Recurrent and metastatic squamous cell carcinoma in lung transplant recipient on voriconazole: Lessons learned

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Key words: adjuvant radiation therapy; high risk squamous cell carcinoma; lung transplantation; voriconazole.

INTRODUCTION

The increased incidence of aggressive cutaneous squamous cell carcinoma (C-SCC) is well known in the immunosuppressed, solid organ transplant population. Heart and lung transplant recipients are particularly at risk for aggressive C-SCC development given their more intensive immunosuppression regimens and older age at time of transplant.[1] In organ transplant recipients, the risk of metastasis is also higher than that in the general population and estimated to be approximately 7% to 8%.[2,3] Here we describe a patient who underwent bilateral lung transplantation who, after prophylaxis with voriconazole therapy, had uncontrolled, recurrent, and ultimately metastatic C-SCC. This case report illustrates the aggressive nature of transplant-related C-SCC, which may often be accelerated by voriconazole.

We discuss the management decisions that were made and illustrate the challenges in managing large, recurrent tumors. We also briefly review the current literature on voriconazole-associated squamous cell carcinomas (SCCs), and propose that early, aggressive surgical management may have prevented poor outcomes.

CASE

A 63-year-old white man with a history of end-stage lung disease secondary to emphysema underwent a bilateral lung transplant in June 2009. Immediately after the transplant the patient was treated with intravenous basiliximab and a 3-drug immunosuppression regimen consisting of prednisone at 15 mg daily, tacrolimus at 4 mg twice daily,

Abbreviations used:	
C-SCC:	cutaneous squamous cell carcinoma
MMS:	Mohs micrographic surgery
SCCs:	squamous cell carcinomas

and azathioprine at 150 mg daily. Voriconazole for antifungal prophylaxis was also initiated at 200 mg twice daily. The prednisone dose was weaned to 5 mg daily by the fourth month postoperatively.

In February 2011, his transplant team referred him to the dermatology department to evaluate a large, growing lesion of his left forearm. Physical examination found a 7.0-cm × 5.5-cm exophytic tumor without background actinic keratosis or field disease (Fig 1, *A*). Punch biopsy of the left forearm lesion found poorly differentiated C-SCC infiltrating to the subcutaneous fat (Fig 1, *B* and *C*). There was also evidence of perineural invasion (not shown). Mohs micrographic surgery (MMS) was performed, and the lesion was cleared with negative margins after 2 stages. This finding was confirmed on permanent formalin-fixed sections of the resected tissue. The defect was subsequently repaired with a full-thickness skin graft. At this time, voriconazole was also discontinued, and azathioprine was decreased to 50 mg daily with eventual discontinuation at tumor recurrence.

In May 2011, the patient was hospitalized after a motor vehicle accident. During that time, he was found to have recurrence of the primary C-SCC on the left forearm (Fig 1, *D*) along with newly developed in-transit metastases to the elbow. Positron emission tomography scan at the time
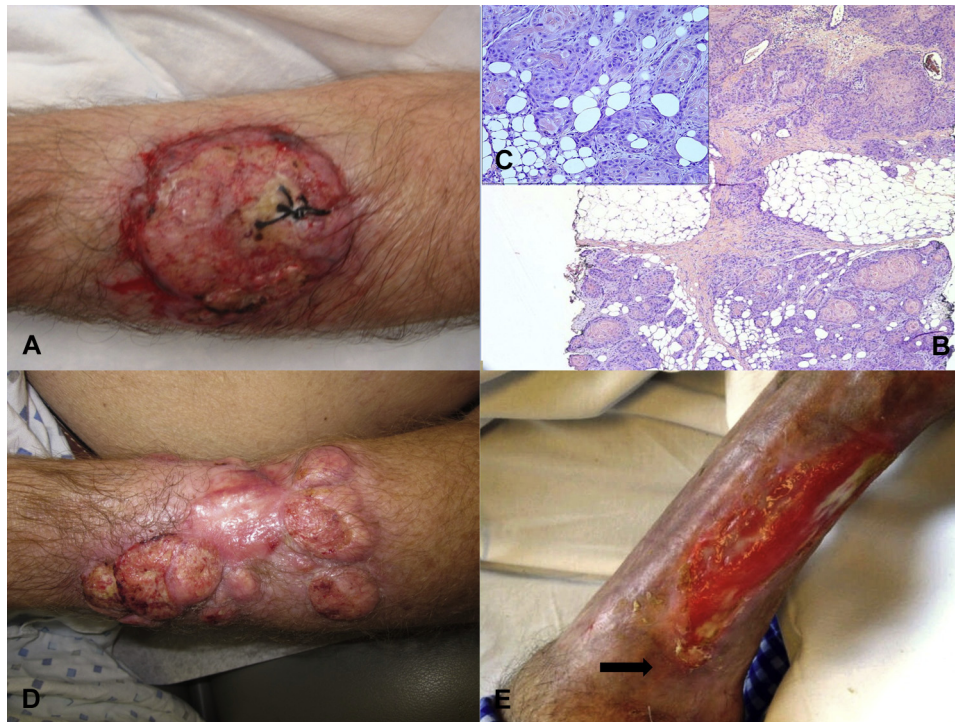
Fig 1. A, SCC in double-lung transplant recipient on voriconazole. There is no background actinic keratosis or field disease. **B** and **C**, Biopsy results show poorly differentiated SCC deeply infiltrating to subcutaneous fat on high-power view (**C**, inset). There was evidence of perineural invasion (not shown). **D**, Recurrence of aggressive SCC 2 months after MMS with negative margins confirmed on formalin-fixed tissue. **E**, Recurrence at radiation site.

showed several areas of increased metabolic activity within the left upper extremity concerning for metastases. Fine-needle aspiration was attempted but was unsuccessful because of difficulty accessing the lymph nodes, as the patient sustained a compound fracture of the left humerus. The patient was referred to the surgical oncology and radiation oncology departments for further treatment. The collective decision was to proceed with preoperative radiation therapy before further surgical intervention. In the months following, the patient was treated with radiation (total dose, 52 Gy) to only the primary site, to which he showed incomplete response. Because of difficulties mobilizing his arm after his accident, the other lesion near his elbow could not be irradiated.

In October 2011, his recurrent tumor measured approximately 10 × 8 × 1 cm on his left forearm, and the tumor on his left elbow measured approximately 5 × 4 × 2 cm. He also had palpable adenopathy by this time. The 2 tumors were surgically removed and 2 left epitrochlear nodes were biopsied. Both nodes were positive for SCC. A complete lymph node dissection was subsequently performed in the left axilla; 3 of 28 lymph nodes were positive with extranodal extension. In November and December,

there was evidence of clinical recurrence in the irradiated area, in the axilla, and 3 satellite lesions surrounding the primary tumor site in the left forearm (Fig 1, *E*). All of these were resected. His immunosuppressive medications were revised to sirolimus at 2 mg daily (from tacrolimus). By now, the patient also had a painful lesion on the dorsal part of the right hand. MMS was offered for this lesion, and the hematology/oncology department recommended starting cetuximab/radiation therapy for axillary disease and recurrence. However, the patient declined further treatments. Despite medical advice, he voluntarily discontinued all his immunosuppressive medications and died as a result of septic shock secondary to multilobar pneumonia.

DISCUSSION

This case illustrates advanced C-SCC in an immune-suppressed double-lung transplant recipient after voriconazole prophylaxis. Voriconazole is a widely prescribed antifungal medication used for prevention and treatment of invasive fungal infections in organ transplant recipients.[4] Many case reports describe skin cancer, particularly C-SCC, after photosensitivity reactions in both adult and pediatric patients receiving long-term voriconazole

therapy.[5-11] Almost all patients were immunosuppressed, including stem cell and solid organ transplant recipients. The large number of reported cases inspired several cohort studies that established voriconazole as an independent risk factor for the development of cutaneous malignancy in lung transplant recipients.[4,12-15]

One case-control study of lung transplant recipients identified long-term voriconazole (median cumulative dose, 76 g) and residence in areas of strong sun exposure as independent risk factors for C-SCC.[14] Another study suggests that voriconazole-associated C-SCC was more aggressive compared with non—voriconazole-associated C-SCC.[15] Although the mechanisms by which voriconazole may predispose to skin cancer are not entirely clear, phototoxicity associated with voriconazole has been reported, and primary metabolite voriconazole N-oxide may be involved.[5,16] A recent review synthesizes the current data on this topic.[16]

Currently, no guidelines exist to standardize prophylactic administration of voriconazole. However, because of the potential risk of skin cancer in long-term voriconazole use, the US Food and Drug Administration has altered its labeling to state that voriconazole should be used carefully for durations greater than 6 to 9 months, particularly among patients with risk factors for skin cancer. In general, for patients requiring prolonged voriconazole, diligent skin examinations, avoidance of excess sunlight, and liberal use of ultraviolet protectants are advisable.

For a patient with transplant-associated C-SCC, MMS with clear margins is the recommended approach to achieve locoregional control.[17,18] In the transplant population, C-SCCs have a higher propensity to recur and metastasize.[3,19] Therefore, treating C-SCCs at an early stage and achieving locoregional control is crucial in the treatment of these patients.[20] Nodal metastases are more likely to occur when a combination of high-risk features are present.[20] These features include size (>2 cm), depth of invasion, poor differentiation, previous radiation therapy, perineural invasion, and recurrence.[17,21] This profile is consistent with that of the patient we describe.

Adjuvant radiotherapy is often proposed for postsurgical management when excision is incomplete, for a nonsurgical candidate, or in the setting of dermal metastases to improve local control and prevent recurrence.[20,22] In this patient, radiotherapy was chosen to reduce the size of the tumor followed by surgical extirpation. However, given the aggressive nature of the tumor, radiation therapy may not have been optimal. Particularly with high-risk, recurrent C-SCCs, expedited surgical extirpation with wide margins, followed by radiation therapy, may have offered a better opportunity for disease control.

All patients exposed to voriconazole should be educated about the increased risk of skin cancer and should have regular dermatologic follow-up for skin cancer screening. Physicians caring for lung-transplant recipients should consider alternatives to voriconazole in patients at risk for skin cancer. Treatment for transplant-associated C-SCC should include aggressive surgical intervention. Finally, awareness of the patient's quality of life and respect for patient autonomy cannot be overlooked. The morbidity associated with transplant-related aggressive skin cancer is considerable, and we must also respect the patient's decision to discontinue care.

REFERENCES

1. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol*. 2011;65(2):253-261. quiz 262.
2. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47(1):1-17.
3. Sheil AG, Disney AP, Mathew TH, Amiss N. De novo malignancy emerges as a major cause of morbidity and late failure in renal transplantation. *Transplant Proc*. 1993;25:1383-1384.
4. Singer JP, Boker A, Metchnikoff C, et al. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. *J Heart Lung Transplant*. 2012;31(7):694-699.
5. Cowen EW, Nguyen JC, Miller DD, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *J Am Acad Dermatol*. 2010;62(1):31-37.
6. Ibrahim SF, Singer JP, Arron ST. Catastrophic squamous cell carcinoma in lung transplant patients treated with voriconazole. *Dermatol Surg*. 2010;36(11):1752-1755.
7. Wong JY, Kuzel P, Mullen J, et al. Cutaneous squamous cell carcinoma in two pediatric lung transplant patients on prolonged voriconazole treatment. *Pediatr Transplant*. 2014;18(6):E200-E207.
8. Epaulard O, Saint-Raymond C, Villier C, et al. Multiple aggressive squamous cell carcinomas associated with prolonged voriconazole therapy in four immunocompromised patients. *Clin Microbiol Infect*. 2010;16(9):1362-1364.
9. Vanacker A, Fabre G, Van Dorpe J, Peetermans WE, Maes B. Aggressive cutaneous squamous cell carcinoma associated with prolonged voriconazole therapy in a renal transplant patient. *Am J Transplant*. 2008;8(4):877-880.
10. Morice C, Acher A, Soufir N, et al. Multifocal aggressive squamous cell carcinomas induced by prolonged voriconazole therapy: a case report. *Case Rep Med*. 2010;2010:351084.
11. McCarthy KL, Playford EG, Looke DF, Whitby M. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. *Clin Infect Dis*. 2007;44(5):e55-e56.
12. Zwald FO, Spratt M, Lemos BD, et al. Duration of voriconazole exposure: an independent risk factor for skin cancer after lung transplantation. *Dermatol Surg*. 2012;38(8):1369-1374.

13. Epaulard O, Villier C, Ravaud P, et al. A multistep voriconazole-related phototoxic pathway may lead to skin carcinoma: results from a French nationwide study. *Clin Infect Dis*. 2013;57(12):e182-e188.

14. Vadnerkar A, Nguyen MH, Mitsani D, et al. Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients. *J Heart Lung Transplant*. 2010;29(11): 1240-1244.

15. Feist A, Lee R, Osborne S, Lane J, Yung G. Increased incidence of cutaneous squamous cell carcinoma in lung transplant recipients taking long-term voriconazole. *J Heart Lung Transplant*. 2012;31(11):1177-1181.

16. Williams K, Mansh M, Chin-Hong P, Singer J, Arron S. Voriconazole-associated cutaneous malignancy: a literature review on photocarcinogenesis in organ transplant recipients. *Clin Infect Dis*. 2014;58(7):997-1002.

17. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol*. Aug 2011;65(2):263-279. quiz 280.

18. Stasko T, Brown M, Carucci J, et al. Guidelines for the management of squamous cell carcinoma in organ transplant recipients. *Dermatol Surg*. 2004;30:642-650.

19. Carucci JA, Martinez JC, Zeitouni NC, et al. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics, management, and outcome in a series of 21 patients. *Dermatol Surg*. 2004;30:651-655.

20. Veness MJ, Harris D. Role of radiotherapy in the management of organ transplant recipients diagnosed with non-melanoma skin cancers. *Australas Radiol*. 2007;51(1):12-20.

21. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. *Dermatol Surg*. 2002;28:268-273.

22. Babington S, Veness MJ, Cakir B, Gebski VJ, Morgan GJ. Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision? *ANZ J Surg*. 2003;73:621-625.