Keratinocyte carcinomas arising near arteriovenous fistulas: Case series and safety considerations for dermatologic surgery

A report of the International Transplant Skin Cancer Collaborative

Olivia M. Lucero, MD,[a] Claudia Flores Echaiz, MD,[b] Fatemeh Jafarian, MD,[b] Matthew C. Fox, MD,[c] John T. Vetto, MD, FACS,[d] Reid V. Mueller, MD,[d] Pedro G. Teixeira, MD,[e] Fiona O. Zwald, MD,[f] and Justin J. Leitenberger, MD[a]
Portland, Oregon; Montreal, Canada; Austin, Texas; and Atlanta, Georgia

Key words: arteriovenous fistula; arteriovenous graft; basal cell carcinoma; hemodialysis access; renal transplant; skin cancer; squamous cell carcinoma.

INTRODUCTION

The prevalence of end-stage renal disease and renal transplants has risen dramatically over the past decade.[1] Patient populations with these conditions are of particular concern to dermatologists, given the increased risk for cutaneous malignancy in patients on dialysis and those with a kidney transplant.[2]

After renal transplantation, a functioning arteriovenous fistula or graft (AVF) is often maintained for potential future use. Ten-year renal transplantation graft failure rates have been reported as high as 36%.[3] AVFs are usually placed on the upper extremity, positioning a high-pressure circulatory network near the dermis in an area with ultraviolet exposure, which can present a problematic milieu for malignancies. Transplant patients are often immunosuppressed through endogenous and exogenous means with immunomodulatory agents that can be carcinogenic, further raising skin cancer risk.[4] Long-term AVFs might predispose patients to malignancy, considering that increased lymphatic workload with the potential for focal immunosuppression and frequent iatrogenic trauma both accelerate carcinogenesis.[5,6] Van Hoek et al, who described multiple squamous cell carcinomas (SCCs) arising distal to an AVF site, concluded that regional ischemia from distal hypoperfusion resulted in an accumulation of immunosuppressive agents and oxidative damage.[7] Although an analysis of 68 renal transplant patients did not reveal a significant difference between the number of cancers on limbs with and without fistulas, it is not surprising that cancers occur near fistulas given the collective risk.[5] Although poor outcomes have not yet been reported in the literature, thoughtful and strategic care is necessary given the potentially devastating complications that could arise from damage to an AVF during cutaneous surgery.

Abbreviations used:

AVF:	arteriovenous fistula or graft
CT:	computed tomography
KC:	keratinocyte carcinoma
MRI:	magnetic resonance imaging
SCC:	squamous cell carcinomas

From the Department of Dermatology, Oregon Health and Sciences University, Portland[a]; Division of Dermatology, McGill University Health Center, Montreal[b]; Department of Dermatology, Dell Medical School, University of Texas at Austin[c]; Department of Surgery, Oregon Health and Sciences University, Portland[d]; Department of Surgery and Perioperative Care, Dell Medical School, University of Texas at Austin[e]; and Piedmont Healthcare, Atlanta.[f]

Funding sources: None.
Conflicts of interest: None disclosed.
Previously presented: Oregon Dermatology Society meeting in Portland, Oregon in November 2017.

Correspondence to: Justin J. Leitenberger, MD, Oregon Health and Sciences University Center for Health and Healing, 3303 SW Bond Ave, Ste 16D, Portland, OR 97239. E-mail: leitenbe@ohsu.edu.

JAAD Case Reports 2019;5:7-11.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.08.021

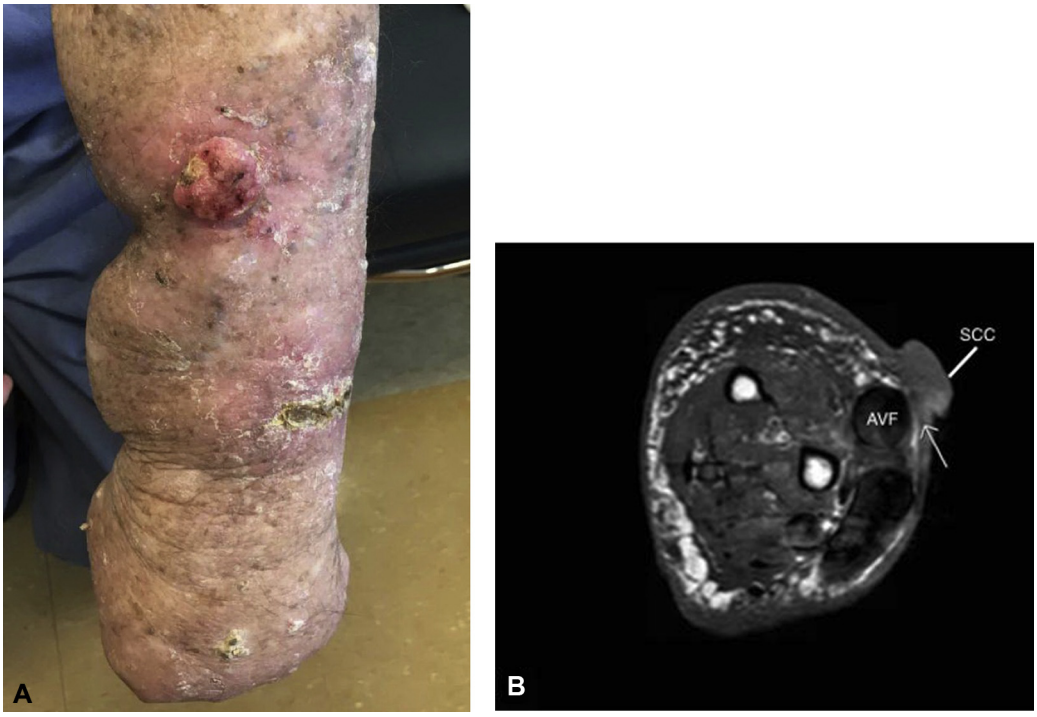

Fig 1. Clinical image (**A**) and magnetic resonance image (**B**) of patient 1, illustrating SCC overlying patent AVF on edematous arm. *Long arrow* delineates border of SCC, indistinct due to edema and lack of contrast. *AVF*, Arteriovenous fistula or graft; *SCC*, squamous cell carcinoma.

CASE SERIES

Patient 1

A 74-year-old incarcerated man presented with an enlarging 4 x 3—cm SCC located over a radiocephalic AVF on his left forearm (Fig 1, *A*). His history was significant for an AVF placed in 1988 for end-stage renal disease, a renal transplant in 1989, and multiple keratinocyte carcinomas (KCs). He had lymphedema of the ipsilateral limb attributed to the fistula. Magnetic resonance imaging (MRI) without gadolinium (due to low glomerular filtration rate) showed a superficial skin nodule, although evaluation of its extension was limited by lack of contrast and edema (Fig 1, *B*). Given the tumor proximity to the AVF, the patient was referred to surgical oncology for excision under general anesthesia. Vascular surgery was available to ligate the fistula intraoperatively; however, the tumor was successfully excised without disturbing the AVF. The wound underwent a linear repair. His postoperative course was complicated by a superficial bacterial infection treated with sulfamethoxazole/trimethoprim, and he was noted to have healed without complication 6 months later.

Patient 2

A 61-year-old woman with a history of cystinosis, 2 renal transplantations (performed in 1971 and 2008), and multiple KCs presented with a 5 x 5—cm fungating and eroded nodular basal cell carcinoma on the left forearm over a previously utilized functional radiocephalic AVF (Fig 2, *A*). An MRI revealed no vessel invasion (Fig 2, *B*). Plastic and vascular surgery planned a joint procedure under anesthesia. The fistula was ligated intraoperatively due to concern of positive deep margins, and she underwent successful excision of the tumor with 2-cm margins. The defect was repaired with a split thickness skin graft. The patient recovered well with no complications from her ligation noted 6 months later.

Patient 3

A 71-year-old woman with a history of polycystic kidney disease and renal transplantation in 2005 presented with a firm, enlarging poorly differentiated SCC on her left forearm located 2 mm from a previously utilized functional brachiocephalic loop graft. Ultrasound demonstrated a 3.8-mm distance between the deepest lesion margin and the AVF. During vascular surgery, the lesion was excised with 1-cm peripheral margins with depth to the level of the AVF under general anesthesia. Intraoperatively, the portion of the specimen directly overlying the graft was sharply dissected to achieve negative margins, resulting in complete visualization of the

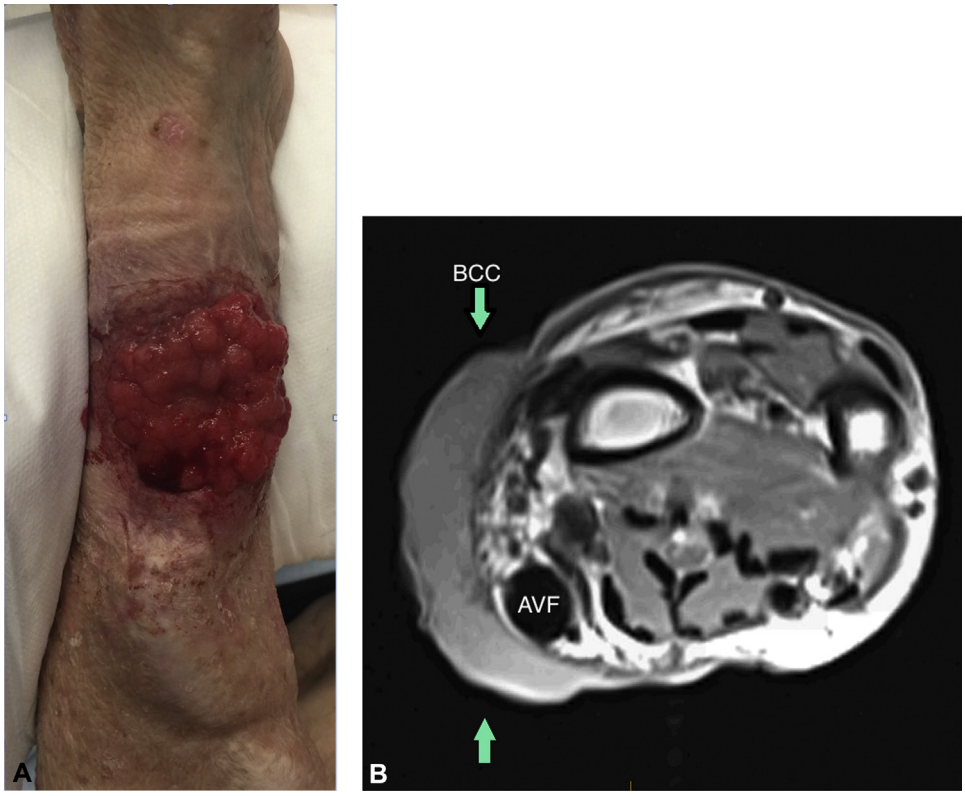

Fig 2. **A**, Clinical picture of basal cell carcinoma (*arrows*) of patient 2 before intraoperative AVF ligation and excision. **B**, Magnetic resonance image demonstrates a predominantly cutaneous and subcutaneous mass with proximity but no invasion of fistula. *AVF*, Arteriovenous fistula or graft.

Fig 3. Clinical picture of SCC of patient 4 (*circled*). The border of the brachial artery proximal to the arteriovenous fistula or graft is delineated by *red dashed lines*. Patient details have been obscured. *SCC*, Squamous cell carcinoma.

surface of the AVF. The wound underwent a linear closure with a fully functioning and intact AVF. Pathology confirmed negative margins.

Patient 4

A 71-year-old woman with a history of multiple KCs and a renal transplant in 2011 presented with a 1-cm SCC on her left anterior shoulder overlying the proximal segment of a previously utilized functional brachiobasilic AVF placed in 2008 (Fig 3). The tumor was able to be displaced from the vessel, and Mohs micrographic surgery was successfully undertaken with linear repair and no damage to the vessel. The area healed well, and no complications were noted 3 months postoperatively.

DISCUSSION

The skin overlying an arteriovenous hemodialysis access site can present a unique challenge in dermatologic surgery. Given the potential complications of laceration and hemorrhage in the outpatient surgical setting, thoughtful and strategic presurgical planning should be undertaken.

Organ transplant recipients and those with iatrogenic immunosuppression are at risk for high-risk cutaneous malignancies, including locally recurrent and metastatic disease. Initial evaluation should include a regional lymph node exam to evaluate

for locoregional progression.[4] Tumor staging with high-risk features, particularly SCC in the Brigham and Women's Hospital T2b category or higher, warrant additional staging workup with imaging for metastatic disease.[8] The presence of palpable lymph nodes should prompt evaluation by fine needle aspiration or a core biopsy and imaging.[9]

Physical examination should also include evaluation of the AVF. The most common location for vessel anastomosis is between the radial artery and the cephalic vein or between the brachial artery and the cephalic or basilic vein.[10] This anatomic knowledge is key as excessive dilation of the vessel can occur proximally and distally to the site of anastomosis, complicating cutaneous intervention along the entire length of the limb. Case 4 highlights the subtle challenges that occur when patients do not have a visually apparent AVF, which might offer an illusion of safety while performing cutaneous surgery. Determination of vessel patency is important, considering that stenosis can occur in the absence of a ligation procedure.[11] Mature AVFs will often have a palpable thrill that indicates a functioning circuit. Imaging should be used when the examination is not revealing or reassuring.

If the tumor is mobile and the skin displaces easily away from the AVF, then excisional surgery, curettage, and electrodessication might be appropriate. Tumors tethered and immobile or those of unclear depth require imaging to determine AVF proximity. Imaging modalities to assess KC extension and aid in preoperative planning include MRI, computed tomography (CT), and ultrasound. MRI is the most useful in assessing soft tissue extension and involvement of critical structures, such as nerves and ligaments, while also enabling the determination of the margin proximity to the AVF.[12] Creatinine level should be obtained before using contrast because many renal transplant patients have a decreased glomerular filtration rate.[13] Ultrasound, as demonstrated in patient 3, can also adequately determine tumor margins and proximity to vascular structures.[14] CT is best to use when concerned about bony invasion but, compared with MRI, lacks the contrast achieved in soft tissue assessment.[9,12] Of note, multiple imaging modalities, including positron-emission tomography/CT scanning, might be necessary when evaluating for metastatic disease.

Thoughtful preparation for repairing the wound might be indicated before surgery. Tissue laxity availability to close the defect away from the fistula prevents adhesion to the underlying vessel during healing. Furthermore, therapeutic access to a utilized AVF should not be impaired with postoperative bandages.

If the tumor is nondisplaceable above the fistula or if the repair requires extensive undermining for closure of the defect, surgical care in the operating room setting is often preferred. A nephrology consultation to determine utility of the fistula is important. Maintenance of a nonfunctioning AVF in a transplant patient is not always necessary nor advisable, given potential consequences of increased cardiac output and pulmonary artery pressure.[15] Vascular surgery specialists may recommend temporary or permanent intraoperative ligation should the need arise from bleeding or a positive deep margin, the latter of which was the case for patient 2. Complete histologic clearance should be achieved. Patients that have positive margins despite surgical intervention should be considered for adjuvant therapy as guided by the National Cancer Center Network.[9]

Caution should be considered for use of photodynamic therapy or topical 5-fluorouracil due to the risk for ulceration, necrosis, or inadequate penetration.[16,17] Electron beam radiation therapy should also be used with caution because of the risk for soft tissue necrosis, although this has been successfully used with multidisciplinary planning in a case of SCC arising over an AVF.[6,18] Radiation oncologic specialists can titrate electron energy to optimize treatment depth so as to not penetrate the vessel.[6] For basal cell carcinoma, smoothened inhibitors may be a considered; however, necrosis, incomplete response, and recurrence are limitations to its use.[19] A delay in definitive treatment could result in further vertical growth.

A discussion of the risks of surgical intervention, as is appropriate for informed consent, is warranted before beginning the procedure. This includes the risks of AVF ligation and general anesthesia, as well as the complications of infection, recurrence, scar, nerve damage, pain, and bleeding.

In conclusion, these cases demonstrate the importance and success of a strategic, thoughtful, and multidisciplinary approach to KCs arising over an AVF to prioritize patient safety.

REFERENCES

1. United States Renal Data System. *2016 USRDS annual data report: an overview of the epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016. Available at: http://www.usrds.org/2016/view/.
2. Shang W, Huang L, Li L, et al. Cancer risk in patients receiving renal replacement therapy: a meta-analysis of cohort studies. *Mol Clin Oncol*. 2016;5(3):315-325.
3. United States Renal Data System. *2014 USRDS annual data report: an overview of the epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health,

National Institute of Diabetes and Digestive and Kidney Diseases; 2014. Available at: http://www.usrds.org/2014/view/
4. Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. *Br J Dermatol*. 2008;158(2):217-224.
5. Bordea C, Cortina-Borja M, Wojnarowska F, Morris PJ. Distribution of upper limb skin cancers in relation to arteriovenous fistula side in renal transplant recipients. *Transplantation*. 2001;71(1):143-145.
6. Nath NS, Gilmore BF, McCann RK, Mosca PJ. Management of a cutaneous squamous cell carcinoma overlying an AV fistula. *BMJ Case Rep*. May 6, 2017;2017. pii:bcr-2016-218932.
7. Van Hoek F, Van Tits HW, Van Lijnschoten I, De Haas BD, Scheltinga MR. Multiple carcinomas in the hemodialysis access induced ischemic hand of a renal transplant patient. *Eur J Dermatol*. 2010;20(2):214-216.
8. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol*. 2013;149(4):402-410.
9. National Comprehensive Cancer Network. Squamous cell skin cancer (version 2.2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed June 1, 2018.
10. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis*. 2006;48(Suppl 1):S2-S90.
11. Teodorescu V, Gustavson S, Schanzer H. Duplex ultrasound evaluation of hemodialysis access: a detailed protocol. *Int J Nephrol*. 2012;2012:508956.
12. Humphreys TR, Shah K, Wysong A, Lexa F, MacFarlane D. The role of imaging in the management of patients with nonmelanoma skin cancer: when is imaging necessary? *J Am Acad Dermatol* 2017;76(4):591-607.
13. Gourishankar S, Hunsicker LG, Jhangri GS, et al. The stability of the glomerular filtration rate after transplantation is improving. *J Am Soc Nephrol*. 2003;14:2387-2394.
14. Song WJ, Choi HJ, Lee YM, et al. Clinical analysis of an ultrasound system in the evaluation of skin cancers: correlation with histology. *Ann Plast Surg*. 2014;73(4):427-433.
15. Voorzaat BM, van Schaik J, Siebelink HM, Tordoir JH, Rotmans JI. The pros and cons of preserving a functioning arteriovenous fistula after kidney transplantation. *J Vasc Access*. 2016;17(1):S16-S22.
16. Sturm HM. Bowen's disease and 5-fluorouracil. *J Am Acad Dermatol*. 1979;1(6):513.
17. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol*. 2013;27(5):536-544.
18. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. *Int J Radiat Oncol Biol Phys*. 2001;51(3):748-755.
19. Guo D, Kossintseva I, Leitenberger J. Neoadjuvant vismodegib before Mohs: lack of tissue sparing and squamous differentiation of basal cell carcinoma in a patient With chronic lymphocytic leukemia. *Dermatol Surg*. 2016;42(6):780-783.