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## **Conversion Therapy for Advanced Penile Cancer with Tislelizumab Combined with Chemotherapy: A Case Report and Literature Review**

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### **Abstract**

#### **BACKGROUND**

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

#### **CASE SUMMARY**

We describe a locally advanced PSCC 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 PSCC, 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.

### **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

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not entirely clear; however, there is a strong association with human papillomavirus (HPV) <sup>1, 2</sup> and a chronic inflammatory state of the foreskin and glans <sup>3, 4</sup>. According to previous studies, partial or total excision of the penis is the primary treatment for localized tumors<sup>5</sup>. 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 extranodal extension, surgery alone offers little benefit, and the prognosis is very poor<sup>6-8</sup>. 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<sup>9</sup>, but multiple small cohort studies have demonstrated that nearly half of patients do not benefit from neoadjuvant chemotherapy alone, highlighting the urgent need to find new and effective treatments <sup>10, 11</sup>.

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 <sup>12-16</sup>. By inhibiting programmed cell death protein 1 (PD-1) or PD-1 Ligand (PD-L1), ICIs block the inhibition of CD8<sup>+</sup> 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) <sup>17</sup>. For some unresectable tumors, neoadjuvant immunotherapy offers a potential solution by mediating tumor regression to the point of becoming operable or even cured<sup>18, 19</sup>. Accumulating evidence in lung and breast cancer has demonstrated that neoadjuvant immunotherapy increases the rate of pathological response and improves overall survival<sup>20, 21</sup>. However, immunotherapy combined with chemotherapy for patients with unresectable locally advanced PSCC has rarely been reported.

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## **CASE PRESENTATION**

### ***Chief complaints***

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

### *History of present illness*

On February 2019, the patient went to Hubei Provincial People's Hospital 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 days 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 x 2.5 cm (Figure 2A). 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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### *History of past illness*

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

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### *Personal and family history*

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

### *Physical examination*

A poor general condition, ECOG (Eastern Cooperative Oncology Group) score of 2 points. A subpreputial mass located in the left groin palpable was detected, with the size of 10 cm x 6 cm and characterize of 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 shown normal.

### *Imaging examinations*

The patient was admitted to the West China Hospital of Sichuan University 21 days 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 x 2.5 cm (Figure 2A). 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 2B). 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 tumor mass was found (Figure 2C).

### **FINAL DIAGNOSIS**

Locally advanced penile squamous cell carcinoma (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 1.

Tislelizumab, a humanized IgG4 anti-PD-1 monoclonal antibody<sup>22</sup>, was added to the chemotherapy regimen. After 3 cycles of treatment with tislelizumab plus chemotherapy, the inguinal ulcer in the patient healed. Moreover, enhanced pelvic CT (Figure 2D) 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 necrotic and 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 2E) 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 (PFS) and disease-specific survival (DSS) rates of 12% and 28%, respectively<sup>10, 23, 24</sup>. 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<sup>12-16</sup>.

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<sup>25</sup>. 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<sup>26</sup>. In addition, the preoperatively induced systemic immune response generates long-term immune memory and prevents tumor recurrence<sup>27</sup>. These results suggest that immunotherapy combined with chemotherapy is a promising translational treatment strategy.

Numerous factors are involved in the effectiveness of immunotherapy. To explore treatment options, we performed immunohistochemistry and next-generation sequencing (NGS) 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<sup>28</sup> and with fewer tumor-infiltrating lymphocytes (TILs) in tumor tissue<sup>29</sup>. The PD-L1 expression score for our patient was 40% (tumor proportion score, TPS), which provides 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 tumor cells per megabase (MB) of DNA in tumor cells. <sup>6</sup> PSCC is a heterogeneous disease, harboring approximately 5.45 genomic alterations per tumor<sup>30</sup>. TMB has been suggested as a promising immunotherapeutic marker in many cancer types<sup>31</sup>. However, the TMB cutoff values are not the same in different cancers<sup>32</sup>. In our case, the patient had a TMB of 5.0 mutations per megabase (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<sup>33</sup>. Microsatellite instability high (MSI-H) is another valid marker of sensitivity to ICIs. In our case, the tumor was microsatellite stable (MSS); the literature reports a low incidence of MSI-H in PSCC<sup>34</sup>.

More interestingly, laboratory testing for our patient revealed the presence of human papillomavirus (HPV) 16 DNA. Patients with HPV<sup>+</sup> PSCC have a better prognosis than those with HPV<sup>-</sup> disease<sup>35</sup>. The possible mechanism is that the virus increases the production of neoantigens while increasing the number of infiltrating CD8<sup>+</sup> T cells in the tumor microenvironment<sup>36</sup>. 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<sup>-</sup> and HPV<sup>+</sup> PSCC are minimal<sup>28</sup>.

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 IHC is frequent in PSCC<sup>37</sup>. High expression of EGFR may be associated with poor prognosis, implying the potential for better effects upon targeting EGFR<sup>38</sup>. Retrospective studies<sup>39</sup> 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. NGS 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<sup>40</sup>.

## **CONCLUSION**

In conclusion, this case report describes HPV<sup>+</sup> 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 and was confirmed to achieve a



pathological complete response. Postoperative disease-free survival (DFS) 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.

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