Parenchymal Anaplastic Astrocytoma presenting with Visual Symptoms due to Bilateral Optic Nerve Sheath Involvement

Running title: anaplastic astrocytoma spread to optic nerve sheaths

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The authors have no conflict of interest to disclose

Dr. Moss receives support from NIH grant number K12 EY021475

Keywords: anaplastic astrocytoma, optic nerve edema, leptomeningeal spread

Abstract

A 23 year old man presented with transient visual obscurations and was found to have optic nerve edema and a thalamic lesion that did not enhance on magnetic resonance imaging. Lumbar puncture opening pressure was normal. Subsequent magnetic resonance images demonstrated optic nerve sheath enhancement. Pathological diagnosis of the thalamic mass was anaplastic astrocytoma (WHO grade III). Visual symptoms were attributed to spread of high grade parenchymal glioma to the optic nerve sheaths causing intraorbital optic nerve compression.

Dear Editor,

We read with interest the recent report by Traynis et al et al regarding glimoatosis cerebri presenting through anterior visual pathway involvement (1). We contribute a distinct, though similar, case that further expands the spectrum of presentation of the primary neuro-ophthalmic presentations of central nervous system gliomas.

Case Report

A 23 year old man presented with transient visual obscurations (TVOs). Visual acuity was normal. Visual fields showed mild blind spot enlargement. There was bilateral optic disc elevation. Magnetic resonance imaging (MRI) of the brain demonstrated a left thalamic lesion with increased T2 signal and no enhancement. Multiple MRIs during the next 5 months were stable. 5.5 months after presentation the TVOs became more frequent. He developed peripheral vision loss in both eyes. He denied headaches and fevers. His past medical history, social history, and family history were unremarkable.

Visual acuities were 20/50 OD and 20/200 OS. Visual fields were constricted. Posterior segment exam revealed marked elevation of both optic nerves with vessel obscuration and subretinal fluid extending to the macula. There were no hemorrhages or cotton wool spots. Neurological and ophthalmic examinations were otherwise normal.

Serial lumbar punctures (LP) had opening pressures of 23 and 22 cm of water. Cerebrospinal fluid (CSF) had 13 white blood cells/μL with monocytic predominance, 46 mg/dL protein, normal glucose, negative cultures, negative venereal disease research laboratory, no oligoclonal bands, normal angiotensin converting enzyme (ACE) and no

malignant cells. CSF cytology from a third LP revealed rare spindle cells with mild atypia.

Blood tests including anti-nuclear antibody, anti-aquaporin 4 antibody, and ACE levels were all within normal limits. Studies investigating an infectious etiology including for Lyme, coxsackie virus, varicella-zoster virus, arbovirus, West Nile virus, Bartonella henselae, syphillis, Cryptococcus neoformans, toxoplasmosis, coccidioides and human immunodeficiency virus were negative.

MRI brain demonstrated a stable, non-enhancing left thalamic mass (Fig. 1). MR spectroscopy to further evaluate the thalamic mass showed decreased signal intensity associated with N-acetyl aspartate resonance and increased signal intensity associated with the choline resonance, consistent with a low-grade tumor or inflammatory process. MRI orbits showed increased fluid space in the optic nerve sheaths and new enhancement of bilateral optic nerve sheaths (Fig. 2). Brain MR angiography and venography and spine MRI were within normal limits. Computed tomography of the chest, abdomen and pelvis did not demonstrate mass lesions or lymphadenopathy. Gallium scan did not reveal areas with abnormal activity.

Visual fields and visual acuity worsened despite empiric treatment with steroids. Stereotactic biopsy of the left thalamic lesion and left frontal meninges revealed parenchymal anaplastic astrocytoma, World Health Organization (WHO) grade III, in thalamic tissue samples, along with changes suggestive of leptomeningeal glioma spread in the left frontal leptomeningeal biopsy (Fig. 3). Immunohistochemistry studies from the thalamic tissue samples indicated that tumor cells were positive for GFAP and were negative for LCA, CD68, CD3, and CD20. Many tumor cells stained with p53 consistent

with the presence of p53 mutation in tumor cells. The Ki-67 proliferation marker stained more than 5% of tumor cells. The leptomeningeal sample demonstrated focal staining of a low number of cells with GFAP, p53 and Ki-67.

Follow up orbital MRI showed enhancement of bilateral optic nerve sheaths that extended intracranially, new T2 hyperintensity within both optic nerves and volume loss of the right optic nerve. Left transconjunctival optic nerve sheath fenestration with biopsy of the nerve sheath was performed to evaluate for optic nerve sheath involvement of the tumor to aid in treatment planning. This did not show frank neoplasia. Immunohistochemistry was positive for p53 in a few cells along with occasional LCA and CD68-positive inflammatory cells. Due to the detection of a small number of p53-positive cells, involvement of the optic nerve sheath by glioma could not be ruled out.

He was treated for six weeks with concurrent temozolomide 75mg/m^2 (160 mg) daily and whole brain radiation at 45 Gray in 1.8 Gray fractions. One month after completion of concurrent chemoradiation, he was placed on maintenance chemotherapy with temozolomide 200mg/m^2 (400mg) daily for 5 days every 28 days for a planned total of 6 cycles.

His visual acuity stabilized at hand motion with the right eye and bare LP with the left eye. There was some expansion of the right eye visual field following therapy. Ophthalmoscopic examination showed bilateral optic nerve pallor. Repeat imaging of brain and orbits revealed slight interval decrease in size of the thalamic tumor with reduction in mass effect on the third ventricle. There was interval development of enhancement within bilateral optic nerves. During the second cycle of maintenance chemotherapy, the patient experienced left buttock pain, which progressed to bilateral,

unrelenting back pain. MRI showed new leptomeningeal enhancement within the thoracic spine suggestive of further tumor spread.

Discussion

Anaplastic astrocytomas are part of the glioma family of malignant brain tumors with an age adjusted incidence rate of 0.36: 100000 and median survival of 2-5 years (2, 3). Optic nerve head edema is a non-specific finding that can be due to nerve head infiltration, optic nerve head ischemia, intra-orbital optic nerve compression by high subarachnoid space pressure, or compression by optic nerve sheath lesions. We present a unique case of parenchymal anaplastic astrocytoma with spread to the optic nerve sheaths presenting with transient visual obscurations. This is distinct from the recently published case (1) due to the association with a high grade parenchymal tumor, and initial symptomatology attributable to compressive, rather than infiltrative optic neuropathy.

The literature supports the challenge of confirming pathological diagnosis of tumor spread to optic nerve sheaths ante-mortem and reinforces the importance of maintaining a high suspicion for tumor spread as a cause of enigmatic symptoms (4-8). Though we do not have pathological confirmation of leptomeningeal spread to the optic nerve sheaths, aspects of the optic nerve sheath biopsy, CSF analysis and clinical course provide supportive evidence. None of the biopsy specimens or clinical investigations suggested an alternative etiology for optic nerve head edema and optic nerve sheath enhancement.

Leptomeningeal spread of malignant astrocytomas is well described, though presentation through optic nerve sheath involvement has only been alluded to. A study of

high-grade gliomas (33 anaplastic astrocytoma and 35 glioblastoma multiforme) reported that 25% had intracranial dissemination and 6 had spinal dissemination (9). All cases with spinal dissemination had thalamic or temporal lobe primary tumors and the authors proposed proximity to CSF circulation as a risk factor for dissemination. In a case series of post-mortem confirmed cases of leptomeningeal infiltration, 18 of 63 cases were associated with an intracranial mass lesion and 7 of these were astrocytomas (further subdivision was not specified) (10). Of the 18 cases associated with an intracranial mass lesion, CSF contained malignant cells in only 21% and presenting signs included optic nerve edema in 45% cases. The authors' proposed that papilledema may have represented either elevated intracranial pressure or neoplastic optic nerve compression, but did not have sufficient clinical data to make this distinction. In our patient elevated intracranial pressure was excluded by serial lumbar punctures.

The non-enhancing appearance of the thalamic mass on imaging and its stability on serial scans in our patient led to the initial consideration that it was a low grade tumor unrelated to his neuro-ophthalmic symptoms and signs. Several case series reinforce that imaging characteristics do not reliably predict histological grade. In both retrospective and prospective studies of parenchymal brain lesions without enhancement between 35 and 45% are WHO grade III on histological examination (11,12). Though the majority of anaplastic astrocytomas demonstrate MRI enhacement, on study estimated that 9% of malignant supratentorial gliomas lacked contrast enhancement (13). Some studies have suggested that advanced imaging techniques such as perfusion-weighted imaging and MR spectroscopy may provide additional insight into the malignant potential of intracranial lesions (14-16). However, the false negative predictions of these techniques, as shown by

our case, limits their utility as a screening test. One possible reason for the imaging and histological discrepancy in our case and others is heterogeneity within the tumor with focal high-grade transformation (17).

Transient visual obscurations related to optic disc edema caused by compressive optic neuropathy by leptomeningeal spread of parenchymal anaplastic astrocytoma is a unique presentation of primary central nervous system glioma to our knowledge. An additional instructive aspect of this case is the seemingly benign radiographic features of the malignant parenchymal tumor.

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Figure Legends:

Figure 1. MRI of thalamic lesion five months after symptom onset. FLAIR axial images of left thalamic lesion with T2 hyperintensity. The lesion was isointense on T1 and did not demonstrate enhancement after gadolinium administration.

Figure 2. Parasagittal MRI of optic nerves five months after symptom onset. T1 post-contrast with fat saturation images demonstrating variable thickening and enhancement of both optic nerve sheaths.

Figure 3. Thalmic(left), leptomeningeal (center) and optic nerve sheath (right) Biopsy specimens. Hemotoxylin & eosin stains 200x (main) demonstrating significant pleomorphism and glial nuclear atypia, as well as increased cellularity and scattered mitotic figures in the thalamic specimen and small focal collections of atypical cells in the subarachnoid space of the leptomeningeal specimen, but not the optic nerve sheath specimen. P-53 immunohistochemistry (insets) demonstrating staining of many thalamic tumor cells, atypical leptomeningeal cells and rare optic nerve sheath cells.