Title: Melanoma brain metastasis pseudoprogession after pembrolizumab treatment

Running head: Brain pseudoprogession after pembrolizumab

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Abstract

The role of immunotherapy in treatment of brain metastases is unknown since most trials exclude patients with active brain lesions. As new immunomodulating agents gain approval for many malignancies, it is important to know if they have unique effects in the central nervous system (CNS). Here we present a case of a patient with progressing brain metastases treated with a single cycle of pembrolizumab, who presented with mental status changes 11 days thereafter. MRI of the brain showed enlargement of CNS lesions with intense central enhancement and diffuse perilesional edema. Histologic evaluation of a resected lesion revealed isolated clusters of tumor cells surrounded by reactive astrocytosis, scattered inflammatory cells and an abundance of microglial cells. Given the increasing use of immune checkpoint inhibitors in patients with brain metastases from melanoma and other diseases, recognition of pseudoprogression and management with immune suppression is essential.

Introduction

Ten to 40% of metastatic melanoma patients develop brain metastases (1). Standard management of brain metastases involves surgery or radiotherapy, depending on size and number (2). Although systemic therapy might have a role in treating brain metastases, the ability of newer systemic therapies to cross the blood brain barrier (BBB) remains unknown and is the subject of ongoing investigations (1, 3). Most systemic therapy trials exclude patients with active brain metastases due to their expected poor prognosis, concerns about confounding neurological symptoms, and possible inability of drugs to cross the BBB (4, 5). In recent years a few systemic therapy trials have been tailored specifically to brain metastasis patients (6-11). All of these studies were small with the exception of the BREAK-MB trial (dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastastic to the brain) which enrolled 172 patients.
Drugs with known ability to cross the BBB, fotemustine and temozomide, both alkylating agents, have shown limited activity, with brain metastasis response rates of 25% and 6%, respectively (12-14). Most of the experience in treating melanoma brain metastases with immune therapy has been with ipilimumab. There is evidence that T cells activated by the CTLA-4 inhibitor ipilimumab cross the blood brain barrier, resulting in intracerebral antitumor responses. A phase 2 trial of patients with asymptomatic and symptomatic brain metastases showed median overall survival of 7 and 3.7 months, respectively, with 2 year survival rates of 10% (15). Activity in asymptomatic patients was thus similar to that of patients without brain metastases (16).

As immunomodulating antibodies play an increasing role in treatment of melanoma and other cancer types, the effects of these agents on brain metastases needs to be assessed. Magnetic resonance imaging (MRI) is the most commonly used modality for assessing response of brain metastases, but the range of imaging responses of brain metastases to immunotherapy is not well studied. We present a case of metastatic melanoma to the brain associated with significant pseudoprogression after treatment with the PD-1 inhibitor, pembrolizumab.

Case Presentation

A 56-year-old female presented with BRAFV600E mutant metastatic melanoma to subcutaneous tissues, axillae, and adrenal glands four years after excision of a 2.13mm, non-ulcerated primary lesion. She was treated with vemurafenib for four months with disease progression in the brain. She received whole brain radiation followed by induction ipilimumab without response and was switched to dabrafenib and trametinib (BRAF and MEK inhibitors, respectively), to which she had a mixed response. She then developed innumerable new, small brain metastases, seen on surveillance MRI, for which radiosurgical salvage was not easily achievable. To facilitate safe management, one of her intracranial lesions was resected. She was enrolled on a trial of pembrolizumab for melanoma patients with active brain metastases (NCT02085070), receiving
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her first dose of 10mg/kg of pembrolizumab. She presented to the emergency room 11 days later with mental status changes. MRI showed significant worsening of cerebral edema surrounding all of her brain lesions, many of which were larger on post-gadolinium T-1 imaging. The enlarging lesions showed unusual target-like appearances (Fig. 1). Given the MRI and the speed of imaging growth that was atypical for tumor progression, we resected a representative accessible small left parietal-occipital lesion. Histopathology of this second lesion showed small clusters of tumor cells surrounded by an admixture of hemorrhage, reactive astrocytosis, scattered inflammatory cells and an abundance of microglial cells, as identified by CD68 immunostaining—all changes consistent with response to treatment rather than tumor growth (Fig. 2). CD45 staining highlighted scattered inflammatory cells, of which surprisingly few were CD8+ T cells. Sparse tumor cells showed reactivity to S100, HMB45, and Melan A. She passed away three weeks later. No autopsy was done, and the pathologic disease status could not be determined.

Discussion

Immune checkpoint inhibitors, alone and in combination, are currently the focus of intense study for a wide range of malignancies, including melanoma and lung cancer - diseases that metastasize to the brain frequently. Patients with brain metastases have previously been excluded from these trials, and literature describing effects of immunomodulating antibodies on brain lesions and microenvironment consequently remains sparse. There is evidence that T cells activated by ipilimumab may cross the BBB, enabling an intracerebral antitumor response (17, 18). Several studies have shown a positive effect of ipilimumab on selected patients with small, asymptomatic brain metastases not requiring steroid therapy (7, 15, 16, 19-22). Hodi et al, (23) described one patient with brain metastases from melanoma who did not respond to ipilimumab. Pathological review of a resected brain metastasis following ipilimumab showed focal necrosis with marked tumor infiltration by lymphocytes and an abundance of melanophages and CD8+ tumor-
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infiltrating lymphocytes with a paucity of FoxP3+ regulatory cells. The lesion in our patient showed only small clusters of tumor cells with similar reactive brain changes. The inflammatory infiltrate in our patient was composed predominantly of activated microglial cells and scattered CD8+ T cells. While the effects of pembrolizumab on normal brain and brain metastases are largely unknown, it might cause an inflammatory response similar to that of ipilimumab, as supported our pathology.

Many studies have investigated effects of radiosurgery on brain tumors. Interpretation of imaging after radiosurgery may be difficult even without additional effects of immunotherapy. In patients treated with Gamma Knife Stereotactic Radiosurgery (GKRS), re-increase in size of enhancing lesions on T-1 MRI is thought to be due to tumor regrowth. Our institution reported that regrowth of lesions on MRI after GKRS can histologically show either tumor recurrence or post-radiation inflammation (24) and often it is impossible to differentiate these entities using MRI. Rauch et al, (25) reported histopathologic changes in 10 patients with symptomatic growing lesions 8-17 months after GKRS and increased FLAIR signal on MRI. There were radiation-induced leukoencephalopathic changes (inflammatory infiltrate, demyelination, coagulative necrosis, and reactive astrocytosis) and vasculitic pathology, without evidence of tumor, indicative of treatment-related changes.

Our case demonstrates that lesion enlargement on gadolinium-enhanced T-1 MRI associated with increased perilesional FLAIR on MRI in a patient treated with pembrolizumab may not necessarily reflect true tumor progression, but can also be an inflammatory effect. Patients may become symptomatic from this inflammation and management of the inflammation with corticosteroids might be necessary despite diminishing the immune effect. Recognition of the possibility of pseudoprogression is therefore crucial for management of these patients. Moreover, correct interpretation of effects of immunomodulatory agents such as pembrolizumab on brain
Brain pseudoprogression after pembrolizumab metastases and correct classification of patients by clinical trial response criteria (RECIST or RANO) remains a challenge.
References

Figure 1: MRI: Pre and Post Treatment with pembrolizumab

(A) Post-contrast T1-weighted image revealed several enhancing metastatic lesions within the brain parenchyma prior to initiation of treatment. (B) Post-contrast T1-weighted image acquired 11 days after onset of treatment with pembrolizumab revealed increase in size of many of the metastatic lesions with a target-like appearance. The lesions demonstrate a central densely enhancing area with a ground glass zone surrounding it. (C and D) Post-contrast T1-weighted imaging before and on therapy. The arrows show the lesion that was resected.

Figure 2: (A) A representative hematoxylin and eosin (H&E) section from one of the patient’s brain lesions prior to pembrolizumab treatment showing diffuse area of malignant cells (10X). (B) HMB-45 immunostaining of the lesion depicted in part A showing diffuse positivity consistent with metastatic melanoma (10X). (C) A representative H&E section post-pembrolizumab treatment showing small clusters of melanoma cells admixed with areas of hemorrhage (20X). (D) Immunohistochemical staining with HMB-45 of the lesion depicted in part C highlighting scattered foci of melanoma cells (20X). (E) Reactive astrocytosis and infiltration of macrophages in surrounding brain tissue of the lesion in part C (40X). (F) CD45 immunohistochemical staining showing scattered perivascular and interstitial inflammatory cells as well as activated microglial cells (20X). (G and H) CD8 immunostaining highlighting infiltration of cytotoxic lymphocytes (40X and 20X). (I) CD4 immunostaining showing only rare helper T lymphocytes (20X). (J) CD68 immunostaining showing microglial/macrophagocytic cells (20X).
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