Regression of intracranial meningioma following treatment with nivolumab: Case report and review of the literature

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The treatment of refractory meningiomas remains a challenge for both neurosurgeons and neuro-oncologists. There have been no clinical reports of the use or effects of anti-PD-1 therapy in patients with meningioma.

We describe a patient whose intracranial meningioma decreased significantly in size after treatment with nivolumab, a monoclonal antibody targeting PD-1, for a concomitant advanced lung cancer. This is the first clinical report suggesting that antibodies targeting PD-1 are effective in treating meningioma. It should encourage further research into the use of checkpoint inhibitors in meningioma.

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1. Introduction

Meningiomas account for over one-third of all primary central nervous system (CNS) tumors in adults. They rarely present in childhood, and the incidence increases with age, peaking in the seventh decade of life [1]. Between 70% and 80% of meningiomas are considered benign grade I according to the World Health Organization (WHO) classification system and, if suitable for surgical resection, they generally show good outcome following surgical treatment [2]. However, atypical WHO grades II and anaplastic WHO grade III meningiomas are characterized as having aggressive behavior, resulting in a high recurrence rate and significant morbidity and mortality [3].

The significant subset of patients with poor local control has been the target of several studies searching for systemic therapy for meningiomas. A great number of agents have been investigated, including hormonal, chemotherapeutic, biological and molecularly targeted therapies, but none has been found to definitively prolong progression-free or overall survival [4–8].

Encouraging responses of non-CNS malignant tumors to immune modulator therapeutics, such as immune checkpoint antibodies, have stimulated interest in studying local immune responses in the lesion’s microenvironment. Meningiomas express the programmed-death ligand 1 (PD-L1), which, together with regulatory T (Treg) cells, contribute to the immunosuppressed tumor microenvironment [9]. Moreover, PD-L1 expression levels reportedly correlate with the aggressive phenotype of the tumor and increase with the grade of the meningioma [9]. Anti-PD-1 therapies were shown to have a long-lasting effect on tumor regression and stabilization in other solid tumors, such as non-small-cell lung carcinoma and melanoma [10,11]. There have been no clinical reports of the use or effects of anti-PD-1 therapy in patients with meningioma. We report a 66-year-old female whose previously known intracranial meningioma decreased in size after treatment with nivolumab for a concomitant stage IV lung adenocarcinoma.

2. Case report

2.1. History and examination

A 66-year-old, woman was referred to the neurosurgery outpatient clinic complaining of visual deterioration in the right eye. Her medical history was significant for progressive stage IV metastatic lung adenocarcinoma and a large right sphenoid wing meningioma (Fig. 1. Panels A and D), both diagnosed 18 months ago. The patient reported a worsening of vision, which had progressed over the past month to near total blindness in her right eye. She also complained

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of mild headache. Her visual acuity was 20/1000 in the right eye and 20/20 in the left eye. Pupillary examination showed a right relative afferent pupil defect, and fundus examination revealed temporal atrophy of her right optic nerve and a normal appearing left optic nerve. Repeat brain magnetic resonance imaging (MRI) study demonstrated significant enlargement of the known dural-based, extra-axial, right sphenoid wing meningioma (Fig. 1. Panel B) associated with worsening vasogenic brain edema and significant mass effect (Fig. 1. Panel E). An area of hypointensity in the dorsal aspect of the lesion (Fig. 1. Panel B, asterisk) suggested accelerated growth of the tumor. The tumor encased the right optic nerve as it entered the optic canal, explaining the patient’s visual deterioration. In addition, there were 2 small new intra-axial ring enhancing lesions located in the left temporal lobe and left posterior frontal parasagittal area, suggestive of metastatic lesions.

In light of progressive metastatic lung disease resistant to three lines of previous therapy, it was decided to treat her lung cancer with nivolumab, a PD-1 inhibitor, and postpone any treatment of the meningioma. Low-dose dexamethasone (2 mg once per day) was initiated to control edema.

After six months of treatment with nivolumab, the patient reported a significant improvement in well-being and cessation of headaches. Chest CT demonstrated a regression of the known lung disease. Brain MRI demonstrated a significant reduction in the mass effect and midline shift. FLAIR images (Fig. 1. Panel F) showed decreased signal intensity in the right frontal lobe and anterior corpus callosum, compatible with reduction of vasogenic brain edema. Following contrast administration (Fig. 1. Panel C), there was a 24% reduction in the volume of the meningioma compared with the previous examination (Fig. 1. Panel B).

3. Discussion

Complete surgical resection has been the standard of care for meningioma. However, a significant subset of patients cannot be successfully managed by surgery alone or safely undergo complete resection due to proximity of the tumor to eloquent brain regions. The treatment of refractory disease, mostly associated with grades WHO II and III meningiomas or cases not amenable for resection, remains a challenge for both neurosurgeons and oncologists. Multiple agents have been investigated in clinical trials for the treatment of meningiomas. They include cytotoxic agents (e.g., hydroxyurea and irinotecan) [5], hormonal agents (e.g., progesterone receptor antagonists and estrogen receptor antagonists) [6], growth factor receptor antagonists (e.g., EGFR and PDGFR inhibitors) [8], angiogenesis inhibitors [7] and immunomodulators (e.g., interferon alfa-2b) [4]. None have shown a significant response, sustainable tumor control or the prolongation of survival.

With increased understanding of the underlying mechanisms involving the immune response towards tumor cells, multiple novel immunotherapeutic agents and strategies are currently being investigated for the treatment of cancer. Checkpoint inhibitors that are aimed at enhancing the function of T cells by blocking
the negative regulators of T cell immunity have demonstrated durable control of advanced cancer as well as improved overall survival [10,11]. One important immunologic checkpoint that shows promising results in cancer treatment is the programmed cell death protein 1 pathway (PD-1/PD-L1) [12]. PD-1 is a cell surface receptor of the CD-28 family that is expressed on T cells and professional antigen-presenting cells. It appears to modulate T cell activity in peripheral tissue through interaction with its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) that are expressed on hematopoietic cells as well as on non-hematopoietic cancerous tissues. Upon interaction of PD-1 with its ligand, PD-1 inhibits kinase-signaling pathways leading to the attenuation of T cell activity and the inhibition of T-cell proliferation, causing down-regulation of anti-apoptotic molecules. It is assumed that by expressing PD-L1 molecules, tumor cells can down-regulate anti-tumor T-cell activity and thus evade immune response [12]. This may be the reason for the correlation between high expression of PD-L1 molecules in tumor cells and poor prognosis, as seen in malignant melanoma and lung cancer. The antibodies developed to interfere with the PD-1 pathway are divided into anti-PD-1 and anti-PD-L1 antibodies [12]. Nivolumab is an anti-PD1 antibody that shows durable response rates with minimal toxicity among patients with advanced melanoma [13], non-small cell lung carcinoma [14], renal cell carcinoma [14] and other solid tumors [11].

Unlike other types of solid cancer, the role of immunotherapy and, particularly, checkpoint inhibitors in the treatment of meningiomas is unknown. Du et al. [9] recently found that T cells are the main tumor-infiltrating lymphocytes in meningiomas. However, they observed a clear decrease in the total number of T-cells, including CD4+ and CD8+ cells, along with an increase in the number of FOXP3 expressing regulatory T cells in high-grade meningiomas (e.g., WHO III anaplastic meningioma), which suggests an immunosuppressed tumor microenvironment [9]. Moreover, those findings have been linked to elevated expression of PD-L1 mRNA and protein in high-grade meningioma cells, supporting the attenuated local immune response and suggesting that the PD-1 pathway may be a promising target for treatment of these tumors.

To date, there have been no reports of clinical application of PD-1 antibodies for the treatment of meningioma. We believe that the current case is the first demonstration of a significant clinical response of meningioma to a single-agent therapy with nivolumab. The timeline of lung cancer therapies given to our patient clearly showed a significant reduction in the meningioma’s size and resolution of the associated brain edema only after the termination of previous therapies and after the initiation of nivolumab. Although we had no tissue diagnosis to confirm the pathology of the meningioma, the imaging studies are pathognomonic for that diagnosis. The possibility of a collision tumor with a meningioma, harboring a lung cancer metastasis, is unlikely. It is considered a rare event, which more commonly involves breast cancer metastases [15].

4. Conclusion

This is the first report suggesting that antibodies targeting PD-1 are effective in treating meningioma. This report should encourage further research into meningioma immunotherapy and the clinical trials of checkpoint inhibitors, specifically, antibodies targeting the PD-1 pathway, for treatment of meningiomas with aggressive biologic behavior.

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