PD-1 Inhibition Achieves a Complete Metabolic Response in a Patient with Malignant Peripheral Nerve Sheath Tumor

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Abstract

High-grade malignant peripheral nerve sheath tumors (MPNST) have a poor prognosis with limited responsiveness to systemic therapy. We document a case of a complete metabolic response to pembrolizumab monotherapy in metastatic disease. Tumor molecular profiling identified programmed-death ligand-1 (PD-L1) positivity. This characteristic provided a rationale for immune-checkpoint therapy. Treatment with pembrolizumab resulted in a complete metabolic response after four cycles of therapy. Patients with PD-L1-positive, metastatic MPNST may be candidates for immune-checkpoint therapy, which may produce a durable complete remission. Future study of anti–PD-1/PD-L1 therapy is warranted.

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are rare neoplasms that most often arise around major nerve roots in proximal areas of the upper and lower extremities (1, 2). Approximately 50% of cases occur in patients with neurofibromatosis type 1 (NF1), with about 40% to 47% of MPNST cases developing spontaneously and the remaining 10% to 13% arising as a secondary malignancy following therapeutic irradiation (3). Standard treatment for localized high-grade MPNST involves surgical resection and adjuvant radiation, but local recurrence and distant metastases occur in 40% to 65% and 30% to 60% of patients, respectively (2). The overall prognosis of high-grade MPNST is poor, with 5-year survival rates ranging from 34% to 77% (4–6). Standard-of-care treatment for MPNST includes complete surgical excision with clear margins, often followed by adjuvant radiotherapy for tumors >5.0 cm, to reduce local recurrence (7). Cytotoxic chemotherapy has limited efficacy, inducing response rates of about 21% against MPNST, and is limited to patients with unresectable or metastatic disease (8). The most active agents include doxorubicin and ifosfamide, although tumor response rates to the combination are <25% (8). Whereas the addition of ifosfamide to doxorubicin chemotherapy can improve progression-free survival, it does not prolong overall survival in metastatic soft-tissue sarcomas (9).

Several molecular pathways are dysregulated in MPNST and may serve as therapeutic targets, although no specific effective target has been identified. Downregulation of tumor suppressors neurofibromin 1 (NF1), phosphatase and tensin homolog (PTEN), and TP53, upregulation of oncogenes epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF-1R), and mitogen-activated protein kinases (MAPK), activation of PI3K/AKT/mTOR and Wnt/b-catenin signaling pathways, and aberrations in inhibitors of cyclin-dependent kinase 2 (CDKN2A, CDKN2B) have been implicated in the pathogenesis of MPNST (2, 7). Trials of agents that target these signaling pathways are ongoing.

Immunotherapy with checkpoint inhibitors has dramatically increased survival of patients with certain solid and hematologic malignancies (10). Therapeutic monoclonal antibodies that interfere with the interaction between programmed cell death protein-1 (PD-1) and its ligands, programmed cell death protein 1 ligand (PD-L1) and programmed cell death protein 2 ligand (PD-L2), can overcome immune suppression and produce durable objective tumor responses (11). Biomarkers that are predictive of tumor response to treatment with immune-checkpoint inhibitors can be used to identify patients who are most likely to benefit from therapy. In the treatment of sarcomas, potential biomarkers include tumor-infiltrating lymphocytes (TIL), tumor mutational load, and expression of PD-1 and PD-L1 (12), although utility of PD-1 and PD-L1 as a biomarker of response to immune-checkpoint inhibitors in different solid tumors has been variable.

To date, investigations of these biomarkers in MPNST have been limited. PD-L1 expression and CD8+ lymphocytic infiltration positivity in NF1- and NF2-associated tumors suggest their potential responsiveness to immunotherapy but also indicate significant tumor heterogeneity (14–16). Results from a correlative study of sporadic and NF1-associated MPNST showed no correlation between PD-L1 expression or CD8+ infiltration and disease-specific or disease-free survival (17). The objective tumor response of metastatic MPNST to single-agent immune-checkpoint therapy and its potential for inducing a durable complete remission have not been described. Herein, we document a case of complete metabolic response in
a patient with MPNST following four cycles of pembrolizumab immunotherapy.

**Results**

**Clinical presentation**

A 22-year-old white male had left groin pain that spread down to the knee, and he was falling frequently. Two months later, X-rays showed "hip impingement." Molecular resonance imaging (MRI) of the left hip without contrast showed a lytic osseous lesion with soft-tissue extension in the medial left femoral head and neck, measuring up to 4.6 cm, with marked perilesional edema and cortical destruction, considered at risk for pathologic fracture. Biopsy was consistent with MPNST. One month later, a PET scan with accompanying contrast-enhanced computed tomography (CT) showed an intensely FDG-avid, lytic mass of the left femoral head with pathologic fracture, FDG-avid left iliac and pelvic lymphadenopathy, and a single FDG-avid, lytic left proximal femur lesion (Fig. 1A–C). A chest CT scan with contrast was negative for metastases. MRI with and without contrast of the left femur and pelvis showed interval progression of tumor involving the left femoral head measuring up to 5.5 cm, with focal soft-tissue extension of tumor into the anterior wall and column of the left acetabulum with possible extension into the posterior column. A small enhancing lesion at the anterior aspect of the left intertrochanteric region was suspicious for local metastasis. There was extensive left femoral neck bone marrow edema and a moderate-sized joint effusion with adjacent synovitis (Fig. 1D and E).

The patient underwent total gross resection with endoprosthetic placement and received postoperative intensity-modulated radiotherapy 54 Gy in 27 fractions to the left pelvis/femur with 9 Gy boost to two PET-positive ipsilateral pelvic lymph nodes. Surgical pathology revealed a high-grade malignant spindle cell/epithelioid neoplasm with multifocal femoral head involvement and extension into adjacent soft tissue (maximum tumor dimension spanning 9.0 cm)—consistent with MPNST. The mitotic rate was 10 per high-power field with necrosis. IHC was positive for vimentin, S100, and SOX10. IHC staining was negative for MelanA, pan-melanoma (Biocare Medical; MART-1, Tyrosinase, HMB-45), BRAF, and CD117 (c-Kit). Caris Life Sciences molecular profiling [DNA next-generation sequencing, RNA sequencing (RNA-seq), protein expression by IHC] was limited due to bone decalcification but showed positive IHC staining intensity (0, 1+, 2+, 3+) for TUBB3 (2+, 100% of cells stained) and PD-L1 (2+, 5% of cells stained; Fig. 2).

Restaging scans at completion of radiotherapy showed post-radiotherapy changes at the left proximal femur primary tumor site but no obvious progressive tumor. Two small pelvic lymph nodes were unchanged in appearance. A thorax CT scan with contrast showed multiple new soft-tissue nodules in the lungs concerning for metastases, with the largest measuring 6 mm in diameter in the left lower lobe (Fig. 3). MRI of the pelvis with and without contrast showed interval resection of the left femoral head tumor, including the intra-articular soft-tissue component, and the new left total hip arthroplasty. There was enhancing bone marrow and soft-tissue edema about the left hemipelvis likely related to postradiation changes without definitive evidence of residual or recurrent tumor. The patient was referred to the Early-Phase Therapeutics Program for evaluation for immune-checkpoint trials.

![Figure 1](image-url)

**Figure 1.** Pretreatment imaging studies. **A,** Pretreatment PET coronal maximum intensity projection (MIP) image shows FDG-avid left iliac lymph nodes (LN) and the left femoral head primary peripheral nerve sheath tumor (F). Pretreatment axial contrast-enhanced CT images of the pelvis show enlarged metastatic left common iliac (B) and external iliac (C) lymph nodes (white arrows). **D,** Coronal fat-saturated T2-weighted MRI shows the large T2 hyperintense primary peripheral nerve sheath tumor centered in the left femoral head with accompanying pathologic fracture (F) and extensive cortical breakthrough and soft-tissue extension along the inferior aspect (ST). **E,** Coronal contrast-enhanced T1-weighted MRI demonstrates the mass, which has marked predominantly peripheral enhancement.
Genomic profiling
Circulating tumor DNA (ctDNA; Guardant 360 liquid biopsy) profiling revealed a single variant, CDK6 Amp 1+ (copy-number amplification, 0, 1+, 2+, 3+) prior to starting therapy.

Treatment and outcomes
Given the patient’s PD-L1 positivity and the possibility of an abscopal effect in the post radiation setting, off-label therapy was initiated with pembrolizumab 200 mg intravenously (over 30 minutes) every 3 weeks. Therapy was well tolerated; the patient’s only symptoms were mild fatigue and mild, occasional loose stools, both unchanged since the onset of radiotherapy.

A whole-body FDG-PET/CT scan without contrast (skull vertex to feet) performed prior to the fifth cycle of pembrolizumab showed a complete metabolic response to therapy (Fig. 4A). CIs showed the previously FDG-avid left pelvic adenopathy had resolved (Fig. 4B and C) and the left lower lobe metastasis had decreased in size to 4 mm with resolution of the other lung metastases (Fig. 4D and E). There were postsurgical changes related to excision of the previously seen FDG-avid mass involving the left femoral head with metallic prosthesis in place and no evidence for FDG-avid recurrent disease. Therapy with pembrolizumab every 3 weeks continued without interruption (completed 21 cycles of therapy). Repeat ctDNA (Guardant 360 profiling) testing after 12 cycles of pembrolizumab showed that the previous CDK6 amplification was not detectable. How immunophenotyping (Supplementary Data) revealed a high frequency of circulating CD8+ T cells, which correlated positively with the favorable outcome observed.

Discussion
This patient with MPNST has experienced a complete metabolic response to single-agent pembrolizumab. Given immunogenic features of MPNST previously reported in the literature, a substantial response to pembrolizumab, as was experienced by our patient, is not unexpected. However, a literature search conducted in PubMed and EMBASE through July 24, 2019, revealed only two accounts thus far of clinical outcome benefit to immune-checkpoint inhibitors in MPNST, and overall data are limited (17, 18). Payandeh and colleagues reported the case of an adult male with spindle cell sarcoma who experienced complete resolution of a mesenteric mass by abdominopelvic CT scan after receiving six cycles of pembrolizumab plus daily procarbazine (17). In a phase I trial of pembrolizumab in patients with advanced solid tumors, one patient with MPNST achieved stable disease but subsequently progressed (18). Surgical specimens (n = 53) of MPNST, of which 33 (62.3%) were from spontaneous tumors, were evaluated for the presence of CD8+ TILs and expression of PD-L1 and PD-1, which were also correlated to clinical findings and treatment outcomes (19). Thresholds for PD-L1 and CD8 positivity were 1% and 5%, respectively. PD-L1 expression was positive in nine of 53 (17%) of the MPNST samples and CD8+ immune infiltrates of at least 1% were present in 30 of 53 (56.6%) tumors. No tissues stained positive for PD-1. PD-L1 expression or CD8+ infiltration did not correlate with disease-specific or disease-free survival (19).

Although we cannot exclude the possibility of an interaction between pembrolizumab and radiation resulting in an abscopal effect, we believe that the tumor response is most likely due to pembrolizumab itself.

Figure 2. Tumor tissue hematoxylin and eosin (H&E) stain. A, H&E staining of MPNST demonstrates hypercellularity (marbled appearance) with accentuated perivascular cellularity. Long fascicles of spindled cells with wavy/buckled, hyperchromatic nuclei and lightly eosinophilic cytoplasm. B, Staining with antibody to PD-L1 [Ventana PD-L1 (SP142) Assay, Ventana, provided by Caris Molecular Profiling] shows 2+ (0, 1+, 2+, 3+ scale) staining of MPNST cells.

Figure 3. Pretreatment CT images of lung metastases. Axial CT images of the lungs show new metastases (white arrows) in the left upper lobe (A) and in the right middle and left lower lobes (B).
attributable to pembrolizumab. The interval between completion of radiotherapy to the tumor bed and the two PET-positive lymph nodes and initiation of pembrolizumab was 5.5 weeks. An optimal time window between radiation and immunotherapy has not been established; intervals in published studies range from concurrent to immunotherapy started 3 to 5 days after radiation (20, 21). The response noted in the pelvic lymph nodes can be explained by the radiation alone.

The tumor immunologic microenvironment of MPNST has yet to be deciphered. However, previous reports highlighted that, despite low PD-1 and PD-L1 expression in tumor tissue, 57% of samples had cytotoxic T-cell infiltration in the MPNST microenvironment (7). The aforementioned highlights a potential role for a checkpoint inhibitor combined with a different immune-based modulatory treatment. An inflamed tumor microenvironment with increased T-cell infiltration into the tumor appears critical for an antitumor immune response to PD-1 blockade. Tumor immunogenicity could be promoted using various strategies, such as cytotoxic chemotherapy, targeted therapies, oncolytic viruses, and nanoparticles, to stimulate proinflammatory cytokines and immunogenic cell death, induce tumor neoantigens, and generate CD8⁺ lymphocyte infiltration. We believe that these strategies may increase PD-L1 expression and/or synergize with PD-1 blockade (22). Studies investigating these approaches have reported encouraging results (23).

Tumor responses in unselected soft-tissue sarcomas to PD-1/PD-L1 inhibitors have been mixed but encouraging (24–26). This case report highlights the potential for a durable objective response to checkpoint inhibitor therapy, which warrants further study in this disease. There is currently an ongoing phase II trial of pembrolizumab in nonresectable MPSNT patients (NCT02691026) as well as a clinical trial investigating the role of nivolumab plus ipilimumab in patients with rare tumors including MPNST (NCT02834013). We look forward to results of those trials.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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