Reviewer's report

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

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**Reviewer:** Cedric Lamirel

**Reviewer's report:**

This report presents a case of bilateral non-arteritic anterior ischemic optic neuropathy (NA-AION) during FOLFOX chemotherapy for a stage 3B colorectal cancer. Before the NA-AION the patient experienced several bilateral transient visual losses. According to the authors, these transient visual losses argue for the role of 5FU known as a vasospastic agent.

I found the clinical presentation very interesting and of relevant value for clinician. The transient visual losses that preceded the permanent visual loss are very important to suspect a vascular mechanism of the toxicity of 5FU for the optic nerve. This case should be published to help clinicians dealing with patients presenting with transient visual symptoms in the setting of 5FU chemotherapy.

However major revisions are needed before publication.

**Major revisions:**

1 - In the abstract (p2): “to report a case of bilateral NA AION” and in the history. From the history provided, there was only a left NA AION and disc edema on the right eye. There was no visual field loss or visual acuity loss or color vision loss on the right eye to account for an optic neuropathy. From the clinical presentation, we can only found that there was disc edema on the right. Was there some RNFL loss in the right eye after resolution of the disc edema to confirm that this was a right optic neuropathy with minimal signs?

2 - In the abstract (p2) : " This is the first case to our knowledge of a potential association between 5-fluouracil and ischaemic optic neuropathy”.

Others cases of optic neuropathy from 5FU have been reported, even with disc edema, but were not classified as NA-AION because it always difficult to confirm the mechanism:

According to the “Clinical Ocular Toxicology” from FT Fraunfelder, FW Fraunfelder, WA Caembers. Saunders, Elsevier. 2008: “There are several cases of possible optic nerve toxicity secondary to 5FU in the literature and in the USA National Registry (Portland, Oregon, www.eyedrugregistry.com)”

I think authors should not present their case as being the first one.

They should address the ischemic mechanism only in their discussion and in the conclusion as the possible mechanism. In the case presentation, the mechanism should not be addressed and the author should only write “optic neuropathy with disc edema”

To be of relevant clinical value, the report should be a review of the cases in the literature and in the registry and authors should rewrite the article on how their case if very interesting to argue for the ischemic mechanism from vasospasm from 5FU because of the transient visual loss before the optic neuropathy.

3 - Abstract (p2) and in clinical presentation: the term “amaurosis” should not be used as it is used for transient visual loss from embolic mechanism. Author should rather use the general term of transient visual loss.

4 – in the Background (p3): “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.”.

There is literature about these cases, and the USA national registry should be reviewed as well as the pharmaceutical company for all the other cases found in the world. See comment #2

5- In the Background (p3): “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.”

Avoid the use of “amaurosis fugax”. The mechanism should not be address in the background. We do not know clearly the pathophysiology of the NAION, and so “infarctus of the retrolaminar portion” is not relevant.

6- In case presentation (p4):

The timing of the transient symptoms, the initial examination and the persistent visual loss are not clearly stated.

When the initial examination was performed: after symptoms of the 9th round of chemo? How long after regression of symptoms?

When did the transient symptoms occur regarding the beginning of the chemo rounds? After the bolus of the 5FU? During the infusion of the 5FU? After the infusion?
Did the persistent visual loss occur during the 10th round of chemo? Or did it occurred 2 weeks after the last chemo? If so, the delay between the 5FU infusion and the persistent loss should be discussed.

7- In case presentation (p4):
On initial examination, was there a disc at risk? This is very relevant as the NA AION is the possible mechanism. On figure 1, the ocular fundus photos should be added if they are available.

8- In case presentation (p4):
The figure 2 should contain the total and individual deficit map and not the grey scale map of the visual fields. As the authors think the optic neuropathy was bilateral, this is important to know whether there was some mild defect in the inferior field of the right eye. There should be a comment on the visual field of the right eye in the text.

9- In case presentation (p4-5) and about the investigations performed and differential diagnosis.
Given the presentation, giant cell arteritis is a possible explanation of AION with transient visual losses before the persistent visual loss. How this was ruled out? How was the sed rate, the CRP, the platelets? Other symptoms or signs of GCA? Was a fluorescein angiogram performed?
Was there any arterial hypotension episode recorded during the transient visual loss? During the infusion of the chemo?
As no photos of the ocular fundus are available, for the reader another possible explanation is a retinal artery embolism. The retinal infarction is not always visible depending on the timing between the symptoms and the eye examination. Because of the history of transient visual loss, this mechanism is high on the differentials diagnosis. OCT scan of the superior compared to the inferior part of the macula at the acute phase and/or at the atrophic phase would help the reader to be convinced that the mechanism was not at retinal infarction given the altitudinal visual field defect.

10 – In case presentation (p5) and about the evolution.
Avoid the use of “amaurosis”.

Nothing it mentioned about the right optic disc. If there was no pallor or no RNFL thinning, author cannot write that the optic neuropathy was bilateral. From the article, I can only be convinced that there was some RNFL thickening on the right eye from disc edema, but not a true right optic neuropathy.

11 – in conclusion (p5-6).
This part should be rewrite with:
- The mention of the previous optic neuropathies related to the 5FU published or
reported and what were the possible mechanisms mentioned (comment #2 and 4)

- How this case can be suggestive of the ischemic mechanism because of the transient visual loss before the persistent visual loss.

- Discuss the presence or the absence of disc at risk in this case.

- Somewhere the role of the oxaliplatin and leuvoroin should be mentioned, even to be rule out if no previous report of optic nerve toxicity related to these drugs is found.

No mention of “retrolaminar infarct” should appear as the true pathology of AION is not clearly established.

Minor revision:

12- In case presentation (p4) : “The patient did not possess any atherosclerotic risk factors (e.g. smoking, hypercholesterolaemia, hypertension, diabetes), suffer from episodes of hypotension, or obstructive sleep apnoea.”

This should be place at the beginning of the case presentation as part of the past medical history. Was the sleep apnoea treated?

13- In conclusion (p5): “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.”

I think there is a typo.

This should be rewrote as: “We propose that the episodes of bilateral simultaneous altitudinal field defects and resultant left optic neuropathy may in fact be the result of arterial vasospasm induced by 5-FU in the short posterior ciliary arteries.”

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I received honorarium for lecture from Allergan France, and MSD France. But none are related to this article