dose of lenvatinib was increased to 8 mg daily.

The patient also had stenosis of the brachiocephalic trunk, which was managed conservatively. In view of disease progression, treatment was shifted to Cabozantinib 40 mg once daily.

Approximately six weeks after initiation of cabozantinib therapy, the patient reported symptomatic improvement with reduced fatigue but developed painful scrotal erosions. There was no history of fever, trauma, sexually transmitted disease, or prior similar lesions.

Dermatological examination revealed multiple superficial ulcers over the scrotal skin with polycyclic borders and mild surrounding erythema. No vesicles, fluid-filled lesions, purulent discharge, necrosis, or crepitus were noted.

Clinical evaluation revealed no evidence of systemic infection or Fournier gangrene. Based on the temporal relationship between cabozantinib therapy and lesion onset, along with exclusion of infectious causes, cabozantinib-induced scrotal ulceration was suspected.

Cabozantinib was discontinued immediately, and conservative management including local wound care, analgesics, and supportive measures mupirocin ointment, moisture soft cream, Megaheal gel). Progressive healing was observed following drug withdrawal, with complete resolution of the lesion during follow-up and supporting a positive de-challenge.

3 DISCUSSION

Cabozantinib inhibits angiogenesis through VEGF pathway blockade, thereby impairing endothelial repair and tissue perfusion. Although this mechanism contributes to antitumor activity, it may also predispose patients to ischemic cutaneous injury and ulcer formation. Anti-angiogenic effects can impair wound healing and tissue perforation, potentially causing skin ulceration, necrosis, and delayed wound healing.

Cutaneous adverse effects associated with cabozantinib commonly include palmar-plantar erythrodysesthesia, xerosis, mucositis, and delayed wound healing. Genital ulceration is rarely described in the literature. Similar ulcerative lesions have been reported with other antiangiogenic agents, suggesting that VEGF inhibition may play a central role in the pathogenesis.

The case report published by **Rena C Zubo et al** 41 consecutive patients who received cabozantinib, 30 (73%) developed 1 or more cutaneous toxic effects. Adverse events included hand-foot skin reaction (22 [54%]), generalized pigment dilution and/or hair depigmentation (18 [44%]), xerosis (8 [20%]), scrotal erythema/ulceration (6 [15%]), and nail splinter haemorrhages (5 [12%]). Eighteen patients (44%) had 2 or more cutaneous adverse events. Reactions developed in 17 of 30 patients (57%) during the first month of cabozantinib treatment and in 24 of 30 (80%) by the second month. Of patients with skin toxic effects, dose reduction was required for symptom management in 9 of 30 patients (30%), and treatment discontinuation was required in 4 of 30 (13%).[8]

Another study conducted by **Arun Somasundaram et a**l cabozantinib known side effects is hand–foot syndrome (HFS), also known as palmar–plantar erythrodysesthesia. In addition to HFS, reported that known side effects of cabozantinib include xerosis, scrotal erythema, subungual splinter haemorrhages, and pigment dilution or hair greying. Behçet's disease can also manifest with scrotal ulcers; however, the patient did not have a history of recurrent oral aphthous ulcers or symptoms involving the eyes or joints. Other potential causes of acute scrotal ulcers include herpes infection, syphilis, chikungunya, certain drugs (such as all-trans retinoic acid and hydroxyurea), and trauma. In our patient, these other causes were ruled out because the ulcers developed after starting cabozantinib and healed completely once the drug was discontinued. Recognising and managing these side effects is crucial for the effective care of patients on cabozantinib, allowing for appropriate interventions and minimising the need for active treatment.[9]

The differential diagnosis in this patient included Fournier gangrene, infectious genital ulcers, vasculitis, pressure ulcers, and malignant skin infiltration. However, absence of fever, purulent discharge, crepitus, or systemic toxicity made infectious etiologies less likely.

The diagnosis of cabozantinib-induced scrotal ulceration was supported by:

- A clear temporal association between initiation of therapy and lesion onset
- Exclusion of alternative causes
- Complete healing after discontinuation of the drug (positive de-challenge)

According to the WHO-Uppsala Monitoring Centre (WHO-UMC) and Naranjo adverse drug reaction causality scales, the reaction was categorised as "probable." The outcome of the reaction was found to be "recovering".

Early recognition of this uncommon toxicity is clinically important because continuation of therapy may result in worsening ulceration, secondary infection, and significant impairment in quality of life. It can be prevented by alternate therapy, monitoring recommendations, and dose reduction.

Abbreviations

- HCC: Hepatocellular Carcinoma
- WHO: World Health Organization

4 CONCLUSION

Cabozantinib can rarely cause severe scrotal ulceration in patients receiving treatment for advanced Hepatocellular Carcinoma. Clinicians prescribing cabozantinib should maintain a high index of suspicion for genital ulceration in patients presenting with painful scrotal lesions, and early drug withdrawal may prevent progression and avoid unnecessary surgical intervention.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

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

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