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Case Report

Redefining the treatment of metastatic uveal melanoma with immunotherapy – A case report

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ABSTRACT

Cancer immunotherapy originated in the early 1900s with the understanding of cancer immune surveillance and host immune defense mechanisms against cancer cells. Immunotherapy has provided a ray of hope in patients with uveal melanoma, a subtype of melanoma that has a poor prognosis once it has metastasized. Metastatic uveal melanoma (MUM) lacks a standard protocol for the treatment. Systemic chemotherapy has not shown any potential benefit. Moreover, its high toxicity has limited its use. Immunotherapy has changed the approach to treating these patients and has significantly prolonged the overall survival as well as the quality of life. We, hereby, present an interesting case of a patient presenting with MUM after an unusually long time from the primary treatment and showing an exceptional response to immunotherapy.

Keywords: Metastatic uveal melanoma, Immunotherapy, Nivolumab, Ipilimumab

INTRODUCTION

Uveal melanomas (UM) represent 3–5% of all melanoma cases with an incidence rate of 5 per million individuals. It is generally a tumor of old age, more common in males and non-Hispanic whites.[1] Metastasis in UM is not an uncommon occurrence. It mostly involves the liver, lungs, bone, and skin. Once it metastasizes, overall survival reduces to 4–6 months irrespective of chemotherapy.[2] We, hereby, present an interesting case of a patient presenting with MUM after an unusually long time from the primary treatment and showing an exceptional response to immunotherapy.

CASE REPORT

A 50-year-old gentleman, known hypertensive, presented to us in December 2017 with complaints of mild dull aching pain in the left lower abdomen for 2 months. He gave no history of fever, weight loss, loss of appetite, or abdominal distension. He had undergone left eye enucleation 16 years ago. Histopathology report was suggestive of malignant melanoma of choroid, chronic mixed type, and predominantly epithelioid type with no extrascleral or intrascleral extension. He had been disease-free until his presentation to us. On examination, he had a left eyeball implant, and no pallor, icterus, or pedal edema. Abdominal examination revealed a palpable, soft, and non-tender mass in the right iliac fossa.

He was further investigated with whole-body PET-CT which showed increased FDG uptake in multiple serosal and mesenteric nodes, largest 6.1 × 5.5 × 6.3 cm at L3, L4 levels in the abdominal cavity. Multiple parenchymal, pleural-based, and subpleural nodules were seen in bilateral lung fields. His complete blood count, liver function tests, and thyroid function tests were within normal limits. CT-guided trucut biopsy from peritoneal nodules showed metastatic malignant melanoma, S100, Melan A and HMB 45 positive, and CK negative (consistent with an origin from a primary in the eye). BRAF mutation (RTPCR) was negative. C-KIT: Exon 9,11,13,17 (RTPCR) was of wild type. PD-L1 (Ventana SP263 antibody clone) showed a tumor proportion score of 0%.

He was advised cytotoxic chemotherapy with taxanes and platinum or Dacarbazine which he refused. Hence, alternative treatment with immunotherapy was proposed which he accepted. Since ipilimumab was unavailable in India, he was started on single-agent IV Nivolumab 3mg/kg once every 14 days and was re-evaluated with PET-CT imaging every 3 months. The patient showed signs of stable disease for the first 8 months and the first sign of response in the form of necrosis of pelvic nodules was documented after 8 months of immunotherapy. By the end of 1 year, there was complete resolution of all pelvic nodules [Figures 1 and 2]. Considering excellent response with Nivolumab, it was decided to continue the same regimen until unequivocal clinical and radiological progression of the disease or until the patient had intolerable toxicities.

Post 2 years of immunotherapy, trucut biopsy from the abdominal mass showed a predominantly necrotic tumor with no viable carcinoma cell. PET-CT showed a reduction in lung metastases and overall stable disease. Hence, it was decided on the patient's request to increase the duration of immunotherapy from every 15 days to once every 2 months with close observation.

After 6 months of following the schedule, the patient showed disease progression with metastases in the brain and gluteal muscle. Formalin-Fixed Paraffin-Embedded (FFPE) blocks made from the gluteal nodes were analyzed to detect mutational burden using semiconductor-based next-generation sequencing (NGS). The FFPE was subjected to target enrichment by multiplex polymerase chain reaction amplification using a panel targeting 409 oncogenes and tumor-suppressing genes. Enriched DNA sequences were ligated with platform-specific adaptor molecules and were sequenced using a semiconductor P1 chip. The sequencing data were analyzed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v7.5. The report showed activating mutations in GNAQ (thereby a possible potential benefit from MEK inhibitors, e.g., trametinib and cobimetinib), inactivating

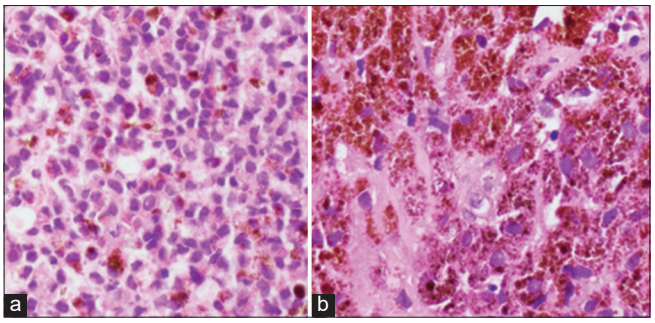

Figure 1: A 50-year-old man came with complaints of the left lower abdomen pain for 2 months: (a) Pathological finding with hematoxylin and eosin staining (H and E) of abdominal node biopsy done on initial presentation showing malignant melanoma cells. (b) Pathological finding with hematoxylin and eosin staining (H and E) done on abdominal nodes post 1-year immunotherapy show mostly necrotic tissue with pigmentation.

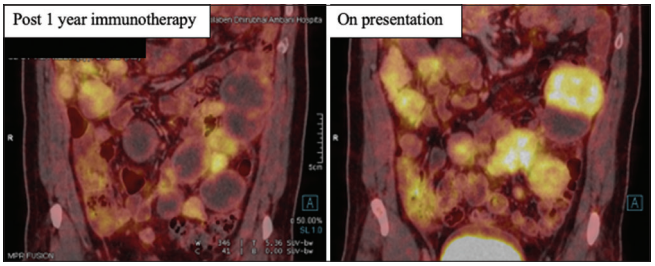

Figure 2: Interim PET-CT scan post 1 year of immunotherapy with Nivolumab showing a reduction in FDG uptake of previously demonstrated multiple soft tissue mass lesions noted in the abdominal cavity.

mutations in SMARCA4, neurofibromatosis 2 gene (thereby suggesting a potential benefit from oxaliplatin, carboplatin, cisplatin, temsirolimus, and everolimus), SF3B1, and CDH1 genes. In addition, tumor mutational burden analysis showed a low tumor mutation burden (2.96 mutations/Mb) suggesting a possible no response to immune checkpoint inhibitors such as Nivolumab. Hence, the patient was started on palliative chemotherapy with Nab-Paclitaxel and Carboplatin, of which he took six cycles, showed stable disease and was put on oral temozolamide maintenance therapy which was discontinued post six cycles due to intolerable toxicity and disease progression. As Ipilimumab became available, it was decided to start a combination therapy with IV 3 mg/kg Ipilimumab and IV 1 mg/kg Nivolumab every 21 days for four cycles followed by maintenance IV Nivolumab. Full body PET-CT after four cycles showed stable disease, and hence, it was decided to proceed with the maintenance of 3 mg/kg IV Nivolumab. Post 4th maintenance therapy patient showed disease progression, and hence, IV Nivolumab was stopped and Tab Trametinib was started. Two months later, the patient died due to carcinomatosis.

DISCUSSION

UM accounts for 80–90% of all ocular malignancies. Despite being the most commonly occurring ocular tumor, the complexity and nature of the disease make it challenging for many oncologists to effectively treat the patient. To add on, half of the patients end up developing metastatic disease.[1] Around 32% of patients who develop metastases remain asymptomatic, leading to an already advanced disease stage at the time of presentation.[3] The liver is the most common site of metastasis and is commonly seen within 4 years after treatment of the primary tumor.[4] Our patient presented with metastases in the pelvis and lungs, 17 years after enucleation, underlining the interesting possibility of dormant metastatic cells in the body from the primary tumor, which got activated years later.[5]

Furthermore, metastatic uveal melanoma (MUM) lacks a standard protocol for management. Conventionally used systemic chemotherapeutic agents do not improve patient survival significantly and include dacarbazine, temozolamide, fotemustine, and other agents such as liposomal vincristine and paclitaxel.[6] Due to all these factors, the overall prognosis remains poor with survival of only 6–8 months from the onset of metastatic disease irrespective of the chemotherapy given.[1] Based on these facts, our patient's expected survival on presentation was also predicted to be around 4–6 months.

With the advent of immunotherapy, the approach toward treating MUM has been redefined. It is well-established that cancer cells misuse immune checkpoint receptors such as CTLA4 and PD1 and upregulate them to escape immune surveillance.[7] A retrospective study of 64 patients with MUM who received combined immunotherapy with IV Ipilimumab (CTLA4 inhibitor) and IV Nivolumab (PD1 inhibitor) showed a median overall survival of 16.1 months and median duration of response of 25.5 months.[8] Another retrospective study in patients with MUM receiving only IV Nivolumab showed a median overall survival of 12 months with complete response in one, partial response in three and stable disease in five patients.[9] Our patient received single-agent IV Nivolumab 3 mg/kg once every 14 days as Ipilimumab was unavailable in India and he had an overall survival of 54 months and a median duration of response of 22 months and 5 months when he was rechallenged with the combination of Nivolumab and Ipilimumab later during his illness. This observation reinforces that immunotherapy, specifically Nivolumab, can be given despite molecular analysis (tumor mutational burden/PDL1/microsatellite instability testing) showing a possible low/negligible response to immunotherapy and can be reinitiated if required. Notably, on both occasions, an NGS study done on our patient showed a potential lack of benefit from immunotherapy.

PD-L1 inhibitors are known to induce mild immune-related adverse effects such as fatigue, rash, and pruritis. Grade IV/V toxicities are seen in <1% of the patients.[10] Although the occurrence of toxicity increases by 18–19% using combination therapy as compared to monotherapy, most side effects are easily manageable with antipyretics, non-steroidal anti-inflammatory agents, and corticosteroids or require no intervention.[11] Our patient had no toxicity with IV Nivolumab monotherapy despite receiving it for more than 2 years. With combination therapy, he had mild adrenal insufficiency and mild perioral skin depigmentation as the only side effect. With systemic chemotherapy, he had intolerable toxicities such as fatigue, loss of appetite, and gastrointestinal disturbances, especially with oral temozolamide which had to be discontinued.

CONCLUSION

Immunotherapy appears to give promising results for MUM patients. Patients can be given the benefit of upfront immunotherapy specifically Nivolumab, irrespective of NGS report, considering its mild side effects and toxicity as compared to systemic chemotherapy. Furthermore, our case, further, reinforces the need of identifying more reliable biomarkers to define the suitability of a patient for immunotherapy. The discoveries in this field will allow for the improvement of MUM treatments/therapies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: Epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol 2017;11:279-89.
2. Woodman SE. Metastatic uveal melanoma: Biology and emerging treatments. Cancer J 2012;18:148-52.
3. Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH, Chapman PB. Variates of survival in metastatic uveal melanoma. J Clin Oncol 2005;23:8076-80.
4. Midena E. Isolated brain metastasis of malignant choroidal melanoma 27 years after enucleation. Arch Ophthalmol 1999;117:1553.
5. Shields JA, Augsburger JJ, Donoso LA, Bernardino VB Jr.,

Portenar M. Hepatic metastasis and orbital recurrence of uveal melanoma after 42 years. Am J Ophthalmol. 1985;100:666-8.
6. Polak ME, Borthwick NJ, Johnson P, Hungerford JL, Higgins B, Di Palma S, *et al.* Presence and phenotype of dendritic cells in uveal melanoma. Br J Ophthalmol 2007;91:971-6.
7. Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, *et al.* Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res 2013;1:32-42.
8. Heppt MV, Amaral T, Kähler KC, Heinzerling L, Hassel JC, Meissner M, *et al.* Combined immune checkpoint blockade for metastatic uveal melanoma: A retrospective, multi-center study. J Immunother Cancer 2019;7:299.
9. Nomura M, Oze I, Masuishi T, Yokota T, Satake H, Iwasawa S, *et al.* Multicenter prospective phase II trial of nivolumab in patients with unresectable or metastatic mucosal melanoma. Int J Clin Oncol 2020;25:972-7.
10. Tacar SY, Selcukbiricik F, Yilmaz M, Erturk K, Sarici AM, Gulturk I, *et al.* Nivolumab for metastatic uveal melanoma: A multicenter, retrospective study. Melanoma Res 2021;31:449-55.
11. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, *et al.* Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26:2375-91.

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