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## Sustained complete response of metastatic cutaneous squamous cell carcinoma by immune checkpoint inhibition in a renal transplant patient: a case report

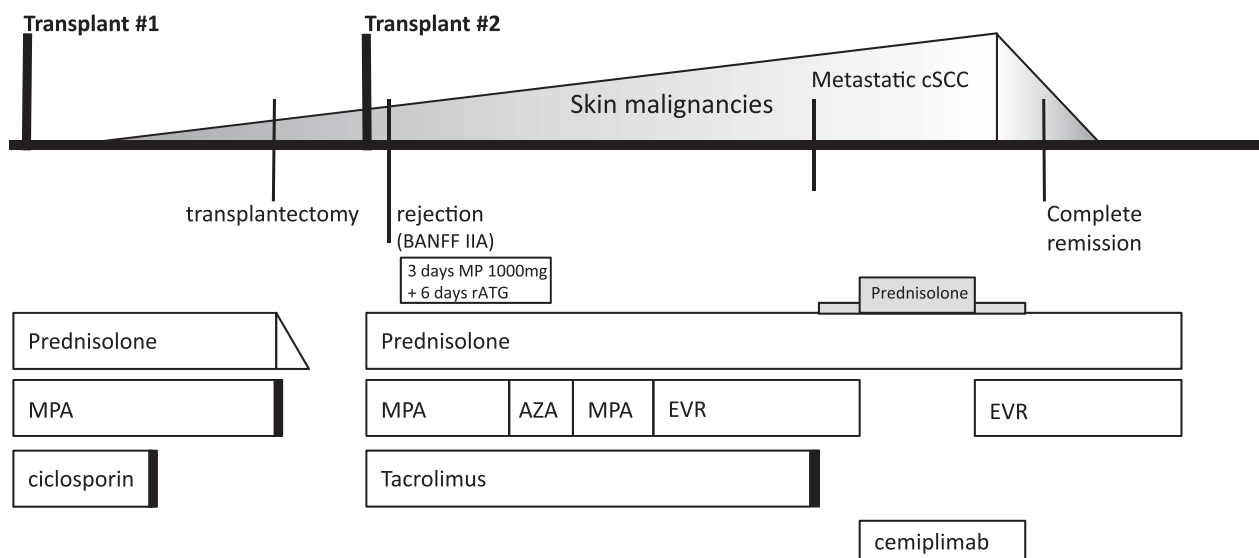
Editor,

A 69-year-old kidney transplant patient was referred for treatment of a recurrent cutaneous squamous cell carcinoma (cSCC) on the right jaw, after two irradiated excisions in another clinic.

Her medical history reported a first kidney transplant (at age 54) due to membranous glomerulonephritis, and a second kidney transplant 9 years later, complicated by successfully treated acute vascular rejection. Her immunosuppressive regimen consisted of prednisolone, mycophenolic acid (MPA) and tacrolimus (Fig. 1). During the last 7 years, she also had 25 cSCCs (of which 16 *in situ*) and seven basalomas.

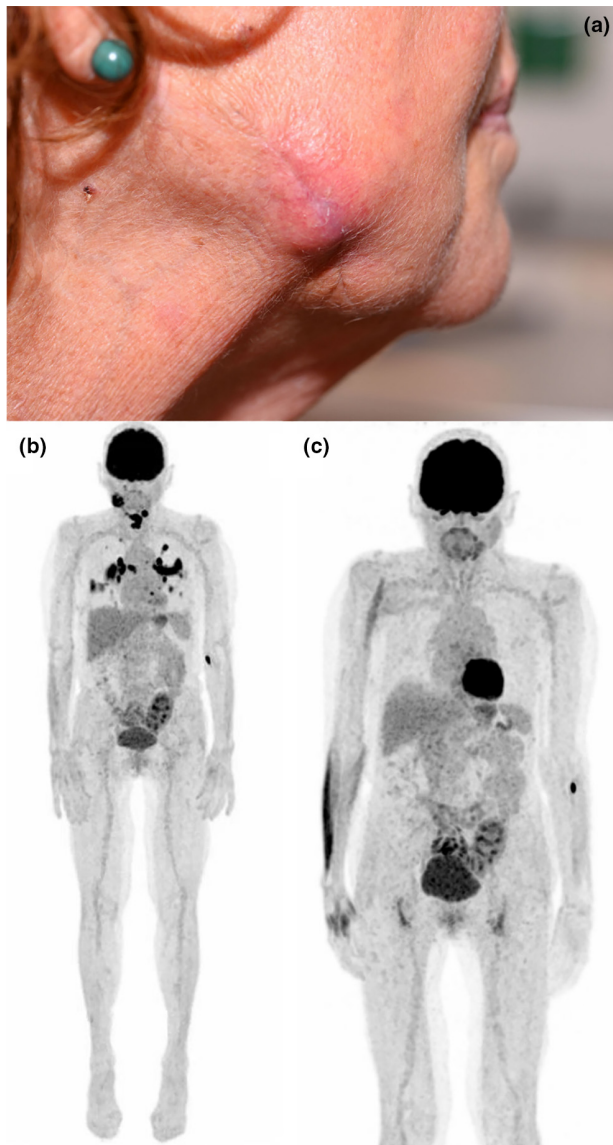
On the right jaw a firm erythematous nodule was located measuring 4 × 4 centimetres (Fig. 2a). A CT scan showed a 3 mm unspecified nodule in the inferior lobe of the right lung for which follow-up was decided. After multidisciplinary consultation, surgical excision was performed, which was incomplete. The tumour had an invasion depth of 30 millimetres, moderate differentiation and no perineural invasion. Post-operative radiotherapy (66 Gray in 33 fractions) followed. MPA was changed to everolimus because of its proposed anti-neoplastic properties.<sup>1</sup>

Three months later, a follow-up PET-CT scan revealed progression of the unspecified nodule in the right lung and multiple new nodules suspected of metastases in both lungs (Fig. 2b). After multidisciplinary board discussion, immunosuppression was minimized to prednisolone 7.5 mg/day and everolimus and treatment with the immune checkpoint inhibitor (ICI) cemiplimab was suggested. The choice of treatment with a programmed cell death-1 inhibitor (PD-1i) was extensively discussed with the patient because it has been reported to provoke graft rejection.<sup>2,3</sup> The chance of durable tumour control was, however, most important to her and she accepted this risk with possible need to restart dialysis. Immunosuppression was further reduced to monotherapy prednisolone 15 mg/day and cemiplimab (350 mg intravenously



MPA=mycophenolic acid; MP=methyl-prednisolone; AZA= azathioprine; EVR= everolimus; cSCC= cutaneous squamous cell carcinoma

**Figure 1** Immunosuppressive regimen.



**Figure 2** (a) A firm erythematous node located on a scar on the right jaw. (b) Pulmonary and cervical metastasis on the PET scan before the start of immunotherapy. (c) Complete metabolic response on PET scan after four courses of cemiplimab.

1×/3 weeks) was initiated. After four courses a complete metabolic response was achieved (Fig. 2c). Afterwards, everolimus was re-introduced to reduce prednisolone dose (tapered to 7.5 mg/day). After seven courses, there was a sustained complete response and cemiplimab was discontinued. No complications or side-effects during treatment were observed and graft function was stable. To date, 17 months later, there still is complete remission with excellent graft function.

Cemiplimab, a human IgG4 monoclonal antibody, is the first drug approved for the systemic treatment of advanced cSCC

when surgery and radiotherapy are no curative options. It has shown a response rate of 50%.<sup>4</sup> By blocking PD-1 binding to PD-L1 and PD-L2 ligands, cemiplimab induces an enhanced anti-tumour response by activated T cells. However, in transplant recipients, this immune response by ICI can provoke transplant rejection up to 40% as shown in previous case reports and series.<sup>2</sup>

Studies of treatment of transplant recipients with cemiplimab are limited. Results range from complete response or stable disease without complications<sup>5,6</sup> to partial response and graft failure.<sup>7</sup> Del Bello *et al.*<sup>3</sup> reported graft failure due to a cytokine storm induced by a single dose of PD-1i in a renal transplant patient.

It is still not well understood which factors predict clinical response and preservation of graft function. History of allograft rejection is associated with higher rejection rates after ICI treatment.<sup>2,8</sup> Interestingly, despite the history of organ rejection, our patient's graft function was preserved, demonstrating the need for a better understanding of predictors of outcome.

In transplant recipients with advanced cSCC a multidisciplinary team is essential. Shared decision-making is important, since graft failure is possible. In case of renal transplantation, dialysis may replace kidney function, but it can indeed lead to a reduction in quality of life. Our patient opted for treatment for her metastatic malignancy, accepting the risk of having to undergo dialysis again, which ultimately proved unnecessary.

### Acknowledgements

The patient described in this study has given written informed consent to publication of her case details.

### Funding sources

None.

### Conflicts of Interest

The authors of this manuscript have no conflicts of interest.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Birt-Hogg-Dubé syndrome: association with bilateral metachronous seminomas

Editor,

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant genodermatosis caused by inactivating mutations in the *FLCN* gene encoding the protein folliculin.<sup>1</sup> BHD has wide phenotypic heterogeneity but is typically characterized by skin, lung and renal involvement. The exact incidence is

unknown but it is likely underdiagnosed due to the wide phenotypic variability.<sup>2</sup>

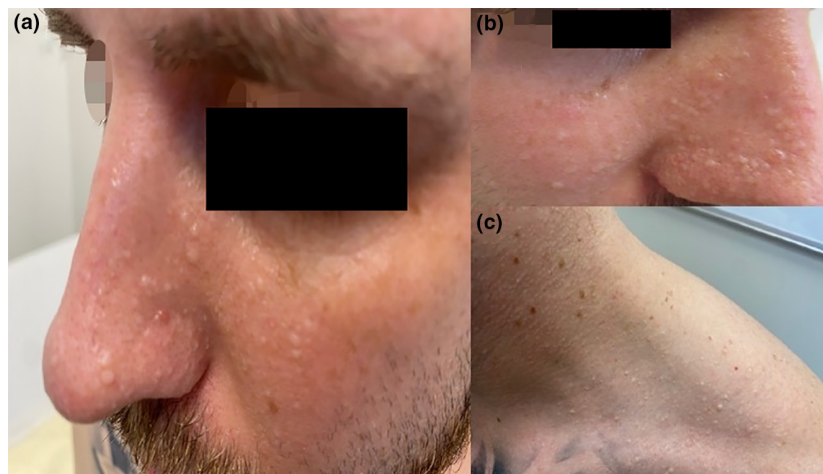
A 34-year-old male presented with an 8-year history of fibrous papules on the central face, extending to the neck and upper chest, and acrochordons on the neck (Fig. 1). He had a history of two left-sided spontaneous pneumothoraces at the age of 16 requiring pleurodesis. He was diagnosed with a left-sided testicular seminoma at the age of 29, treated by orchidectomy. Staging scans performed at that time detected a renal oncocytoma. At the age of 34, he was diagnosed with a right-sided testicular seminoma also treated by orchidectomy. A review of his family history revealed similar skin manifestations in his paternal grandfather, father, paternal uncle and two of his sisters. His paternal uncle had been diagnosed with a melanoma.

Biopsy of the facial papules showed superficial dermal vascular ectasia and concentric fibrosis accompanied by plump and stellate stromal fibroblasts consistent with an angiofibroma (Fig. 2).

Genetic testing revealed a heterozygous pathogenic frameshift mutation in *FLCN* on chromosome 17 (c.927dupA) confirmed by Sanger sequencing, consistent with BHDS.

The diagnostic criteria set out by the European Birt-Hogg-Dubé consortium state that patients should fulfil one major or two minor criteria for the diagnosis of BHDS.<sup>2</sup> Major criteria are (i) five fibrofolliculomas with at least one confirmed histologically and (ii) detection of a pathogenic *FLCN* mutation. Minor criteria are (i) presence of multiple lung cysts, (ii) early-onset renal cancer, bilateral or multifocal neoplasms or characteristic histological forms and (iii) a first-degree relative with BHDS.

BHDS is caused by an inactivating mutation in *FLCN* gene found on the short arm of chromosome 17 (17p11.2) which encodes the protein folliculin.<sup>1</sup> *FLCN* is a tumour suppressor gene implicated in cell growth, proliferation and survival *via* interactions with the energy-sensing mammalian target of



**Figure 1** (a and b) Pale dome-shaped fibrous papules on nose and cheeks (c) Acrochordons and fibrous papules on neck and shoulders.