

Teaching Case

Use of Immunotherapy and Radiation Treatment in the Management of Metastatic Melanoma With Rhabdomyosarcomatous Differentiation



Apar Gupta, MD, MBA,^{a,*} Raquel Wagman, MD,^b
Aditya Kuwadekar, MD,^c Michael Scoppetuolo, MD,^d
Michael Dardik, MD,^c and Franz Smith, MD^e

^aDepartment of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; ^bDepartment of Radiation Oncology, Saint Barnabas Medical Center, Livingston, New Jersey; ^cDepartment of Pathology, Saint Barnabas Medical Center, Livingston, New Jersey; ^dDepartment of Medical Oncology, Saint Barnabas Medical Center, Livingston, New Jersey; and ^eDepartment of Surgery, Saint Barnabas Medical Center, Livingston, New Jersey

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Introduction

Melanoma with rhabdomyosarcomatous differentiation is a rare phenomenon in which malignant melanoma undergoes rhabdomyoblastic transformation with accompanying morphologic and immunophenotypic features of striated muscle. Due to its rarity, there have only been 11 pathologically confirmed cases of melanoma with rhabdomyosarcomatous differentiation (Table 1).¹⁻⁸ In these reports, the emphasis has been placed on pathologic diagnosis, although limited details have been given regarding patients' clinical course and management. Although immunotherapy and radiation treatment (RT) have been successfully used in metastatic melanoma, they have been seldom used in the management of this rare melanoma variant. Moreover, the efficacy of RT for this disease remains unknown and the use of hypofractionated RT has not been tested. We seek to describe the use of immune checkpoint blockade therapy and

hypofractionated RT in our case of melanoma with rhabdomyosarcomatous differentiation.

Case Presentation

A 72-year-old man presented to his dermatologist with a pigmented lesion on his left lateral scalp that was biopsied and found to be superficial spreading malignant melanoma. He then underwent wide local excision and pathology revealed malignant melanoma with a 3.1-mm depth of invasion, mitotic rate of 3/mm², nonbrisk tumor infiltrating lymphocytes, negative margins, and no ulceration or perineural or lymphovascular invasion. The patient had a negative staging workup and final staging was pT3aN0M0.

Four months after surgery, the patient presented with an intensely pruritic rash overlying the surgical bed. On examination, the skin surrounding the surgical site was found to be thick and mildly nodular with a violaceous and erythematous component extending up to 10 cm in diameter (Fig 1 A). CT and MRI imaging of the head demonstrated skin thickening with dense subcutaneous enhancement infiltrating the scalp. Punch biopsy revealed rhabdomyosarcomatous differentiation of melanoma (Fig 2) indicating dedifferentiation at the time of recurrence. Programmed death ligand (PD-L1) assay was

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* Corresponding author: Apar Gupta, MD, MBA; E-mail: ag1363@cinj.rutgers.edu

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Table 1 Published cases of melanoma with rhabdomyosarcomatous differentiation and classification of treatment response

Author	Age/sex	Site of primary lesion	Molecular marker status	Sites of distant metastases	Surgery	Systemic therapy	TR	Immune checkpoint blockade	TR	Radiation therapy	TR	OS
Gharpuray-Pandit et al, 2007 ¹	21/F	Chin		Neck, mediastinum	Neck dissection	Interferon	PD			Yes, no details given		10 mo
Gharpuray-Pandit et al, 2007 ¹	90/M	Ear		None	WLE							
Gattenlöhner et al, 2008 ²	41/M	Forehead		Neck, lung, mediastinum, abdomen	WLE	Dacarbazine	PD			56 Gy to neck	PD	6 mo
Reilly et al, 2014 ³	59/M	Abdomen	BRAF mutated	Trunk, axilla, groin	WLE/ALND	Vemurafenib	CR			36 and 50 Gy to supraclavicular and axillary regions, respectively		
Shenjere et al, 2014 ⁴	67/F	Chest	BRAF WT	Lung	WLE							24 mo
Shenjere et al, 2014 ⁴	51/F	Uterine cervix	BRAF WT	Abdomen, pelvis	TAH/BSO	Ifosfamide, vincristine, actinomycin, doxorubicin	PR					
Agaimy et al, 2016 ⁵	69/F	Unknown	BRAF WT, NRAS WT	Jejunum								
Agaimy et al, 2016 ⁵	24/F	Scalp	BRAF mutated	Lung								
Antonov et al, 2016 ⁶	75/M	Postauricular region		Neck, lung, chestwall	WLE	Doxorubicin, ifosfamide	PD					7 mo
Campbell et al, 2018 ⁷	52/F	Back	BRAF mutated	Axilla, bone, kidney	WLE/ALND	Interferon, dabrafanib, trametinib	PR	Ipilimumab, pembrolizumab	PR			48 mo
Current case	72/M	Scalp	BRAF WT, NRAS WT, KIT WT, NF1 mutated	Neck, mediastinum, liver, kidney, bone	WLE	Temozolamide	PR	Nivolumab	PR	30 Gy to scalp and bilateral neck	CR	15 mo

Abbreviation: ALND = axillary lymph node dissection; CR = complete response; OS = overall survival; PD = progressive disease; PR = partial response; TAH/BSO = total abdominal hysterectomy/bilateral salpingo-oophorectomy; TR = treatment response; WLE = wide local excision; WT = wild-type.



Figure 1 Initial presentation of local recurrence after wide local excision (A), increasing nodularity after 6 weeks of nivolumab therapy (B), and complete resolution after 2 fractions of RT (C).

performed which showed PD-L1 expression of 90%. Next-generation sequencing was also performed and showed a NF1 mutation and wild-type BRAF, KIT, and NRAS.

The patient's disease continued to progress rapidly on the scalp, with increasing nodularity, enlarging area of erythema, and onset of facial and periorbital edema. Nivolumab 240 mg every 2 weeks was initiated and the patient initially appeared to have a modest response; however, after 3 cycles, the nodular densities continued to progress, becoming more bulky, fluctuant, and friable, leading to ulceration and easy bleeding (Fig 1 B). Although pseudo-progression could not be ruled out, the patient became increasingly symptomatic, and thus he was referred to radiation oncology for disease progression.

Although the lesions were superficial, electron beam therapy was not thought to be adequate given the thickness of the nodules and the convexity of the scalp which would preclude sufficient dose homogeneity. He was planned to undergo intensity-modulated radiation treatment with 30 Gy in 5 biweekly fractions, using 6 MV photons and 0.5 cm of bolus (Fig 3). After 2 fractions, the patient was hospitalized owing to an unrelated accident; RT and nivolumab were held during this time, but a remarkable response was noted with complete resolution of the thick nodular densities (Fig 1 C). After a prolonged hospitalization lasting more than a month, 2 nodules redeveloped on the scalp and were treated with a small electron field of 6 MeV electrons in 3 remaining fractions.

The patient did not experience any acute or late toxicities from radiation treatment.

The patient had a sustained complete response on the scalp, but he developed disease progression outside the irradiated fields approximately 2 months after completion of RT. Examination was notable for a 4-cm left postauricular mass, 3-cm right preauricular mass, and bilateral cervical lymphadenopathy. He was restarted on nivolumab and he again had a modest initial response with some tumor regression, though slow progression was then noted over the following 6 weeks. The patient continued to progress symptomatically in the upper neck, with pain and loss of hearing. Nivolumab was discontinued and he was treated with a second course of intensity-modulated radiation treatment to 30 Gy in 5 fractions to the pre- and postauricular areas and bilateral upper necks using 6 MV photons (Fig 4). During RT, a dramatic response was again noted, with complete and sustained clinical resolution of disease in the treated field. Less than 1 month after RT, disease progression outside of the targeted areas was noted, for which he was placed on temozolamide monotherapy with a partial response at some sites but an overall progressive course of disease.

Discussion

Melanoma with rhabdomyosarcomatous differentiation is an extremely rare disease in which the tumor cells dedifferentiate and form rhabdomyoblastic components

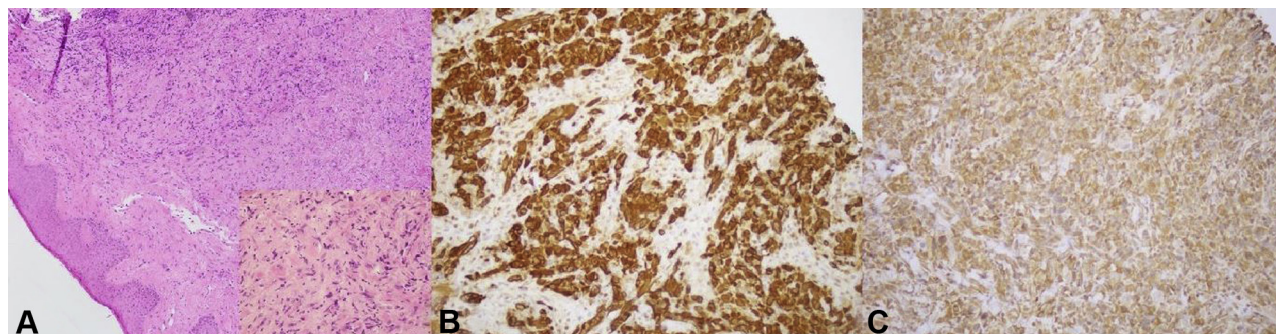


Figure 2 Biopsy revealed the dermis to be infiltrated by neoplastic cells with brightly eosinophilic cytoplasm and eccentric nuclei (A) with desmin (B) and vimentin (C) stains strongly and diffusely positive, consistent with rhabdomyosarcomatous differentiation.

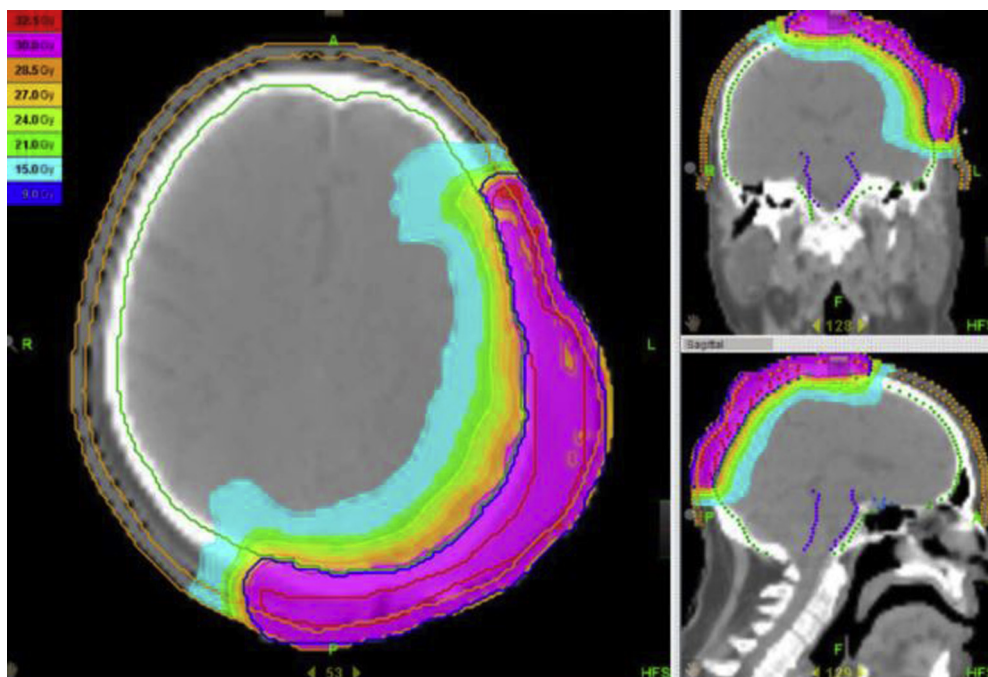


Figure 3 Intensity-modulated radiation treatment plan to 30 Gy in 5 fractions to the left lateral and posterior scalp.

with variable loss of melanocytic features. Histopathologic and immunohistochemical diagnosis have been described in great detail,⁹ yet there has been relatively little data on disease management, including a clear lack of use of immunotherapy and RT. Of the previously reported cases, immune checkpoint blockade was only used in one case, with what is suggested to be a good initial

response with eventual relapse.⁷ RT was used in 3 cases, 2 of which were in the adjuvant setting and one in which there was gross disease. In this sole case of gross disease, there was no account of treatment response, but a poor overall outcome with progressive disease was described.² Moreover, it does not seem that hypofractionated RT was used in any of the previous cases. Finally, before our case,

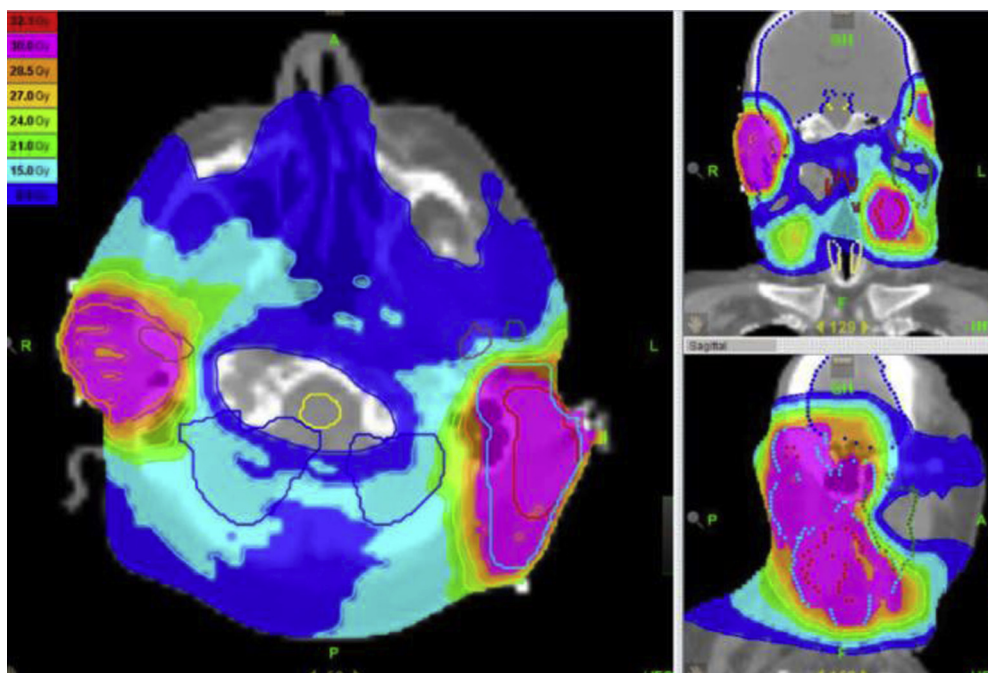


Figure 4 Intensity-modulated radiation treatment plan to 30 Gy in 5 fractions to the left postauricular and right preauricular regions and the bilateral upper neck.

there has only been one complete response documented, in a patient who was treated with vemurafenib and without the use of any RT.³

Melanoma has generally been considered to be a radio-resistant disease, but RT has still been effective in controlling advanced unresectable or metastatic disease, particularly with higher biologically effective doses.¹⁰ The use of a hypofractionated regimen delivering 30 Gy in 5 biweekly fractions was tested adjuvantly in a trial of postoperative melanoma cases and has since become the most widely used regimen in the treatment of metastatic melanoma.^{11,12} Conversely, rhabdomyosarcoma is largely a cancer of the pediatric population and data on the use of palliative RT for metastatic sites is limited. Single institutional retrospective studies have reported local control rates of 64% to 100% for conventionally fractionated RT.^{13,14} Given the rarity of melanoma with rhabdomyosarcomatous differentiation and the lack of RT use, it was difficult to predict if there would be any response to RT; our case with 2 separate complete responses in the targeted areas suggests that this disease may be amenable to radiation therapy.

Past reports have described melanoma with rhabdomyosarcomatous differentiation as being refractory to chemotherapy, concordant with the long-standing experience of metastatic melanoma being poorly responsive to traditional chemotherapeutic agents. However, immune checkpoint blockade has been found to significantly improve outcomes compared with chemotherapy in patients with metastatic melanoma. In one trial, nivolumab significantly improved response rate and overall survival compared with chemotherapy.¹⁵ In our case, nivolumab demonstrated an early response that then led to slow progression of disease; however, in the report by Campbell et al it seems that ipilimumab and pembrolizumab may have had longer durations of response.⁷

Biopsy was not performed at the time of suspected clinical progression, thus the possibility of pseudoprogression cannot be ruled out. Up to 15% of melanoma cases have demonstrated pseudoprogression after initiation of checkpoint inhibitor therapy, characterized by T-cell infiltration as a result of immune activation.^{16,17} However, clinical deterioration does not typically accompany pseudoprogression,¹⁷ and in our case, the patient became increasingly symptomatic with increased pain and bleeding, prompting multidisciplinary discussion of change in management course and decision to proceed with RT. Hyperprogression, or rapid tumor growth in a short time interval, has been another recently recognized phenomenon with initiation of checkpoint inhibition, including nivolumab.¹⁷ Without biopsy, it remains unknown whether the patient was experiencing pseudoprogression or hyperprogression.

Furthermore, there is a possibility that the favorable response seen was in part owing to a delayed response to nivolumab. In the landmark CheckMate trials testing the use of nivolumab for melanoma, response rates of 27% to

44% were noted at 9 to 12 weeks, and some responses were seen as late as 1 year after treatment initiation.^{15,18,19} The possibility of a delayed response to nivolumab, especially in light of the patient's highly PD-L1 positive tumor, along with an abbreviated first course (limited by an unrelated accident) prompted a trial with a second course of nivolumab at disease progression.

It is also interesting to note that hypofractionated RT has been shown to have more prominent immunomodulatory activity than conventionally fractionated RT,²⁰⁻²² which may have contributed to the excellent response seen in our patient. Clinical studies have also shown the benefit of combination therapy with RT and immunotherapy. In a retrospective study of 59 patients who received anti-PD-1 immunotherapy for metastatic melanoma, it was found that those who received RT had a significantly higher response rate and nonsignificantly improved overall survival than those who did not receive RT.²³ Conversely, the tumor may have shown exquisite radiosensitivity and responded to RT alone without any contributory or delayed effects from checkpoint inhibition.

Nevertheless, this rare melanoma variant remains a rapidly progressive disease with poor prognosis. In the 11 cases that have been reported, all patients presented with initially localized disease, only to develop rapid appearance of distant metastases in all but one case (in which the patient was lost to follow-up).¹ Our patient had an overall survival of 15 months from initial diagnosis. Three cases reported overall survival between 6 to 10 months,^{1,2,6} and 2 cases reported substantially longer survival of 24 to 48 months.^{4,7}

Conclusions

Immunotherapy and RT may play promising roles in the control of melanoma with rhabdomyosarcomatous differentiation. Hypofractionated RT twice produced an excellent response in our case, which may have been in part due to an additive or delayed effect from immune checkpoint blockade therapy, although no synergism or abscopal effect was seen. This combination should be further studied in future cases.

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