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The Need to Enhance Intimacy Care in Immunosuppressed Patients: A Case Report of Neglected Penile Cancer in a Long-term Lung Transplant Recipient

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It has long been established that prolonged immunosuppression increases the risk of cancer, especially of epithelial origin and of infectious organism-related oncogenesis.^{1,2} Penile cancer is a rare disease, with an incidence of 0.94 of 100 000 in Europe.³ It is strongly associated with human papillomavirus (HPV) infection, which is the primary risk factor.⁴ Studies have shown that immunosuppression increases the incidence of penile cancer with an odds ratio of 15.6,² even when specifically considering solid organ transplant and possible pre-existing factors.^{5,6} The increasing risk could be dependent of the kind of immunosuppressive drug used, where calcineurin inhibitors could lead to higher incidence. Switching from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors has been shown to reduce the overall risk of cancer, particularly squamous cell carcinoma (SCC), in which we find penile SCC.⁷ However, data on lung transplant recipients remain scarce and this benefit has been mainly studied on kidney transplant recipients. Caution must be taken with mTOR inhibitors regarding wound healing and surgical intervention. mTOR inhibitors should be discontinued at least 1 wk before elective surgery and not restarted until 10–15 d afterward.⁸ The ideal timing for introducing everolimus should be carefully discussed and planned by the medical team, particularly when surgery is anticipated, as everolimus can delay wound healing. Other risk factors include phimosis, lichen sclerosis,

smoking, UV A phototherapy, and low socioeconomic status.⁹ Immunosuppressed patients are more susceptible to HPV infection because of their compromised immune response against the virus.¹⁰ Vaccination against HPV is therefore recommended for transplanted patients, typically using a 3-dose vaccination regimen.¹¹ Early diagnosis of penile carcinoma is most often feasible as the lesions are typically clinically apparent. However, in case of phimosis, some lesions may remain hidden beneath the foreskin for extended periods, complicating detection. Additionally, benign-looking lesions can be initially misjudged, further delaying diagnosis. A retrospective study of 254 patients showed that initial symptoms commonly include wart-like lesions or tumors (20%), ulceration (17.7%), induration (15%), and superficial fissures (8.7%).¹² Data are scarce on the combination of immunosuppressive therapy and penile SCC, but for cutaneous SCC studies show more aggressive behavior, adverse pathologic features and more extended disease in organ transplant recipients.¹³

Psychological factors such as embarrassment and denial can also contribute to delays in seeking medical advice, with delays >6 mo in 65% of patients.¹⁴ Lack of awareness exacerbates these psychological barriers, whereas knowledge of risks and symptoms is crucial for prompt recognition and seeking of medical attention. Moreover, the sensitive nature of the affected area may further inhibit patients from openly discussing their symptoms.¹⁵ Delays in diagnosis often result in more advanced disease at the time of diagnosis.¹²

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CASE PRESENTATION

We present the case of a 67-y-old patient who underwent bilateral sequential lung transplantation 17 y earlier because of Gold IV chronic obstructive pulmonary disease (forced expiratory volume in 1 s <30%). The posttransplant follow-up was free of major problems for a decade, in terms of lung allograft function, immunosuppression side effects, and quality of life. However, he developed a chronic kidney disease induced by cyclosporine. At 10 y posttransplant, he developed noticeable and multiple cutaneous warts on both hands and feet, which were treated with acitretin upon dermatological advice. Four years later, he presented with a SCC of the left index finger, which was initially conservatively treated but finally required partial amputation of the distal phalanx. He received an HPV

vaccination with the recommended 3 doses. He was last evaluated by the dermatologist in September 2023, still showing cutaneous warts on both hands, but with his feet being free from relapse.

At the time of his referral, his immunosuppressive treatment included low-dose methylprednisolone (2 mg daily), mycophenolate mofetil 750 mg BID, and cyclosporine 100 mg BID, with target trough concentrations (C0) of 150–200 µg/L and 2-h postdose levels (C2) of 800–1000 µg/L. At referral, his C0 and C2 levels were measured at 180.6 and 632.9 µg/L, respectively.

He presented in urology in October 2023 for a phimosis that had been present for at least a year but was now causing dysuria and pain upon retraction. No hematuria, infection, or any other symptom was evident. The physical examination revealed a visibly swollen and abnormally shaped glans, with palpation showing tenderness. There was a clearly indurated lesion measuring approximately 2 cm in diameter at the junction of the glans and the corpus cavernosum (Figure 1). Cavernosal invasion was suspected although not clinically apparent. Examination of the inguinal region did not reveal suspicious lymph nodes. Subsequently, an MRI was performed to assess the extent of invasion, which indicated a suspicion of right corpus cavernosum involvement. Lymph node assessment was negative. As the patient had been sexually inactive for years, no new sexually transmitted disease tests were conducted, as prior test were negative. A thoracic computed tomography (CT) scan performed a few weeks prior, as part of his transplant follow-up, showed several nonspecific pulmonary nodules, which exhibited hypermetabolism on the Positron emission tomography-CT scan that was done as part of the pulmonary workup. The penile tumor was also hypermetabolic, as were the right mediastinal hilum lymph nodes.

The case was discussed in a multidisciplinary meeting, which recommended a surgical intervention for the primary penile tumor, primarily for symptom relief, along with an endobronchial ultrasound-guided biopsy of the mediastinal lymph nodes.

The penile tumor surgery consisted in a total penectomy with perineal urostomy because of the T3 clinical stage, with residual penile length inferior to 2 cm. A dynamic sentinel lymph node dissection associating technetium-99m and patent blue dye was also conducted. The pathologic examination

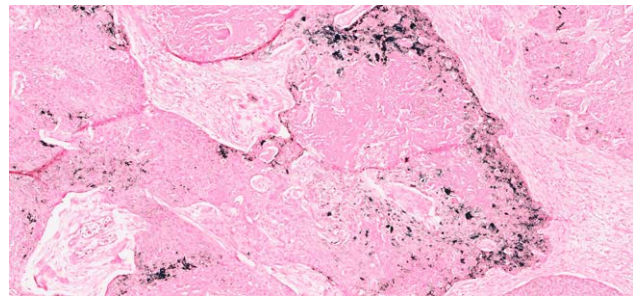


FIGURE 2. Hybridization in situ for human papillomavirus (HPV) 16, 18, and 31.

revealed extensive infiltration of the corpora cavernosa, corpus spongiosum, and urothelium by a moderately differentiated SCC with negative surgical margins (pT3). The sentinel lymph nodes were free of involvement. In situ hybridization demonstrated expression of oncogenic HPV 16, 18, and 31 in the tumor cells (Figure 2). Postoperative recovery was easy, and follow-up at 1, 3, and 6 mo indicated satisfactory functional outcomes concerning urinary function and wound healing. The immunosuppressive regimen was adjusted, with mycophenolate mofetil being replaced by everolimus only after surgery and satisfactory wound healing, to avoid any delays in the healing process. The target cyclosporine levels were reduced to 70–100 µg/L for C0 and 400–500 µg/L for C2.

Mediastinal lymph node biopsies obtained by endobronchial ultrasound were inconclusive. Three months later, the chest CT control revealed enlargement of the previously observed lesions, and the patient finally consented to undergo a transbronchial biopsy, which provided positive pathology for a SCC metastasis, making the cancer final staging pT3 N0 M1. The patient started taxane- and platinum-based chemotherapy, while immunotherapy was not considered because of the risk of allograft rejection.

DISCUSSION

This case report highlights the importance of better informing both patients and practitioners about urogenital diseases that may arise during prolonged immunosuppressive treatment. While occurrences of penile carcinoma in transplant recipients have been reported before, this case emphasizes the need for heightened awareness and proactive monitoring, especially for those developing other HPV-associated tumors. The increased frequency of penile carcinoma among transplant recipients underscores the significance of educating patients about this risk. Awareness of symptoms and potential risks can empower patients to self-diagnose and seek medical advice promptly. However, in sensitive areas such as sexual health, the fear of embarrassment may prevent patients from spontaneously discussing these concerns with their healthcare providers.

In the case described, despite regular contact with healthcare providers, including a dermatologist, and awareness of the risk of cutaneous lesions and oncologic transformation because of previous experiences with SCC and HPV vaccination, neither the patient nor the physicians raised or identified a penile issue. Furthermore, in this case, the first diagnosis of SCC should have prompted a modification of



FIGURE 1. Penile tumor.

the immunosuppressive regimen by switching from calcineurin inhibitors to mTOR inhibitors, although the benefit of such a change on SCC, primarily reported mainly in kidney transplantation recipients, has not yet been confirmed in lung transplantation. Patient and practitioner vigilance remain crucial in detecting potential complications of immunosuppressive therapy during medical follow-up, including in private or sensitive areas like the anus or penis, which are not seen even when the patient is wearing only underwear. Proactive monitoring should extend to these areas to avoid delays in recognition and treatment and their impact on patient survival.

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