Immune checkpoint inhibitor therapy in a liver transplant recipient with autoimmune disease and metastatic cutaneous squamous cell carcinoma

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INTRODUCTION

Clinical trials investigating immune checkpoint inhibitors (ICIs) largely excluded solid organ transplant recipients (SOTRs), as immunostimulation by these drugs may subvert host tolerance to the transplanted tissue, potentially leading to allograft rejection.[1] Consequently, data concerning the safety and efficacy of ICIs in these patients remain limited. ICI trials also routinely excluded patients with preexisting autoimmune disease given the concern for possible disease exacerbations, resulting in similarly limited data in this population.[2] We report a unique case of a SOTR with ulcerative colitis (UC) and metastatic cutaneous squamous cell carcinoma (SCC) who was successfully treated with anti-programmed cell death protein 1 ICI therapy, initially with nivolumab, then with cemiplimab, which is approved by the US Food and Drug Administration for advanced cutaneous SCC.[3]

Abbreviations used:

ICI:	immune checkpoint inhibitors
SCC:	squamous cell carcinoma
PET-CT:	positron emission tomography-computerized tomography
RT:	radiation therapy
SOTR:	solid organ transplant recipient
TMB:	tumor mutational burden
UC:	ulcerative colitis

CASE REPORT

A 58-year-old man with longstanding UC underwent a liver transplant at the age of 37 for primary sclerosing cholangitis-related liver disease and was subsequently on tacrolimus 1 mg daily for immunosuppression. His UC was well-controlled with long-term prednisone 10 mg daily and infliximab 400 mg every 8 weeks. In November 2016, he developed a 7-mm hyperkeratotic papule on the left forearm. Shave biopsy, electrodessication, and curettage were performed. Histopathology demonstrated a moderately differentiated cutaneous SCC and the lesion was considered to be fully treated.

In June 2017, he developed a 6 x 6-cm left axillary mass. Ultrasound-guided fine needle aspirate revealed a poorly differentiated epithelial malignancy with extensive necrosis. Complete resection of the mass was performed, and pathology demonstrated a metastatic moderately differentiated SCC. Extensive extranodal involvement, and perineural and lymphovascular invasion were identified. Staging computerized tomography (CT) showed no sites of disease elsewhere. Cisplatin was initiated but was discontinued after one dose due to symptomatic ototoxicity. He subsequently completed adjuvant

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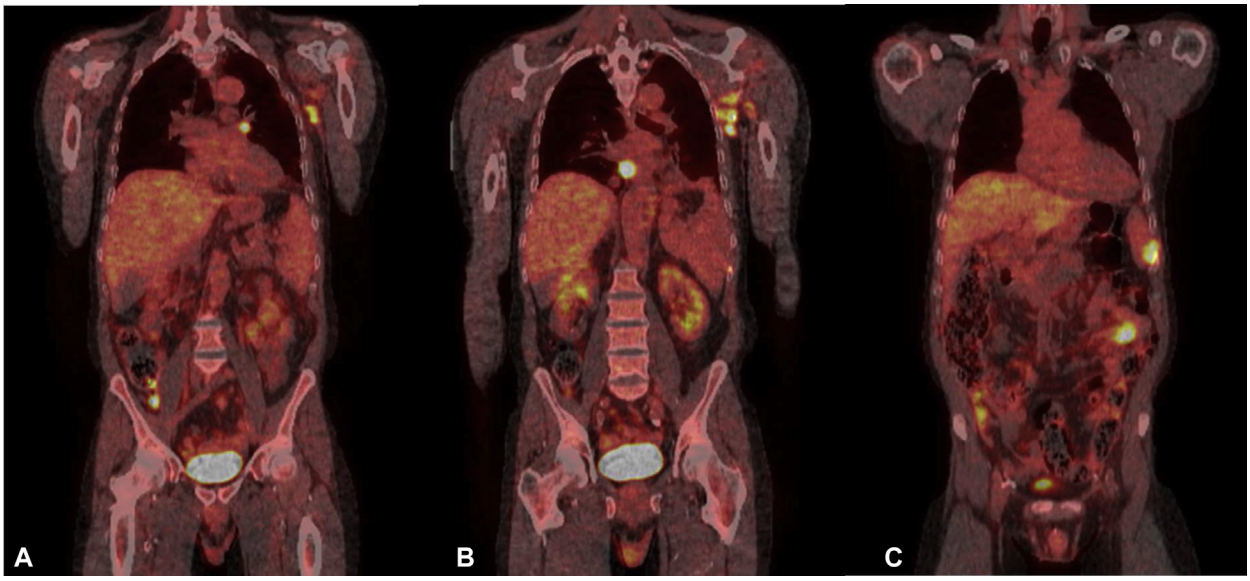

Fig 1. A-C, Cutaneous squamous cell carcinoma; axillary lymphadenopathy with metastases to the left hilar region, right subcarinal/paraesophageal region, and left chest wall, prior to nivolumab initiation (PET-CT). *PET-CT*, Positron emission tomography-computerized tomography.

radiation therapy (RT) (30 fractions of 6000 cGy to the left axilla) with concurrent chemotherapy (7 cycles of cetuximab).

Restaging positron emission tomography-CT (PET-CT) in January 2018 showed hypermetabolic lymphadenopathy in the left axilla and new hypermetabolic pleural, subpleural, and retrocrural deposits, consistent with metastatic disease progression. Nodal biopsies confirmed metastatic SCC. Tacrolimus dose was decreased from 1.0 to 0.5 mg to improve the antitumoral immune response. For his UC, vedolizumab was initiated and infliximab was discontinued to decrease systemic immunosuppression associated with antitumor necrosis factor therapy. He remained on prednisone 10 mg daily. Four cycles of carboplatin and paclitaxel were administered and then discontinued due to a severe UC flare. Follow-up PET-CT in April 2018 demonstrated a worsening of metastatic disease with enlarging axillary lymphadenopathy, as well as new and enlarging left hilar, right subcarinal/paraesophageal, and left chest wall deposits (Fig 1, *A-C*).

Genome evaluation with TempusXT and FoundationOne CDx platforms was pursued to investigate actionable treatments, revealing a high tumor mutational burden (TMB) of 44 mutations/megabase.[4] High TMB ($\geq$10 mutations/megabase) is a treatment indication for immunotherapy and more than half of cutaneous SCC tumors exhibit high TMB.[5] Understanding the risks of liver allograft rejection and severe colitis, a decision was made to begin nivolumab. In preparation, mycophenolate 1000 mg daily was added to his immunosuppression regimen of tacrolimus and prednisone. In May 2018, he initiated nivolumab 240 mg every 2 weeks. One month later, he completed hypofractionated RT to the left axilla, right paraesophageal lymph node, and left posterior chest wall to induce an intended abscopal effect. Six months following nivolumab initiation, PET-CT revealed a small area of uptake in the left axilla but no other sites of residual disease. Biopsy of the left axillary mass again revealed metastatic SCC, following which he received 5 fractions of 3000 cGy RT to the area. Subsequent imaging every 3 months demonstrated a continued but decreased uptake in the left axilla, with no other sites of disease (Fig 2).

The patient remained on nivolumab for 15 months with brief interruptions but without significant toxicity, colitis, or evidence of liver allograft rejection. For his UC, he remained on vedolizumab throughout nivolumab therapy. Based on the favorable clinical response and potential side effects of triple immunosuppression, nivolumab was discontinued in August 2019. Follow-up PET-CT in June 2020 showed further evolution of metastatic disease in the left axilla. The patient restarted immunotherapy but was switched to cemiplimab 350 mg every 3 weeks. At present, he has completed 2 cycles. Repeat imaging to assess response is scheduled following the completion of 4 cycles; however, cemiplimab is currently on hold due to a

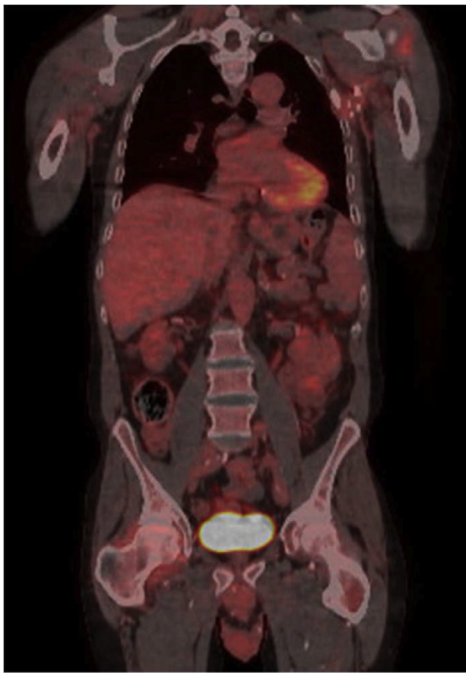

Fig 2. Cutaneous squamous cell carcinoma; continued but decreased uptake in the left axilla with no other sites of active disease, demonstrating durable response after 15 months of treatment with nivolumab (PET-CT). *PET-CT*, Positron emission tomography-computerized tomography.

hospitalization for stroke and left axillary wound infection. We hope that with reinitiation of immunotherapy, the tumor can be controlled without subjecting the patient to aggressive surgical procedures, such as limb amputation.

DISCUSSION

This case adds to the growing but still limited body of literature concerning ICI therapy in SOTRs and those with autoimmunity. The concurrence of both autoimmune disease and history of liver transplantation in our patient made the decision to initiate immunotherapy particularly challenging. However, failure of chemoradiation and high TMB supported immune checkpoint blockade as a reasonable therapeutic strategy. High TMB is a common feature of cutaneous SCC, and given that tumors with high TMB are particularly susceptible to ICIs,[5] they are now considered to be first-line therapies for advanced cutaneous SCC.[6]

All the target areas in our patient sustained an excellent treatment response except for the left axilla. The treatment resistance of the left axilla may have been due to impaired lymphatics and/or vasculature from prior radiation and surgery, preventing the trafficking of the immune cells to the area.[7] Although, radiation may have played an immunostimulatory role in regions outside the irradiated fields by enhancing tumor cell lysis and exposing neoantigens to CD8 T cells, thereby potentiating the antitumoral effects of ICI therapy. This synergism between RT and immunotherapy, known as the abscopal effect, is an increasingly recognized phenomenon in metastatic malignancies,[8] and possibly contributed to our patient's positive response to therapy.

While greater immunosuppression potentially counteracts the intended cell-mediated effects of ICIs, multiple reports exist of SOTRs on multiagent immunosuppression who experienced positive responses to immunotherapy.[1,9] In our patient, ICI therapy was generally well tolerated and he displayed no evidence of allograft rejection or colitis, which may be attributed to his multidisciplinary pretreatment optimization of antirejection medications. In SOTRs on ICIs, the rate of allograft rejection is lower in patients on multiple immunosuppressive medications than in those on single-agent therapies.[1]

Approximately 40% of SOTRs who receive ICIs for metastatic cancer experience graft rejection, which carries a high mortality risk.[1,9] However, a systematic review revealed more deaths resulting from metastatic disease progression than from graft failure in these patients, providing support for the use of immunotherapy in SOTRs with aggressive forms of cancer.[9] Our patient's excellent response with minimal toxicity underscores the promise of ICIs in SOTRs with metastatic cancer and concomitant autoimmunity. However, the lack of rejection in our patient cannot necessarily be extrapolated to all organ allografts, such as kidney and heart, which are more accessible to lymphoid infiltration and may consequently be more prone to rejection in the setting of ICI therapy. In this unique population of SOTRs with autoimmunity and metastatic cancer, optimization of immunosuppression regimens and close monitoring for signs of graft rejection and/or autoimmune disease exacerbations are essential.

Conflicts of interest

None disclosed.

REFERENCES

1. Kumar V, Shinagare AB, Rennke HG, et al. The safety and efficacy of checkpoint inhibitors in transplant recipients: a case series and systematic review of literature. *Oncologist*. 2020; 25(6):505-514.
2. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med*. 2018;168(2):121-130.

3. Barrios DM, Do MH, Phillips GS, et al. Immune checkpoint inhibitors to treat cutaneous malignancies. *J Am Acad Dermatol*. 2020;83(5):1239-1253.
4. Avila M, Meric-Bernstam F. Next-generation sequencing for the general cancer patient. *Clin Adv Hematol Oncol*. 2019;17(8): 447-454.
5. Chan TA, Yarchoan M, Jaffee E, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol*. 2019;30(1):44-56.
6. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. *Eur J Cancer*. 2020;128:83-102.
7. Botticelli A, Mezi S, Pomati G, et al. The impact of locoregional treatment on response to nivolumab in advanced platinum refractory head and neck cancer: the need trial. *Vaccines (Basel)*. 2020;8(2):191.
8. Buchwald ZS, Wynne J, Nasti TH, et al. Radiation, immune checkpoint blockade and the abscopal effect: a critical review on timing, dose and fractionation. *Front Oncol*. 2018; 8:612.
9. Fisher J, Zeitouni N, Fan W, Samie FH. Immune checkpoint inhibitor therapy in solid organ transplant recipients: A patient-centered systematic review. *J Am Acad Dermatol*. 2020;82(6):1490-1500.