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CASE REPORT

Case Report and Literature Review on Skin Toxicity Induced by PD-1 Inhibitor in a Penile Cancer with Massive Ulceration of Chemoradiotherapy-Resistant and Successful Treatment by Immunotherapy

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Abstract: Penile cancer is a rare malignant tumor with a poor prognosis in advanced stages. Immune checkpoint inhibitors (ICIs) have demonstrated promising efficacy in patients with advanced penile cancer, but it can also induce immune-related adverse events (irAEs). This article reports a patient who achieved almost a complete response to the PD-1 inhibitor sintilimab as third-line treatment for advanced penile squamous cell cancer with massive ulceration of chemoradiotherapy-resistant, and successful treatment by immunotherapy. One year into maintenance therapy with sintilimab, skin toxicity in the form or grade-2 skin rashes and grade-3 pruritus occurred. Sintilimab was permanently discontinued. The skin toxicity was effectively controlled by oral prednisone at a daily dosage of 15 mg. At the last follow-up of 16 months after sintilimab discontinuation, the patient remained in partial response, with total progression-free survival exceeding 30 months. We also conducted a comprehensive literature search, and summarized skin toxicity of ICIs administration. These articles suggested that immune-related skin toxicity may be indicative of good treatment response.

Keywords: penile cancer, immune checkpoint inhibitors, sintilimab, skin toxicity, immunotherapy, case report

Introduction

Penile cancer is a rare cancer with varying incidence across different countries and regions, from 0.1–1 per 100,000 men in Europe and the USA to 2.8–6.8 per 100,000 men Africa, Asia, and South America.[1,2] Penile squamous cell carcinoma (PSCC) accounts for 95% of the cases. The prognosis of penile cancer is closely associated with staging and lymph node metastasis. The 5-year overall survival rate was high as 90% for localized penile cancer, 80% in patients with unilateral superficial inguinal lymph node (N1 or N2) metastasis, 10–20% in patients with bilateral or pelvic lymph node involvement (N2 or N3), and <10% in the presence of extranodal extension.[3] Platinum-based chemotherapy is the standard treatment for advanced PSCC but is associated with only 15–55% objective response rate (ORR) and <12 month overall survival.[2]

Immune checkpoint inhibitors (ICIs) have demonstrated promising efficacy in patients with advanced penile cancer exhibiting microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR) or high PD-L1 expression.[4,5] However, ICIs can also induce immune-related adverse events (irAEs), most frequently involving the skin, gastrointestinal tract, lungs and endocrine glands, it may also potentially manifest as neurologic, hepatic, rheumatological, renal and cardiac

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toxicities,[6–8] as well as rare adverse reactions such as Reiter's syndrome and myasthenia gravis, autoimmune hemolytic anemia.[9–11] Skin toxicity (eg, rash, pruritus, and vitiligo) represents the most common irAEs associated with ICIs. Potentially life-threatening skin irAEs include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash or reaction with eosinophilia and systemic symptoms (DRESS).[6,12,13] There may be a positive correlation between the occurrence of irAEs and the antitumor response to ICIs.[14] Herein, we report a case of metastatic penile cancer patient with chemoradiotherapy-resistant who achieved an excellent response to third-line treatment with the PD-1 inhibitor sintilimab (Tyvyt®), with delayed immune-related skin adverse reactions.

Case Description

A 59-year-old male patient was found to have a penile mass with purulent discharge. Physical examination revealed a palpable enlarged lymph node of 5 cm*3 cm in the right inguinal region. The patient had undergone surgery for a right-sided hernia 10 years ago and had a circumcision 8 years ago, with no family history. Needle biopsy confirmed PSCC, with pathology showing (penile mass) moderately to poorly differentiated squamous cell carcinoma. Due to the large size of the lymph nodes and concerns for complications, the patient refused an inguinal lymphadenectomy, he underwent partial penectomy and urethral meatus formation. Postoperative pathology: (partial penile and mass) moderately to poorly differentiated squamous cell carcinoma. Lymph node fine-needle aspiration biopsy, pathology revealed (right inguinal lymph node) metastatic or invasive squamous cell carcinoma. He was diagnosed with penile malignant tumor (pT3N2Mx). Lung CT showed small pulmonary nodules (it could not be determined whether they are lung metastases). He underwent postoperative chemotherapy (40-mg cisplatin on days 1–3 and 120-mg docetaxel on day 1 of each 21-day cycle) plus concurrent radiotherapy (52 Gy in 26 fractions to the planning target volume (PGTV) containing the metastatic lymph nodes, and 48.5 Gy in 26 fractions to the PTV covering the lymph node regions). The disease progressed after two cycles of concurrent radiochemotherapy, and chemotherapy was switched to tegafur and oteracil (60 mg twice daily on days 1–14 of each 21-day cycle). The patient developed skin ulcer with a foul odor after completing one treatment cycle, Abdominal CT scan showed enlarged bilateral inguinal lymph nodes, and the lung CT indicated an enlargement of pulmonary lesions (compared to the preoperative lung CT). The Eastern Cooperative

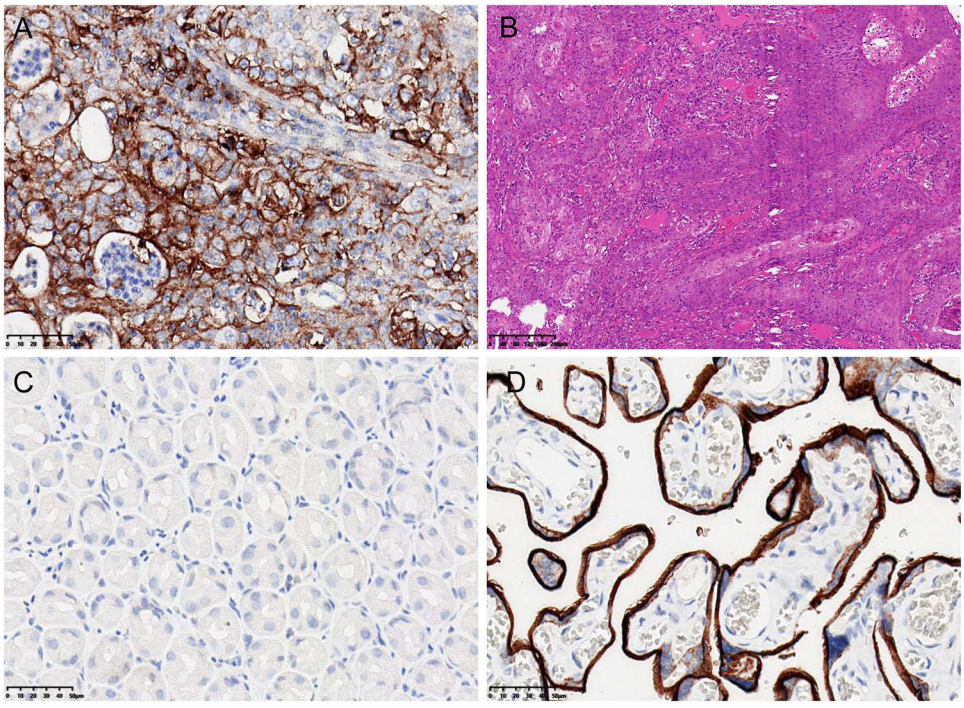

Figure 1 Programmed cell death 1 ligand 1 immunohistochemistry (PD-L1 IHC). (**A**) Sample (inguinal lymph node) 400×. (**B**) Sample (HE) 100×. (**C**) Negative Control 400×. (**D**) Positive Control 400×.

Oncology Group (ECOG) score was 2, and tegafur/oteracil was discontinued. Due to the high tumor proportion score (TPS) of PD-L1 protein expression (90%) (Figure 1), sintilimab treatment was initiated at a dose of 200 mg once every three weeks. Serum squamous cell carcinoma antigen (SCCA) decreased from 9.4 ng/mL to 5.8 ng/mL (normal standard: Serum SCCA < 1.8 ng/mL) after one sintilimab treatment cycle, and after two cycles, it dropped within the normal range. Skin ulcers also showed significant improvement. The ECOG score improved to 0. Imaging showed partial response: significant reduction in the lesion on the right inguinal region, Imaging showed partial response: significant reduction in the lesion on the right inguinal region, bilateral inguinal lymph nodes, and lung metastases. After 8 cycles of sintilimab treatment, the lesion on the right inguinal region had healed completely, bilateral inguinal lymph nodes shrank, and lung metastases disappeared (Figure 2).

One year into sintilimab treatment, red, scaly and itchy skin patches started to appear on all four limbs. An assessment based on the Common Terminology Criteria for Adverse Events (CTC-AE) rated the maculo-papular skin rash as grade 1. Symptomatic treatment was initiated and sintilimab treatment proceeded as planned. Four weeks later, skin rashes worsened to grade 2, with grade-3 pruritus (Figure 3). At the recommendation by a multidisciplinary team (MDT), sintilimab was permanently discontinued, and the patient was treated with prednisone (30 mg/d). The skin rash and itching rapidly dissolved rapidly. A skin biopsy revealed mild epidermal hyperplasia with excessive keratinization, alkaline degeneration of superficial elastic fibers in the dermis, minimal inflammatory cell infiltration around blood vessels, and immunohistochemistry showing CD4+/CD8+ lymphocytes and CD68+ tissue cells (Figure 4). The skin rash deteriorated upon an attempt to taper prednisone to 5 mg/d, and stabilized when prednisone dosage was adjusted back to

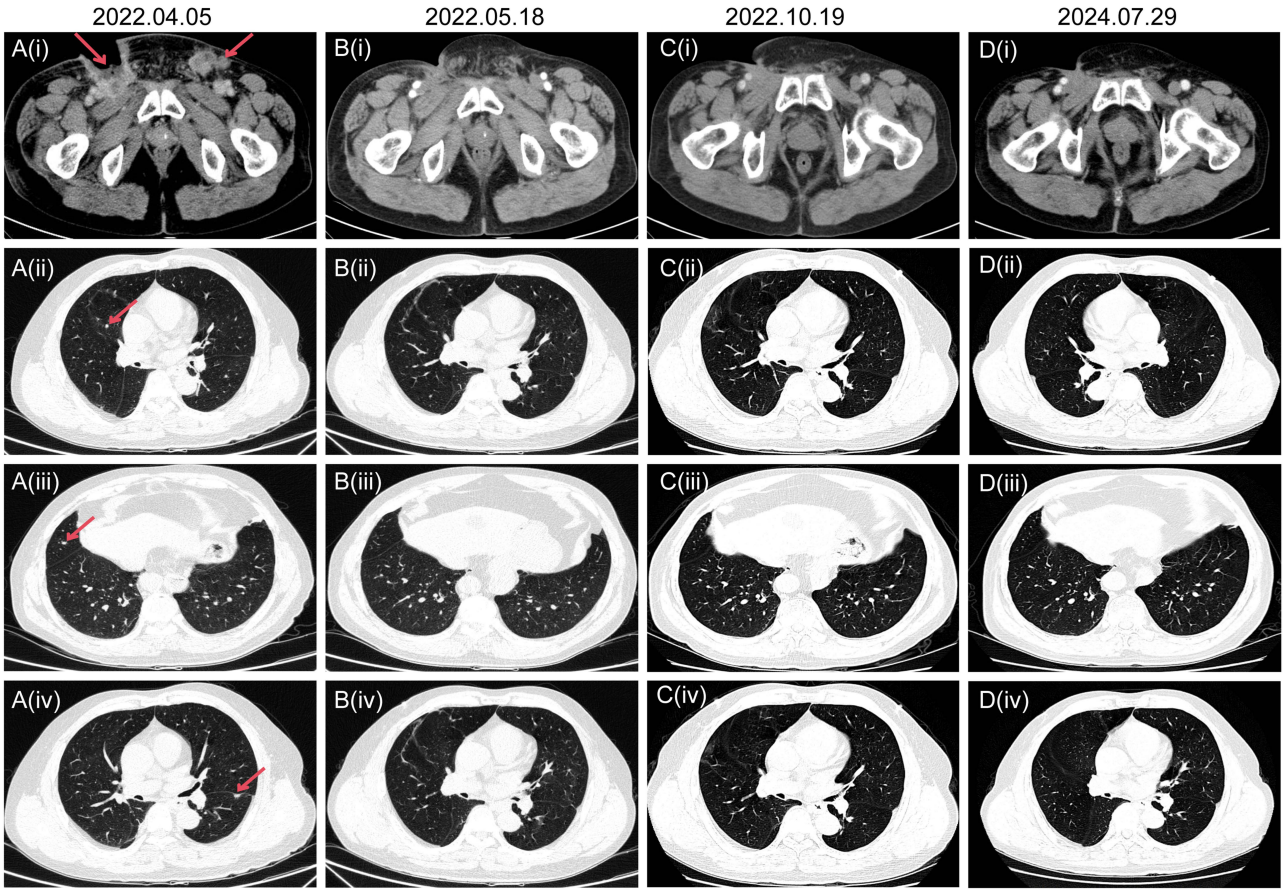

Figure 2 CT scans prior to and after sintilimab. (**A**) Prior to sintilimab. (**A(i)**) Abdominal CT scan showed enlarged bilateral inguinal lymph nodes, local skin ulceration in the right inguinal region (red arrow). (**A(ii)–A(iv)**) Lung CT scan showed metastatic lesions in the lungs (red arrow). (**B**) After two cycles of sintilimab treatment, (**B(i)–B(iv)**) Abdominal CT and lung CT scan showed significant reduction in the lesion on the right inguinal region, bilateral inguinal lymph nodes, and lung metastases. (**C**) After 8 cycles of sintilimab treatment, (**C(i)**) Abdominal CT scan showed the lesion on the right inguinal region had healed completely, bilateral inguinal lymph nodes shrank, (**C(ii)–C(iv)**) Lung CT scan showed lung metastases disappeared. (**D**) CT scans at the last follow-up (2024-07-29), (**D(i)**) Abdominal CT scan showed complete improvement in the lesion on the right inguinal region, bilateral inguinal lymph nodes continue to decrease, (**D(ii)–D(iv)**) Lung CT scan showed lung metastases disappeared.

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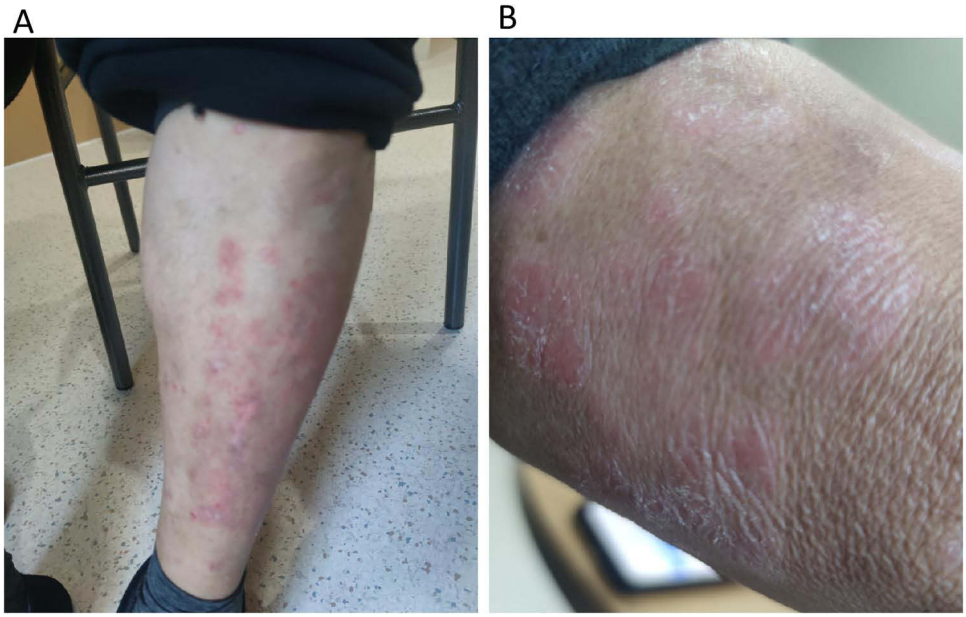

Figure 3 The skin lesions. (**A**) The left foot. (**B**) The right arm.

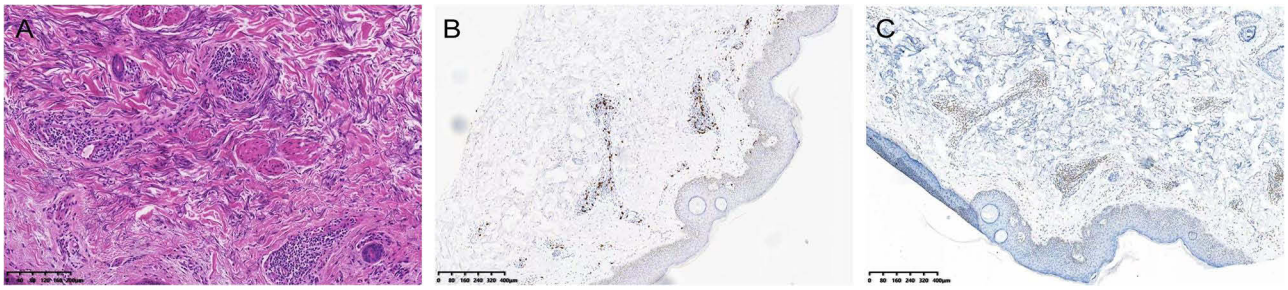

Figure 4 Biopsy of the skin lesion. (**A**) hematoxylin and eosin (HE) staining. (**B**) CD8+ T lymphocyte infiltration in the skin lesion (EnVision). (**C**) CD4+ T lymphocyte infiltration in the skin lesion (EnVision).

15 mg/d. At the last follow-up (16 months after sintilimab discontinuation), complete improvement in the lesion on the right inguinal region, lung metastases had disappeared, bilateral inguinal lymph nodes continue to decrease. The patient remained in Partial Response (PR), good performance status (PS) (ECOG 0), total progression-free survival exceeding 30 months. The latest follow-up date: 2024-7-29.

Discussion

Penile cancer has a low incidence and poor prognosis. The case report demonstrate that withdrawal of immunotherapy drugs due to adverse reactions might also continuously benefit advanced penile cancer patient with chemoradiotherapy-resistant who have successful treatment by immunotherapy. Platinum-based chemotherapy is the standard treatment for advanced PSCC, and the NCCN 2024 guidelines recommend the paclitaxel, ifosfamide and cisplatin (TIP) regimen as the first-line treatment.[15] For patients with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) or high tumor mutation burden (TMB-H) with TMB ≥10, and no other alternative after tumor progression, NCCN guidelines recommend considering immunotherapy.[15] Sintilimab is a PD-1 inhibitor approved for various malignancies, including Hodgkin lymphoma, non-small cell lung cancer (NSCLC), hepatocellular carcinoma, esophageal squamous cell carcinoma, and gastric or gastroesophageal junction adenocarcinoma in China. The use of sintilimab for advanced penile cancer is off-label, but limited studies have shown promising efficacy in the immunotherapy of penile cancer.[5,16] Keren et al[17] reported that ICIs had demonstrated greater effective than conventional cytotoxic or platinum-based

chemotherapies in a real-world experience. Nine patients were screened, and three patients who were not suitable for chemotherapy and received Cemiplimab as first-line therapy in advanced PSCC, the efficacy evaluation showed almost a complete response (CR) in all three patients after cycles of immunotherapy.

PD-L1 high expression is one of the most widely studied biomarkers selecting patients for ICIs treatment. The KEYNOTE-042 trial[18] demonstrated that in advanced NSCLC, patients with high TPS had a significant survival benefit with immunotherapy compared to standard chemotherapy. The KEYNOTE-028 trial[19] showed high PD-L1 expression correlates with clinical response to pembrolizumab immunotherapy in 20 types of solid tumors. Baweja and Mar[5] reported significant therapeutic response to nivolumab and ipilimumab immunotherapy after TIP regimen failure in an advanced penile cancer patient with high PD-L1 expression (TPS ≥90%). High PD-L1 expression in penile cancer is also a biomarker for immunotherapy.[20] In the index patient, the TPS of PD-L1 protein expression was 90% is compatible with the remarkable treatment response to sintilimab. Most notably, PR was sustained for at least 16 months after discontinuation of sintilimab.

Skin toxicity is a common adverse event associated with immune checkpoint inhibitors, with an incidence ranging from 30% to 60%.[6] The occurrence of skin toxicity varies among different immune checkpoint inhibitors, with CTLA-4 inhibitors having a higher incidence than PD-1 or PD-L1 inhibitors, and combination therapy having a higher incidence than monotherapy.[7] The rate of skin toxicity associated with sintilimab monotherapy and combination therapy have been reported to be <3% and <5%, respectively, with 0.3–1.3% mortality.[21] The treatment of skin toxicity caused by ICIs should be based on the severity of the condition. For Grade1, oral antihistamines or topical glucocorticoids can be administered. While Grade 2 – Grade 4, oral or intravenous glucocorticoids should be added.[22] Reports suggest the rituximab, tocilizumab, dupilumab, and traditional Chinese medicine formulations can be administered when glucocorticoids resistance.[7] Most skin toxicities can be managed appropriately without affecting the continued use of ICIs. However, if grade 4 skin toxicity occurs, such as SJS/TEN or TEN syndrome, ICIs should be permanently discontinued.[22] Therefore, it is crucial for clinicians to identify and intervene promptly at an early stage.

Skin toxicity associated with immune checkpoint inhibitors typically occur early in treatment, usually within 2–5 weeks after initiation.[23] In the index case, the skin rash appeared as late as one year after the initiation of sintilimab treatment. Such a profile may be related to the relatively long half-life of sintilimab (21 days) and the requirement of up to 15 treatment cycles before reaching steady-state.[24]

Another important feature in this case is the sustained PR after sintilimab discontinuation due to skin toxicity. Such a phenomenon was previously reported in a patient undergoing sintilimab treatment for NSCLC.[25] The case was treated with sintilimab for lung adenocarcinoma for 5 cycles. The drug was discontinued due to cardiac and skin toxicity, and the efficacy remained at PR for more than 3 months. The curative effect was evaluated as PR.[25] The occurrence of immune-related adverse events (irAEs) may have a positive correlation with the antitumor response to ICIs.[14] Early-onset immune-related adverse reactions could be predictive factors for the improved response of tumors to immunotherapy. Walid Shalata et al reported on the treatment of non-small cell lung cancer (NSCLC) with pembrolizumab; seven patients discontinued treatment prematurely due to severe adverse effects, yet they still demonstrated favorable and sustained therapeutic responses, with a minimum progression-free survival (PFS) of 30 months.[26] Growing research suggests that cutaneous immune-related adverse events (cirAEs) is associated with favorable outcomes among individuals with cancer who receive immune checkpoint inhibitor treatment, compared with patients who lack toxicity, those who have experienced skin toxicity show significant improvements in progression-free survival (PFS) and overall survival (OS),[27] with patients experiencing lower grade skin toxicity reactions (Grades 1–2) derived the more prognosis and those with grades 3–4 had less benefits.[28] We conducted a literature review on the association between skin toxicity induced by ICIs and clinical outcomes: including systematic reviews and meta-analyses, randomized controlled trials (RCTs), and retrospective analyses, all of which included subgroup analyses on the relationship between skin toxicity and treatment outcomes. The results are summarized in Table 1.[27–36]

There are still some shortcomings in this article. Due to the low incidence of penile cancer, the limited number of cases, and this being a case report, the therapeutic effect of ICIS on penile cancer, as well as the relationship between skin toxicity reactions and the treatment response in patients with penile cancer, requires further investigation with larger sample studies.

Table 1 Studies Comparing Outcomes in Malignancy Patients on Treatment with ICIs

Author	Study Design	Sample Size	Population	Checkpoint Inhibitor(s) Used	Onset Time of Skin Toxicity	Survival Endpoints Between Patients With and Without Cutaneous irAES
Yaxin Du et al 2023[27]	Systematic Review and Meta-Analysis	22749 (23 studies)	Pan-Cancer	ICIs	/	OS (HR 0.61; 95% CI 0.52–0.72; P < 0.001) PFS (HR 0.52; 95% CI 0.41–0.65; P <0.001)
Yaowen Zhang et al 2024[29]	Systematic review and meta-analysis	6148 (27 studies) Cutaneous 14.5% 95% CI (10.6–19.7)	Renal cell carcinoma (RCC) and urothelial carcinoma (UC)	ICIs	/	OS (HR0.51; 95% CI 0.36–0.73; P<0.01) PFS (HR 0.45; 95% CI 0.31–0.65; P<0.01)
Ahmad A Tarhini et al 2021[28]	RCT (E1609)	1673 (Rash 536)	Melanoma	Ipilimumab	/	Grades 1–2 Rash: OS (HR 0.70; 95% CI 0.55–0.89; p=0.004) RFS (relapse-free survival) (HR 0.75; 95% CI 0.62–0.90; p=0.002) Grades 1–4 Rash: OS (HR=0.74; 95% CI 0.59–0.94; p=0.012) RFS (HR 0.77; 95% CI 0.65–0.92; p=0.004)
Guihong Wan et al 2024[30]	Retrospective	13086 (MGBD) 26172 (TriNetX)	Pan-Cancer	ICIs	/	MGBD cohort: OS (HR 0.61; 95% CI 0.46–0.81; p=0.0007) TriNetX cohort: OS (HR 0.62; 95% CI 0.48–0.82; p=0.0007)
Koji Haratani et al 2017[31]	Retrospective	134 (skin 43)	NSCLC	Nivolumab	5.7 (0.4–36.2) weeks	OS (6-week landmark): HR (0.209; 95% CI 0.049–0.618; p = 0.003) PFS (6-week landmark): HR (0.476; 95% CI 0.232–0.912; p = 0.03)
Ying Yu et al 2023[32]	Retrospective	425 (skin 42)	NSCLC	Anti-PD-1/PD-L1 monotherapy	38.5 (1–439) days	OS (HR 0.49; 95% CI 0.31–0.76; p=0.001) PFS (HR 0.53; 95% CI 0.36–0.76; p=0.001)
George Raynes et al 2023[33]	Retrospective	262 (skin 19)	NSCLC	Pembrolizumab	3.0 (1.4–7.9) months	OS (HR 0.35; 95% CI 0.19–0.67; p=0.001) PFS (HR 0.37; 95% CI 0.20–0.69; p=0.002)

(*Continued*)

Table 1 (Continued).

Author	Study Design	Sample Size	Population	Checkpoint Inhibitor(s) Used	Onset Time of Skin Toxicity	Survival Endpoints Between Patients With and Without Cutaneous irAES
Yuzhong Chen et al 2023[34]	Retrospective	301 (Skin 58)	NSCLC	anti-PD-1	Median 12.1 weeks	OS 31.5 months (95% CI: 23.3–Not reached), 21.1 months (95% CI: 18.9–23.4; p = 0.010) PFS 15.7 months (95% CI: 12.2–22.3), 10.8 months (95% CI: 9.7–11.6; p = 0.001)
Inga Van Buren et al 2023[35]	Retrospective	20163 (Dermatologic toxicity 1001)	Pan-Cancer	ICIs	/	Median [IQR] OS, 26.4 (11.9 to not reached) months
Kimberly Tang et al 2022[36]	Retrospective	7008	Malignant neoplasms of digestive organs, bronchus or lung, melanoma of skin, and urinary tract	Anti-PD-1/PD-L1	/	Median [IQR] OS, cirAE group was 1278 days (558-not reached) control group: 1024 days (455-not reached)

Abbreviations: CI, confidence interval; HR, hazard ratio; RCC, Renal cell carcinoma; UC, urothelial carcinoma; RFS, relapse-free survival; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1.

Conclusion

Penile cancer has a low incidence and poor prognosis. This report describes a case of skin toxicity caused by sintilimab in a penile cancer with chemoradiotherapy-resistant and successful treatment by immunotherapy, literatures suggested that immune-related skin toxicity may be indicative of good treatment response.

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Ethics Approval and Informed Consent

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. The need for ethics committee approval was waived, as this is a case report.

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Disclosure

The authors report no conflicts of interest in this work.

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