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Review article

# Iatrogenic solid tumors following immunosuppressive therapy

Kossivi Dantey[a], Liron Pantanowitz[b,*]

[a] Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212-4756, United States
[b] Department of Pathology, Presbyterian Shadyside Hospitals, University of Pittsburgh Medical Center, 5230 Centre Avenue Pittsburgh, PA 15232, United States

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ABSTRACT

Immunosuppression induced by chronic medication, such as occurs post-transplantation, may increase a patient's risk of developing solid tumors. These are often rare tumors characterized by odd presentations. This review focuses on commonly encountered iatrogenic, non-hematopoietic solid tumors following immunotherapy and provides a practical approach to their diagnosis. All of the malignancies covered in this review are viral-induced. They include human papillomavirus (HPV)-associated carcinomas, Epstein-Barr virus (EBV)-associated tumors, Merkel cell polyomavirus (MCPyV)-related Merkel cell carcinoma, and Human Herpesvirus 8 (HHV8)-related Kaposi sarcoma. The complementary diagnostic role of ancillary studies, such as immunohistochemistry and in-situ hybridization that target these oncogenic viruses, is addressed.

## Introduction

The goal of immunosuppressive therapy (IT) is the reduction of normal immune response. IT is used in organ transplantation, bone marrow transplantation and to manage autoimmune diseases. The refinement of transplantation is one of the great achievements in modern medicine.[1,2] Immunosuppression can be produced by medication, surgery, plasmapheresis and/or radiation. IT has allowed significant improvement in the overall survival of transplant recipients and patients afflicted with debilitating autoimmune disease. The downside of chronic IT is that it exposes patients to potential long-term complications. One such complication is the increased risk of developing malignancy, including solid tumors, compared with that of the general population.[3] Iatrogenic solid tumors following IT can be of hematopoietic or non-hematopoietic origin. This review focuses on common iatrogenic non-hematopoietic solid tumors, mainly carcinomas (excluding cutaneous basal cell carcinomas) and sarcomas.

Most of the malignancies covered in this review are viral-induced. These include human papillomavirus (HPV)-associated carcinomas, Epstein-Barr virus (EBV)-associated tumors, Merkel cell polyomavirus (MCPyV)-related Merkel cell carcinomas, and Human Herpesvirus 8 (HHV8)-related Kaposi sarcomas. Other, more rare, entities that may be encountered in immunosuppressed patients are EBV-associated inflammatory pseudotumors (IMT),[4] cytomegalovirus (CMV)-associated pseudotumors,[5] histoplasmosis spindle cell tumors,[6] and EBV-associated interdigitating dendritic cell sarcomas.[7]

The surgical pathologist may face unique challenges in the evaluation of iatrogenic solid tumors following immunotherapy. These are often rare lesions characterized by odd presentations that exhibit morphologic overlap with comparable tumors. However, there are now novel ancillary tests that can be employed to complement morphology in order to render an accurate diagnosis. This review will discuss commonly encountered iatrogenic solid tumors following immunotherapy and provide a practical approach to their diagnosis.

## Incidence

According to a large cohort study of solid organ transplant recipients from the US, researchers noted that the most common non-hematopoietic malignancies were lung, liver and kidney cancer.[3] This study also found that the incidence of specific malignancies varied with the organ transplanted. For example, the incidence of lung tumors among lung transplant recipients was increased whereas for kidney transplant recipients there was an increase in the frequency of kidney cancer. In addition, cancerous skin lesions and uroepithelial carcinomas are also common among renal transplant recipients.[8] Table 1 lists the incidence of selected solid tumors reported in transplanted patients.

* Corresponding author.
*E-mail addresses:* Kossivi.Dantey@AHN.ORG (K. Dantey), pantanowitzl@upmc.edu (L. Pantanowitz).

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**Table 1**
Increased incidence of solid tumors after transplantation and immunotherapy.

| *Tumor* | *Incidence* |
|---|---|
| Kaposi sarcomas | 0.5–5.3%[9] |
| Merkel cell carcinomas | 0.4%[9] |
| EBV-related smooth muscle tumors | 1.67%[10] |
| Skin cancers (squamous cell carcinomas) | 7%[11]–82%[12] |

## Pathogenesis

The pathogenesis of iatrogenic solid tumors following IT is initiated by several factors including those directly related to IT (type of immunosuppressive drug, duration of immunosuppression) and other factors such as sun exposure, associated viral infection,[13] and in patients undergoing renal transplantation pre-transplantation dialysis.[14] Sun exposure combined with fair phenotypic features plays an important role in skin tumors after transplant, because of UV-induced p53 tumor-suppressor gene mutations.[15,16] HPV, EBV, MCPyV and HHV8 are all well-known carcinogenic viruses that plague immunosuppressed patients.[17,18] HHV8 is also known as Kaposi sarcoma-associated herpesvirus (KSHV). Even though these viruses belong to different families and exploit diverse strategies to promote cancer development, they share several features. One key attribute is their ability to infect, but not kill, their host cell and thereby establish long-term persistent infections. This sets the stage for a variety of molecular events that ultimately contribute to virus-mediated tumorigenesis. The identification of these viruses in IT-associated solid tumors can often help confirm their diagnosis.

## Carcinomas

### *HPV-associated squamous cell carcinomas (HPV-SCC)*

The development of HPV-associated carcinomas involving the genital (cervix, vagina, vulva, penis) and/or anal region is a major burden for patients on IT. Some authors have reported increased standardized incidence ratios (SIR) of such HPV-associated cancers in transplant patients compared to the general population.[19] The incidence of vulvar and vaginal carcinoma is highest (SIR 22.8) compared to cancer of the penis (SIR 15.7), cervix (SIR 2.1), and anus (SIR 4.9).[19] Non ano-genital skin in these patients can also be involved.[20] In fact, patients on IT are at risk for multiple cutaneous HPV-SCC that may behave aggressively.[21] Clinically, HPV-SCC presents as well circumscribed exophytic papules that may be flat or pedunculated.

Microscopic examination of HPV-SCC in immunosuppressed patients shows features that are morphologically similar to those seen in patients from the general population. Hence, they are infiltrative with moderate parakeratosis, epidermal cytologic atypia (Fig. 1, image 1), and keratin pearl formation. Malignant cells are characterized by having a moderate amount of eosinophilic cytoplasm and enlarged nuclei with hyperchromasia. High-risk features such as poor differentiation, acantholysis, spindled morphology, and perineural invasion can be present.[22] Cytokeratin immunoreactivity may be needed to differentiate poorly differentiated SCC from other tumors (e.g. melanoma, myeloid sarcoma). HPV positivity using immunocytochemistry or in-situ hybridization (Fig. 1, image 2) is very useful.

The differential diagnosis includes pseudoepitheliomatous hyperplasia, metastatic carcinoma (e.g. HPV-associated oropharyngeal SCC, lung or urothelial SCC), basal cell carcinoma (BCC), adnexal carcinomas, and melanoma. Exaggerated vulvar pseudoepitheliomatous hyperplasia may be associated with herpes infection in immunocompromised patients. A high index of suspicion and clinical presentation can help differentiate primary from metastatic disease. BCC can be distinguished by searching for specific morphologic features such as the presence of nests and islands of basaloid cells with palisading, and sometimes the attachment of tumor to overlying epidermis. Melanocytic immunohistochemical markers (e.g. S-100 protein, SOX-10, Melan-A, tyrosinase) are valuable for diagnosing melanoma.

### *Merkel cell carcinomas (MCC)*

MCC is a relatively rare cutaneous tumor that shows neuroendocrine differentiation. The head and neck area and extremities are most commonly involved. Clinically these lesions present as a solitary nodule or multiple dermal nodules ranging from 0.8 to 4 cm. It is now well established that patients exposed to long-term immunosuppression after organ transplant have an elevated risk of developing MCC.[18] Compared to sporadic cases, immunocompromised patients with MCC appear to manifest earlier and exhibit a more aggressive course of disease with poorer outcomes.[23] This might be due to the fact that MCPyV infection, which plays a role in the development of MCC, is exacerbated with an impaired immune system.[24]

Histological examination of MCC shows a proliferation of small round blue tumor cells arranged in a medullary (sheet-like) pattern (Fig. 2, image 1). Trabecular and organoid growth is less common. These cells have scant cytoplasm and round nuclei with slightly irregular nuclear contours and finely granular chromatin with inconspicuous nucleoli. Nuclear molding, frequent mitotic figures, and tumor necrosis are common. There can uncommonly be squamous or sarcomatous differentiation (Fig. 2, image 2). Immunohistochemical studies are usually needed to confirm the diagnosis. MCC has characteristic perinuclear staining with CK20. Neuroendocrine markers (CD56,

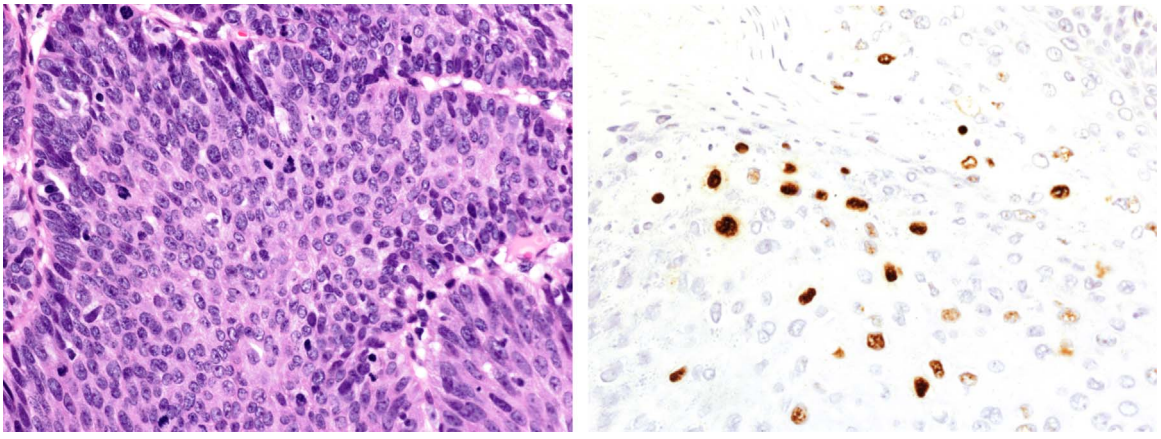

**Fig. 1.** Squamous cell carcinoma. (1) Invasive nest of squamous epithelium with moderate nuclear atypia and increased mitotic figures (H & E, 40 × magnification). (2). In-situ hybridization for HPV is positive in tumor cells (ISH, 40 × magnification).