CLINICAL VIGNETTE

Carboplatin Induced Papilledema Successfully Treated with Acetazolamide

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Case

A 73-year-old retired male ophthalmologist initially presented to his primary care physician with rapidly progressive weight loss and failure to thrive. He had vague upper GI symptoms including early satiety, increased belching, and post-prandial nausea. Ultimately, the patient underwent a diagnostic, contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis. The scan revealed a 4.2 x 3.7 x 5.6 cm mass in the body of the pancreas. Additionally, there was hepatomegaly noted with innumerable hepatic lesions and upper abdominal lymphadenopathy. A CT-guided core biopsy of a liver lesion revealed poorly-differentiated neuroendocrine carcinoma. The patient had normal baseline renal and hepatic function and no history of hypertension.

He initiated palliative chemotherapy with intravenous carboplatin (AUC 5 mg/ml x min) on day 1 with intravenous etoposide 100 mg/m2 on days 1, 2, and 3 of a 21-day cycle. After 4 of 6 planned cycles of chemotherapy, repeat CT scans showed responding disease. The chemotherapy regimen was well tolerated with mild cytopenias, manageable nausea, and typical chemotherapy related fatigue and malaise. The patient obtained significant clinical benefit with chemotherapy with resolution of his GI symptoms, improved functional status, and weight gain.

One week after his fifth cycle of carboplatin and etoposide, the patient noted a pulsatile, partial scotoma in his left temporal field. The following day he noted similar, but more subtle symptoms in his right eye. His wife, a retired academic ophthalmologist, performed direct ophthalmoscopy and noted flattening of the temporal disc margins bilaterally.

The patient was seen by a neuro-ophthalmologist. Examination confirmed bilateral optic nerve edema, greater on the left than on the right. Optical coherence tomography (OCT) demonstrated marked elevation of optic nerve thickness, confirming optic nerve edema. Magnetic resonance imaging (MRI) of the brain and orbits with and without contrast demonstrated no mass or abnormal enhancement, ruling out metastatic disease as a cause. However, the bilateral optic nerve sheaths were dilated with flattening of the posterior globes. This was interpreted as strongly suggestive of intracranial hypertension.

He was diagnosed with carboplatin-induced intracranial hypertension with bilateral papilledema and started on acetazolamide. Within 2 weeks of starting acetazolamide, his symptoms had resolved and direct ophthalmoscopy demonstrated improving optic nerve edema. Repeat OCT was also consistent with resolving optic nerve edema.

Given the response to carbonic anhydrase inhibition and the patient's response to chemotherapy, the decision was made to proceed with the sixth and final cycle of carboplatin and etoposide. The patient completed the final cycle while on acetazolamide and experienced no recurrent visual symptoms. He subsequently discontinued acetazolamide and follow up examination with neuro-ophthalmology 4 months later was normal. One year after his initial diagnosis, he has normal vision.

Discussion

Papilledema reflects optic disc swelling that results from an increase in intracranial pressure (ICP). Typically, patients present with symptoms attributable to increased ICP, such as headache, and not with visual symptoms. Visual symptoms if present, are typically transient partial visual field losses, lasting seconds. The visual symptoms tend to be unilateral. If the increase in ICP and papilledema are not resolved, visual symptoms may progress and can lead to permanent vision loss. Papilledema may occur secondary to any cause of increased ICP.[1]

Platinum chemotherapy agents – oxaliplatin, carboplatin, and cisplatin – are used to treat numerous malignancies. Oxaliplatin and cisplatin are known for causing neurotoxicity, in particular, sensory neuropathy and in the case of cisplatin, otoxocity as well. At standard AUC doses, carboplatin infrequently causes neurotoxicity.

There are two case reports of high-dose carboplatin, doses double that given to this patient causing acute onset cortical blindness. The mechanism is thought to be direct neuro toxic effect of the carboplatin. The patients in these reports had a normal neurological examination at time of visual loss, a history of hypertension, and either a history of chronic kidney disease or acute deterioration in glomerular filtration. In both cases, vision improved with stopping carboplatin.[2]

One case report described the development of bilateral carboplatin-induced papilledema in a woman receiving standard-dose carboplatin, AUC = 5, for metastatic ovarian carcinoma.

The patient noted bilateral visual symptoms during her 4th cycle of therapy when she developed acute kidney injury due to obstructive uropathy. As in our case, direct ophthalmoscopy demonstrated bilateral papilledema. The patient was treated with an additional cycle of carboplatin and started on a prednisolone taper. Two years later, left eye vision had improved, while right eye vision was stable. Examination at 2 years disclosed bilateral optic nerve atrophy.[3]

In our patient given his aggressive metastatic malignancy the initial concern was for a metastatic brain lesion and/or lepto-meningeal carcinomatosis as a cause of his optic symptoms. As the MRI was not consistent with metastatic disease, the differential was carboplatin-induced intracranial hypertension, malignant hypertension, or a toxic injury to the optic nerve from carboplatin. Malignant hypertension was ruled out as the patient had no history of poorly controlled hypertension with normal blood pressures during previous visits. The prompt response to acetazolamide and no recurrence with carboplatin re-challenge also ruled out toxic injury to the optic nerve secondary to chemotherapy. Therefore, carboplatin was determined to be the cause of his papilledema.

Our case highlights an infrequent complication of platinum-based chemotherapy, optic nerve toxicity. The initial symptoms of optic nerve toxicity are often subtle and likely underreported by patients. It is probable this patient's diagnosis was made because both the patient and his wife were ophthalmologists and promptly identified his symptoms. Early recognition of ocular toxicity can lead to stopping of the offending drug before permanent visual injury occurs and also allows for effective treatment if the optic nerve injury is reversible as is the case in papilledema.

This case demonstrates that carboplatin-induced papilledema can be effectively treated with acetazolamide and that the carboplatin can be safely continued without lasting optic nerve injury. Moreover, it is the first case describing carboplatin-induced papilledema occurring with standard dosing and no antecedent renal injury.

REFERENCES

1. **Bienfang DC**. Overview and differential diagnosis of papilledema. In: *UpToDate*, Post TW (Ed), *UpToDate*, Waltham, MA, 2020.
2. **O'Brien ME, Tonge K, Blake P, Moskovic E, Wiltshaw E**. Blindness associated with high-dose carboplatin. *Lancet*. 1992 Feb 29;339(8792):558. doi: 10.1016/0140-6736(92)90384-f. PMID: 1346911.
3. **Fischer N, Stuermer J, Rodic B, Pless M**. Carboplatin-Induced Bilateral Papilledema: A Case Report. *Case Rep Oncol*. 2009 Apr 25;2(1):67-71. doi: 10.1159/000212087. PMID: 20740148; PMCID: PMC2918832.