

Tislelizumab Combination With Chemotherapy Successfully Converted Unresectable Advanced Penile Cancer Into Complete Surgical Excision: a Case Report and Literature Review

Xiang-Yu Long

Sichuan University

Shuang Zhang

Sichuan University

Lian-sha Tang

Sichuan University

Xiang Li

Sichuan University

Jiyan Liu (✉ ljy19722021@163.com)

Sichuan University

Case report

Keywords: Case report, Conversion therapy, immunotherapy, PD-1 blockade, Penile squamous cell carcinoma

Posted Date: October 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-889417/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Locally advanced Penile squamous cell carcinoma (PSCC) with unresectable inguinal lymph nodes has a poor prognosis, and benefits from surgical treatment alone. Effective conversion therapy regimens are urgently needed.

Case Presentation: We report a locally advanced PSCC patient with bulky, fixed inguinal lymph node metastasis complicated within genital skin ulcers, who completed inguinal lymph node dissection and achieved pathologically complete response via conversion therapy by immunotherapy plus chemotherapy.

Conclusion: For unresectable locally advanced PSCC, neoadjuvant immunotherapy combined with chemotherapy is a potential treatment approach. Biomarkers of immune efficacy need to be explored. At the same time, clinical trials are needed to test the notions.

Background

Penile carcinoma is a rare tumor in the male genitourinary system and the main histopathological type is squamous cell carcinoma. For locally advanced penile squamous cell carcinoma (PSCC) patients with bulky, fixed, bilateral inguinal lymph node metastases and extra-nodal extension, it is difficult to benefit from surgery alone and the prognosis is very poor[1–3]. The use of multiple strategies reducing pathological staging, even convert to operability can improve prognosis and increase survival rate. Neoadjuvant chemotherapy is the usual treatment for this kind of patients[4], but multiple small size cohort studies have demonstrated that nearly half of patients do not benefit from neoadjuvant chemotherapy alone, which made it urgent to find new and effective treatments.

In recent years, immune checkpoint inhibitors (ICIs) have become a hot topic in oncology treat and even became the standard of care for tumors such as melanoma and lung cancer. By inhibiting the Programmed death-1 receptor (PD-1) or PD-1 ligand (PD-L1), ICIs block the inhibition of CD8⁺ effector T cells and reverse the suppressive tumor microenvironment, which may improve the prognosis for patients resistant to other treatment modalities (e.g. chemotherapy/radiotherapy). For some unresectable tumors, neoadjuvant immunotherapy offers a potential solution by mediating tumor regression to make them operability or even curable. Currently, evidence has accumulated in lung and breast cancers demonstrated that neoadjuvant immunotherapy increases the rate of pathological response and improves overall survival. However, immunotherapy combined with chemotherapy for patients with unresectable locally advanced PSCC has rarely been reported.

Case Presentation

Here, we present a 58-year-old male patient who was admitted to the local hospital for sub-preputial mass and fixed lymphadenopathy in the left inguinal region. Distal penectomy and biopsy of the left inguinal lymph node were done subsequently. The postoperative pathological biopsy showed high-/medium-

differentiated squamous carcinoma of the penis invading the penile corpus cavernosum, with no involvement of the uroepithelium. Pathological biopsy of the left inguinal lymph node present loss of normal lymph node structure and multifocal cancerous infiltration of fibrous tissue. Also, the final pathological staging was IV (pT3N3M0).

21 days after surgery, the patient was admitted to the West China Hospital of Sichuan University, where an enhanced CT of the pelvis showed multiple enlarged lymph nodes in the left inguinal region, and the largest lymph node section was 4.0 x 2.5 cm (Fig. 2A). After multidisciplinary collaboration consultation, it was difficult to perform a complete inguinal lymph node dissection. The patient was enrolled in a clinical trial on EGFR monoclonal antibodies. However, a larger inguinal lesion was developed after 6 cycles of EGFR monoclonal antibodies. And the lesion was evaluated as progressive disease by CT scanning (Fig. 2B). Next, the patient received paclitaxel 240mgD1 plus cisplatin 40mgD1-3 chemotherapy after withdrawing from the clinical trial. After the 1st cycle of chemotherapy, no change of tumor mass was found (Fig. 2C).

Tislelizumab, a humanized IgG4 anti-PD-1 monoclonal antibody[5], was added with the chemotherapy regimen. After 3 cycles of treatment with tislelizumab plus chemotherapy, the patient's inguinal ulcer healed. Moreover, pelvic enhancement CT (Fig. 2D) indicated that the inguinal mass was significantly reduced, and the effect of conversion therapy was obvious. Based on the effects of the combination therapy, bilateral inguinal lymph node dissection was performed. Postoperative pathological examination indicated no tumor occurring in 21 inguinal lymph nodes on the left side and 18 inguinal nodes on the right side. Some lymph nodes present necrotic and multinucleated giant cell reaction, which demonstrated complete response to the treatment strategy. After surgery, the patient continues taking tislelizumab 200mg alone for three cycles and requested to discontinue immunotherapy due to abhorrence of side effects diarrhea/abdominal pain. The patient had no evidence (Fig. 2E) of tumor recurrence at regular postoperative follow-up for 12 months.

Discussion And Conclusion

Chemotherapy is commonly used as a translational therapy strategy for patients with locally advanced unresectable PSCC. However, despite the meaningful response to systemic chemotherapy, long-term survival rates were disappointing, with 2-year progression-free survival (PFS) and disease-specific survival (DSS) probabilities of 12% and 28%, respectively. Moreover, patient resistance to chemotherapy have a worse prognosis. Therefore, there is a urgent need to find new translational therapeutic strategies with higher efficacy and low toxicity profile. Referring to the experience with advanced non-small cell lung cancer and melanoma, PD-(L)1 blockade plus chemotherapy may be a promising option.

Theoretically, in the primary tumor, PD-(L)1 blockade relieves the suppressive immune microenvironment, restores the activity of exhausted cytotoxic T cells, and mediates tumor regression. Simultaneously, chemotherapy causes tumor cell necrosis and releases more tumor antigens. In the presence of ICIs, dendritic cells can present antigens to T cells more efficiently, initiating tumor-specific T cell proliferation

and activation. Activated T cells leave the tumor-draining lymph nodes into the bloodstream and migrate to tumor sites and distant micro-metastases, shrinking the primary lesion and reducing postoperative distant recurrence[6]. In addition, the preoperatively induced systemic immune response generates long-term immune memory and prevents tumor recurrence[7]. These suggest that immunotherapy combined with chemotherapy is a promising translational treatment strategy.

Numerous factors are involved in the effectiveness of immunotherapy. To explore the treatment options, we performed immunohistochemistry and next generation sequencing (NGS) analysis on our patient. PD-L1 expression in tumor tissues is validated companion diagnostic test for predicting efficacy of treatment with ICIs. Several studies have shown that 40–60% of PSCC patients express PD-L1 (PD-L1 positivity defined by > 5% tumor expression), and high PD-L1 expression positive associated with worse staging and prognosis [8]. It is also associated with lower numbers of Tumor-infiltrating lymphocytes (TILs) in tumor tissue. The PD-L1 expression of our patient was 40%(Tumor Proportion Score, TPS), and these findings provide a rationale for the use of ICIs as a treatment option for patients with PSCC. Tumor mutation burden (TMB) is also a promising immunotherapeutic marker in many cancer types. However, the TMB cut-off values are not the same in different cancers. In our case, the patient had a TMB of 5.0 mutations per mega base (Muts/Mb), slightly higher than the median value (4.5 Muts/Mb) in PSCC, and a recent report suggests that mutations in select genes may be a better predictor than TMB. Microsatellite instability high (MSI-H) is another valid marker of sensitivity to ICIs. Our case was microsatellite stable (MSS), the literature reports a low incidence of MSI-H in PSCC[9].

More interesting, patient's laboratory testing got human papillomavirus (HPV) 16 DNA. Patients with HPV⁺ PSCC have a better prognosis than those with HPV⁻. The possible mechanism is that the virus increases the production of neo-antigens, while increasing the number of infiltrating CD8⁺T cells in the tumor microenvironment[10]. Does this mean that the HPV virus could be a meaningful biomarker for immunotherapy? Considering the impact of HPV on the tumor, several clinical trials of combinatorial immunotherapy augmented with HPV-targeted vaccines have been conducted in HPV-associated malignancies. Current results regarding the association between the status of HPV and the expression of PD-L1 are conflicting and need to be confirmed by more studies. However, the differences in TMB between HPV⁻ and HPV⁺ PSCC patients are minimal[8].

In addition, patient in current case had high expression of epidermal growth factor receptor (EGFR) by immunohistochemistry and was treated experimentally with EGFR monoclonal antibody. Several studies have shown that high EGFR expression detected by IHC is frequently seen in PSCC [11]. High expression of EGFR may be associated with poor prognosis, implying better effects by targeting EGFR. Retrospective studies[12] have shown that the use of Cetuximab or dacomitinib (a pan-HER tyrosine kinase inhibitor) provide benefit to only a small number of patients. Our patient had disease progression after attempting EGFR monoclonal antibodies. NGS of this case showed a mutation in PIK3CA p.E453K. In colon cancer, PIK3CA mutations are significantly associated with clinical resistance to EGFR monoclonal antibodies[13].

In conclusion, current case present with HPV⁺ locally advanced inoperable PSCC that responded well to ICI plus chemotherapy, converted to operable, and underwent inguinal lymph node dissection, which was pathologically confirmed to achieve a complete response. Postoperative disease-free survival (DFS) exceeded 12 months and continued the trend of prolongation. For this group, immunotherapy combined with chemotherapy is a promising translational treatment option. However, more clinical trials are needed to validate this notion and effective biomarkers need to be further explored.

Abbreviations

Not applicable.

Declarations

Funding

Supported by the Key Research and Development Program of Guang'an, China (2019ZYZF0121).

Acknowledgements

Not applicable.

Ethics approval and consent to participate

Ethical approval was given by the medical ethics committee of the West China Hospital of Sichuan University.

Consent for publication

Written informed consent was obtained from the patient's parent for publication of this Case report and any accompanying images.

Competing interests

The authors have stated that they have no conflict of interest.

Authors Contributions

JY.L and X.L contributed to design and supervise the current investigation. XY.L, S.Z and LS.T collected clinical data, and XY.L was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available from the corresponding author on request.

References

1. Graafland NM, van Boven HH, van Werkhoven E, Moonen LM, Horenblas S: **Prognostic significance of extranodal extension in patients with pathological node positive penile carcinoma.** *J Urol* 2010, **184**:1347-1353.
2. Pandey D, Mahajan V, Kannan RR: **Prognostic factors in node-positive carcinoma of the penis.** *J Surg Oncol* 2006, **93**:133-138.
3. Wang JY, Zhu Y, Tang SX, Zhang HL, Qin XJ, Zhang SL, Dai B, Ye DW: **Prognostic significance of the degree of extranodal extension in patients with penile carcinoma.** *Asian J Androl* 2014, **16**:437-441.
4. Bandini M, Pederzoli F, Necchi A: **Neoadjuvant chemotherapy for lymph node-positive penile cancer: current evidence and knowledge.** *Curr Opin Urol* 2020, **30**:218-222.
5. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, Hu H, Huang J, Zhu S, Jin J, et al: **Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma.** *Cancer Sci* 2021, **112**:305-313.
6. Topalian SL, Taube JM, Pardoll DM: **Neoadjuvant checkpoint blockade for cancer immunotherapy.** *Science* 2020, **367**.
7. Keung EZ, Ukponmwan EU, Cogdill AP, Wargo JA: **The Rationale and Emerging Use of Neoadjuvant Immune Checkpoint Blockade for Solid Malignancies.** *Ann Surg Oncol* 2018, **25**:1814-1827.
8. Ottenhof SR, Djajadiningrat RS, Thygesen HH, Jakobs PJ, Jóźwiak K, Heeren AM, de Jong J, Sanders J, Horenblas S, Jordanova ES: **The Prognostic Value of Immune Factors in the Tumor Microenvironment of Penile Squamous Cell Carcinoma.** *Front Immunol* 2018, **9**:1253.
9. Stoehr R, Wendler O, Giedl J, Gaisa NT, Richter G, Campean V, Burger M, Wullich B, Bertz S, Hartmann A: **No Evidence of Microsatellite Instability and Loss of Mismatch-Repair-Protein Expression in Squamous Cell Carcinoma of the Penis.** *Pathobiology* 2019, **86**:145-151.
10. Ahmed ME, Falasiri S, Hajiran A, Chahoud J, Spiess PE: **The Immune Microenvironment in Penile Cancer and Rationale for Immunotherapy.** *Journal of clinical medicine* 2020, **9**.
11. Gu W, Zhu Y, Ye D: **Beyond chemotherapy for advanced disease-the role of EGFR and PD-1 inhibitors.** *Transl Androl Urol* 2017, **6**:848-854.
12. Necchi A, Lo Vullo S, Perrone F, Raggi D, Giannatempo P, Calareso G, Nicolai N, Piva L, Biondi D, Catanzaro M, et al: **First-line therapy with dacomitinib, an orally available pan-HER tyrosine kinase inhibitor, for locally advanced or metastatic penile squamous cell carcinoma: results of an open-label, single-arm, single-centre, phase 2 study.** *BJU Int* 2018, **121**:348-356.
13. Sartore-Bianchi A, Martini M, Molinari F, Veronese S, Nichelatti M, Artale S, Di Nicolantonio F, Saletti P, De Dosso S, Mazzucchelli L, et al: **PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies.** *Cancer Res* 2009, **69**:1851-1857.

Figures

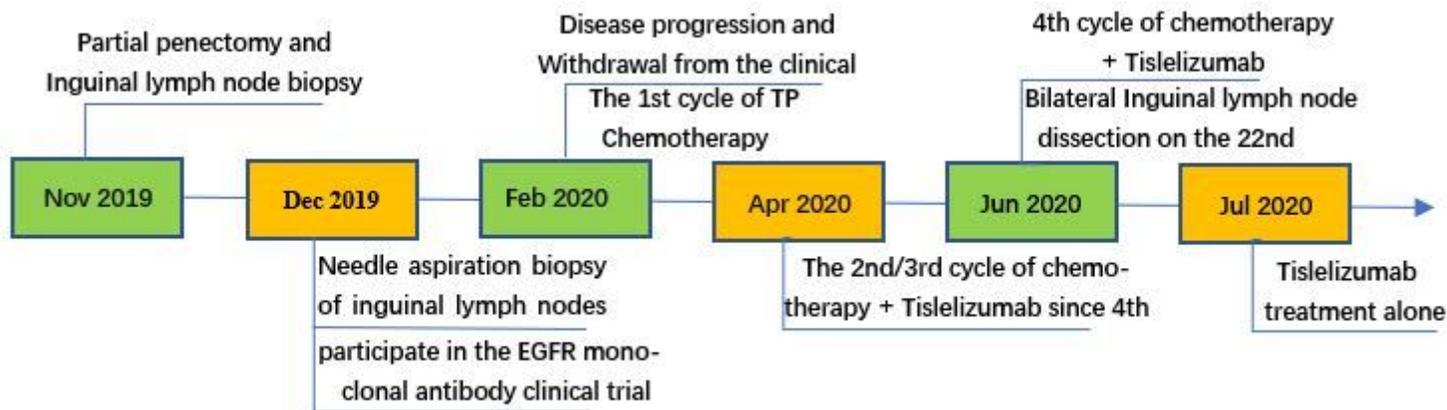


Figure 1

The time pipeline of treatment procedure

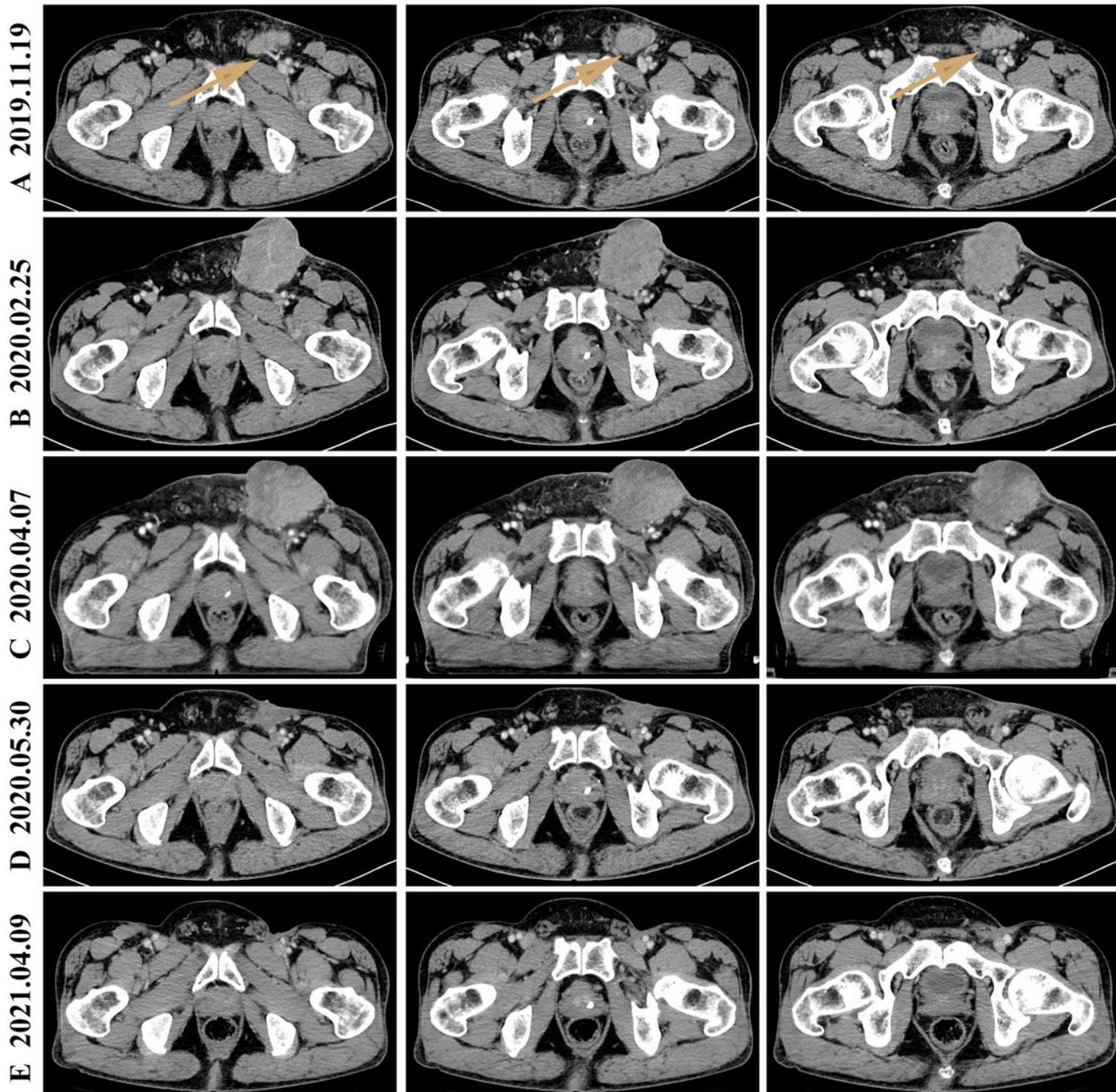


Figure 2

CT images of different treatment periods. A) November 19, 2019: CT images before EGFR monoclonal antibody therapy. B) February 25, 2020: CT images before chemotherapy after EGFR monoclonal antibody treatment. C) April 7, 2020: CT imaging evaluation of tumor lesions after the first chemotherapy alone. D) May 30, 2020: CT imaging of preoperative evaluation after third immunotherapy combined with chemotherapy treatment. E) April 09, 2021: CT images of follow-up at 10 months after bilateral inguinal lymph node dissection