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Case Report

CASE REPORT

Response to anti-PD1 immunotherapy in patients with metastatic cutaneous sarcoma: case reports and literature review

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Abstract

Dermal sarcomas represent a group or rare malignancies of mesenchymal origin. Although surgical excision with wide margins can be curative, in the advanced/metastatic setting, treatment options are limited and the benefit from anthracycline-based chemotherapy or targeted agents is usually short-lived. Tumor mutational burden and PD-L1 expression scores can be used as predictive biomarker for response to immunotherapy in some metastatic cancers. The role of immune-checkpoint blockade for sarcoma patients remains investigational. Here we present three cases of dermal sarcomas with high TMB and PD-L1 expression and responses to anti-PD1 agents in two of them.

INTRODUCTION

Pleomorphic dermal sarcoma (PDS) shares pathological, clinical and immunophenotypical features with atypical fibroxantoma (AFX) and characteristically affects sun-damaged skin, with a strong predilection for the scalp. Epithelioid sarcoma (ES) is a rare soft tissue tumor, with epithelial and often mistaken for chronic inflammatory processes, necrotizing granulomas and various fibrohistiocytic tumors. Usually, it has a propensity for local recurrence, regional lymph node involvement and distant metastases [1]. For patients with advanced disease, systemic treatment are associated with limited and often short-lived responses [2, 3]. Front line response rates are typically about 15–18% with a median PFS of 4–6 months [4]. Efficacy beyond front-line therapy is even worse; ORR is usually $< 10\%$ and median PFS is about 2–4 months [5, 6].

The advent of immune checkpoint inhibitors (ICIs) resulted in improved survival and robust antitumor responses in a growing number of solid tumors. However, its efficacy in sarcomas remains to be defined. PD-L1 expression and high tumor mutational burden (TMB), have been associated with higher response rates and improved benefit in patients treated with immunotherapy [7]. Herein, we report two cases of cutaneous aggressive sarcomas that presented either high

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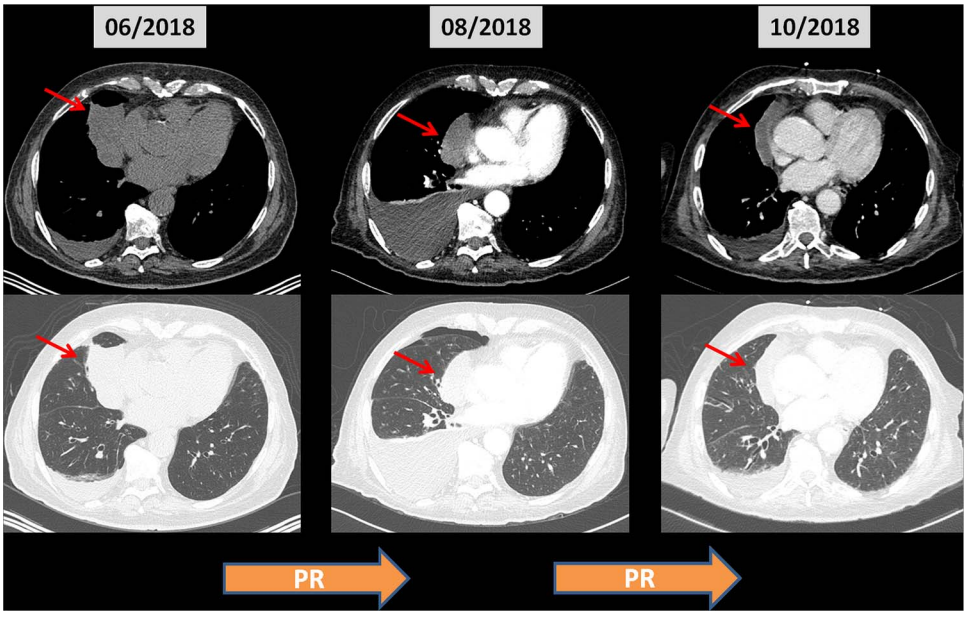

Figure 1: Chest CT demonstrating progressive response after initiating immunotherapy, with reduction of middle lobe pulmonary mass (red arrow).

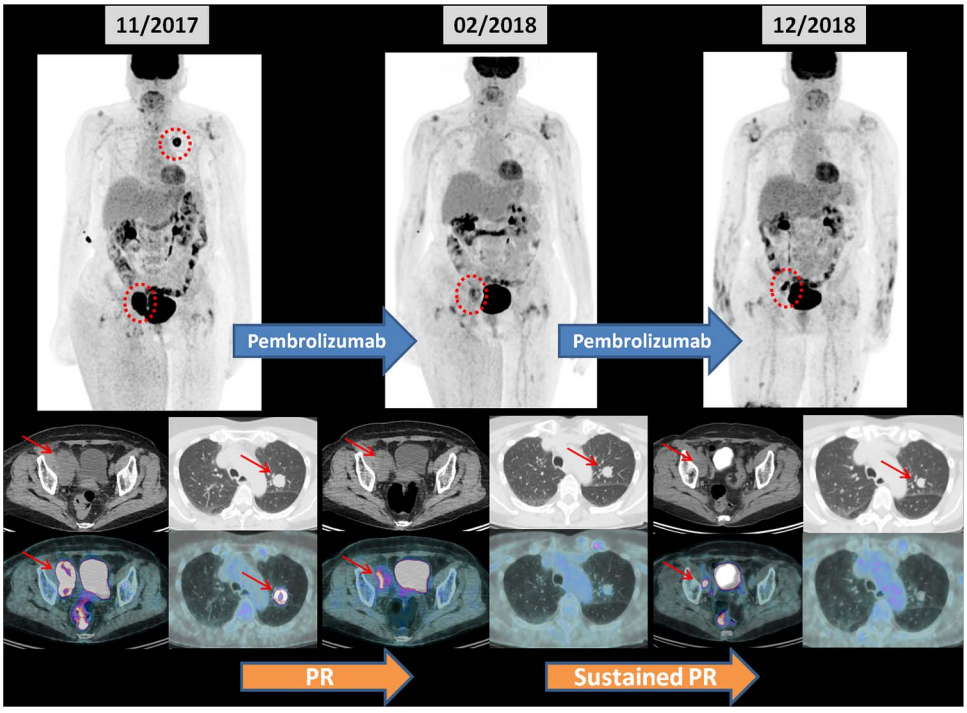

Figure 2: FDG PET/CT scans during treatment demonstrating partial response in the first response assessment scan (after 3 cycles) characterized by complete metabolic response in the pulmonary nodule (dashed circle) and partial metabolic and morphologic response in the right pelvic lymph node enlargement (red arrow in D). These finding had similar and sustained partial response in following scan (after 18 cycles) as shown in image C.

PD-L1 expression or high tumor mutational burden and response to anti PD-1 immunotherapy.

Case 1

An 87-year-old Caucasian gentleman presented to our clinic 5 months following the wide excision of a scalp lesion consistent with PDS, immunohistochemical staining (IH) was positive for CD10, with a Ki-67 index of 80%. He underwent adjuvant radiotherapy to a total dose of 30 Gy given in 10 fractions. During follow-up, imaging prompted by dyspnea revealed a hypermetabolic mass on right middle lobe of the lung associated with pleural effusion. A CT-guided biopsy was positive for metastatic sarcoma. Pazopanib 800 mg daily was prescribed for 2 cycles, but interrupted due to intolerance. PD-L1 expression in the tumor was investigated by IH and was strongly positive in 95% of tumor cells. Pembrolizumab was initiated at 200 mg IV given every 3 weeks. After 2 cycles, the patient presented a marked clinical

and radiologic response (Fig. 1). Nevertheless, the patient developed severe immune mediated myositis and cardiomyopathy 6 weeks following the first dose of pembrolizumab, leading to his death.

Case 2

A 75-year-old woman presented in 2014 with a nodular lesion in the medial aspect of the right thigh. Initial excision performed at an outside institution was consistent with fibroma. The patient developed a locoregional recurrence with nodal involvement after 3 years, and underwent a complete surgical resection and inguinal lymphadenectomy. Pathology report showed a high-grade pleomorphic sarcoma with epithelioid features; IH was positive for caldesmon, CD10 and FXIIIA and negative for CD31, CD34 S100, AML and HMB 45, with a Ki-67 index of 60%. Due to early nodal and pulmonary recurrence, she received first-line chemotherapy with pegylated-liposomal doxorubicin, with disease progression following 2 cycles. A tumor sample was obtained for directed next-generation sequencing through a commercially available test, and showed a high tumor mutation burden, with 29 Muts/Mb. Based on these results, the patient was started on pembrolizumab, showing an expressive response after 3rd, 6th and 18th cycles (Fig. 2). She remained on therapy for 28 cycles, followed by disease progression in the form of new pulmonary nodules.

DISCUSSION

Although the role of immune checkpoint blockade in sarcomas remains investigational, here we report two cases in which anti-PD1 agents were recommended based on potential biomarkers, resulting in significant benefit. In the phase II trial SARC028, pembrolizumab was evaluated in advanced soft-tissue and bone sarcomas. Regardless that the efficacy was limited in the entire population, this anti-PD1 agent showed encouraging activity in the cohort of patients with undifferentiated pleomorphic sarcomas [8]. The Alliance trial compared nivolumab monotherapy versus combination therapy with nivolumab plus ipilimumab in unselected advanced heavily treated patients with sarcoma. In the combination group, the proportion of patients achieving an objective response with combination therapy was 16%, while the monotherapy group did not achieve response [9].

Potential markers associated with increased benefit from immune checkpoint blockade have emerged over the past years, including the PD-L1 expression by immunohistochemistry and TMB. It is believed that higher PD-L1 expression is related to increased response rate and clinical benefit in the anti-PD1/PD-L1 therapy [9]. Some sarcomas express PD-L1, with reported expression of positive PD-L1 cells ranging from 12 to 65% [7]. This variability poses a challenge in the use of PD-L1 expression as a prognostic biomarker. Additionally, clinical data from patients treated with checkpoint inhibitors have suggested that patients can benefit from this therapy irrespective of PD-L1 expression [8]. However, limited evidence exists on the activity of checkpoint inhibitors in sarcoma and the low clinical activity of pembrolizumab alone in most sarcoma subtypes suggests that this agent cannot adequately activate suppressed effector T cells in these patients [9]. Undifferentiated pleomorphic sarcoma is an inflamed tumor characterized by high numbers of tumor infiltrating lymphocytes, which could explain the clinical activity of pembrolizumab noted in this subgroup of sarcoma patients [9]. In our case 1, we described a patient with high expression of PD-L1, which presented with remarkable response but died of severe immune related toxicity. The second case illustrates a woman with high TMB with a consistent and meaningful response to anti-PD1 agent. TMB is associated with genome instability and immunogenicity, which has been reported to play an important role in the efficacy of ICIs. The cutoff number defining high TMB is still controversial and is likely to vary for different histologies. However, higher TMB has shown to be associated with longer overall survival across multiple cancer types [10]. Utilizing TMB as a biomarker may help select such patients for immunotherapy. Prospective basket trials evaluating patients with uncommon tumors harboring high TMB are needed.

CONCLUSION

PDS and ES are rare, aggressive, cutaneous tumors. The presence of predictive biomarkers for immunotherapy such as high PDL-1 expression or high TMB make these rare entities as attractive targets for anti-PD1/PDL-1 based immunotherapy, and may have a role in the selection of patients in a scenario of scarse treatment options.

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REFERENCES

1. Tardío JC, Pinedo F, Aramburu JA, *et al*. Pleomorphic dermal sarcoma: a more aggressive neoplasm than previously estimated: Pleomorphic dermal sarcoma. *J Cutan Pathol*. 2016;**43**:101–12. doi: 10.1111/cup.12603.
2. Cormier JN, Pollock RE. Soft tissue sarcomas. *CA Cancer J Clin*. 2004;**54**:94–109. doi: 10.3322/canjclin.54.2.94.
3. Jones RL, Constantinidou A, Olmos D, *et al*. Role of palliative chemotherapy in advanced epithelioid sarcoma. *Am J Clin Oncol*. 2012;**35**:351–7. doi: 10.1097/COC.0b013e3182118cf7.
4. Seddon B, Strauss SJ, Whelan J, *et al*. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol*. 2017;**18**:1397–410. doi: 10.1016/S1470-2045(17)30622-8.
5. van der Graaf WT, Blay J-Y, Chawla SP, *et al*. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*. 2012;**379**:1879–86. doi: 10.1016/S0140-6736(12)60651-5.
6. Schöffski P, Chawla S, Maki RG, *et al*. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *The Lancet*. 2016;**387**:1629–37. doi: 10.1016/S0140-6736(15)01283-0.
7. D'Angelo SP, Shoushtari AN, Agaram NP, *et al*. Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol*. 2015;**46**:357–65. doi: 10.1016/j.humpath.2014.11.001.
8. D'Angelo SP, Mahoney MR, Van Tine BA, *et al*. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol*. 2018;**19**:416–26. doi: 10.1016/S1470-2045(18)30006-8.

9. Pollack SM, He Q, Yearley JH, *et al*. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas: sarcoma immune microenvironment. *Cancer*. 2017;**123**:3291–304. doi: 10.1002/cncr.30726.

10. Goodman AM, Kato S, Bazhenova L, *et al*. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;**16**:2598–608. doi: 10.1158/1535-7163.MCT-17-0386.