Value of cemiplimab in progressive metastatic cutaneous squamous cell carcinoma after kidney transplantation: a case report

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Abstract Cutaneous squamous cell carcinoma (CSCC) is the most frequent post-transplant tumour entity resulting from immunosuppression treatment that is needed to prevent organ rejection. Solid organ transplant (SOT) recipients are at higher risk for CSCC and vulnerable for aggressive disease or a fatal course. Here, we report on a case of post-kidney transplant metastatic CSCC, demonstrating efficacy of cemiplimab in achieving complete remission after previous disease progression under cetuximab treatment. Unfortunately, the patient developed severe pneumonia, which was only later diagnosed as cemiplimab-associated pneumonitis. Due to a rapidly evolving septic condition, intensive care treatment was required and resulted in a fatal outcome. The patient’s transplant remained intact, yet first-line treatment of advanced CSCC, such as with cemiplimab, should be weighed critically in SOT recipients, as transplant rejection may occur. However, the present case underlines the feasibility of cemiplimab as a second-line treatment option in this patient collective.

Conflict of interest CG is a member of the advisory board of and has received honoraria and travel expenses from Amgen, BioNTech, BMS, GSK, Immunocore, MSD, Novartis, Pierre-Fabre, Roche, Sanofi and Sysmex. CG is the co-founder of Dermagnostix.

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What does this study add?
- Kidney transplant recipients are at high risk for advanced cutaneous squamous cell carcinoma.
- Second-line cemiplimab is a feasible treatment option in selected patients.
- First-line cemiplimab should be critically weighed against risk of transplant rejection.
- Close consultation with a transplant nephrologist and thorough discussion with the patient is indispensable.

Case presentation
A 69-year old woman presented at University Skin Cancer Center Hamburg with two rapidly evolving subcutaneous tumour masses in the left axilla and the dorsal left forearm in April 2019. She had been previously diagnosed with incompletely resected cutaneous squamous cell carcinoma (CSCC) of the left axilla (G2, pT3, R1).

Her medical history was most notable for an allogenic renal transplantation in 2004. She had received immunsuppressive treatment with tacrolimus, mycophenolate mofetil and methylprednisolone for prevention of organ rejection since (Fig. 1). Further dermatological history included multiple CSCC in various locations over the course of several years. Among these, recurrent sternal CSCC (G3, pT3, L0, V1 and Pn1), ulcerated muscle-infiltrating CSCC (G3, pT3, L0, V0 and Pn0) at the upper left back and supraclavicular CSCC (G3, pT3, L0, V0 and Pn0) were remarkable.

Upon presentation to our centre, suspicious pleural foci were detected in computed tomography (CT; Figs 1 and 2). The interdisciplinary dermatological tumour board strongly suspected metastatic disease, possibly originating from multiple previously resected CSCC tumour sites. Surgical exploration and tumour reduction in the left axilla revealed recurrent multifocal subcutaneous CSCC infiltrates, most suitably representing local recurrence at the site of prior tumour resection, and lymph node metastases without capsule-penetrating growth. Due to
infiltration of the left axillary vein and brachial plexus, it was not possible to completely resect the tumour.

Histopathological analysis after extirpation of the tumour mass at the dorsal left forearm identified SCC without precursor lesions and without connection to the overlying epidermis, most likely representing a metastasis, rather than primary CSCC. CT-guided biopsies of the pleural lesions showed infiltrates of poorly differentiated SCC. TP53 gene sequencing analysis confirmed pleural metastases to exhibit the same point mutation as the axillary CSCC lesion.

Together, the patient was classified stage IVA (pT3 pN3b M1) according to the AJCC 2017 classification system and radiotherapy of the left axilla was conducted.

Cetuximab 400 mg/m² body surface area (BSA) IV was initiated in June 2019, and the patient subsequently received nine doses of 250 mg/m² BSA IV weekly (Fig. 1). Re-staging with cranial magnetic resonance imaging (cMRI) and CT of thorax and abdomen revealed progressive disease (PD) with pleural carcinoma and osseous filiae of the spine in September 2019 (Fig. 3).

After interdisciplinary risk-benefit assessment, cemiplimab 350 mg Q3W was initiated in October 2019 (Fig. 1). The supervising transplant nephrologist discontinued immunosuppressive treatment with tacrolimus and mycophenolate mofetil and gradually reduced methylprednisolone to 2 mg/day. Renal transplant function remained stable under this therapeutic regime.

In January 2020, CT and cMRI follow-up staging revealed complete remission of lung and pleural foci as well as partial remission of osseous metastases. The patient’s status remained well under this treatment, and consecutive repetitive radiological follow-up assessments showed stable disease (SD; Figs 1–3). By the end of January 2021, the patient suddenly developed progressive respiratory insufficiency requiring hospital admission in an external hospital. There, she was diagnosed with severe bilateral pneumonia and was treated with intravenous piperacillin/tazobactame. Due to a rapidly declining status, she was transferred to the intensive care unit in the respective hospital. A CT of the thorax showed pneumonitis rather than pneumonia, and thus, high-dose intravenous prednisolone treatment was initiated.

**Figure 1** Timeline illustrating the course of a kidney transplant recipient with metastatic CSCC. Periods of years are indicated where applicable. Months from start of cemiplimab treatment are depicted below the timeline. CR, complete remission; CSCC, cutaneous squamous cell carcinoma; CT, computed tomography; ICU, intensive care unit; IS, immunosuppression; MMF, mycophenolate mofetil; PD, progressive disease; PR, partial remission.

**Figure 2** Radiological assessment of pleural metastases. (a–c) Computed tomography images of the thorax are shown. Yellow arrows indicate pleural foci. (a) Identification of pleural foci upon presentation to centre in April 2019. (b) Progressive disease after 3 months of cetuximab treatment in September 2019. (c) Complete radiological remission of foci after 10 months of cemiplimab treatment in August 2020.
However, the patient quickly became septic and succumbed to multi-organ failure in early February 2021.

**Discussion**

This case demonstrates the current therapeutic challenge of addressing aggressive metastatic CSCC in a kidney transplant patient. Clinical trials that have led to the approval of immune checkpoint inhibitors, for example cemiplimab, explicitly excluded SOT recipients. As studies on the use of ICI treatment in SOT recipients remain sparse, there are currently no clear recommendations for this patient cohort. A recent pooled analysis of published cases of ICI treatment in kidney transplant patients estimated an allograft rejection rate of about 44%, while anti-PD-1 ICI treatment seemed to exhibit a higher risk of transplant rejection compared with anti-CTLA-4 ipilimumab.

For a comparatively reduced risk of transplant rejection compared to ICI, cetuximab was initiated as first-line treatment in the present case. Unfortunately, PD warranted for therapeutic alternatives. Based on an interdisciplinary consensus and after thorough discussion with the patient, cemiplimab treatment was established. Alongside, the supervising transplant nephrologist adapted the concurrent immunosuppressive medication to a minimum required for prevention of organ rejection.

Cemiplimab was tolerated well over a period of about 14 months without any signs of organ rejection. Complete remission of the pleural foci occurred after 3 months of treatment. Further progression of the osseous lesions could also be prevented, and some lesions even showed partial remission. Remarkably, the patient reported a significant amelioration of quality of living under cemiplimab treatment.

Only recently, repetitive measurement of quantitative donor-derived cell-free DNA (dd-cfDNA) blood levels has been identified as a useful biomarker for detecting allograft injury and rejection among anti-PD-1 ICI treatment in a kidney transplant patients. This promising biomarker should be evaluated in a broader study setting, as it holds a high potential for better monitoring of kidney transplants under ICI treatment. High dd-cfDNA levels may indicate high risk of allograft rejection and could thus help to identify the optimal time point of discontinuation of anti-PD-1 ICI in hopes of retaining the transplanted organ. Alternatively, kidney retransplantation may be a feasible option for selected individuals after allograft rejection under anti-PD-1 ICI treatment.

In the presented case, cemiplimab treatment response was promising and did not result in allograft rejection. Had the patient developed rejection, it should be noted that complete remission of metastatic CSCC, specifically of the osseous lesions, had not yet been achieved. The latter would not have qualified the patient as a suitable candidate for kidney retransplantation.

However, transplant rejection is not the only risk to keep in mind. Severe immune-related adverse events are a common, potentially life-threatening, complication of ICI treatment, and SOT recipients are no exception. A recent retrospective analysis of six SOT recipients with metastatic CSCC under cemiplimab treatment has revealed severe adverse events in two cases. Interestingly, one of these cases was severe pneumonitis. Due to the late diagnosis of pneumonitis at the external hospital and a rapidly evolving septic condition with multi-organ failure, our patient’s condition could not be stabilized despite intensive care treatment with high-dose glucocorticosteroids. Data on differences in occurrence of adverse events and their severity in SOT recipients compared to non-transplant cohorts are limited and warrant large-scale examination. Investigations in the SOT recipient cohort rather focused on safety and efficacy in respect to transplant rejection rather than adverse events due to ICI treatment so far.

In summary, this report underlines the potential of cemiplimab treatment for progressive metastatic CSCC and suggests its suitability as a second-line treatment option in selected kidney transplant recipients. However, both allograft rejection and rare, but not uncommon severe fatal immune-related adverse events, remain a serious risk. The use of cemiplimab, especially as a first-line regimen, should therefore be critically evaluated and discussed with the respective patient.

[Figure 3](#) Radiological assessment of osseous metastases. (a, b) Computed tomography images of thorax and abdomen. Yellow arrows indicate osseous metastasis of the spine. (a) Identification of osseous metastases after 3 months of cetuximab treatment in September 2019. (b) Partial remission of osseous metastases after 10 months of cemiplimab treatment in August 2020.
Additionally, close collaboration with a transplant nephrologist is indispensable.

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