1. Title Page

Category: Case Report

Title: Bilateral non-arteritic anterior ischaemic optic neuropathy in the setting of FOLFOX chemotherapy

Running Header: NAION and 5-Fluouracil

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2. Abstract:

Background: To report a case of bilateral non-arteritic anterior ischaemic optic neuropathy in the setting of FOLFOX chemotherapy. This is the first case to our knowledge of a potential association between 5-fluouracil and ischaemic optic neuropathy.

Case Presentation: A case of a 57-year-old male being treated with FOLFOX chemotherapy for stage 3B colorectal cancer, who developed bilateral non-arteritic anterior ischaemic optic neuropathies, is described. The patient presented following cycles 7, 8 and 9 of chemotherapy with a history of bilateral intermittent inferior altitudinal episodes of amaurosis. These episodes progressed to optic nerve swelling and a subsequent persistent left sided inferior altitudinal defect. The patient’s symptoms of amaurosis and swelling regressed with discontinuation of chemotherapy.

Conclusion: This is the first report of a potential association between 5-fluoruracil and non-arteritic anterior ischaemic optic neuropathy. It highlights that 5-fluorouracil may have the potential to cause arterial vasospasm outside the cardiac vasculature, resulting in and end-organ ischaemia.

Keywords: Non-arteritic anterior ischaemic optic neuropathy, FOLFOX, Fluorouracil
3. Background

The following case report highlights the presence of a bilateral non-arteritic anterior ischaemic optic neuropathy (NAION) in the setting of FOLFOX chemotherapy. FOLFOX chemotherapy consisting of oxaliplatin, fluorouracil and leucovorin has been used for the treatment of stage three colorectal cancer since the release of early data from the phase III MOSAIC trial in 2003[1]. 5-Fluorouracil (5-FU) is an antimetabolite inhibiting the action of thymidylate synthase ultimately interfering with DNA replication[1]. 5-FU has been shown to have significant arterial vasospastic properties, involving predominantly the coronary arteries, resulting in ischaemia and subsequent infarction of the myocardium, arrhythmias and sudden cardiac death[2-4].

With respect to ophthalmic complications of this agent, product information outlines the occurrence of transient visual disturbance and optic neuritis, but no literature exists stating the nature of these transient visual disturbances or the proposed mechanisms of these disturbances. We present the case of a patient who experienced bilateral amaurosis fugax with simultaneous inferior altitudinal visual field defects lasting seconds that subsequently progressed to a NAION with infarction of the retrolaminar portion of the superior disc on the left side.

Case Presentation:

A 57-year-old male with stage 3B colorectal cancer was referred by medical oncology to the Royal Brisbane Hospital Ophthalmology department, with a four-week history of simultaneous transient bilateral inferior altitudinal defects that would last up to 10 seconds in duration. The patient was receiving FOLFOX adjuvant chemotherapy and was on cycle 8 of 12 with
curative intent. The patient’s dosing schedule was oxaliplatin 165mg (Day 1), fluouracil 780mg bolus dose (Day 1) with a subsequent infusion of 1170mg over 48 hours, and leucovorin 390mg (Day 1+2). The patient’s symptoms had occurred with cycles 7, 8 and 9 of chemotherapy and had not occurred in the periods between cycles. On initial examination the patient’s visual acuity was 6/5 bilaterally. Ophthalmic examination, computerized perimetry and OCT retinal nerve fiber layers were unremarkable.

The patient represented two weeks later with a persistent complete left inferior altitudinal defect. Ophthalmic examination at this time revealed visual acuities of right 6/5-1, left 6/7.5 with a left relative afferent papillary defect. Dilated fundal examination revealed diffuse left sided optic disc swelling and swelling of the superior quadrant of the right disc (Figure 1: OCT RNFL Optic Discs Initial). The patient subsequently went on to have formalized fields, which confirmed the left inferior altitudinal defect (Figure 2: CP24-2 Initial). At this stage, the patient’s chemotherapy was ceased after careful discussion with the medical oncology team, who with their expertise felt that the threat of further visual loss was greater than the potential benefit to be gained from further chemotherapy in reducing recurrence.

Investigations were subsequently undertaken to rule out secondary causes of the optic disc swelling (i.e. toxic, infiltrative). The patient did not possess any atherosclerotic risk factors (e.g. smoking, hypercholesterolaemia, hypertension, diabetes), suffer from episodes of hypotension, or obstructive sleep apnoea. The patient underwent blood examination (including paraneoplastic panel screen), duplex carotid ultrasound, holter monitor, MRI brain and orbits and lumbar puncture. All
investigations were unrevealing. The patient was commenced on low dose aspirin 100mg/day and brimonidine tartate 2 times/day. Over the course of approximately three months the patient’s symptoms did not progress with the cessation of chemotherapy and the patient ceased to experience any further episodes of amaurosis. Serial ophthalmic examination revealed a stable visual acuity with resolution of optic disc swelling and the gradual appearance of a pale superior left optic nerve. Repeat fields showed a stable left inferior altitudinal defect with no progression.

Conclusions:

We propose that the episodes of bilateral simultaneous altitudinal field defects and resultant infarction of the left superior retrolaminar portion of the optic disc may in fact be the result of arterial vasospasm. Arterial vasospasm induced by 5-FU in the short posterior ciliary arteries. 5-FU has been proven to result in arterial vasospasm, with animal and human studies demonstrating a dose dependant relationship that abates with cessation of drug administration[4, 5]. Imaging studies have demonstrated that this vasospasm is not specific to the coronary vasculature and in fact has been shown to be present within peripheral arteries. Ultrasound evidence does exist demonstrating the occurrence of arterial vasospasm in the brachial arteries following administration of 5-FU [6, 7]. Furthermore, 5-FU has also been shown in vitro to induce vasoconstriction of vascular smooth muscle cells via activation of protein C, which resolves with administration of protein kinase inhibitors[4]. This highlights a biological plausibility to our case. Moreover, the episodes of amaurosis occurred in conjunction with the 5-FU infusion, reflecting a close temporal relationship between drug delivery and the
development of symptoms that also disappeared with cessation of the infusion. These symptoms of amaurosis recurred with subsequent cycles of reinfusion ultimately resulting in sufficient ischaemia to produce infarction in the form of a NAION. Upon cessation of the chemotherapy the symptoms of amaurosis settled and there was failure of the ischaemic optic neuropathy to progress.

It is not possible to prove from a single case that 5-FU causes short posterior ciliary artery vasospasm and ultimately NAION. However, given the biological plausibility of the mechanism and the close temporal association, we think this should be at least considered. 5-FU is known to cause transient visual disturbance, yet the cause or specifics of this disturbance have never been elucidated in academic literature. It is proposed that the transient visual disturbance experienced in the setting of 5-FU infusion is in fact a result of short-posterior ciliary artery vasospasm resulting in transient episodes of ischaemia to the optic nerve. These patients may never come to the attention of ophthalmologists as the disturbances are generally thought of as transient, with no long lasting effects. Our case may represent an individual who experienced these transient visual disturbances and whose arterial vasospasm may have been more severe than usually encountered to result in permanent ischaemia and necrotic tissue damage to the optic nerve head. We believe that all patients undertaking FOLFOX chemotherapy who experience visual disturbances should be examined by an ophthalmologist to determine the exact nature of these disturbances and to further elucidate evidence to identify a potential cause.
4. Competing Interests

We have no competing interests

5. Authors Contributions

LT initially identified the case and after discussion with JH decided to write up the case. A literature review was conducted by LT and subsequently a manuscript was formulated by LT and JH. Both parties approved the final manuscript.

6. Acknowledgment

I would like to take this opportunity to thank the Redcliffe Oncology department for referring this patient to the Royal Brisbane and Women’s Hospital Ophthalmology department and for the patient allowing me to write up this case.

7. Requesting Consent Statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
8. References


Figure 1

RNFL Thickness

μm

OD

RNFL Thickness

OS