

## CASE REPORT

# Case report of penile cancer recurrence treated with cetuximab combined with anlotinib

Shuang Dai<sup>1</sup>  | Yan-Yang Liu<sup>1</sup> | Tao Liu<sup>2</sup> | Yu Zhang<sup>3</sup> | De-Yun Luo<sup>4</sup><sup>1</sup>Lung Cancer Center, Department of Medical Oncology, West China Hospital, Sichuan University, Chengdu, China<sup>2</sup>Department of Oncology, The First Affiliated Hospital of Chengdu Medical College, Chengdu Medical College, Chengdu, China<sup>3</sup>Department of Pathology, West China Hospital, Sichuan University, Chengdu, China<sup>4</sup>Department of Abdominal Oncology, West China Hospital, Sichuan University, Chengdu, China**Correspondence**

De-Yun Luo, Department of Abdominal Oncology, West China Hospital, West China Medical School, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan Province 610041, China.  
Email: luodeyun999@163.com

**Funding information**

None.

**Abstract**

Penile squamous cell carcinoma with pelvic lymph node metastases/recurrence has a poor prognosis. We reported a case with recurrent pSCC was administered cetuximab and anlotinib after failure of first-line treatment and achieved an effective response. Cetuximab combined with anlotinib may be a new choice for relapsed pSCC.

**KEYWORDS**

chemotherapy, metastases, penial squamous cell carcinoma, recurrence, targeted therapy

## 1 | INTRODUCTION

Penile squamous cell carcinoma (pSCC) is the most common type of penile cancer, and its incidence is generally low, but it remains a serious health problem in developing countries. Patients with advanced/recurrent pSCC in the inguinal region carries a dismal prognosis, especially these patients with pelvic lymph node (PLN) metastases, with a 5-year survival rate of 0%–17%.<sup>1,2</sup> Currently, cisplatin-based chemotherapy in combination with radiotherapy is regarded as a standard treatment among these patients with PLN metastases/recurrence.<sup>3,4</sup> However, there is no clear consensus on the optimal second-line treatment upon disease progression or deterioration of the patient's general condition after advanced first-line treatment. In this context, we reported a clinical case of cetuximab (an

anti-EGFR monoclonal antibody) combined with anlotinib (a multi-targeted small-molecule tyrosine kinase inhibitor) in the treatment of recurrent penile squamous cell carcinoma.

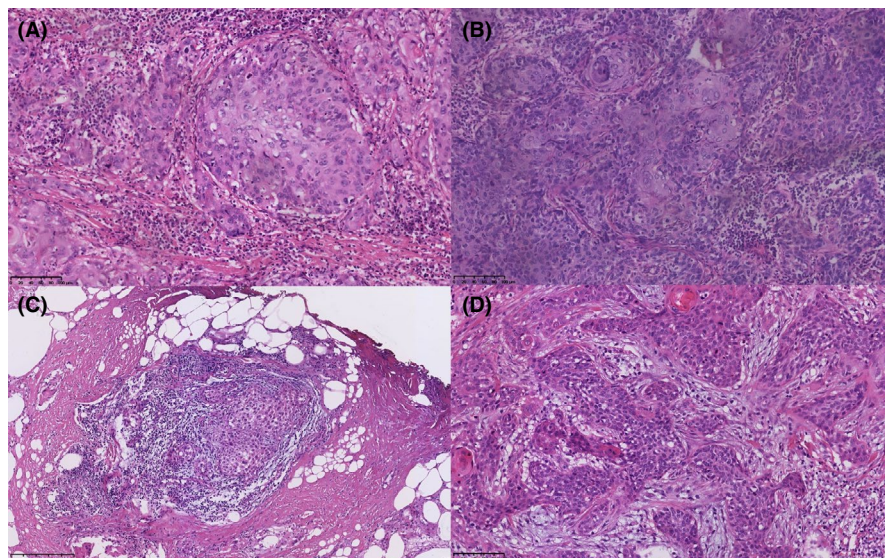
## 2 | CASE PRESENTATION

A 36-year-old man unintentionally found a palpable, visible lesion on the penis in September 2012, and was further diagnosed with pSCC invading into corpus cavernosum in January 2013, through biopsy (Figure 1A), and treated with partial penectomy. Later, in February 2013, just one month after the diagnosis of pSCC, the patient found the enlarged lymph nodes in the left groin (1 cm\*1 cm\*1 cm) without pressure pain. At that time, the bilateral inguinal

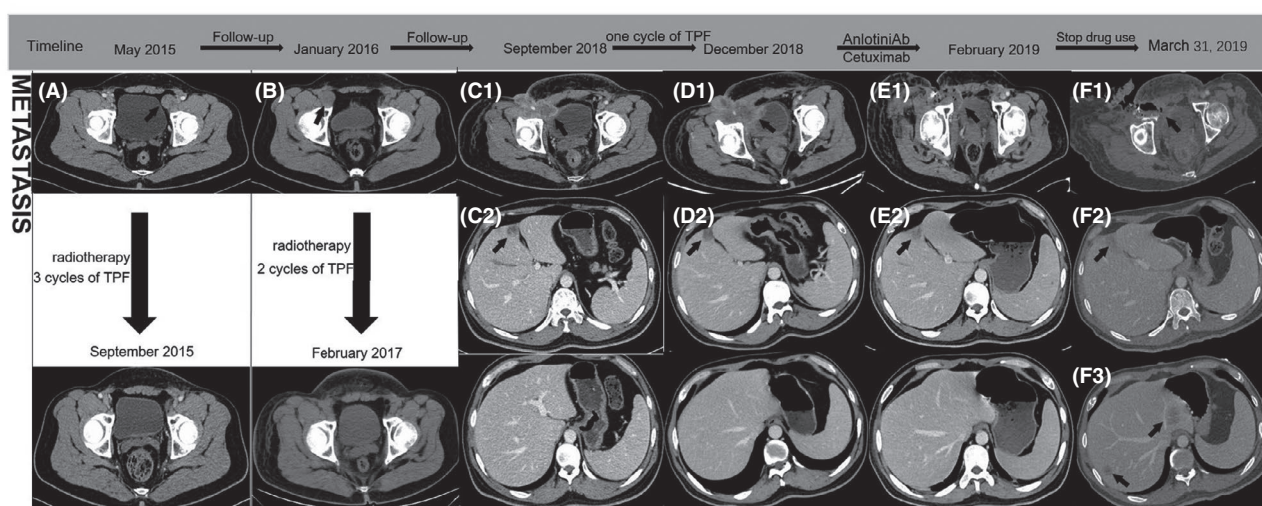
Shuang Dai and Yan-Yang Liu contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.



**FIGURE 1** (A) Nest of invasive squamous cell carcinoma; (B) Histology of inguinal lymph node metastasis; (C) Finding squamous cell carcinoma in the dermis and subcutaneous fibrous adipose tissue; (D) Histology of the root of the penis metastasis. (A to D): H&E, 20X, respectively



**FIGURE 2** Treatment timeline after postoperative recurrence. (A) Left inguinal nodal metastasis; (B) Right inguinal nodal metastasis; (C1) Multiple adjacent tissue and organ metastases; (D1) Tumor progressed rapidly; (C2, D2, E2, F2) Fatty deposition; (E1) The right inguinal soft tissue lesion shrank and the edema of right left reduced after two cycles of anlotinib and cetuximab. (F1,F3) Progression after stopping anlotinib and cetuximab

lymph node dissection was performed again. The postoperative pathological examination indicated that tumor invasion was positive in the left inguinal lymph node, revealing IIIA stage (pT2N1M0) (Figure 1B). In January 2014, eleven months after surgery, he again found a dorsal subcutaneous mass at the root of the penis with pressure pain and a hard node in the left inguinal area without redness, swelling, and bleeding. Subsequently, the biopsy revealed squamous cell carcinoma (moderate to low differentiation) with focal keratinization at the root of the penis (Figure 1C,D), which suggested tumor recurrence. He received excision of the penile root mass and left inguinal region mass on February 20, 2014, with complete resection of the lesion and no evaluable lesion postoperatively. Furthermore, after surgery, he continued to receive

postoperative chemotherapy including five cycles of TPF regimen chemotherapy with paclitaxel ( $120 \text{ mg/m}^2$ , day 1), cisplatin ( $25 \text{ mg/m}^2$ , days 1–3), and fluorouracil ( $500 \text{ mg/m}^2$ , days 1–5), repeated every 3 weeks. He was followed up regularly afterwards and remained in a stable condition for half of the year.

On May 16, 2015, contrast-enhanced computerized tomography (CT) of the abdomen revealed a metastatic lymph node (largest approximately  $2.6 \text{ cm} \times 2.5 \text{ cm}$ ) adjacent to the left external iliac vessels (Figure 2A). He received radiotherapy with 60 Gy/30 fractions and three cycles of TPF chemotherapy. At the end of treatment, on Sep 28, 2015, CT suggested complete remission (CR). However, after only three months of stability, the lesion recurred in January 2016. Contrast-enhanced CT of the abdomen

suggested additional enlarged lymph nodes in the right external iliac artery. Considering the patient's previous chemo-radiotherapy was effective, two cycles of TPF chemotherapy in combination with radiotherapy (64 Gy/32 fractions) was added, and the efficacy was assessed as CR.

Twenty months after remission, until September 20, 2018, CT scans indicated metastases in the right inguinal soft tissue. The tumor invaded the right wall of the bladder, the right external iliac artery, the right ureter, and the left lateral wall of the rectum (Figure 2C1). The patient was retreated with one cycle of TPF regimen. However, the cancer progressed rapidly leading to severe symptoms and much worse physical status (Figure 2D1). The patient developed severe right leg edema, which severely limited his daily work activities (Figure 3A). In this situation, the patient still requested aggressive treatment. The patient had already undergone chemo-radiotherapy in the past and that any further change in chemotherapy regimen would have low efficiency and would be difficult to tolerate due to the high toxic side effects. Based on limited clinical experience,<sup>5-7</sup> cetuximab monotherapy or cetuximab in combination with anlotinib may be effective. He was administered cetuximab (400 mg/m<sup>2</sup> on day 1, every week) and anlotinib (12 mg on day 1–14) in December 2018. After one cycle, the edema of right leg obviously reduced (Figure 3B). Follow-up CT scans (Figure 2E1) after two cycles discovered that metastasis center was significantly shrank. The patient continued to receive treatment. But his right femoral artery was suddenly ruptured and hemorrhaged, and underwent immediate interventional endovascular therapy. Anlotinib and cetuximab were discontinued in March 2019. Less than a month after the drug was stopped, metastatic lesions were found in the liver (Figure 2F3), and he died on May 25, 2019. Patients survived for more than 6 months from the start of treatment with anlotinib and cetuximab.

### 3 | DISCUSSION

The degree of lymph node involvement in the inguinal region is an important indicator for assessing the prognosis

of pSCC. The five-year cancer-specific survival rate can reach 85%–100% for patients without inguinal lymph node metastases; 79%–89% for patients with a single inguinal lymph node metastasis; 17%–60% for patients with bilateral or multiple inguinal lymph node metastases; 0%–17% for patients with pelvic lymph node metastases.<sup>8</sup> Chemotherapy in combination with radiotherapy is regarded as a standard treatment among these patients with tumor recurrence or metastases after lymph node dissection and partial resection in the inguinal region. Patients with tumor recurrence have significantly prolonged survival time after radiotherapy intervention.<sup>9-11</sup> In terms of chemotherapy, cisplatin-based regimens is the first-line option. In line with adjuvant indications, both TIP (paclitaxel, ifosfamide, and cisplatin) and TPF (using 5-FU instead of ifosfamide) are recommended as reasonable options.<sup>12-16</sup> TPF regimen can contribute to durable remission up to 52.6% after a median follow-up of 42 months, and was recommended for adjuvant chemotherapy of patients with N2-N3 stage in the 2020 EAU (European Association of Urology) guideline.<sup>17</sup> Herein, after complete surgical resection, we chose TPF as adjuvant chemotherapy and observed a sustained response. Because there are virtually no consistent data on systemic treatment options. Upon disease progression, TPF continued to be used as the first or subsequent line therapy of advanced/relapsed pSCC. Tumor growth was successfully controlled for a long time. Our patient had survived over 5 years.

Anlotinib, a novel multi-targeted small-molecule tyrosine kinase inhibitor (TKI), targets vascular endothelial growth factor receptor (VEGFR2/3), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), and plays an important role in inhibiting tumor angiogenesis and suppressing tumor growth.<sup>18</sup> Currently, anlotinib treatment has been reported in advanced non-small cell lung cancer, soft tissue sarcoma, renal cell carcinoma, and other solid tumors.<sup>18,19</sup> In addition, the EGFR-RAS-RAF signaling pathway plays an important role in tumor cell proliferation, invasion, and metastasis. Recently, it has been reported that cetuximab, an anti-EGFR monoclonal antibody, has antitumor activity in metastatic penile cancer and may enhance

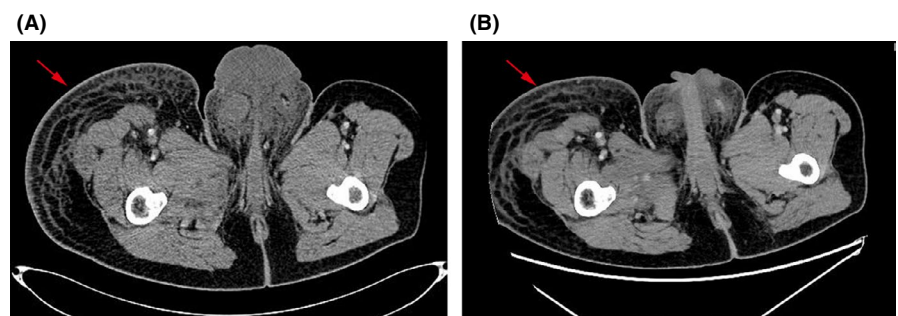


FIGURE 3 Edema of right leg. (A) is a pre-treatment image; (B) is a post-treatment image



the effect of cisplatin-based chemotherapy.<sup>6,20</sup> The median overall survival with EGFR-targeted therapy can reach 29.6 weeks in metastatic squamous carcinoma.<sup>20</sup> Our patient had difficulty tolerating subsequent chemoradiotherapy, and we used anti-angiogenesis agents and observed an effective response, which may provide a new strategy for metastatic/recurrent pSCC, especially for patients who have no more chemotherapy options available or refuse to continue chemotherapy.

Of note, prior to the use of anlotinib and cetuximab, the tumor has invaded and encircled the blood vessels. Furthermore, the edema subsided rapidly, and the center of the tumor shrank significantly after treatment. These two factors may be the cause of femoral artery rupture and bleeding. It is generally believed that anlotinib is an effective and safe drug for cancer patients that shows tolerable and manageable toxicity.<sup>21</sup> However, to date, one case has been reported in which the drug was discontinued due to gastrointestinal bleeding during the use of anlotinib.<sup>22</sup> So the possibility of bleeding caused by anti-angiogenic drugs cannot be ruled out either. On the other hand, some studies indicated that the adverse effects of anti-angiogenic drugs may be correlated with their efficacy.<sup>23</sup> All in all, this treatment is not recommended for patients with a bleeding tendency. Before using it, you must carefully assess bleeding risk including whether the tumor invades the vessel wall and the degree of invasion.

In conclusion, the available drugs to treat advanced/recurrent pSCC are very limited. Here, the efficacy of anlotinib and cetuximab was verified, and the results suggest a potential treatment option for advanced or refractory pSCC, which deserves further in-depth study and exploration.

## ACKNOWLEDGEMENT

None.

## CONFLICT OF INTEREST

The author reports no conflict of interest in this work.

## AUTHOR CONTRIBUTIONS

All authors take responsibility for the integrity and accuracy of the data, and approved the final version. S.D, Y.Y.L, T.L, and Y.Z involved in data acquisition; S.D and Y.Y.L wrote original draft; Pro. L involved in writing, review and editing.

## ETHICAL APPROVAL

We have obtained the informed consent of patient's family for the use of data and publication of this study, and approvals from concerned review boards/committees (human) are documented.

## CONSENT

Written patient consent was signed and collected in accordance with the journal's patient consent policy.

## DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

## ORCID

Shuang Dai  <https://orcid.org/0000-0002-4294-2712>

## REFERENCES

1. Djajadiningrat RS, van Werkhoven E, Horenblas S. Prophylactic pelvic lymph node dissection in patients with penile cancer. *J Urol*. 2015;193:1976-1980. doi:10.1016/j.juro.2014.12.019
2. Pandey D, Mahajan V, Kannan RR. Prognostic factors in node-positive carcinoma of the penis. *J Surg Oncol*. 2006;93:133-138. doi:10.1002/jso.20414
3. Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. *Lancet Oncol*. 2004;5:240-247. doi:10.1016/s1470-2045(04)01427-5
4. Pizzocaro G, Nicolai N, Milani A. Taxanes in combination with cisplatin and fluorouracil for advanced penile cancer: preliminary results. *Eur Urol*. 2009;55:546-551. doi:10.1016/j.eururo.2008.07.014
5. Granados-García M, Aguilar-Ponce JL, Maldonado-Magos F, et al. Advanced squamous cell carcinoma of the head and neck: the current role of cetuximab. *ORL J Otorhinolaryngol Relat Spec*. 2016;78:320-333. doi:10.1159/000455891
6. Wu J, Cheng K, Yuan L, et al. Recurrent penile squamous cell carcinoma successfully treated with cetuximab, chemotherapy, and radiotherapy. *Clin Genitourin Cancer*. 2016;14:e135-e137. doi:10.1016/j.clgc.2015.10.010
7. Yang D, Xu F, Lai X, et al. Combined treatment with anlotinib and chemotherapy for advanced esophageal squamous cell carcinoma improved patient survival: a case report. *Am J Transl Res*. 2020;12:6578-6583.
8. Leone A, Diorio GJ, Pettaway C, et al. Contemporary management of patients with penile cancer and lymph node metastasis. *Nat Rev Urol*. 2017;14:335-347. doi:10.1038/nrurol.2017.47
9. Robinson R, Marconi L, MacPepple E, et al. Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer: a systematic review by the european association of urology penile cancer guidelines panel. *Eur Urol*. 2018;74:76-83. doi:10.1016/j.eururo.2018.04.003
10. Tang DH, Djajadiningrat R, Diorio G, et al. Adjuvant pelvic radiation is associated with improved survival and decreased disease recurrence in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. *Urol Oncol*. 2017;35:605.e17-605.e23. doi:10.1016/j.urolonc.2017.06.001
11. Winters BR, Kearns JT, Holt SK, et al. Is there a benefit to adjuvant radiation in stage III penile cancer after lymph node dissection? Findings from the national cancer database. *Urol Oncol*. 2018;36:92.e11-92.e16. doi:10.1016/j.urolonc.2017.11.005
12. Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol*. 2010;28:3851-3857. doi:10.1200/jco.2010.29.5477

13. Di Lorenzo G, Buonerba C, Federico P, et al. Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis. *BJU Int*. 2012;110:E661-E666. doi:10.1111/j.1464-410X.2012.11453.x
14. Nicholson S, Hall E, Harland SJ, et al. Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). *Br J Cancer*. 2013;109:2554-2559. doi:10.1038/bjc.2013.620
15. Nicolai N, Sangalli LM, Necchi A, et al. A combination of cisplatin and 5-fluorouracil with a taxane in patients who underwent lymph node dissection for nodal metastases from squamous cell carcinoma of the penis: treatment outcome and survival analyses in neoadjuvant and adjuvant settings. *Clin Genitourin Cancer*. 2016;14:323-330. doi:10.1016/j.clgc.2015.07.009
16. Hakenberg OW, Comp erat E, Minhas S, Necchi A, Protzel C & Watkin N. Watkin EAU guidelines on penile cancer. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3. <https://uroweb.org/guideline/penile-cancer/>
17. Giannatempo P, Paganoni A, Sangalli L, et al. Survival analyses of adjuvant or neoadjuvant combination of a taxane plus cisplatin and 5-fluorouracil (T-PF) in patients with bulky nodal metastases from squamous cell carcinoma of the penis (PSCC): results of a single high-volume center. *J Clin Oncol*. 2014;32:377-377. doi:10.1200/jco.2014.32.4\_suppl.377
18. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. *Cancer Sci*. 2018;109:1207-1219. doi:10.1111/cas.13536
19. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol*. 2018;11:120. doi:10.1186/s13045-018-0664-7
20. Carthon BC, Ng CS, Pettaway CA, et al. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. *BJU Int*. 2014;113:871-877. doi:10.1111/bju.12450
21. Si X, Zhang L, Wang H, et al. Quality of life results from a randomized, double-blinded, placebo-controlled, multi-center phase III trial of anlotinib in patients with advanced non-small cell lung cancer. *Lung Cancer*. 2018;122:32-37. doi:10.1016/j.lungcan.2018.05.013
22. Shi Y, Chen J, Chen H, et al. Sarcomatoid carcinoma of the gallbladder: a case report. *J Int Med Res*. 2020;48:300060520935283-300060520935283. doi:10.1177/0300060520935283
23. Kollmannsberger C. Sunitinib side effects as surrogate biomarkers of efficacy. *Can Urol Assoc J*. 2016;10:S245-S247. doi:10.5489/cuaj.4315

**How to cite this article:** Dai S, Liu Y-Y, Liu T, Zhang Y, Luo D-Y. Case report of penile cancer recurrence treated with cetuximab combined with anlotinib. *Clin Case Rep*. 2022;10:e05443. doi:[10.1002/ccr3.5443](https://doi.org/10.1002/ccr3.5443)