

# A case of metastatic basal cell carcinoma treated with continuous PD-1 inhibitor exposure even after subsequent initiation of radiotherapy and surgery



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**Key words:** basal cell carcinoma; metastasis; pembrolizumab; programmed cell death protein-1 inhibitors.

## INTRODUCTION

Advanced basal cell carcinomas (BCCs) resistant to Smoothed inhibitor (SI) therapy represent a treatment challenge.<sup>1</sup> Recently, case reports showed that BCCs can be responsive to systemic immunotherapy,<sup>2-4</sup> specifically programmed cell death protein-1 (PD-1) inhibitors. These cases are highly encouraging as salvage therapy after resistance to SI therapy. In 2 metastatic BCC cases, shrinkage of all lesions occurred, specifically lung lesions<sup>3</sup> in one and liver lesions in the other.<sup>4</sup> Currently, it is unknown whether metastatic BCC can exhibit differential response or resistance to PD-1 inhibitors. Here we report a case of a patient with metastatic BCC whose lung lesions were rapidly and completely responsive to PD-1 inhibition but whose bony lesions were not. This case is presented to (1) highlight the need for serial monitoring of BCC patients on systemic immunotherapy and (2) illustrate the utility of combining immunotherapy overlapping with radiotherapy and surgery in SI-refractory metastatic BCC.

## CLINICAL CASE

A man in his 50s presented with a history of BCC on the shoulder skin that was excised 5 years ago. Subsequent recurrence in the skin overlying and involving the sternum and clavicle required en bloc resection. One year later, computed tomography (CT) imaging showed lung nodules with

### Abbreviations used:

BCC:	basal cell carcinoma
CT:	computed tomography
PD-1:	programmed cell death protein-1
PD-L1:	programmed cell death ligand-1

BCC histology on biopsy. The patient started the SI, vismodegib, but experienced disease progression after 3 months. He enrolled in a clinical trial with a different SI, taladegib, but the clavicular BCC recurred. Genetic analysis of the recurrent BCC showed mutations in *TP53* (G245D, in the zinc binding domain) and *PTCH1* (L758fs\*32, in the 12th transmembrane region; foundation 1 solid tumor panel), although the latter mutation did not lead to clinical tumor response to the 2 previous SIs.

High levels of programmed cell death ligand-1 (PD-L1) expression have been associated with response to PD-1 inhibitors in melanoma<sup>5</sup> and increased number of prior treatments in BCCs.<sup>5</sup>

Because of the lack of good treatment options, and high levels of PD-L1 expression in the recurrent BCC and its immune infiltrate (Fig 1, A), the patient started off-label use of the PD-1 inhibitor, pembrolizumab, at 2 mg/kg every 3 weeks. After 6 weeks of pembrolizumab, CT scan showed resolution of

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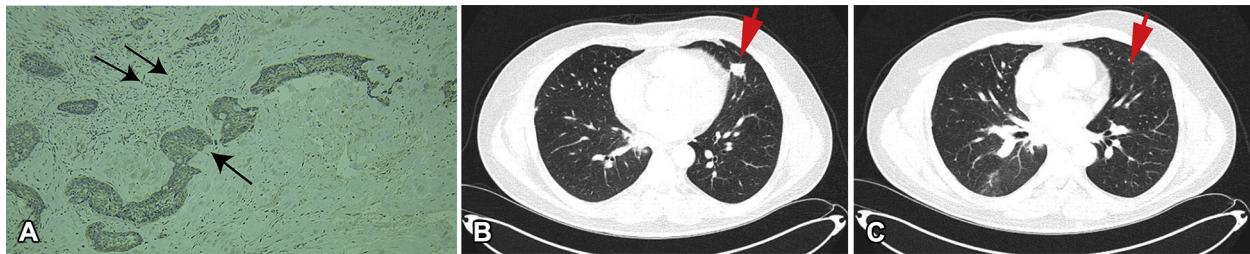
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**Fig 1.** Immunohistochemical and radiographic findings in a patient with metastatic BCC treated with pembrolizumab overlapping with radiotherapy and surgery. **A**, Significant PD-L1 expression in the recurrent shoulder BCC (arrow) and peritumoral infiltrate (double arrow) using mouse anti-PD-L1 monoclonal antibody, clone 2B11D11, Proteintech). (Original magnification:  $\times 200$ .) **B**, CT image of pulmonary metastases with arrow indicating example lesion before pembrolizumab (red arrow). **C**, After 6 weeks of pembrolizumab, this lesion completely resolved (red arrow).

multiple lung lesions with continuing response at 12 months (Fig 1, B is an example lesion [arrow] before pembrolizumab treatment; Fig 1, C shows resolution of lesion after 6 weeks of treatment). The patient reported no adverse events to pembrolizumab.

However, 16 weeks after pembrolizumab initiation, the patient had severe back pain requiring opioid analgesia. CT scan showed a new 5-cm mass on the T8 vertebral body. Because the pulmonary metastases continued to respond to pembrolizumab, the patient did not wish to stop this treatment. Hence, stereotactic external beam radiation therapy was initiated to the T8 lesion (20 Gray total dose). The patient reported significant reduction in pain, enabling him to discontinue opioid analgesia. Subsequent magnetic resonance imaging showed reduction in tumor size to 4.7 cm, and he underwent a laminectomy of the T8 vertebra to excise the remaining tumor, which confirmed basal cell histology. Immunohistochemistry found minimal PD-L1 expression on the tumor cells and peritumoral infiltrate. The patient is currently alive and is 6 months postradiotherapy.

## DISCUSSION

This case illustrates dramatic response of metastatic BCC to PD-1 inhibitor in the lungs but subsequent resistance of bony disease, a phenomenon not previously reported. Although a case report of a BCC patient with PD-L1 amplification of bone metastasis showed exceptional response to PD-1 inhibition,<sup>3</sup> our patient had loss of PD-L1 expression in the vertebral metastasis, with associated lack of response to pembrolizumab. The mechanism of resistance by the bone metastasis to PDL-1 inhibition in this case is unclear. However, there is

evidence that tumor cells can develop the ability to evade the immune system during the process of adapting to the bony microenvironment.<sup>6,7</sup> Currently, the rate of resistance to PD-1 inhibitors in BCCs is unknown.

Although treatment is ongoing for this patient, we present this case to share a potential treatment combination that is palliative and clinically beneficial. Close clinical monitoring and serial imaging are critical to detect resistance after PD-1 inhibitor initiation for metastatic BCC so that additional treatments can be expeditiously initiated. Resistance to PD-1 inhibitor therapy is under ongoing investigation and may affect up to 60% of treated patients; the mechanism of resistance is indeterminate; however, tumor-intrinsic inhibition of tumor-directed T cells likely play a role.<sup>8</sup> Future research will likely identify mechanisms of PD1 inhibitor resistance in metastatic BCCs. Additional cases combining immunotherapy with other treatment modalities in advanced BCCs will better delineate the potential benefits and harms of this integrated approach.<sup>9</sup>

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