 doi:10.20944/preprints202207.0296.v1

Case report

Sintilimab-Induced Diabetic Ketoacidosis in A Patient with Radiation and Multichemorefractory Penile Cancer: A Case Report and Literature Review

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Abstract: Penile squamous cell carcinoma (SCC) is a rare disease. Treatment options for advanced penile cancer are often limited and prognosis remains poor. We reported a 52-year-old male recurrent and metastatic penile SCC patient with high PD-L1 expression(90%) and TMB(14.4 muts/Mb). He had undergone penectomy, bilateral inguinal lymph node dissection and excision of the abdominal wall mass during two surgeries. Despite cisplatin-based concurrent chemoradiotherapy and sequential chemotherapy with docetaxel plus cisplatin were then carried out, the carcinoma still had progressed. The patient then obtained progression free survival exceeding 32 months with continuous sintilimab, although new onset of ICI-induced diabetes after 24 cycles of sintilimab and required sustained insulin treatment. He didn't have positive type 1 diabetes associated autoantibodies, but had susceptible HLA genotype DR3-DQ2 haplotype. This is the first patient with radiation and multichemorefractory penile SCC obtained remarkable anti-tumor effect of partial regression exceeding 32 months during continuous sintilimab and anlotinib.

Keywords: Autoimmune diabetes; PD-1 inhibitor; Sintilimab; Penile carcinoma

1. Background

In recent years, immune checkpoint inhibitors (ICIs), a novel class of drugs for tumor immunotherapy, have emerged as beneficial weapon for various malignancies. ICIs can activate the autoimmune response to tumor cells and block immune escape of tumor by inhibiting negative immune regulation proteins, including cytotoxic T cell associated antigen 4 (CTLA4), programmed cell death protein 1 (PD-1) and programmed cell death protein ligand 1 (PD-L1)[1]. However, inhibition of immune checkpoints sometimes also damage self-tissues, causing immune-related adverse events, including dermatological, pulmonary, gastrointestinal, cardiovascular and endocrine system[2]. Type 1 diabetes mellitus(T1DM) is a rare adverse effect and seldom reported[3], especially in patients with penile cancer. Sintilimab (Innovent Biologics, Suzhou, China), a type of PD-1 antibodies, was included in the 2019 edition of The Lymphoma Diagnosis and Treatment Guide of The Chinese Society of Clinical Oncology[4]. Here we report the first case of new-onset autoimmune diabetes who received sintilimab plus anlotinib for treating radiation and multichemorefractory penile squamous cell carcinoma(SCC).

2. Case report

A 52-year-old man was pathologically diagnosed with squamous cell carcinoma of the penis and inguinal lymph node metastases by biopsy of glans penis mass and right inguinal lymph node in Dec 8th 2017. Then he underwent partial amputation of penis and

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bilateral inguinal lymph node dissection. Four months after the surgical procedure, he received concurrent chemotherapy (cisplatin[40mg/m2] for 5 weeks) and radiotherapy(2.0 Gy/fraction, total 60 Gy). 2 weeks after radiotherapy, sequential chemotherapy regimen(docetaxel[120 mg/m2 day 1] plus cisplatin[40 mg/m2 day 1-3], 4 cycles) was provided for him. In Nov 23th 2018, he was performed with percutaneous cystostomy because of dysuria. Nearly two months after that, the squamous cell carcinoma of the penis relapsed, with metastases in left inguinal and iliac lymph nodes, right pelvic wall lymph nodes, together with the abdominal skin on the right side of the external orifice of cystostomy tube. Due to severe pain, he had undergone total penectomy and excision of the abdominal wall mass which were pathologically proved as squamous cell carcinoma(**Figure 1**). Unfortunately, less than five months since the second surgery, he became physically weak with the eastern cooperative oncology group(ECOG) score of 4. The abdominal computed tomography (CT) showed that the carcinoma had spread to the perineum area with infection, with metastases in bilateral inguinal and pelvic wall lymph nodes and the left external iliac vein invaded.

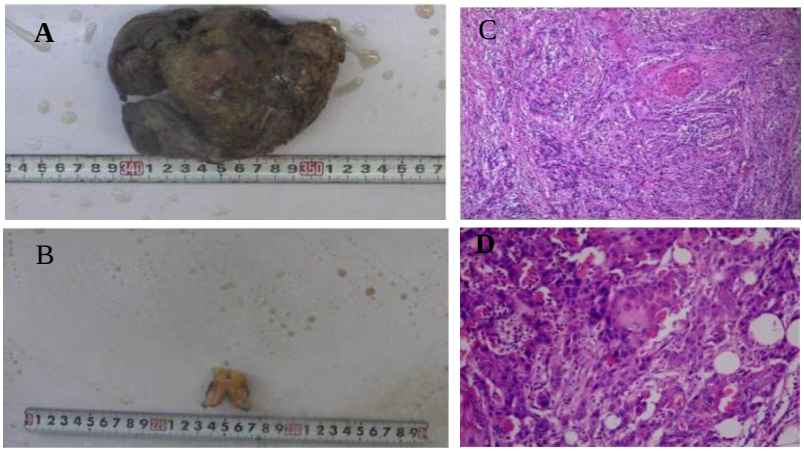

Figure 1. Pathology images of postoperative tissues after recurrence. The picture of penis tumor tissue (A) and wall tumor tissue(B); H&E staining of penis tumor tissue sample(C) and abdominal wall tumor tissue sample(D).

Subsequently, next-generation sequencing and PD-L1 immunohistochemistry were performed to seek potential therapeutic options. Results indicated positive PD-L1 expression(90%), combined positive score(CPS) of 110, microsatellite stable and a tumor mutational burden(TMB) of 14.4(muts/Mb). Tumor tissue sample genomic analysis showed a 2.3 times amplification of epidermal growth factor receptor. The patient was then started on anlotinib treatment (12mg/day for two weeks, then stopped for one week) on August 1st 2019. Fourteen days later, he voluntarily started to receive 200mg of sintilimab every 3 weeks. He signed informed consent for the off-label use of sintilimab. Several days later, his physical strength and mental status improved significantly. Four months after receiving sintilimab, abdominal CT showed that tumor nodule had shrunk dramatically (**Figure 2**). During the following sixteen months, the patient's ECOG score was 1.

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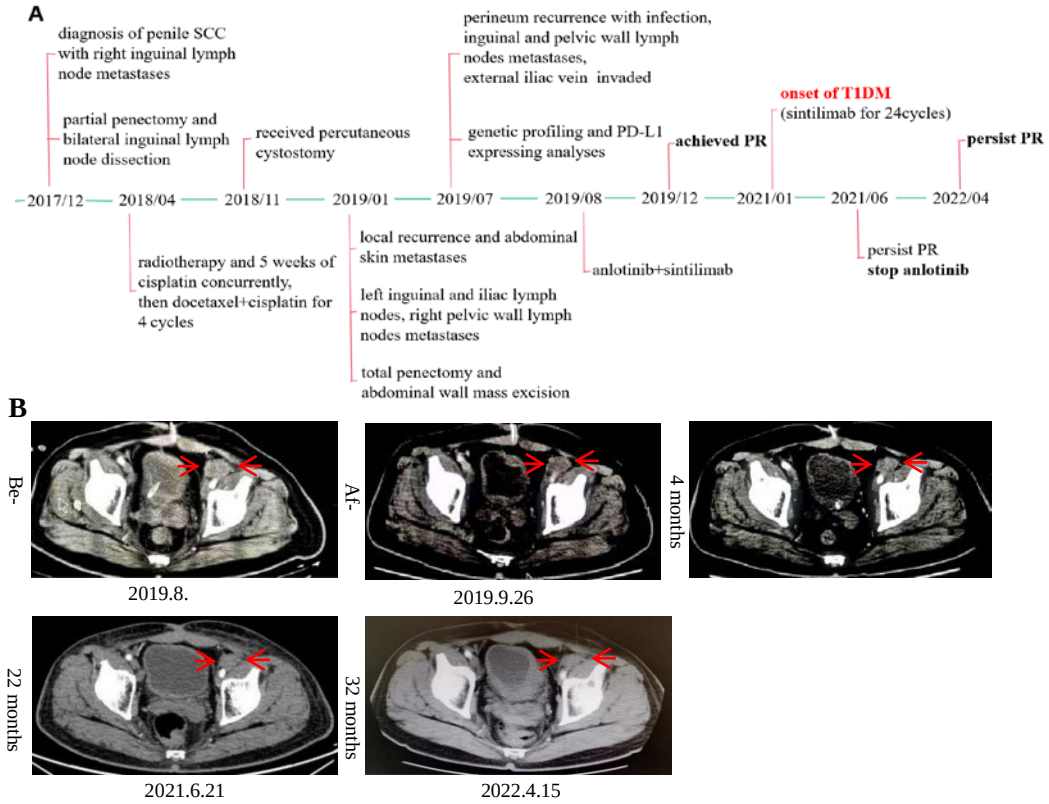

Figure 2. Courses of the patient's treatments and CT image. (A)Scheme shows the time course of the patient in diagnosis and the therapy. (B)Contrast-enhanced abdominal computed tomography assessments of pelvic wall tumor nodule during each period. Red arrows indicate the tumors.

Nevertheless, on January 27th 2021, after 24 cycles of sintilimab, he complained of polyuria, thirsty and fatigue. Two days later, he admitted to the emergency department for nausea and vomiting. No abnormality was found on physical examination. Blood tests showed that his instant plasma glucose was as high as 24.27 mmol/l with an HbA1c value of 7.3%. Arterial blood gas analysis revealed that he had metabolic acidosis, with an arterial pH of 7.329, serum bicarbonate of 20.2 mmol/L and lactate of 1.3mmol/L. The urine ketone body determination was positive. Thus, diabetic ketoacidosis was diagnosed. He initially received maintaining water, insulin therapy delivered by micropump, acid-base and electrolyte balance and supportive treatment to correct acidosis. Then further blood assessment showed the exhaustion of his islet beta cell function with the fasting C-peptide value of 0.13ng/mL, which further decreased to 0.02ng/mL in one month. There was no medical history or family history of hyperglycemia, infection, autoimmune diseases, endocrine, other systemic diseases and hereditary diseases that could cause hyperglycemia. Consequently, he was diagnosed with sintilimab-induced autoimmune diabetes. However, the anti-glutamic acid decarboxylase antibody(GADA), anti-islet cell antibody (ICA), protein tyrosinephosphatase antibody(IA-2A) and anti-insulin antibody(IAA) were all negative. In addition, human leucocyte antigen (HLA) class I and II type analysis revealed that he had the T1DM-sensitive genotype DRB1*0301-DQB1*0201. He was also identified with five T1DM risk loci, including rs689 in INS, rs2476601 in PTPN22, rs1990760 in IFIH1, rs3757247 in BACH2 and rs11202303 in UBASH3A. For other endocrine function assessments, thyroid hormones showed that the patient's serum free triiodothyronine (FT3) and free thyroxine were normal. Moreover, the levels of anterior pituitary hormones and their regulated hormones were all normal.

Thereafter, he received continuous subcutaneous insulin therapy by insulin pump during his hospital stay. Before discharge, insulin treatment was adjusted daily to the dose

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of once-daily insulin glargine (long-acting insulin, 10 units) plus thrice-daily prandial insulin aspart (fast acting insulin, 5 units). He presented with progression-free of carcinoma, moderate glycemic control and experienced no other side effects during follow-up visits. Thus, anlotinib treatment was stopped in June 2021, but sintilimab administration was continued for him.

3. Literature Analysis

There is no published randomized clinical trials supporting that immunohterapy can benefit patients with advanced penile SCC. Therefore, a comprehensive literature analysis was conducted on PubMed with the keywords"immunotherapy and penile squamous cell carcinoma". Ten manuscripts, reporting on fifteen patients, were discovered and determined eligible for analysis. Our present patient was also included.(**Table 1**).

Table 1. Clinical features of reported cases.

Author	Age	PD-L1 status	MSI status	TMB	Outcome
Baweja et al. [9] (2021)	47	TPS:90%	MSI-high	High(24Muts/Mb)	12-month follow up, **PR**
Trafalis et al. [10] (2018)	47	TPS:≈10%	Stable	High	6-month follow up, **PR**
Hui et al. [11] (2019)	64	UK	UK	UK	6-month follow up, Stable
Hui et al. [11] (2019)	79	UK	UK	UK	24-month follow up, **CR**
Chahoud et al. [12](2020)	64	UK	UK	High(14Muts/Mb)	38-month follow up, **CR**
Chahoud et al. [12](2020)	85	CPS:130	Stable	Low (3Muts/Mb)	18-month follow up, **PR**
Hahn et al. [13] (2021)	76	TPS:10%	MSI-high	UK	38.7-month follow up, **PR**
Hahn et al. [13] (2021)	72	TPS:80%	Stable	UK	8.3-month follow up, PD
Hahn et al. [13] (2021)	66	TPS:1%	Stable	UK	3.8-month follow up, PD,
Denis et al.[14](2021)	75	TPS:＞95%	UK	UK	15.1-month follow up, **CR**
Su et al. [15] (2020)	46	TPS:≥10%	Stable	High(8.87Muts/Mb)	10.5-month follow up, **CR**
Hu et al. [16] (2021)	49	TPS:20~30%	Stable	Low (2.25Muts/Mb)	19-month follow up, **CR**
Li et al. [17] (2022)	76	TPS:≈10%	UK	UK	5-month follow up, **CR**
Mei et al. [18] (2022)	63	TPS:50~60%	Stable	High(17.95Muts/Mb)	28-month follow up, **PR**
Mei et al. [18] (2022)	39	TPS:<1%	Stable	Low(0 Muts/Mb)	24-month follow up, **CR**
Present case (2022)	52	TPS:90%	Stable	High(14.40Muts/Mb)	32-month follow up, **PR**

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MSI, microsatellite instability; TMB, tumor mutation burden; PR, partial response; CR, complete response; PD, progression of disease; UK, unknown; TPS, tumor proportion score; CPS, combined positive score.

4. Discussion

Penile cancer is a rare condition, which mostly affects men in their sixth decade of life. The most common histology is SCC, which is primarily treated by surgical resection. Timely multidisciplinary treatment approach at experienced centers is critical for improving outcomes. Unfortunately, advanced penile cancer represents a significant challenge in clinical practice, as treatment options are often limited and prognosis remains poor[5,6]. Thus, novel molecular and immunotherapeutic targets are actively being sought[5,7]. Targeted therapies and immune checkpoint inhibitors are expected to play a role in advanced penile carcinoma[6,8]. However, there is no published randomized clinical trials for patients with distant metastatic disease who have already received standard chemotherapy, due to the rarity of penile SCC[6].

Baweja et al.[9] report a case of metastatic penile cancer with a dramatic treatment response to ipilimumab and nivolumab, whose tumor molecular profiling showed a high PD-L1 expression, TMB and microsatellite instability. There are also nine patients with metastatic-relapsed penile cancer reported documenting use of immune checkpoint inhibitors, such as nivolumab[10,11], atezolizumab[11], pembrolizmab[12,13] or cemiplimab[14] in few case reports. Comfortingly, six patients presented with partial response or nearcomplete response. In China, Su et al[15]reported a recurrent metastatic penile SCC patient with positive PD-L1 expression (≥10%) and high TMB of 8.87 (Muts/Mb) who obtained significant response to toripalimab, with progression free survival exceeding 10 months. Hu et al[16]reported a 49-year-old recurrent penile SCC patient with medium PD-L1 expression and low TMB obtained complete response after multimodal therapy,

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including resection of palliative right inguinal metastases, four cycles of paclitaxel+bleomycin+cisplatin and continuous sintilimab. However, it was also recently reported that immunotherapy combined with chemotherapy had good therapeutic effect in advanced penile SCC patients[17, 18]. Our patient presented with high PD-L1 expression levels and TMB, microsatellite stable. He was firstly reported obtaining partial response to combined treatment with sintilimab plus anlotinib, with progression free survival exceeding 32 months. In all above case reports, Thirteen patients were reported partially or completely response to immunotherapy. Meanwhile, immunohistochemistry analysis indicated that 90.9% of them had positive PD-L1 expression. Microsatellite status and TMB analysis showed that 66.7% of them were microsatellite stable and 66.7% of them were high TMB(Table 3). Recently, six patients with penile carcinoma were reported receiving treatment with nivolumab and ipilimumab in a multicenter, single-arm, multicohort, phase 2 trial. But none of them presented as partial or complete response, without presenting the expression of PD-L1, TMB and microsatellite status[19]. Thus, positive PD-L1 and high TMB could be potential biomarkers for ICIs treatment in penile SCC. However, evidence of several case reports is limited.

ICIs bring the hope for longer survival and improved quality of life in patients with advanced malignant. However, the excessive activation of immune cells may also cause immune-related adverse events (irAEs), resulting in disorders of multiple endocrine and non-endocrine organs[20]. T1DM is a rare irAE of PD-1 inhibitors and expected to increase with the use of ICIs in clinical practice. Here we report the first case of diabetic ketoacidosis caused by new-onset auto-immune diabetes, during sintilimab plus anlotinib therapy for recurrent metastatic penile SCC after resistance to concurrent chemoradiation. Our present case was consistent with previous reports that the majority of the patients with auto-immune diabetes presented with diabetic ketoacidosis(50.2%) and the onset of diabetes ranged from 5 to 880 days after the first dose of ICIs[21, 22]. Our patient's HbA1c level was high at 7.3%, supporting that some degree of hyperglycemia or significant hyperglycemia during a shorter period had been present prior to the acute[23]. ICI-induced diabetes sometimes resembles fulminant diabetes, the routine blood glucose monitorization may not detect or predict its occurrence. Thus, diabetes education, routine self-monitoring of blood glucose and determination of serum glycated albumin and C-peptide in each treatment cycle may be needed to identify the initial elevations in blood glucose.

Although the physiopathology of auto-immune diabetes associated with ICIs is unknown, activation of autoreactive T cells caused by reduction of PD-1 might resulted in an autoimmune response against islet cells. Previous reviews showed that the most commonly positive islet autoantibody was GAD65, but only detectable in about 51% of patients[21,23]. Our patient presented with negative diabetes related antibodies, supporting that the presence of islet autoantibodies is not an absolute requirement for the diagnosis of ICIs-associated diabetes. In addition to islet autoantibodies, certain HLA genotypes are known predispose to type 1 diabetes. DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 has been identified as high risk genotype in Caucasians. In Asians, haplotypes DRB1*0405-DQB1*0401, DRB1*0802-DQB1*0302, DRB1*0901-DQB1*0303 and DRB1*0802-DQB1*0302 genotype were classified as susceptible to acute-onset and slowly progressive T1DM. In contrast, only DRB1*0405-DQB1*0401 was associated with fulminant type 1 diabetes. In addition, the association of B*4002 with fulminant type 1 diabetes was also identified[24]. Pociot et al[24] reviewed that the primary risk factor for β-cell autoimmunity is genetic, mainly occurring in individuals with either HLA-DR3-DQ2 and/or HLA-DR4-DQ8 haplotypes. The frequency of HLA-DR4 was reported to be more than 60% in ICI-induced T1DM and was much higher than that in conventional T1DM, the frequency of HLA-DR3 was about 30%[20, 26]. HLA typing of our patient revealed DR3-DQ2 haplotype which is a susceptible genotype, supporting that there appears to be a cohort of people at-risk HLA that develops ICIs associated diabetes[27].

5. Conclusions

To our knowledge, this is the first case describing a radiation and multichemorefractory penile SCC, who was treated with sintilimab plus anlotinib and achieved progression free survival exceeding 32 months. Although ICI-induced diabetes persisted and required sustained treatment with insulin, this may provide single immunotherapy as a new option to maximize the benefit for advanced penile cancer patients.

Author Contributions: CL analyzed the patient data, designed the case report, and drafted the manuscript. CW and YZ provided signifificant contributions to the collection of patient data. WL provided significant contributions to the analysis and interpretation of CT imaging. LL provided significant contributions to the analysis of the patient data and designed the case report.

Funding: The study was supported by the National Natural Science Foundation of China(NSFC81800717) and Natural Science Foundation of Liaoning Province. Any errors may affect your future funding(20180530039).

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Written informed consent was obtained from the families of the patients for publication of the case.

Data Availability Statement: The raw data presented in the study is included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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