Scrotal Ulcer Due to Lenvatinib During Treatment of Unresectable Hepatocellular Carcinoma

Úlcera Escrotal Devido ao Uso de Lenvatinib Durante o Tratamento de Carcinoma Hepatocelular Irressecável

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Abstract:

Lenvatinib is used as an anti-cancer drug in patients with unresectable hepatocellular carcinoma (HCC) due to its antiangiogenic activity. This class of targeted therapy has changed the paradigm of HCC treatment, but it also poses an additional challenge due to its distinct side effects compared to conventional chemotherapy.

We present the case of a 58-year-old man with Child-Pugh A alcoholic and dysmetabolic cirrhosis, diagnosed with unresectable BCLC (Barcelona Clinic Liver Cancer) stage C HCC. He was started on lenvatinib, and after 4 months of treatment, a skin ulcer appeared on the scrotum. This led to further investigation into its cause and, eventually, to the discontinuation of lenvatinib. The ulcer resolved with drug withdrawal alone (without the need for specific treatment).

This case highlights the importance of clinicians being aware of adverse skin effects associated with lenvatinib, which most likely result from its antiangiogenic activity.

Keywords: Carcinoma, Hepatocellular/drug therapy; Lenvatinib/adverse effects; Skin Ulcer/chemically induced.

Resumo:

O lenvatinib é um fármaco usado em doentes com carcinoma hepatocelular (CHC) irressecável, devido à sua atividade antiangiogénica. Esta classe de fármacos mudou o paradigma do tratamento do CHC mas apresenta agora um desafio adicional devido aos efeitos secundários significativamente diferentes comparativamente à quimioterapia convencional.

Apresentamos o caso de um homem de 58 anos com cirrose alcoólica e dismetabólica em estádio Child-Pugh A, diagnosticado com CHC irresecável, estadio C segundo o sistema BCLC *(Barcelona Clinic Liver Cancer)*.

O doente iniciou tratamento com lenvatinib e, após 4 meses, desenvolveu uma úlcera cutânea no escroto, o que levou a uma investigação adicional sobre a sua causa e posteriormente à suspensão do lenvatinib. Com a interrupção do fármaco (sem tratamento específico), a úlcera resolveu.

Este caso reforça a importância de vigiar efeitos adversos cutâneos associados ao lenvatinib que resultam provavelmente da sua atividade antiangiogénica.

Palavras-chave: Carcinoma Hepatocellular/tratamento farmacológico; Lenvatinib/efeitos adversos; Úlcera da Pele/induzida quimicamente.

Learning Points

1. This case highlights the unique side effects associated with lenvatinib, particularly skin-related issues like cutaneous ulcers.
2. The development of the ulcer is likely linked to lenvatinib's antiangiogenic properties, which impair normal tissue repair processes.
3. Regular dermatological assessments and patient education regarding skin changes are crucial for early detection and intervention of cutaneous toxicities during treatment.
4. Upon identifying an adverse effect, such as the scrotal ulcer in this case, immediate drug discontinuation may be necessary.

Introduction

Lenvatinib is used since 2018 as an anti-cancer drug in patients with unresectable hepatocellular carcinoma (HCC).[1,2] It is an oral small-molecule multi-kinase inhibitor (TKI) of the vascular endothelial growth factor receptor (VEGFR)[1-3] platelet-derived growth factor receptor-alpha (PDGFR-α), fibroblast growth factor receptor (FGFR),[1-4] and the proto-oncogenes, KIT and rearranged during transfection (RET).[5] It has been shown in preclinical studies that by inhibiting VEGF and FGFR, lenvatinib can act as a potent antiangiogenic agent.[3,4] In recent years, antiangiogenic drugs have represented an enormous improvement in

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https://doi.org/10.60591/crspmi.328

the treatment of several types of cancer and a shift towards personalized and precision therapy. However, they present some side effects that have never been observed with conventional chemotherapy.[6]

Regarding lenvatinib, the known side effects include high blood pressure, diarrhea, fatigue, decreased appetite and weight loss, nausea, vomiting, proteinuria and stomatitis. Severe side effects including aerodigestive fistula or bleeding, have also been reported. In addition to these side effects, there are other known cutaneous adverse effects including palmar-plantar erythrodysesthesia (27% to 32%), skin rash (14% to 21%), alopecia (12%), hyperkeratosis (7%), and wound healing impairment (<1%). The occurrence of cutaneous ulcers during lenvatinib treatment is rare.[5,7-9]

Herein, we present a rare case of a patient who developed a cutaneous ulcer in the scrotal area during lenvatinib treatment for HCC.

Case Report

We present the case of a 58-year-old man with diabetes, showing reasonable metabolic control (HbA1c 7.2%) and no known microvascular or macrovascular complications, and also with a history of advanced chronic liver disease at a compensated cirrhosis stage. This liver disease was in the context of sustained alcohol use disorder and metabolic dysfunction associated with steatotic liver disease. Despite being on a regular ultrasound surveillance program, he was diagnosed with hepatocellular carcinoma (HCC) during regular follow-up. At the time of diagnosis in 2022, he presented with an infiltrative nodular lesion in the liver's caudate lobe, measuring 5.6 cm, with typical radiologic features of HCC as shown on a triple-phase CT scan. Two additional nodules were observed in the right hepatic lobe, measuring 17 mm and 13 mm, along with mesenteric and celiac adenomegaly. He had preserved liver function (Child-Pugh A5 and MELD-Na score of 9) and no evidence of ascites, being thus frameable in Barcelona Clinic Liver Cancer stage C. The patient was fully active, with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0. At the time of diagnosis, the patient weighed 119 kg and had a height of 1.79 m, thus presenting a BMI of 37.1 kg/m^2. The platelet count was 101 000/μL.

The tumor board recommended starting the tyrosine kinase inhibitor (TKI) lenvatinib at the maximum tolerated dose. After one month on 8 mg/day with good tolerance, the dose was increased to 12 mg/day, which was maintained for two months. However, due to recurrent episodes of epistaxis requiring cauterization, the dose was reduced back to 8 mg. Four months after treatment initiation, a computed tomography (CT) scan showed a reduction in tumor size of less than 30% and the presence of a viable tumor area, corresponding to a mRECIST classification of stable disease.

After 2 months of dose reduction and 4 months following the initiation of treatment, the patient reported the development of a painful skin lesion in the scrotal region. The lesion had a white base, no exudates, and measured approximately 2 cm (Fig. 1). It was classified as stage 2 according to the National Pressure Injury Advisory Panel (NPIAP) Pressure Injury Stages. No other associated symptoms were noted. Serology for syphilis was negative.

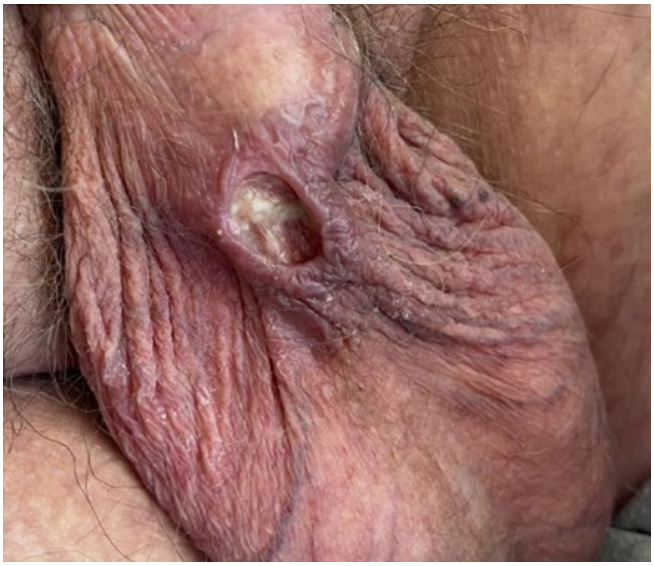

Figure 1: Painful cutaneous ulcer in the scrotal region, 2 cm in diameter, white-based, without exudates.

Considering the known cutaneous side effects associated with Lenvatinib, and a Naranjo scale10 score of 6 (previous reports on this reaction – 1 point; adverse event appeared after the suspected drug was given – 2 points; the adverse reaction improved when the drug was discontinued – 1 point; no alternative causes that could have caused the reaction – 2 points), treatment was discontinued.

Three weeks after discontinuing the drug and without any specific treatment directed at the ulcer, the patient showed significant improvement, with evident healing (Fig. 2). Regarding further treatment for hepatocellular carcinoma, the tumor board recommended starting second-line systemic treatment with an immunotherapy combination of nivolumab and ipilimumab. However, during immunotherapy, the patient developed additional adverse events, including hypophysitis, thyroiditis and phrenic neuropathy, which led to the suspension of treatment. Hereafter, both diseases progressed: cirrhosis decompensated, and HCC progressed, and the patient died approximately 2.5 years after the initial diagnosis.

Discussion

Regarding the development of skin ulcers in patients taking lenvatinib, the literature is scarce, and there are only a few case reports.

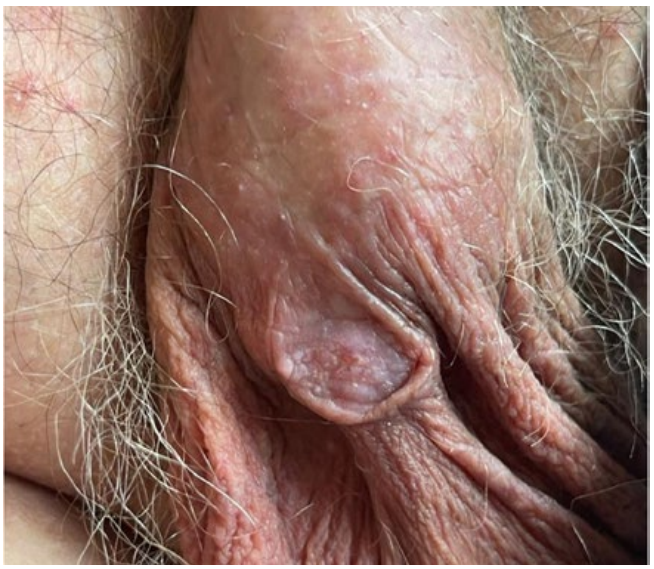

Figure 2: Previous cutaneous ulcer, healing.

To our knowledge, only three cases have been published. One involved a lesion near a metastatic infiltration in the subclavicular area, while the other two, similar to the present case, occurred distant from the primary tumor. The patients were receiving lenvatinib doses ranging from 4 to 24 mg. All cases showed improvement after discontinuing the drug.[9,11,12]

The precise mechanism by which lenvatinib causes cutaneous ulceration is not fully understood. It may be explained by the fact that it works as a VEGFR inhibitor and it is known that the vascular endothelial growth factor (VEGF) signaling pathway is a key regulator of tumor vasculature, mediating endothelial cell proliferation, migration, vascular permeability, and vasodilation.[13] Also, platelet-derived growth factor receptor inhibition by lenvatinib may play a role in impairing the tissue repair process.[9]

Although rare, scrotal erythema and ulceration have also been reported with other VEGFR inhibitors, such as cabozantinib, sorafenib, and sunitinib.[14] Therefore, it is important to conduct a baseline dermatological examination and regularly monitor patients treated with TKIs for cutaneous toxicities. Additionally, patients should be advised to watch for any potential skin alterations.

The low number of cases reported does not allow for a clear idea of the time of exposure or even the dosages at which the risk of developing ulcers arises. Indeed, the reported cases involved a wide range of doses, so individual susceptibility may play a role, although the cofactors remain unknown so far. In this case, despite reasonable metabolic control (HbA1c 7.2%), the patient was diabetic which may constitute an adjuvant factor. Although, in the other case reports, none of the patients were reported as diabetic. Therefore, there is a lack of consistency in this finding. It is also difficult to determine whether it is safe to resume lenvatinib after the ulcer has resolved, or if it actually constitutes an adverse effect that implies a mandatory change in therapy.

In this case, it is also mandatory to evaluate the potential progression to Fournier's gangrene (FG). FG is a type of necrotizing fasciitis that involves the perineal, perianal, and genital areas. Early diagnosis and treatment are crucial for a better outcome, as the mortality of this condition is high.[6] In this patient, since he is diabetic (risk factor) and the lesion is in the scrotal area, a careful assessment of the perineal region is even more relevant.

To our knowledge, there is only one reported case of FG in a patient on Lenvatinib. The starting point was a perianal abscess.[6] However, there are more cases of FG in patients taking bevacizumab, another known vascular endothelial growth factor inhibitor.

Thus, this case shows the importance of clinicians who deal with TKI drugs being aware of adverse skin effects.

Conclusion

Lenvatinib is an antiangiogenic drug indicated for the treatment of hepatocellular carcinoma (HCC). With its introduction, new adverse effects have been identified, including the development of cutaneous ulcers, which are believed to be related to its antiangiogenic activity. The dose or duration of exposure at which the risk of this adverse effect arises remains unclear. However, this case underscores the importance of being aware of potential skin toxicities and, if they occur, considering TKI discontinuation. Alternative treatment options may need to be considered according to therapeutic sequencing recommendations. ■

Contributorship Statement

CM, LR, OP - Designing and writing the article

IFP, JPR - Critical revision of content

All authors approved the final version to be published.

Declaração de Contribuição

CM, LR, OP – Desenho e elaboração do artigo

IFP, JPR – Revisão crítica do conteúdo

Todos os autores aprovaram a versão final a ser publicada.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares

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Received / Recebido: 2024/11/08
Accepted / Aceite: 2025/01/17
Published / Publicado: 2025/03/28

REFERENCES

1. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163-73. doi: 10.1016/S0140-6736(18)30207-1.
2. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76:681–93. doi: 10.1016/j.jhep.2021.11.018
3. Goel A, Singla A. Lenvatinib: A narrative drug review. Cancer Res Stat Treat. 2021;4:709.
4. Matsuki M, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, et al. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. Cancer Med. 2018;7:2641-53. doi: 10.1002/cam4.1517.
5. Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma. Cancer Treat Rev. 2019;77:20-8. doi: 10.1016/j.ctrv.2019.05.004.
6. Barone M, Grani G, Ramundo V, Garritano T, Durante C, Falcone R. Fournier's gangrene during lenvatinib treatment: A case report. Mol Clin Oncol. 2020;12:588-91. doi: 10.3892/mco.2020.2031.
7. Kim BH, Yu SJ, Kang W, Cho SB, Park SY, Kim SU, et al. Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma. J Gastroenterol Hepatol. 2022;37:428-39. doi: 10.1111/jgh.15727.
8. Ikeda M, Kobayashi M, Tahara M, Kaneko S. Optimal management of patients with hepatocellular carcinoma treated with lenvatinib. Expert Opin Drug Saf. 2018;17:1095–105. doi: 10.1080/14740338.2018.1530212
9. Cha S, Kim DW, Choe JW, Kim TH, Kim SY, Hyun JJ, et al. A case report of a patient presented with skin ulcer after treatment of lenvatinib. J Liver Cancer. 2021;21:194–8. doi: 10.17998/jlc.2021.09.20.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45. doi: 10.1038/clpt.1981.154.
11. Dohmen K. Severe ulcerative skin lesions due to lenvatinib. Clin Gastroenterol Hepatol. 2020;18:e113. doi: 10.1016/j.cgh.2019.05.005
12. Kitamura M, Hayashi T, Suzuki C, Hirano S, Tateya I, Kishimoto Y, et al. Successful recovery from a subclavicular ulcer caused by lenvatinib for thyroid cancer: a case report. World J Surg Oncol. 2017;15:24. doi: 10.1186/s12957-017-1096-5.
13. Sally R, Ugonabo N, Nguyen A, Kim RH, Lo Sicco K. Lenvatinib-induced psoriasiform eruption and palmoplantar erythema in a patient with hepatocellular carcinoma. JAAD Case Rep. 2021;15:1-3. doi: 10.1016/j.jdcr.2021.07.001.
14. Zuo RC, Apolo AB, DiGiovanna JJ, Parnes HL, Keen CM, Nanda S, Dahut WL CE. Cutaneous adverse effects associated with the tyrosine-kinase inhibitor cabozantinib. JAMA Dermatol. 2015;151:170–7. doi: 10.1001/jamadermatol.2014.2734.