Case Report: Optical coherence tomography angiography findings in radiation retinopathy [version 1; peer review: 1 approved with reservations]

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Abstract
We report the observation of a 31-year-old patient followed for a nasopharyngeal carcinoma since 2009, treated by locoregional radiotherapy, with a cumulative dose of 70 Gray. This case presented all ocular complications of radiotherapy; radiation retinopathy (RR), which is the most severe complication, could be diagnosed earlier and have a better prognosis if optic coherence tomography angiography (OCTA) was performed. She presented with a progressive decline in bilateral visual acuity. Ophthalmologic examination revealed bilateral posterior subcapsular cataract, radiation retinopathy, and optic neuropathy. The OCT B-scan showed more pronounced macular edema in the right eye. The OCTA revealed enlargement of the central avascular zone and loss of the deep and superficial retinal vascular network. The patient received three consecutive monthly intravitreal injections of anti-vascular endothelial growth factor (VEGF), without improvement in visual acuity. The aim of this case report is to present the contribution of OCT-A in the diagnosis of radiation maculopathy, and attribute these changes to ischemia at the level of the retinal vascular network.

Keywords
Superficial retinal capillary plexus, Deep retinal capillary plexus, Ischemic cascade, Radiation retinopathy, OCT angiography
**Introduction**

Locoregional radiotherapy is the most effective treatment against nasopharyngeal carcinoma (NPC). The proximity with orbit tissues exposes them to severe damages. However, late-onset, sight-threatening ocular complications may occur, including cataract, optic neuropathy, radiation retinopathy (RR), and ocular surface disease. The early diagnosis of these lesions allowed to better prognosis. The optical coherence tomography angiography (OCT-A) allowed to investigate neovascular alteration for patients suffering from RR even before the onset of loss of vision.

We report a case of radiation retinopathy in a 31-year-old female with NPC, treated by locoregional radiation therapy (LRT). She presented all post-radiotherapy ocular complications with late diagnosis of RR and poor prognosis.

The purpose of this case report is to analyze the findings and the usefulness of OCT-A.

**Case report**

A 31-year-old Tunisian, unemployed female with a history of nasopharyngeal carcinoma was diagnosed in 2009 and treated by locoregional radiotherapy. The overall administered dose was about 75 Gy. She presented with adrenal insufficiency, hypothyroidism, and osteonecrosis as side effects of the treatment. She complained of progressive painless loss of vision in both eyes. On examination, her best-corrected visual acuity was 20/40 in both eyes. The ocular motility was full, and no afferent pupillary defect was noted. A symmetrical subcapsular cataract was found. The rest of the anterior segment examination was unremarkable. No vitreous cells were noted. Fundoscopy showed microvascular changes mainly marked by vascular tortuosity and microaneurysms, optic disc pallor, and decreased foveal reflex. Fluorescein angiography was not performed because the patient was allergic to fluorescein. OCT in B-scan showed bilateral macular edema with a central macular thickness of, respectively, 532 μm in the right eye (RE), and 406 μm in the left eye (LE). OCT angiography (OCT-A) disclosed enlargement of the central avascular zone, and hypoperfusion of both superficial and deep retinal capillary networks (Figures 1 and 2). The vessel density was reduced to 38.12 % in the inferior macular area of the RE, and to 39.34 % in the superior macular area of the LE. A systemic workup was performed.

![Figure 1. Right eye. a. Fundoscopy showing vascular tortuosity and dilation of peripheral retinal vessels, the disappearance of foveolar reflection, and mild pallor of the optic disc. b. Optical coherence tomography (OCT) showed macular edema. c. Optical coherence tomography angiography (OCT-A) showing enlargement of the central avascular zone, and hypoperfusion of both superficial and deep retinal capillary network.](image-url)
to rule out other causes of ischemic retinopathy (diabetes mellitus, blood dyscrasias, and carotid insufficiency). Based on medical history, ocular findings, and negative systemic workup the diagnosis of radiation retinopathy was finally established. After informed consent, and a negative pregnancy test, the patient underwent three monthly intravitreal bevacizumab injections (1.25 mg). The improvement of visual acuity was poor.

**Discussion**

Radiation retinopathy (RR) was first described in 1933 by Stallard, as a predictable complication of radiation exposure. It most commonly occurs between six months and three years after irradiation. In this case, the diagnosis was later, twelve years after irradiation. A higher total radiation dose is the highest risk factor, as the incidence of RR increases at doses greater than 45 Gy. This patient received 75 Gy. Histopathological studies have illustrated a vasculopathy with the destruction of the endothelial cells followed by vascular occlusion and capillary dropout. The microvascular alterations are associated with a reduction of retinal oxygenation, blood flow, and ischemia. Contrast sensitivity decrease and visual field impairment were notified in patients treated with radiotherapy. Our patient had gradually decreased bilateral visual acuity, as well as cataract and optic neuropathy. The clinical appearance mimics many lesions of diabetic retinopathy such as microaneurysms, macular edema, cotton-wool spots, retinal neovascularization, vitreous hemorrhage, and tractional retinal detachment. The main tests usually performed on patients are fluorescein fundus angiography (FFA) and optical coherence tomography (OCT). The first exam hallmarks are capillary dilatation and microaneurysms, frequently in combination with ischemia or macular edema. On OCT images, we found a disappearance of the macular depression with macular edema, a significant thinning of the inner plexiform, inner nuclear, and outer plexiform layers. However, FFA is an invasive diagnostic technique. Intravenous dye injection used may cause severe anaphylaxis, particularly in immunocompromised patients. It was not performed on our patient. Besides, OCT cannot capture vessel network status. Recently, OCT-A, has shown to be a safe and non-invasive examination that combines traditional OCT and FFA. It can provide high-resolution images of each layer of the retina and quantify the retinal microvascular networks without the use of exogenous dyes. OCTA has been introduced for the detection of subtle microvascular changes in radiation retinopathy. Vascular abnormalities are manifested by an enlargement of the
central avascular zone and a reduction of vessel density in the deep vascular plexus of the foveal area. Whereas it’s less reduced in superficial layers. The susceptibility of the deep layer can be explained by the direct connection of the superficial capillary plexus to the retinal arterioles with greater perfusion and oxygen supply. This change in structure can be explained by direct compression of the retinal vascular network, deep in the first place, by intra-retinal fluid cysts. Li et al. found that OCTA detects early vascular alterations of the retina in patients with normal-ranged visual acuity. It provided a quantitative measurement of retinal capillary changes which may predict future development of radiation-induced retinal toxicity. They suggested the implementation of OCTA for the early detection and consistent monitoring of RR. In this sense, a grading system was proposed based on clinical findings in OCTA, increased central macular thickness, evident cysts, and ophthalmoscopy findings. The disadvantage is the presence of several artifacts, especially after treatment.

Furthermore, due to the clinical and pathophysiological similarities with diabetic retinopathy, it inspired the treatment of radiation retinopathy. Initially, treatments were based on the use of retinal laser. Sector photocoagulation improves clinical signs, but the visual outcome is poor. Intravitreal injection of anti-VEGF or corticosteroids has been shown to improve visual acuity, reduce cystoid macular edema, and the risk of the development of radiation retinopathy. The visual acuity of our patient didn’t change, probably because she presented with several complications of local radiotherapy, such as cataract and optic neuropathy, and ischemia affecting deep layers. Continuous treatment is necessary to maintain acuity improvement; this requires good patient adherence. The optimal regimen for anti-VEGF therapy is not yet identified. There have been recent preventive efforts to avoid signs that radiation damage has already occurred, particularly since there is still no curative treatment.

Conclusions
Radiation retinopathy manifests itself on OCTA by an enlargement of the foveolar avascular zone and a rarefaction of the vascular network at the level of the deep and vascular networks, even in eyes without clinical evidence of radiation retinopathy.

Data availability
All data are included as part of the article and no additional data are required.

Consent
The patient has consented to the submission of the case report for submission to the journal.

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Version 1

Reviewer Report 31 August 2022

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Helmi Ben Saad
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I read with great interest the case-report entitled “Case Report: Optical coherence tomography angiography findings in radiation retinopathy”. The rationale of the study is interesting. However, a revision is needed.

Here are my remarks:

GENERAL REMARKS

1. I recommend that authors apply the CARE guidelines¹.

2. For the abstract, I recommend that authors apply the IOC plan in the abstract: Introduction, observation, conclusion.

3. All abbreviations should be explained the first time they are used - unless it is a standard unit of measurement - and thereafter the use of abbreviations should be consistent throughout the paper. Avoid excessive use of abbreviations.

4. The paper should be checked by a person fluent in English.

5. Sometimes Gy sometime Gray: please use one term

6. The patient received 70 Gy (see the abstract) or 75 Gy (see the observation and the discussion)?

SPECIFIC REMARKS

1. Abstract:

Some corrections are needed. For example write ‘A 31 year-old female”, delete (RR) and (VEGF), write “The patient presented with...”. Please use OCTA or OCT-A not both.
2. Manuscript:
   - Avoid abbreviating LE and RE, instead using full text: left-eye, right-eye.

   - Misuse of abbreviations: for examples, write “*We report a case of RR in a 31-year-old*”, “history of NPC was”, “treated by LRT”, OCT-A disclosed enlargement’, “diagnosis of RR was finally”, “RR was first described in 1933”, “angiography (FFA) and OCT”, “microvascular changes in RR”, “the treatment of RR8”, “of RR. 3,8 The visual”, “complications of LRT”, “RR manifests itself”, “clinical evidence of RR”.

   - More precision is needed: for example, L3 of the Case report, write ‘The patient complained from’ rather than “She complained from progressive’. In this sentence (L11page 5/6) “retinopathy, it inspired”: it refers to what?

   - In the beginning of the case report, please mention the following sentence “This observation was reported according to the CARE guidelines (ref)”. 

   - Some mistakes related to references: for examples you wrote “by Stallard,3”, but reference 3 is the one of Rose K et al. You also wrote “Li et al1 found”, however the reference number 1 is of Zijing et al?

   - Some sentences are lacking references: for example, add a reference for these sentences: “A higher total radiation dose is the highest risk factor, as the incidence of RR increases at doses greater than 45 Gy”, “However, FFA is an invasive diagnostic technique.”, “Intravenous dye injection used may cause severe anaphylaxis, particularly in immunocompromised patients”.

3. References:

   Please verify all your references, especially references number 1 and 3.

4. Figures:

   Figure 1 Title: c. OCT angiography showing....
   Figure 2 Title: c. OCT angiography showing....

References

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Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Is the case presented with sufficient detail to be useful for other practitioners?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Medical writing skills; physiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Sep 2022

**WAFA AMMARI**, University Hospital Taher Sfar, Mahdia, Tunisia

Thank you for the remarks and the attention paid to this original article.

**General remarks**
1 and 2 we followed the journal recommendations.
3. All abbreviations were explained first time they are used. In ophthalmology, we always used abbreviations.
4. The paper was checked by newspaper experts who appreciated the English used.
5. Gy and Gray are both used, but we rectified this.
6. The patient received 75 Gy. It was a keyboard typo for the abstract.

**Specific remarks:**
1. **Abstract:**
2. **Manuscript:**
   Stallard is the first person to describe this entities and this is mention in the article of Rose K et al.
   The Author's name is Zijing Li
3. **References:**
   All references were verified
4. **Figures:**
   The figures showing multimodal imaging. The OCT-A is the c only.

**For the other remarks, they have been corrected on the article.**

**Competing Interests:** I didn't have any competing interests.
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