Oncology

Penile cancer with visceral metastasis and p16/human papillomavirus positivity: An unusual case of long-term survival

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ABSTRACT

Squamous cell carcinoma (SCC) of the penis is a rare cancer in the industrialized countries, including the United States. Risk factors for these cancers include inflammatory conditions as well as infection with the human papilloma virus (HPV). Treatment modalities are based on TNM staging and may include surgical management or chemoradiation. Patients with local or some regional disease can have a favorable prognosis; however, with extranodal metastasis, survival decreases sharply. Here, we present a case of long-term disease-free survival in a patient with widely metastatic SCC of the penis.

Introduction

Although squamous cell carcinoma (SCC) of the penis is rare in the United States, it is more prevalent worldwide. Tumor involvement of inguinal lymph nodes is the most important predictor of cancer-related death. 1 While patients with metastases confined to inguinal lymph nodes can frequently be cured with aggressive multimodal treatment, those with pelvic lymph node involvement rarely survive long-term. 2 The prognosis for patients who develop distant and/or visceral metastases is dismal, with expected survival less than 12 months. 3

Human papillomavirus (HPV) is one factor in the pathogenesis of some penile cancers. 4 Some studies have suggested better survival outcomes for patients with HPV-related tumors. Unlike head and neck cancers, however, the management of patients with metastatic penile cancer is not dependent on HPV status.

Here we present the case of a man with unusual long-term disease-free survival despite having progressed to widespread metastatic SCC of the penis, with attention to the possible significance of HPV and p16 detection.

Case presentation

A 43-year-old man presented with an exophytic mass on the penis, biopsy showing SCC, grade 2 (of 4), 2.9 cm in maximum dimension. Total penectomy and bilateral ilioinguinal lymph node dissections were performed. Upon surgical staging, right and left superficial inguinal lymph nodes were positive for metastatic SCC, for which he received three cycles of adjuvant chemotherapy (bleomycin, methotrexate, and cisplatin). Tumor recurred approximately one year after diagnosis in bilateral upper thighs for which he underwent palliative radiotherapy with concurrent cisplatin. Approximately three years from diagnosis he underwent resection of a 6-mm tumor recurrence in the previously radiated right groin dermal tissue. He was again without evidence of disease until approximately 3.5 years from diagnosis, when a routine PET/CT detected a cystic mass in the right temporal lobe (Fig. 1). A craniotomy was performed and a 3.6-cm brain metastasis was removed, pathology demonstrating metastatic SCC. He then received post-operative whole-brain radiotherapy (WBRT). Shortly thereafter, he developed biopsy-proven mediastinal lymph node metastases. He was treated with chemotherapy consisting of paclitaxel (130 mg/m^2 day 1), ifosfamide (600 mg/m^2 days 1–3) and cisplatin (12.5 mg/m^2 days 1–3), every 28 days for six cycles. CT chest after the first two cycles showed interval resolution of mediastinal lymphadenopathy (Fig. 2).

The proximal urethra was initially managed with a scrotal urethrostomy in anticipation of penile reconstruction. Early in his clinical course the patient did undergo staged construction of a neophallus and...
neourethra with anastomosis to the native bulbar urethra. After radiotherapy, recurrent strictures in the neourethra eventually required a perineal urethrostomy, which remained patent.

Follow-up: Ten years after his initial diagnosis and with no additional therapy, our patient was alive and had been continuously disease-free for five years. To explore a possible association of the clinical course with HPV, we performed in situ hybridization for HPV DNA (types 16 and 33) and immunohistochemistry for p16 on archived tissue from the prior tumor resections. The results are shown in Fig. 3 and are consistent with an HPV-related tumor.

**Discussion**

Disease-free survival five years after salvage chemotherapy was unexpected, as was the durable tumor control after local therapy for brain metastasis. To our knowledge, no similar case examples exist in the penile cancer literature. As context, the expected median overall survival from the time of progression after chemotherapy for penile cancer...
is less than 6 months. Our investigations show conclusively that this patient’s malignancy was HPV-related, but we can only speculate on whether HPV influenced the response to therapy. Persistent, aggressive treatment was pursued in this case because of the patient’s young age at the time, without knowledge of the HPV status. Our report suggests that HPV-positivity might be useful to guide such treatment decisions.

Chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP) was the last treatment he received and the only intervention accounting for the durable complete response in mediastinal lymph nodes, suggesting that TIP played a crucial role. It is interesting that he had previously received other cisplatin-based chemotherapy with subsequent progression, and that TIP doses were reduced from the usual starting doses in line with the palliative intent of care. Better response to therapy has been associated with HPV in similar tumor types, such as vulvar cancer and SCC of the head and neck, suggesting that enhanced sensitivity to chemotherapy was a factor. An enhanced immune response also may have occurred. Our patient did not receive a checkpoint inhibitor, as they are not standard treatment for penile cancer. Yet, it is possible that the low-dose chemotherapy had an immunomodulatory effect, similar to the proposed mechanism of chemotherapy combined with checkpoint inhibitors in other cancer types.

Conclusion

In summary, our case illustrates that aggressive multimodal therapy for advanced penile cancer can lead to long-term disease-free survival, albeit very rarely. Positive HPV biomarkers may help to identify the patients who are most likely to experience such outcomes. More data are needed to determine whether checkpoint inhibitors are effective in this setting.

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Declaration of competing interest

The authors have no conflicts of interest or disclosures to report.

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