LETTER TO THE EDITOR

To The Editor

Sixth Nerve Palsy as the Presenting Sign of Delayed Melanoma Recurrence

Keywords: Metastatic melanoma, Abducens nerve, Cranial nerve palsy, Cavernous sinus, Diplopia

Neurologic complications are common in metastatic melanoma and can arise through the perineural invasion of a primary tumor, brain metastases, leptomeningeal metastases, and paraneoplastic syndromes. Of all cancers, melanoma has the highest propensity to metastasize to the brain, with nearly 40% of patients with advanced melanoma diagnosed clinically with brain metastases, and up to 75% at autopsy.[1] The presence of neurologic complications suggests a poor prognosis, with a median survival time of 4 months,[2] although this is increasing with the advent of immunotherapeutic agents. A previous case series of 56 melanoma patients with confirmed CNS metastases found the most common neurologic symptoms to be confusion and disorientation, headache or signs of increased intracranial pressure, motor deficits, and focal seizures.[1] Here, we report a unique case of recurrence of melanoma in the cavernous sinus that initially presented as an isolated sixth nerve palsy.

An 85-year-old woman presented with a 1-day history of horizontal binocular diplopia. She had a past medical history of a melanoma on her right fifth toe treated with amputation one year prior to presentation. It was considered pathologic stage pT2b with ulceration, 1 mitosis per square mm with negative sentinel lymph nodes. There was also no regression, lymphovascular invasion, and no microsatellitosis identified and no further treatment was recommended. She also had a history of hypertension and dyslipidemia and her medications included candesartan, amlodipine, and atorvastatin. Examination revealed a visual acuity of 20/20 in both eyes, equal-sized pupils, and an isolated right abduction deficit (Figure 1). External examination was normal without proptosis and her conjunctiva appeared normal. She denied headache or symptoms suggestive of giant cell arteritis, but bloodwork showed elevated sedimentation rate of 60 mm/hr and C-reactive protein (CRP) of 120 mg/L (normal < 5). She denied a change in her appetite, night sweats, but felt more fatigued over the past month. Computed tomography (CT) of the head was reported as normal and she was referred to ophthalmology for a temporal artery biopsy to rule out giant cell arteritis (GCA). Re-evaluation of the CT showed enlargement of the right side of the cavernous sinus and an MRI of the brain and orbits with gadolinium was performed. This showed enlargement in the right cavernous sinus, which was bulkier, dark on T2-weighted images and without enhancement in comparison to the left. The elevated CRP was thought to reflect metastatic disease rather than GCA. CT of the chest, abdomen, and pelvis showed diffuse hepatic metastases and bulky lymphadenopathy consistent with nodal metastases. Her liver function tests revealed a normal AST, ALT, total bilirubin, and ALP was slightly elevated (133 U/L). She opted for palliative care and died 2 months later.

Isolated sixth nerve palsy from recurrence of melanoma in the cavernous sinus is rare and we were unable to retrieve a similar case in the literature. Previous case reports have identified sixth nerve palsy from melanoma located near other parts of the nerve's pathway including the sphenoid sinus, temporal bone, and surrounding leptomeninges. All of these patients had either widespread metastatic disease or other neurological symptoms like severe headache, hearing loss or vomiting. Our literature search revealed only one other case of isolated vertical diplopia, caused by a fourth nerve palsy from melanoma compressing the dorsal midbrain.[3] All other reported presentations of diplopia involved the concurrent involvement of other cranial nerves and neural structures, typically the trigeminal nerve, facial nerve, and meninges. It is important to recognize that the presence of horizontal diplopia in melanoma patients with metastatic disease does not necessarily suggest spread to the brain. More recently, there have been reports of inflammatory cranial nerve palsies in melanoma patients receiving systemic therapy with checkpoint inhibitors.[4]

Melanoma has characteristic features on MRI. These include T1-hyperintensity and T2-hypointensity. In our case, the T1-weighted changes were not appreciated in the cavernous sinus, but there was T2-hypointensity and no contrast-enhancement, which was a significant finding. A differential diagnosis was considered for hypointense signal on T2-weighted sequences and this included acute bleeding or vascular malformations, mucous or protein-containing lesions such as cysts, highly-cellular lesions (e.g. lymphoma, glioma) and the accumulation of minerals (e.g. iron, copper, calcium).[5] However, these lesions were felt to be much less likely in this clinical context.

Another noteworthy feature of this case is that sentinel lymph node biopsy was initially negative at initial toe melanoma diagnosis. Taken together with the other features of the pathology, no further intervention was recommended at that time. In melanoma patients with negative sentinel lymph node biopsies, the probability of distant recurrence is 5%, with a 1% chance of recurrence to the brain.[6] This probability peaks in the first 24 months after biopsy, and begins to drop significantly after 36 months. It is therefore important to recognize that a negative sentinel lymph node biopsy does not preclude future metastatic neurological disease, which can occur at any time. Brain metastases have been reported even after 20 years of diagnosis and treatment.[7] This highlights the importance of a past medical history of melanoma, which should always be taken seriously. Although our patient did not have pathologic confirmation of the cavernous sinus lesion, the widespread metastatic disease allowed this diagnosis to be made with a high degree of certainty.

Patients presenting with an isolated cranial neuropathy together with an elevated ESR and CRP should be evaluated for GCA. However, metastatic melanoma and other metastatic cancers may also demonstrate elevated ESR and CRP levels, as these are nonspecific markers of inflammation. Specifically, patients with metastatic melanoma have been found to have average ESR rates of 31.5 mm/h and CRP levels >3.0 mg/L.[8,9] Therefore, the presentation of an isolated cranial neuropathy alongside these elevated inflammatory markers can invoke the diagnosis of GCA. The temporal artery biopsy was deferred in this case given the initial imaging findings that raised the suspicion of metastatic disease.

In conclusion, we present an 85-year-old woman with a sixth nerve palsy after a one-year recurrence of melanoma in the cavernous sinus. This case emphasizes the importance of considering metastatic melanoma for new neurological symptoms after melanoma diagnosis.

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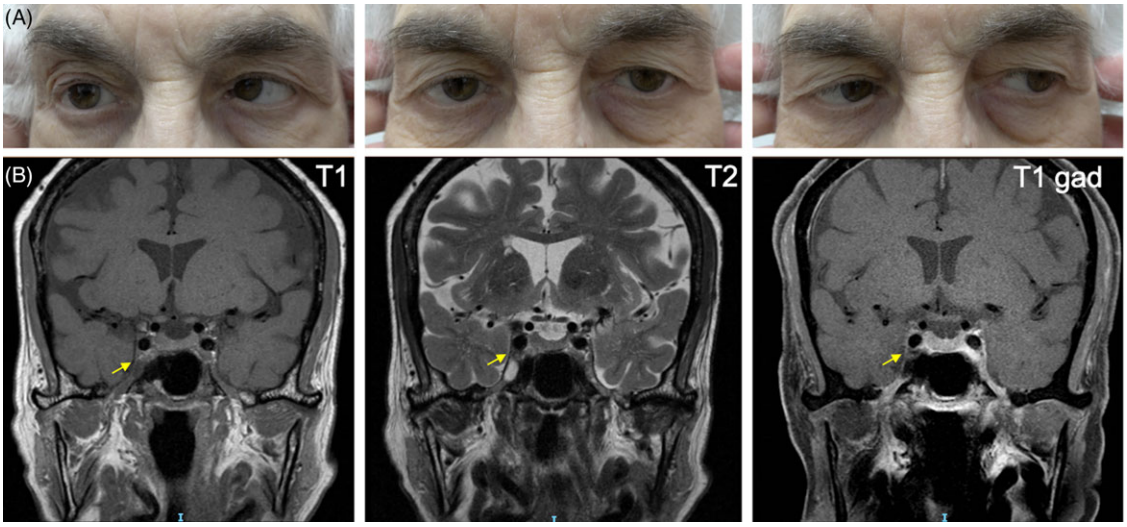

Figure 1: *(A) External photographs demonstrating a limitation of abduction in the right eye. (B) Coronal magnetic resonance imaging (MRI) demonstrating enlargement in the right cavernous sinus (arrows), which was bulkier, dark on T2-weighted images, and without enhancement when compared to the left.*

Conflict of Interest

None.

Statement of Authorship

J.M. selected the case, provided the images, and approved the final version. A.E., J.M., and M.N. performed the literature search, wrote the manuscript, and made revisions.

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