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Conversion therapy for advanced penile cancer with tislelizumab combined with chemotherapy: A case report and review of literature

Xiang-Yu Long, Shuang Zhang, Lian-Sha Tang, Xiang Li, Ji-Yan Liu

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Abstract

BACKGROUND

Locally advanced penile squamous cell carcinoma with unresectable inguinal lymph node metastasis has a poor prognosis, and surgical treatment alone offers limited benefits. Effective conversion therapy regimens are urgently needed.

CASE SUMMARY

We describe a locally advanced penile squamous cell carcinoma patient with bulky, fixed inguinal lymph node metastasis complicated with genital skin ulcers who underwent inguinal lymph node dissection and achieved a pathological complete response with conversion therapy comprising immunotherapy plus chemotherapy.

CONCLUSION

For unresectable locally advanced penile squamous cell carcinoma, neoadjuvant immunotherapy combined with chemotherapy is a potential treatment approach. Biomarkers of immunotherapy efficacy need to be explored, and clinical trials are needed to test these strategies.

Key Words: Conversion therapy; Immunotherapy; PD-1 blockade; HPV; Penile squamous

cell carcinoma; Case report

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Core Tip: Locally advanced penile squamous cell carcinoma with bilateral inguinal lymph node metastases and extra-nodal extension does not respond well to surgical treatment alone, and the prognosis is very poor. In this study, the patient successfully completed inguinal lymph node dissection after conversion therapy of immunotherapy plus chemotherapy. This is the first patient with human papillomavirus 16+ unresectable locally advanced penile cancer treated with immunotherapy plus chemotherapy who eventually achieved a pathologically complete response.

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INTRODUCTION

Penile carcinoma is a rare tumor in the male genitourinary system, and the main histopathological type is squamous cell carcinoma. The etiology of penile carcinoma is not entirely clear; however, there is a strong association with human papillomavirus (HPV)[1,2] and a chronic inflammatory state of the foreskin and glans[3,4]. According to previous studies, partial or total excision of the penis is the primary treatment for localized tumors[5]. Unfortunately, patients with penile squamous cell carcinoma (PSCC) are usually diagnosed in the advanced stage. For locally advanced PSCC patients with bulky, fixed, bilateral inguinal lymph node metastases and extra-nodal extension, surgery alone offers little benefit, and the prognosis is very poor[6-8]. The use of multiple strategies to reduce the pathological stage and even convert the case to operable can improve prognosis and increase the survival rate. Neoadjuvant chemotherapy is the usual treatment for this patient population[9], but multiple small cohort studies have demonstrated that nearly half of the patients do not benefit from neoadjuvant chemotherapy alone, highlighting the urgent need to find new and effective treatments[10,11].

In recent years, immune checkpoint inhibitors (ICIs) have become a hot topic in oncology treatment and the standard of care for cancers such as melanoma and lung cancer[12-16]. By inhibiting programmed cell death protein 1 (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 of patients with disease resistant to other treatment modalities (*e.g.*, chemotherapy/radiotherapy)[17]. For some unresectable tumors, neoadjuvant immunotherapy offers a potential solution by mediating tumor regression to the point of becoming operable or even cured[18,19]. Accumulating evidence in lung and breast cancer has demonstrated that neoadjuvant immunotherapy increases the rate of pathological response and improves overall survival[20,21]. However, immunotherapy combined with chemotherapy for patients with unresectable locally advanced PSCC has rarely been reported.

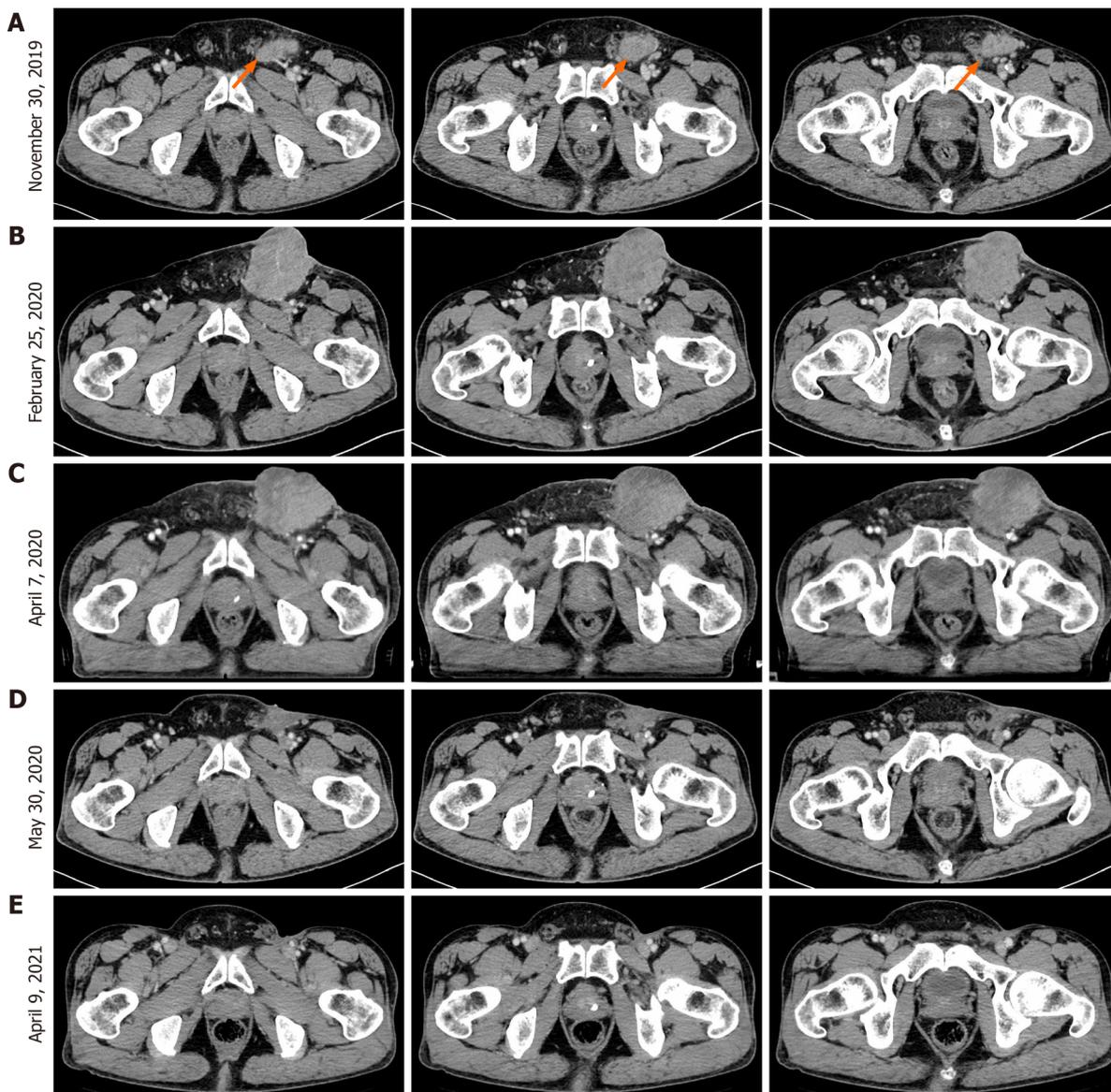
CASE PRESENTATION

Chief complaints

A 60-year-old male patient, who was found to have a subpreputial mass for 1 year, was admitted to the West China Hospital of Sichuan University for 3 mo after the diagnosis of unresectable penile cancer.

History of present illness

In February 2019, the patient went to Hubei Provincial People's Hospital and complained of a subpreputial mass. The patient underwent partial penile resection plus partial biopsy of the left inguinal lymph node on November 12, 2019. The patient was admitted to the West China Hospital of Sichuan University 21 d after surgery, where an enhanced computed tomography (CT) of the pelvis showed multiple enlarged lymph nodes in the left inguinal region; the largest lymph node was 4.0 cm × 2.5 cm (Figure 1A). Inguinal lymph node biopsy was performed on December 11, 2019, and cancer cells were detected. The patient had a repeat CT scan on February 25, 2020, which indicated that the lesion had grown.



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Figure 1 Computed tomography images at different treatment periods. A: November 30, 2019: Computed tomography (CT) images before epidermal growth factor receptor monoclonal antibody therapy; B: February 25, 2020: CT images before chemotherapy but after epidermal growth factor receptor monoclonal antibody treatment; C: April 7, 2020: CT image of tumor lesions after the first round of chemotherapy alone; D: May 30, 2020: CT image for preoperative evaluation after the third round of immunotherapy combined with chemotherapy; E: April 09, 2021: CT images at the 10-mo follow-up after bilateral inguinal lymph node dissection.

History of past illness

The patient had a history of hypertension for 10 years, and the highest blood pressure was 180/100 mmHg. The blood pressure was well controlled by oral amlodipine daily. Also, the patient had multiple sexual partners.

Personal and family history

Family and personal history were unremarkable. He had no significant medical history or drug allergy.

Physical examination

A poor general condition, Eastern Cooperative Oncology Group score of 2 points. A subpreputial mass located in the left groin was palpable, with a size of 10 cm × 6 cm. The mass was hard, fixed and inactive. No other apparently positive signs were found.

Laboratory examinations

The patient was admitted to our hospital, and the relevant blood tests were normal.

Imaging examinations

The patient was admitted to the West China Hospital of Sichuan University 21 d after surgery, where an enhanced CT of the pelvis showed multiple enlarged lymph nodes in the left inguinal region; the largest lymph node was 4.0 cm × 2.5 cm (Figure 1A). After consultation with a multidisciplinary team, the decision was reached that it would be difficult to perform a complete inguinal lymph node dissection. The patient was enrolled in a clinical trial of CDP1, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. However, a larger inguinal lesion developed after 6 cycles of CDP1. The lesion was evaluated as progressive disease by CT scan (Figure 1B). Next, the patient received chemotherapy (paclitaxel 240 mg D1 plus cisplatin 40 mg D1-3) after withdrawal from the clinical trial. After the 1st cycle of chemotherapy, no change in the tumor mass was found (Figure 1C).

FINAL DIAGNOSIS

Locally advanced PSCC with unresectable inguinal lymph node metastasis (T3N3M0, IV).

TREATMENT

Distal penectomy and biopsy of the left inguinal lymph node were subsequently performed. 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 showed loss of normal lymph node structure and multifocal cancerous infiltration of fibrous tissue. The final pathological stage was IV (pT3N3M0), and the timeline of treatment and procedures is shown in Figure 2.

Tislelizumab, a humanized IgG4 anti-PD-1 monoclonal antibody[22], was added to the chemotherapy regimen. After three cycles of treatment with tislelizumab plus chemotherapy, the inguinal ulcer in the patient healed. Moreover, enhanced pelvic CT (Figure 1D) indicated that the inguinal mass was significantly smaller, and the effect of conversion therapy was obvious. Based on the effects of the combination therapy, bilateral inguinal lymph node dissection was performed.

OUTCOME AND FOLLOW-UP

Postoperative pathological examination indicated no tumor in 21 inguinal lymph nodes on the left side or in 18 inguinal nodes on the right side. Some lymph nodes presented as necrotic with multinucleated giant cell reactions, indicating a complete response to the treatment strategy. After surgery, the patient continued taking 200 mg tislelizumab alone for three cycles and requested to discontinue immunotherapy due to irritating side effects (diarrhea/abdominal pain). The patient had no evidence (Figure 1E) of tumor recurrence at regular postoperative follow-ups over 12 mo.

DISCUSSION

Chemotherapy is commonly used as a translational therapy for patients with locally advanced unresectable PSCC. However, despite a meaningful response to systemic chemotherapy, long-term survival rates are disappointing, with 2-year progression-free survival and disease-specific survival rates of 12% and 28%, respectively[10,23,24]. Moreover, patients with disease that is resistant to chemotherapy have a worse prognosis. Therefore, there is an urgent need to find new translational therapeutic strategies with higher efficacy and low toxicity profiles. Based on the experience with advanced non-small cell lung cancer and melanoma, PD-(L)1 blockade plus chemotherapy may be a promising option[12-16].

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[25]. Simultaneously, chemotherapy causes tumor cell necrosis and the release of more tumor antigens. In the presence of ICIs, dendritic cells can present antigens to T cells more efficiently, thereby initiating tumor-specific T cell proliferation and activation. Activated T cells enter the bloodstream from tumor-draining lymph nodes and migrate to tumor sites and distant micrometastases, shrinking the primary lesion and reducing postoperative distant recurrence[26]. In addition, the preoperatively induced systemic immune response generates long-term immune memory and prevents tumor recurrence[27]. These results suggest that immunotherapy combined with chemotherapy is a promising translational treatment strategy.

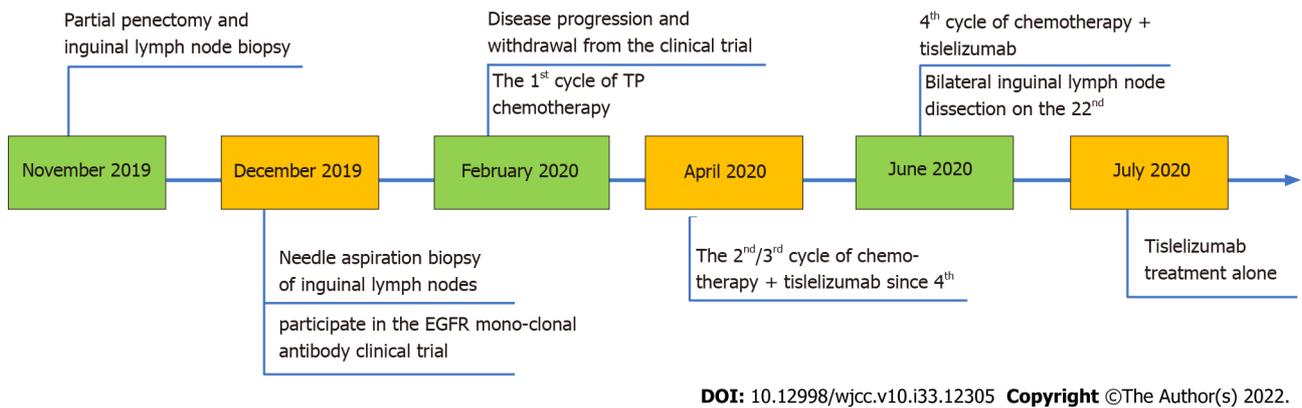


Figure 2 The timeline of treatment and procedures. EGFR: Epidermal growth factor receptor.

Numerous factors are involved in the effectiveness of immunotherapy. To explore treatment options, we performed immunohistochemistry and next-generation sequencing analysis of samples from our patient. PD-L1 expression in tumor tissues is a validated companion diagnostic test for predicting the 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 cell expression), and high PD-L1 expression is positively associated with worse stage and prognosis[28] and with fewer tumor-infiltrating lymphocytes in tumor tissue[29]. The PD-L1 expression score for our patient was 40% (tumor proportion score), which provided the rationale for the therapeutic use of ICIs for patients with PSCC.

Tumor mutation burden (TMB) is the number of nonsynonymous somatic mutations in coding regions of tumor cells per megabase of DNA. PSCC is a heterogeneous disease, harboring approximately 5.45 genomic alterations per tumor[30]. TMB has been suggested as a promising immunotherapeutic marker in many cancer types[31]. However, the TMB cutoff values are not the same in different cancers[32]. In our case, the patient had a TMB of 5.0 mutations per megabase, slightly higher than the median value (4.5 mutations per megabase) in PSCC, and a recent report suggested that mutations in select genes may be a better predictor than TMB[33]. High microsatellite instability is another valid marker of sensitivity to ICIs. In our case, the tumor was microsatellite stable; the literature reports a low incidence of high microsatellite instability in PSCC[34].

More interestingly, laboratory testing for our patient revealed the presence of HPV16 DNA. Patients with HPV⁺ PSCC have a better prognosis than those with HPV⁻ disease[35]. The possible mechanism is that the virus increases the production of neoantigens while increasing the number of infiltrating CD8⁺ T cells in the tumor microenvironment[36]. Does this mean that HPV could be a meaningful biomarker for immunotherapy? Considering the impact of HPV on cancer, several clinical trials of combination immunotherapy 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 patients with HPV⁻ and HPV⁺ PSCC are minimal[28].

In addition, our patient had high expression of EGFR by immunohistochemistry and was treated experimentally with CDP1. Several studies have shown that high EGFR expression detected by immunohistochemistry is frequent in PSCC[37]. High expression of EGFR may be associated with poor prognosis, implying the potential for better effects upon targeting EGFR[38]. Retrospective studies[39] have shown that the use of cetuximab or dacomitinib (a pan-HER tyrosine kinase inhibitor) provides benefit to only a small number of patients. Our patient experienced disease progression after attempting CDP1 therapy. Next-generation sequencing of this case showed the p.E453K mutation in PIK3CA. In colon cancer, PIK3CA mutations are significantly associated with clinical resistance to anti-EGFR monoclonal antibodies[40].

CONCLUSION

In conclusion, this case report described HPV⁺ locally advanced inoperable PSCC that responded well to ICI plus chemotherapy. The tumor was converted to operable, and the patient underwent inguinal lymph node dissection. The patient achieved a pathological complete response. Postoperative disease-free survival exceeded 12 mo, with the expectation of continued prolongation of survival. For this group, immunotherapy combined with chemotherapy is a promising translational treatment option. However, more clinical trials are needed to validate this hypothesis, and effective biomarkers need to be further explored.

FOOTNOTES

Author contributions: Long XY and Liu JY conceived and designed the project; Long XY, Zhang S and Li X were responsible for the sample collection; Long X and Liu JY wrote the manuscript and are responsible for all data present in current research.

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