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

Shali Zhang, MD,[a] David C. Neujahr, MD,[b] and Fiona O. Zwald, MD[c]
Atlanta, Georgia

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.

Abbreviations used:

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

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, 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

From the Department of Dermatology, Emory University School of Medicine[a]; Emory University Transplant Center[b]; and Piedmont Transplant Institute, Dermatology Consultants.[c]

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: Fiona O. Zwald, MD, Piedmont Transplant Institute Dermatology Consultants, PC, 2045 Peachtree Street, Atlanta, GA 30309. E-mail: fiona.zwald@gmail.com.

JAAD Case Reports 2015;1:S12-5.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.09.015

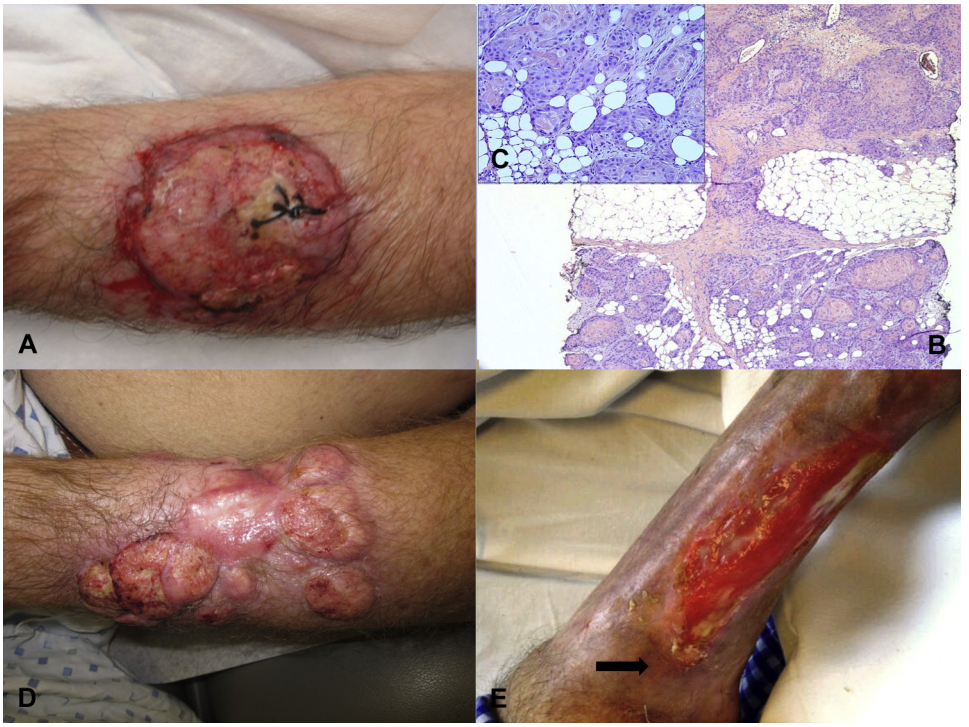

Fig 1. A, SCC in double-lung transplant recipient on voriconazole. There is no background actinic keratosis or field disease. **B** and **C**, Biopsy results show poorly differentiated SCC deeply infiltrating to subcutaneous fat on high-power view (**C**, inset). There was evidence of perineural invasion (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 $10 \times 8 \times 1$ cm on his left forearm, and the tumor on his left elbow measured approximately $5 \times 4 \times 2$ 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