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Case Report

Objective Responses in Metastatic Pleomorphic Rhabdomyosarcoma Treated with Combination of Doxorubicin and Pembrolizumab: A Case Series

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Keywords

Rhabdomyosarcoma · Pleomorphic rhabdomyosarcoma · Immune checkpoint · Pembrolizumab · Doxorubicin · Case series

Abstract

Introduction: Pleomorphic rhabdomyosarcoma is a rare subtype of rhabdomyosarcoma, a soft tissue sarcoma with skeletal muscle differentiation. Although rhabdomyosarcoma is typically seen in the pediatric population, the pleomorphic variant most frequently presents in adulthood and is characteristically aggressive with no currently established treatment regimen in the setting of metastatic disease. There has been growing interest in the application of immune checkpoint inhibitors alongside conventional chemotherapeutic agents in the treatment of pleomorphic rhabdomyosarcoma. ***Case Presentation:*** In the present case series, we report 2 patients with metastatic pleomorphic rhabdomyosarcoma treated with combination doxorubicin and pembrolizumab who had confirmed objective responses. Of note, these 2 patients had variable PD-L1 status – negative and low positive. Duration of treatment response was notable at 14 months and 9 months, respectively, with the first patient remaining on maintenance pembrolizumab therapy and the second patient subsequently achieving complete response with third-line trabectedin. Both patients are currently undergoing routine interval imaging with no evidence of disease at this time. ***Conclusion:*** This report highlights and discusses the

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potential role of PD-1 blockade in the treatment of pleomorphic rhabdomyosarcoma and also discusses burgeoning immunological data that may explain the clinical responses seen in these 2 cases.

Introduction

Soft tissue sarcomas are a group of rare, heterogeneous tumors that comprise approximately 1% of all adult malignancies. While malignancies within the sarcoma family share a common origin – mesenchymal (connective) tissue – they otherwise represent a widely diverse group of cancers that comprise over 150 distinct subtypes [1].

One of these many subtypes of sarcoma – and the subject of the present case series – is rhabdomyosarcoma. Rhabdomyosarcomas are high-grade neoplasms of skeletal myoblast-like cells. Current WHO classification guidelines recognize four distinct subtypes of rhabdomyosarcoma: (1) embryonal, (2) alveolar, (3) spindle cell/sclerosing, and (4) pleomorphic [2].

Pleomorphic rhabdomyosarcoma (PMRS) occurs almost exclusively in adults and carries a particularly poor prognosis. PMRS is more common in males and typically presents in the fifth to sixth decades of life [3]. Anatomically, lesions occur most often in the deep soft tissues of the lower extremities but have been reported in numerous other tissues. While wide surgical resection is the mainstay treatment for localized disease, there is no existing standard regimen for advanced (metastatic) disease, in large part due to the rarity of PMRS, and most retrospective studies group together different subtypes of rhabdomyosarcoma. Thus, there remains an unmet need to continue investigating drugs that provide a sustained clinical response. Several studies in the last few years have yielded promising results with doxorubicin and pembrolizumab combination therapy, with particularly notable efficacy seen in undifferentiated pleomorphic sarcomas [4–6]. We describe 2 patients with PMRS who were treated with combination doxorubicin and pembrolizumab and showed a confirmed objective response. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535959).

Methods

A retrospective search of patients with a pathologically confirmed diagnosis of PMRS who were treated with combination doxorubicin and pembrolizumab yielded 3 patients from 2018 through 2022. Two patients provided written and informed consent for this report. Our Institutional Review Board waived review and approval.

Case 1

A 55-year-old woman developed subacute pain in her right mid-thigh. MRI imaging revealed a soft tissue mass, and subsequent biopsy was notable for malignant spindle cell neoplasm favoring sarcoma. CT imaging showed no evidence of metastasis. The patient underwent excision of the right thigh mass with tumor involvement of the posterior margin. Pathology results from this gross specimen demonstrated high-grade (FNCLCC grade 3 of 3) PMRS with a mitotic count of 38 per 10 high power field (Fig. 1).

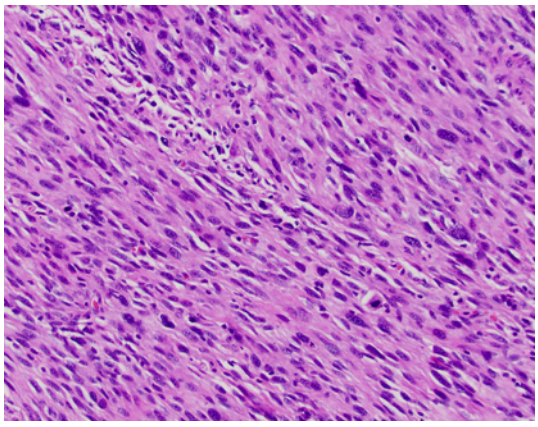

Fig. 1. Histology of a gross specimen demonstrating high-grade (FNCLCC grade 3 out of 3) PMRS with a mitotic count of 38 per 10 high power field (HPF); ×200 magnification.

The patient subsequently underwent adjuvant radiation treatment (66 Gy in 33 fractions) to the postoperative bed. Five months after the completion of her radiation treatment, surveillance CT imaging revealed multiple bilateral pulmonary nodules concerning for metastasis. Molecular testing of the original tumor specimen showed no relevant fusion transcripts and no genetic variants with potential clinical significance. PD-L1 testing by immunohistochemistry was negative (Fig. 2).

The patient was subsequently treated with combination therapy with doxorubicin and pembrolizumab. The patient began doxorubicin chemotherapy (75 mg/m^2) and pembrolizumab (200 mg) during cycle two of doxorubicin. Interval CT CAP imaging after cycle 4 showed an interval decrease in size of her lung nodules consistent with a partial response per Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The patient's treatment course was complicated by hypothyroidism resulting from thyroiditis, which was managed with oral levothyroxine. She also developed a right internal jugular vein thrombus and was started on apixaban. Repeat CT CAP after cycle 6 of doxorubicin (cycle 5 pembrolizumab) showed complete response in the numerous lung nodules and no evidence of new metastatic disease (Fig. 3). After completing six cycles of doxorubicin, the patient continued pembrolizumab (200 mg) maintenance therapy every 3 weeks and is undergoing surveillance imaging every 2 months. Currently, her scans show no evidence of disease at 20 months from diagnosis and 14 months since initiation of combination treatment.

Case 2

A 63-year-old man developed a large mass in his right upper back, with CT chest revealing a 9.5-cm right posterior chest wall soft tissue mass with associated rib reconstruction consistent with malignant neoplasm. A staging body CT imaging revealed no evidence of metastases. Biopsy of the soft tissue mass identified high-grade (FNCLCC grade 3 of 3) PMRS with a mitotic count of 13 per 10 high power field (Fig. 4).

The patient received preoperative radiation treatment (50 Gy in 25 fractions) to the primary mass lesion followed by surgical resection of the mass with negative margins. Of note, tumor testing demonstrated no relevant fusion transcripts, no genetic variants with potential clinical significance, and PD-L1 low-positive (1+/<25%) (Fig. 5).

A restaging CT scan of the chest, abdomen, and pelvis was performed 2 months postoperatively, demonstrating bilateral lung metastases. The patient was started on doxorubicin (75 mg/m^2) and concurrent pembrolizumab (200 mg) treatment. CT CAP after cycle 3 of doxorubicin (cycle 2 of pembrolizumab) demonstrated an interval decrease in size of the lung metastases consistent with a partial response (Fig. 6). The patient experienced significant fatigue, and the doxorubicin dose was lowered to 60 mg/m^2 for cycle 4 and then discontinued

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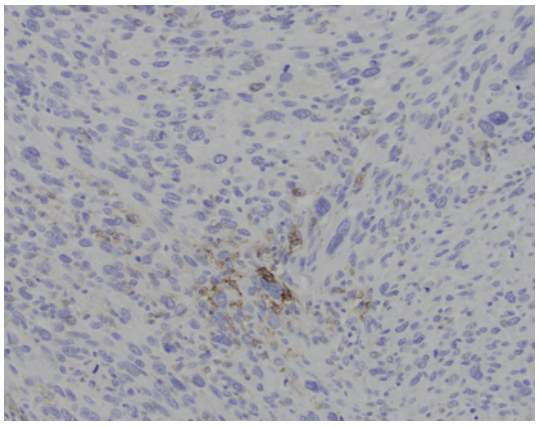

Fig. 2. Immunohistochemical stain demonstrating negative PD-L1 status; ×200 magnification.

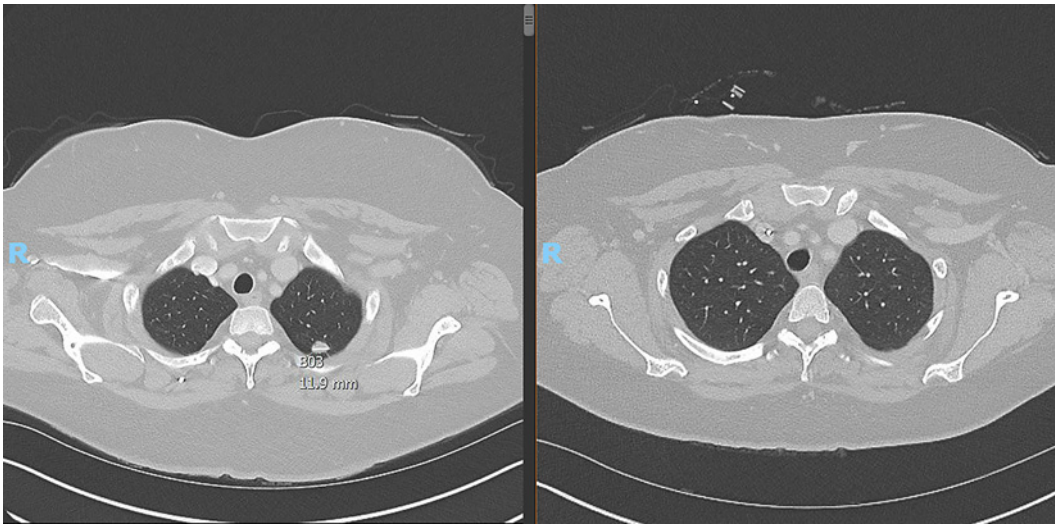

Fig. 3. Single transverse section of a CT chest scan demonstrating complete response; the patient has no evidence of disease to date.

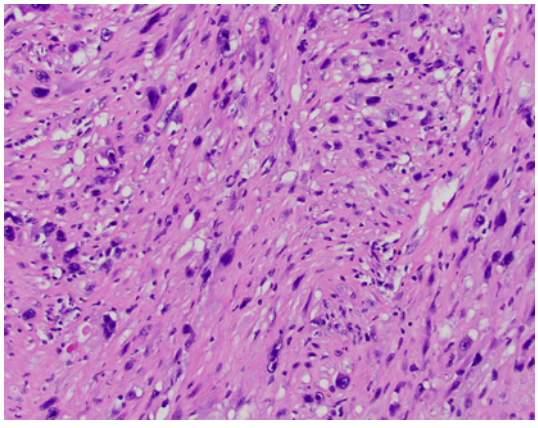

Fig. 4. Histology of a gross specimen demonstrating high-grade (FNCLCC grade 3 out of 3) PMRS with a mitotic count of 13 per 10 high power field (HPF); ×200 magnification.

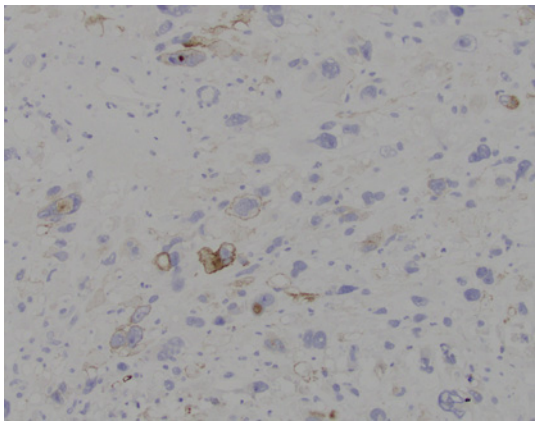

Fig. 5. Immunohistochemical stain demonstrating low-positive PD-L1 status (1+/<25%); ×200 magnification.

after cycle 5. The patient continued on maintenance treatment with pembrolizumab every 3 weeks with interval surveillance imaging. Four months later (a total of 9 months since starting doxorubicin/pembrolizumab), routine imaging demonstrated two new lung nodules concerning for progressive disease. The patient was subsequently enrolled in a clinical trial of cabozantinib/temozolomide but continued to have progression on interval scans. He then underwent stereotactic body radiation therapy (50 Gy in 5 fractions) to the two lung nodules and was started on trabectedin (1.5 mg/m^2). This regimen was continued for 9 months until resolution of disease. The patient remains under observation with no evidence of disease (28 months from original diagnosis; 22 months since initiation of chemotherapy). He currently has no evidence of disease.

Discussion

These 2 cases suggest that combination doxorubicin and pembrolizumab is potentially effective in PMRS. Both patients demonstrated an objective response, with 1 patient having a complete response. The regimen was generally well tolerated, with 1 patient discontinuing doxorubicin due to fatigue. Duration of response has been impressive, at 14 and 9 months to date, with 1 patient subsequently obtaining complete response with third-line trabectedin therapy.

Programmed death-ligand 1 (PD-L1) is a cell surface protein that, when expressed on the tumor surface, inhibits the antitumor activity of activated T-cells. Nevertheless, attempts to predict benefit of PD-1 blockade in soft tissue sarcomas and other cancers have been mixed [7–9]. The 2 patients presented here had differing variable PD-L1 status – negative and low positive – suggesting that the response to immunotherapy may be independent of PD-L1 status. It has been noted that other factors beyond target molecule expression may impact the efficacy of immunotherapeutic agents. In particular, the tumor microenvironment and its role in modulating the immune response are currently under much investigation. One notable study established that IFN-γ-related gene expression in the tumor microenvironment was associated with efficacy of PD-1 checkpoint blockade [10]. These findings were further validated through the application of a tumor inflammation signature (which incorporates IFN-γ activity) to several large clinical trials across a variety of different cancers [11]. These retrospective studies suggest that certain tumors with high tumor inflammation signature may demonstrate improved response to checkpoint inhibitors. Nevertheless, prospective studies and more tumor-specific data are necessary before such findings may be used as reliable guides for therapeutic management.

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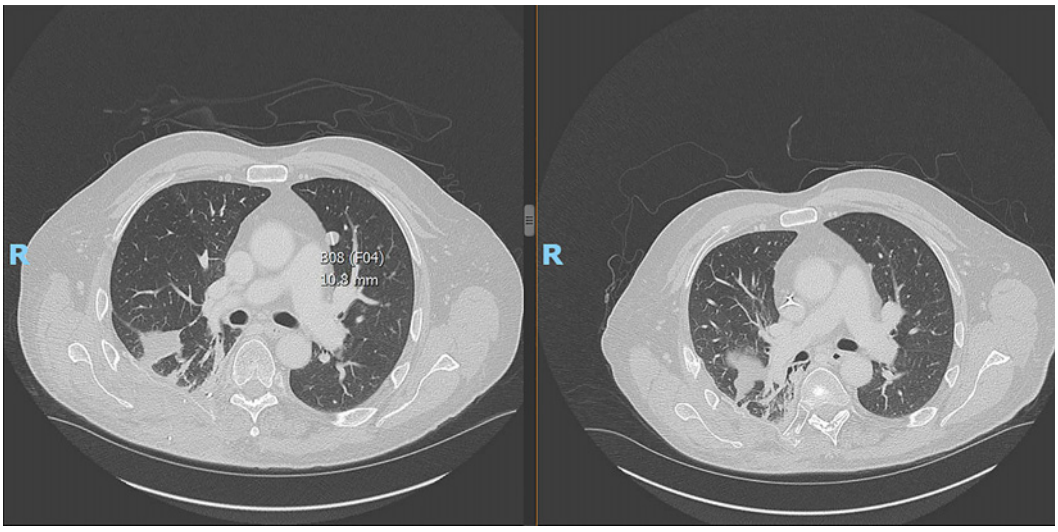

Fig. 6. Single transverse section of a CT chest scan demonstrating partial response; the previously visualized nodule underwent significant decrease in size.

Another seminal study demonstrated that B-cell infiltration of tertiary lymphoid structures within sarcoma tumors (before treatment) is associated with an improved response to immunotherapy [12]. This study also established an immune-based classification for soft tissue sarcomas and identified five distinct immunologic phenotypes with subtype-specific responsiveness to immunotherapy. These findings suggest that B-cells and tertiary lymphoid structures may play key roles in antitumor immune activity, although the mechanism and scope of this phenomenon remains unknown.

It has been noted that soft tissue sarcomas, including PMRS, with complex karyotypes carry a higher tumor mutational burden and a higher degree of immune infiltrates in the tumor microenvironment [13]. Accordingly, there is evidence that these sarcomas may exhibit a better response to immunotherapy.

With regard to the patient presented in case 2, it is notable that although the patient developed progressive disease on combination doxorubicin/pembrolizumab, he had a subsequent complete response to trabectedin and radiation. It has been demonstrated that trabectedin with radiation is effective in soft tissue sarcomas [14]. However, trabectedin and immunotherapy may be synergistic in sarcomas [15–17].

While the use of adjuvant chemotherapy in soft tissue sarcomas is controversial [18–21], there are several ongoing studies – such as the SU2C-SARC032 trial [22] – investigating the role of adjuvant immunotherapy in high-risk sarcoma. Such studies indicate that further elucidation of tumor microenvironments and biomarkers is critical in malignancies such as PMRS, which, like other soft tissue sarcomas, is characteristically heterogenous in nature. Such clarifications will facilitate new and better defined studies investigating the use of immunotherapy in these rare neoplasms.

Conclusions

The patients described here add to the current literature that combination treatment with doxorubicin and pembrolizumab is safe, well-tolerated, and has the potential to provide an objective and durable clinical response in this rare sarcoma subtype. These findings

contribute to the body of evidence demonstrating a potentially expanding role for the use of checkpoint inhibitors in addition to standard chemotherapy in the treatment of PMRS and other advanced soft tissue sarcomas.

Statement of Ethics

Written informed consent was obtained from the participants for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines. All ethical standards of case report publication were adhered to under the policies of the University of Iowa.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. All the co-authors have seen and agree with the contents of the manuscript, and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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Author Contributions

Ioannis Kournoutas wrote the original manuscript and participated in data collection. Varun Monga, Jonathan Davick, and John Reith participated in study conceptualization, data collection, and provided critical edits and revisions of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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