Irreversible bilateral optic neuropathy from gemcitabine-oxaliplatin combination chemotherapy: A case report

We report a case of irreversible optic neuropathy following the use of gemcitabine and oxaliplatin chemotherapy. Ocular side-effects of chemotherapy are relatively rare but have been documented with a wide variety of agents. Although sparse, they are serious because of the potential for loss of vision. Polychemotherapy regimens like gemcitabine and oxaliplatin are commonly used medications, especially for patients with metastatic gall bladder cancer. It is often difficult to arrive at a specific cause-effect relationship between the use of chemotherapeutic drugs and their toxic effects in such cases. Patients on chemotherapy are also often not able to cooperate fully for detailed evaluation and follow-up for the ocular condition due to their frail general condition from the ongoing chemotherapy, and the fact that the management of the systemic disease takes priority in many of these patients.[1]

In December 2021, a 40-year-old woman with no comorbidities from northeast India was referred to us with the diagnosis of metastatic gall bladder cancer. After a histopathological review and a metastatic workup, she was planned for palliative gemcitabine and oxaliplatin-based polychemotherapy. Despite getting infected with the coronavirus disease (COVID-19) during her chemotherapy, she completed four cycles of combination chemotherapy, with a good partial response in April 2022. Chemotherapy was resumed once she tested negative for COVID-19 on the reverse transcription-polymerase chain reaction (RT-PCR) test in January 2022. In April 2022, she returned to her hometown to continue the planned treatment. At the same time, she experienced progressive, painless loss of vision in both the eyes, despite having no previous history of visual impairment. She was referred to an ophthalmologist in her hometown who advised some medication and reassured her, advising her to visit after four weeks.

She returned to our hospital and was admitted through the emergency services in June 2022. After initial evaluation, she was referred to a neurologist and an ophthalmologist

for detailed evaluation. The right eye examination revealed no projection to light, mildly dilated pupils, no reactivity to light, and a small pale disc at ocular pressure 14 mmHg, indicating a relative afferent pupillary defect (RAPD). The left eye fundoscopy showed that she could detect hand movement close to her face; her pupils were slightly dilated and sluggishly reactive to light; and the disc was small and pale at 17 mmHg as shown in Figure 1. Systemic intravenous steroid was started on the second day of admission after the fundus examination.

The ophthalmologist advised an assessment of visual function which was performed by the visual evoked potential (VEP) study. The VEP study revealed no waveform, indicating bilateral retino-optic pathway dysfunction. The automated perimetry test revealed complete loss of vision with constriction of the visual field in the right eye and tunneling of vision with loss of peripheral vision in the left eye, as shown in Figure 2. In Figure 3, the optical coherence tomography (OCT) findings are depicted suggesting thinning of the retinal nerve fiber layer in bilateral eyes (right > left eye).

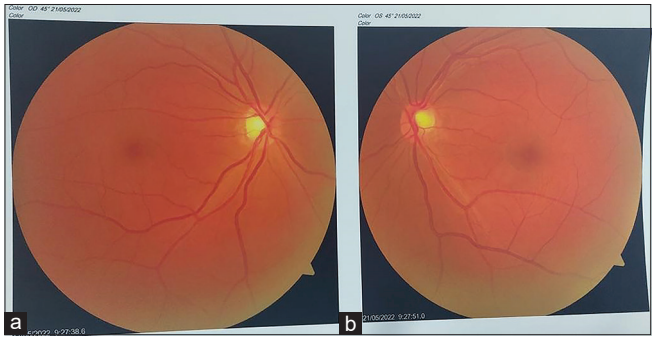

Figure 1: Left (a) and right (b) panels show the color fundus photograph of left and right eye optic disk pallor

The patient was tested to determine the reason for this bilateral edematous optic neuropathy. We first had to rule out intracranial hypertension. Intracranial hypertension could be caused by obstructive hydrocephaly, intracranial metastasis, carcinomatous meningitis, cerebral venous thrombosis, and drug-induced intracranial hypertension. Oxaliplatin has been linked to intracranial hypertension.[2]

The neurologist advised radiological imaging of the brain and the spine. The findings of the magnetic resonance imaging (MRI) of the spine and brain including the orbit, revealed no evidence of active neuritis or infiltration of the optic nerves as shown in Figure 4. A lumbar puncture test revealed an oligoclonal band in both the cerebrospinal fluid and the serum, with no additional band found. Intracranial hypertension was ruled out as the cerebrospinal fluid pressure was 18 cm of H_2O. The neurologist advised serum testing for paraneoplastic inflammatory causes such as multiple sclerosis, neuromyelitis optica, and granulomatosis with polyangiitis. The absence of oligoclonal bands, non-elevation of IgG antibodies in the cerebrospinal fluid, and normal appearance of the MRI brain and spine ruled out the diagnosis of multiple sclerosis. The antinuclear antibody (ANA) screening test was negative, thus ruling out systemic autoimmune rheumatic disease. The serum angiotensin-converting enzyme (ACE) level was within normal limits, which ruled out other rare diseases like sarcoidosis.

Besides oxaliplatin, the second drug, gemcitabine, is an antimetabolite which causes deoxyribonucleic acid (DNA) replication and arrests tumor growth. A literature search in Medline over the last 40 years, did not turn up any reports

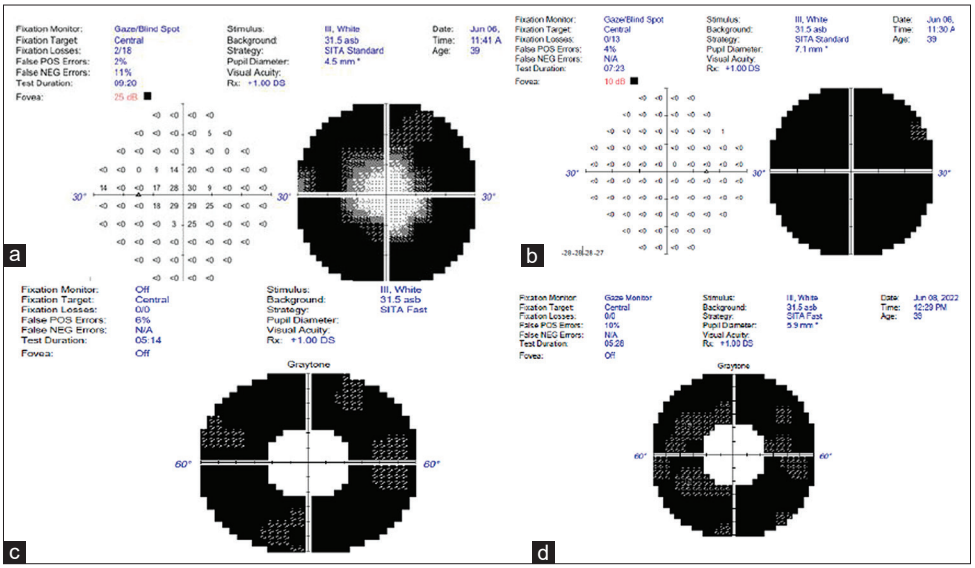

Figure 2: Panels (a) and (c) for the left eye; (b) and (d) for the right eye show the automated perimetry test result. It reveals complete loss of vision with constriction of the visual field in the right eye and tunneling of vision with loss of peripheral vision in the left eye

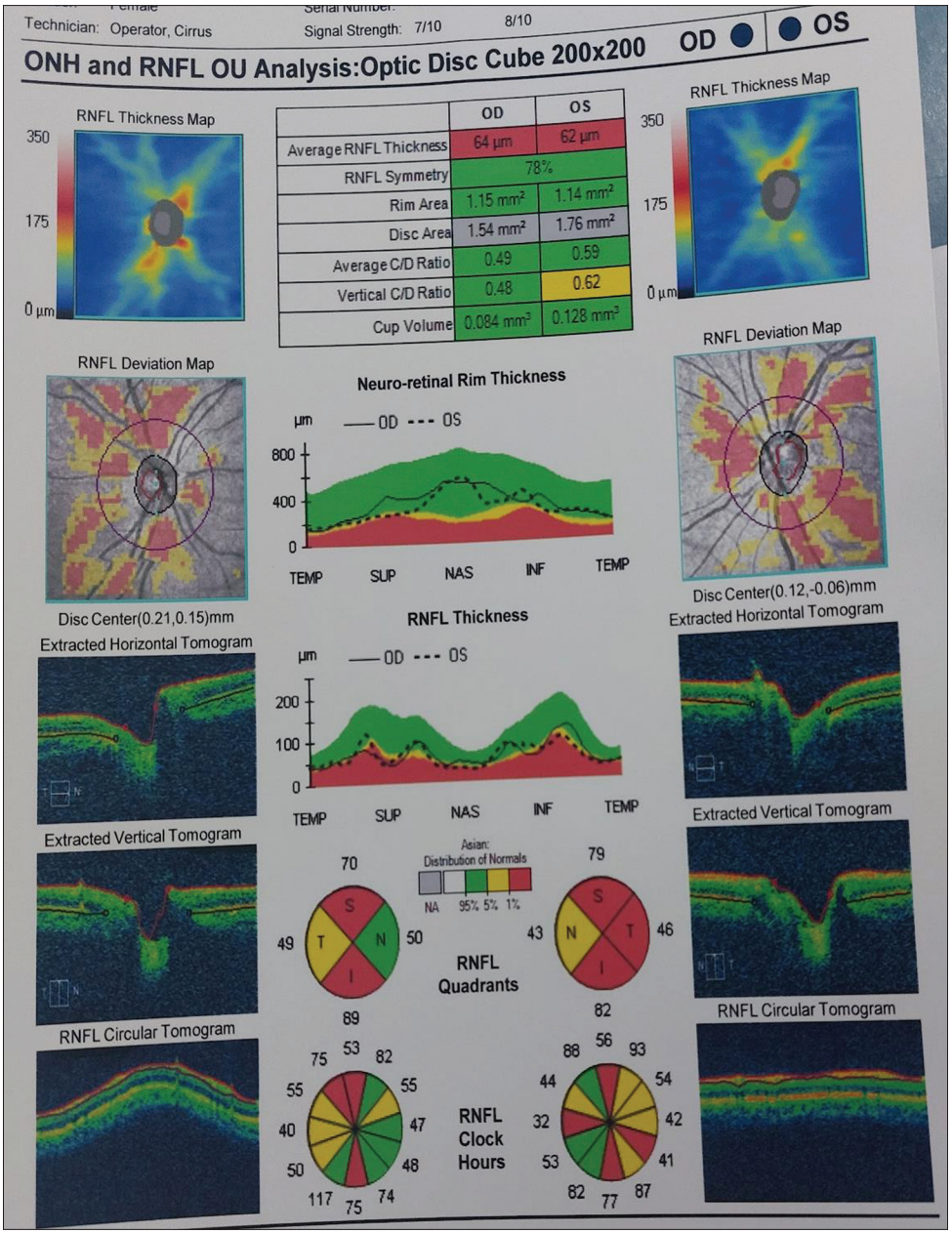

Figure 3: Optical coherence tomography (OCT) findings suggest thinning of the retinal nerve fiber layer in bilateral eyes (right > left eye)

on ophthalmological side-effects related to gemcitabine. However, different antimetabolites with similar mechanisms, such as 5-fluorouracil and cytosine arabinoside, can cause an array of side-effects such as blurring of vision, photophobia, ocular pain, macular edema, and even bilateral vision loss.[3] Though the patient's vision improved marginally in the left eye the day after receiving steroids, there was progressive deterioration of visual acuity in both eyes noted in the subsequent ophthalmologic examination done the following week. Hence, after joint consultation with a neurologist, an ophthalmologist, and an oncologist, it was decided to change to the second line of chemotherapy with oral capecitabine, considering she started exhibiting symptoms of disease progression of gall bladder cancer on a routine abdominal ultrasound. She had a subjective response with lessening of nausea and vomiting and increased appetite after starting oral capecitabine therapy; however, there was no improvement in her vision in either eye. The timeline from diagnosis to the development of bilateral optic neuropathy is presented in Table 1.

Ocular toxicity secondary to systemic chemotherapy is a relatively rare side-effect. Optic neuropathy from chemotherapy-induced optic nerve edema, idiopathic intracranial hypertension, optic atrophy, and optic neuritis, with associated cranial nerve palsies have been reported

Table 1: Timeline from diagnosis to the development of bilateral optic neuropathy

Month and year	Event
Dec 2021	Patient presented to the hospital (AMRI [Advanced Medical Research Institute] Hospital, Kolkata, India) with complaints of pain in the abdomen post-cholecystectomy
Jan 2022	Biopsy confirmed the diagnosis of metastatic gall bladder cancer
Jan 2022	Patient developed coronavirus disease-2019 (COVID-19) infection. He became COVID-19-negative 2 weeks later
Feb 2022	Palliative chemotherapy started with gemcitabine and oxaliplatin
Apr 2022	Good partial response on radiological and subjective evaluation
Apr 2022	Patient decided to return home (to his local place-Aizawl, India) to continue treatment
May 2022	While receiving treatment at local place, the patient developed symptoms of progressive loss of vision in both the eyes. Patient visited an ophthalmologist and was advised observation and close follow-up
Jun 2022	Visited our hospital and reported painless progressive loss of vision in both eyes
Jun 2022	Confirmed diagnosis of irreversible bilateral optic neuritis
Jul 2022	Second-line oral chemotherapy started; however, there was no improvement in vision

Table 2: Various etiologies of optic neuritis

Primary demyelinating	Others
Multiple sclerosis	Infections*
Neuromyelitis optica	Vaccination
	Sarcoidosis
	Autoimmune disease
	Drugs and toxins
	Genetic
	Nutritional

*Infections like bacterial, respiratory, and viral causes including COVID-19 infection

by several authors.[4] The advancement and increased use of chemotherapy have resulted in great improvements in patients' survival; however, we have also started seeing a myriad of ocular adverse symptoms associated with various chemotherapy regimens.

It is often difficult to establish a specific causal relationship between the use of a cytotoxic chemotherapeutic drug(s) and side-effects. Since most of the patients are on several chemotherapeutic drugs with or without radiotherapy, it is difficult to interpret the potential toxic effects of these drugs.

Along with standard cytotoxic chemotherapy, targeted therapy can lead to severe, disabling side-effects. The severity of the symptoms ranges from mild, resolving without intervention, to severe, debilitating, with permanent visual loss, necessitating therapy discontinuation.[4]

Sudden onset ocular symptoms need to be evaluated, and malignancy or paraneoplastic syndromes must be excluded before attributing them to the chemotherapy drug. Several neuro-ophthalmological complications following COVID-19

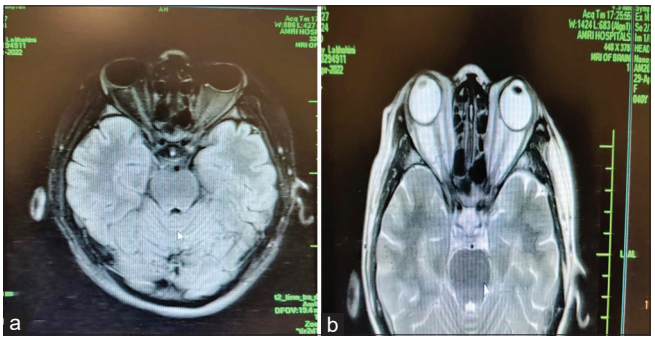

Figure 4: Panels (a) and (b) show MRI scan of the orbit in different axial levels; indicating no evidence of active neuritis or infiltration of the optic nerves

infection like pain, headache, ocular cranial nerve palsies, nystagmus, and other retinal manifestations were ruled out in our patient. The viral RNA can be isolated from the ocular tissue for confirmation of the diagnosis, although the eye as the route of infection has yet to be proven.[5]

Table 2 outlines the medical causes of optic neuritis. The differentials of optic neuropathy in our patient would include toxic, compressive, demyelinating, and infiltrative optic neuropathy. Imaging ruled out the last three causes.

Many of the approved targeted therapies or chemotherapy have been linked to ocular toxicity. Prompt recognition and timely ophthalmologic intervention or referral are of the utmost importance in such cases.

The decision to stop or continue oxaliplatin with or without gemcitabine must be individualized. The benefits of continuing therapy must be weighed against the risks and consequences of toxicities (especially when no effective alternative treatment exists). Ideally, the patient, oncologist, and neuro-ophthalmologist should make the decision together. Inattention to ocular symptoms while focusing exclusively on the systemic disease may result in a delay in the diagnosis of such complications. The reversibility of vision loss is dependent on a number of factors, the most important of which is the time of recognition and immediate intervention. With increased reporting and information available regarding ocular toxicity from chemotherapeutic drugs, baseline ophthalmological examination will help prevent catastrophic complications like bilateral vision loss, as well as protect against medicolegal issues in the future.

Declaration of patient consent

Authors have obtained all appropriate patient consent forms. Patient has given her consent for images and other clinical information to be reported in the journal. The patient

understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Prasenjit Chatterjee, Reshmi Dasgupta, Biplab Sarkar[1]

Department of Oncology, Advance Medicare and Research Institute (AMRI) Hospitals, Salt Lake, West Bengal, [1]Department of Radiation Oncology, Apollo Multispeciality Hospitals, Kolkata, West Bengal, India

Address for correspondence: Dr. Prasenjit Chatterjee, Department of Oncology, Advance Medicare and Research Institute (AMRI) Hospitals, Salt Lake, West Bengal, India.
E-mail: pchat01@rediffmail.com

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