



## Case report

# Classification and treatment follow-up of a juxtapapillary retinal hemangioblastoma with optical coherence tomography angiography



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## ABSTRACT

**Purpose:** Only an endophytic growth pattern in juxtapapillary retinal hemangioblastoma (JRH) is an indication for surgical treatment, but classification of growth types is difficult using conventional imaging techniques. This case report describes the use of optical coherence tomography angiography (OCT-A) features for classification and treatment follow-up in a case with JRH.

**Observations:** The JRH of this patient was easily detected with two different OCT-A methods in both *en-face* and cross-sectional B-scan images, and was classified as a sessile growth type. This growth type excluded the treatment option of vitreoretinal surgery with excision of the lesion or ligation of the feeder vessels. The patient was treated multiple times with intravitreal bevacizumab. Treatment follow-up with OCT-A initially revealed a stable extent of the JRH, with some slight flow deviations in *en-face* visualization, followed by a period of progressive growth of the lesion.

**Conclusions:** OCT-A revealed the depth localization of the JRH and seems to be a valuable tool for JRH classification. Detailed classification may be useful when surgery is considered as a treatment strategy. Furthermore, treatment follow-up is possible with OCT-A, although imaging artifacts should be taken into account.

## 1. Introduction

Retinal hemangioblastomas (RHs) are benign vascular tumors, occurring either isolated or in association with von Hippel-Lindau (VHL) disease.<sup>1,2</sup> The majority of the RHs are located in the peripheral retina, but up to 15% is reported to occur on the optic nerve head or within the juxtapapillary region (juxtapapillary retinal hemangioblastomas, JRHs).<sup>2</sup> For these JRHs, no standardized treatment guidelines are yet established, because of the difficult anatomic location.<sup>3–5</sup> Since JRHs in general have a progressive nature, these lesions will, without treatment, lead to growth of the tumor and complications such as exudation, subretinal fluid accumulation, macular edema, and exudative retinal detachment.<sup>4</sup> Despite this progressive nature, observation is often chosen as initial management. Whenever it becomes symptomatic (i.e. lesion growth or visual deterioration), Saitta et al. (2014)<sup>4</sup> suggested to treat with either intravitreal anti-vascular endothelial growth factor (VEGF) agents, verteporfin photodynamic therapy (PDT), vitreoretinal surgery or a combination of these. Defining the most effective and safe treatment strategy for a patient depends also on the growth type of the

lesion: endophytic, sessile or exophytic. An important feature of the different growth types is the depth-location within the retina. Endophytic tumors are located in the superficial layers (between internal limiting membrane (ILM) and halfway inner plexiform layer (IPL)), sessile tumors in the middle layers of the retina (between halfway IPL and outer nuclear layer (ONL)) and exophytic tumors in the outer layers (between ONL and retinal pigment epithelium (RPE)).<sup>2,6–8</sup> The surgical treatment option is only considered for JRHs with an endophytic growth pattern, due to the superficial location of these lesions.<sup>4,9</sup>

Growth types are based on depth-localization of the JRHs within the retina, which cannot be detected with conventional imaging tools. Currently, the most informative tool for the diagnosis of (J)RHs is fluorescein angiography (FA),<sup>2</sup> which merely provides a two-dimensional dynamic visualization of retinal blood flow with information on leakage, pooling and staining.<sup>10,11</sup> A new imaging technique, optical coherence tomography angiography (OCT-A), is able to create a three-dimensional map of blood flow. This enables the visualization of blood flow in both *en-face* view and on cross-sectional OCT B-scans, which provides information on blood flow location in depth. In addition, no

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invasively administered contrast agents are necessary, which makes it less time consuming, more patient-friendly and easier to conduct for follow-up.<sup>11,12</sup>

In this report, we present a case of a patient with a JRH which was imaged with OCT-A next to conventional imaging techniques. The aim of this report is to evaluate the use of OCT-A in classifying the growth type of this lesion and monitoring its evolution over time.

## 2. Case report

A 46 years old female with VHL disease visited the Rotterdam Eye Hospital (Rotterdam, The Netherlands) because of multiple RHs with tractional and exudative retinal detachment in the periphery in her right eye. At that moment, the visual acuity was 1.0 decimals (Snellen) in the right eye. The left eye was affected by the disease earlier in life and has resulted in complete loss of visual function. Vitreoretinal surgery in the right eye was successfully performed to remove the existing peripheral RHs as well as the tractional membranes, and silicone oil was used as intraocular tamponade. Four weeks after surgery, prior to oil removal, fundus imaging revealed a newly formed JRH, located on the temporal quadrant of the optic nerve head. The visual acuity had decreased to 0.6 decimals, possibly due to the silicone oil within the vitreous cavity. However, because this was her only functional eye, it was treated with intravitreal bevacizumab (1.25 mg/0.05 ml; IVB; Avastin®, Roche Pharma AG, Grenzach- Wyhlen, Germany), in order to reduce the risk of growth of the JRH.

Based on our good experience with early surgical treatment of retinal hemangioblastomas in the retinal periphery,<sup>13</sup> we considered feeder vessel ligation or excision of the JRH during the planned removal of oil. For this reason, imaging by several modalities was performed preoperatively, to determine the growth type of the lesion to be excised. Besides conventional imaging techniques, such as fundus photography (FP), fluorescein angiography (FA) and optical coherence tomography (OCT) (Fig. 1), we also obtained images with the new non-invasive technique, OCT-A, using an experimental 1040nm swept-source Doppler OCT<sup>14</sup> as well as the preliminary research version of Spectralis OCT-A (Heidelberg Engineering, Germany) (Fig. 2). Although FP, FA and OCT were not able to reveal the lesion's location in depth of the retina, superimposed B-scans with flow overlay from OCT-A revealed that the major part of the lesion is located in the middle layers of the retina. Therefore, the growth type of this lesion was defined as sessile. This growth type excluded the option of surgical treatment of the JRH

during the oil removal procedure, which is in accordance with the treatment algorithm approach of Saitta et al. (2014).<sup>4</sup>

The patient was monitored between October 2016 and June 2017 with both OCT-A devices. Table 1 includes an overview of visual acuity, presence of cystoid macular edema (CME) on OCT, lesion growth findings on OCT-A and treatment events in this period, with week 0 being the time of first detection. Treatment consisted of IVB, at certain time points combined with either subconjunctival betamethasone acetate (scBMA, Celestone Chronodose, Schering Co., Kenilworth, NJ) or subconjunctival triamcinolone acetonide (scTCA, Kenacort-A, Bristol-Myers Squibb, NYC) in order to treat the progressed CME. OCT-A *en-face* images of the treatment follow-up are shown in Figs. 3 and 4. Differences in *en-face* images of the lesion between week 1, 4 and 6 are subtle (the eye was treated with IVB between each OCT-A image). From week 10 (one more IVB injection was given at week 8), the lesion seems to be larger on the *en-face* visualization (particularly on Spectralis OCT-A images, Fig. 3), and appeared progressive until week 16 (revealed by Doppler OCT, Fig. 4). Between week 16 and 37, the extent of the lesion seemed to expand slightly more (shown at Doppler OCT images, Fig. 4).

Although the extent of the lesion appeared progressive on OCT-A, there was no substantial visual deterioration (0.8 decimals at week 37) compared to previous visual acuity values (Table 1). Therefore, therapy with IVB continued.

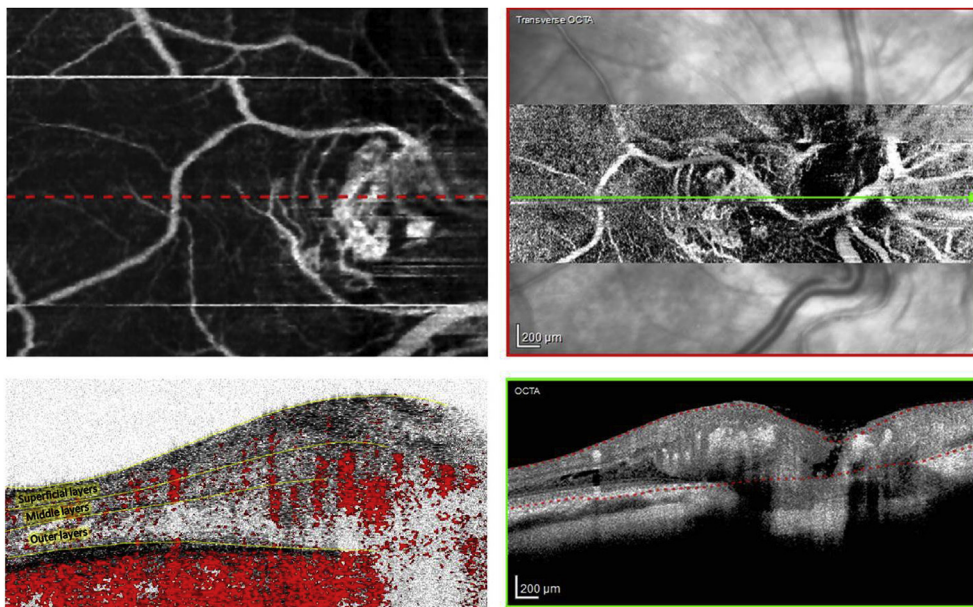
## 3. Discussion

Classification of JRHs is not possible using conventional imaging methods, which is of importance if surgical treatment is considered. In this case report, OCT-A was used to classify the growth type of the lesion and for follow-up of treatment response. Based on OCT-A, this lesion was classified as a sessile growth type (in the middle layers of the retina), which was impossible to do by FA or conventional OCT. This illustrates its contribution in deciding on an optimal treatment strategy. Treatment follow-up was easily performed with OCT-A, providing information on the growth of the lesion.

Since vitreoretinal surgery should only be considered with an endophytic lesion, this treatment option was excluded for this patient. The remaining options were observation, intravitreal anti-VEGF, or intravitreal anti-VEGF combined with verteporfin PDT. The decision for therapy with IVB was based on several reasons: observation was ruled out, because untreated JRHs are in general progressive lesions,<sup>4</sup> which is undesirable in a monocular patient. Treatment with PDT is shown to



**Fig. 1.** Images of the lesion with conventional techniques at week 1. On the left fundus photograph (FP), on the right fluorescein angiogram (FA) at 19 seconds, and underneath a conventional optical coherence tomography (OCT). FP reveals the orange-red colored lesion on the temporal quadrant of the optic disc. FA shows the lesion with hyper-reflection, due to the administered fluorescent dye. OCT shows slight hyper-reflection on the surface, but the hyper-reflection encloses several retinal layers, and does not reveal the precise location in depth.



**Fig. 2.** Doppler optical coherence tomography (OCT) (left) and Spectralis optical coherence tomography angiography (OCT-A) (right) images of week 1. Both *en-face* images are on top with a line that corresponds with the B-scans with flow overlay (bottom images). Flow overlay is illustrated in red on Doppler OCT B-scan, and in white on Spectralis OCT-A B-scan, revealing that the lesion is located in the middle layers of the retina. Note that shadowing artifacts occur in OCT-A below the actual source of the flow. The most inner part of the detected flow is therefore most likely the source of this detected flow and thereby the lesion.<sup>12</sup>

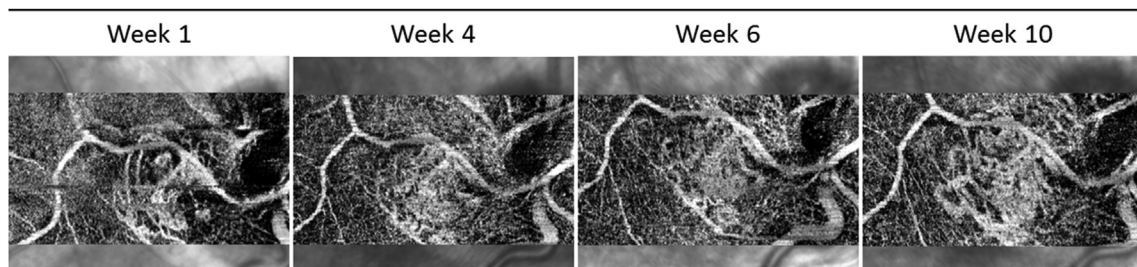
**Table 1**

Overview of the follow-up period with information on the visual acuity, presence of CME, growth of the lesion and the treatment events.

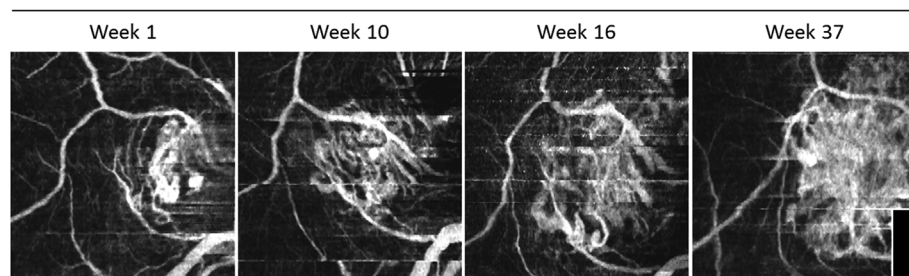
Week	Visual acuity (Snellen decimals)	Presence of CME? (Conventional OCT images)	Growth of the lesion? (OCT-A images) <sup>a</sup>	Treatment
0	N/a	N/a	N/a	IVB
1	0.6	No	Reference	N/a
2	N/a	N/a	N/a	oil removal + IVB
4	N/a	Yes	No	IVB
6	0.9	Yes	No	scBMA
8	0.8	Yes	N/a	IVB
10	0.6	Yes	Yes	N/a
13	0.7	Yes	N/a	N/a
16	0.9	Yes	Yes	IVB + scTCA
17	N/a	N/a	N/a	Laser treatment of new retinal hemangioblastomas in periphery
19	1.0	Yes	N/a	N/a
22	0.9	Yes	N/a	IVB + scTCA
25	0.9	Yes	N/a	N/a
28	0.9	Yes	N/a	IVB
31	0.8	Yes	N/a	Laser treatment of new retinal hemangioblastomas in periphery
34	N/a	Yes	N/a	IVB + scTCA
37	0.8	Yes	Yes	N/a

Note: All the moments the patient was present in the hospital during the follow-up period are included in this table. CME = cystoid macular edema. N/a = not applicable, i.e. this measurement was not performed, or the patient was not treated. IVB = intravitreal bevacizumab. scBMA = subconjunctival betamethasone acetate. scTCA = subconjunctival triamcinolone acetonide.

<sup>a</sup> Compared to the previous OCT-A image.



**Fig. 3.** Spectralis optical coherence tomography angiography (OCT-A) *en-face* images of week 1, 4, 6 and 10, showing slightly more abnormally located blood flow on the temporal side of the lesion in week 10 compared to previous images. Differences between lesion sizes on different images could be observed by taking surrounding vessels as reference.



**Fig. 4.** Doppler optical coherence tomography (OCT) *en-face* images at week 1, 10, 16, and 37 respectively from left to right. The lesion is at week 10, compared to week 1, more dense and slightly expanded towards the superior located vessel. At week 16 the lesion has continued growing, mostly towards the temporal vessel. At week 37, the lesion even crosses the superior and temporal located vessels.

have positive effects on the secondary sequelae of a JRH, such as macular edema, accumulation of lipid exudates and serous retinal detachments. However, results on visual acuity are not consistent<sup>15</sup> and PDT was found too risky for the monocular patient, since it could cause visual damage.

Although there are several cases described that benefit from monotherapy with anti-VEGF,<sup>16–18</sup> in our case the JRH started growing despite the IVB treatment, and the patient developed new peripheral lesions as well. Wong and Chew<sup>19</sup> questioned whether targeting on VEGF would reduce growth and behavior of a JRH that is related to von Hippel-Lindau (VHL) disease, which is in line with the lack of efficacy of anti-VEGF treatment in our case (growth between week 10 and 37). On the other hand, it could also be argued that the IVB may have delayed the growth of the lesion (starting from week 10).

This patient was extensively followed by both OCT-A imaging techniques, Doppler OCT and Spectralis OCT-A. Prior to week 10, the lesion did not show growth and even seemed to diminish slightly. However, the appearance of the lesion on OCT-A *en-face* images of week 1, 4 and 6 differed slightly compared to each other. Although each imaging system, including OCT-A, has to deal with signal variations due to noise,<sup>12</sup> there are some other potential explanations for the slight differences between OCT-A *en-face* images. First of all, IVB treatment may induce deviations in the angiogenesis of the lesion. Furthermore, detection of blood flow could be influenced by thickening of the retina due to CME (first signs of CME at week 4). Moreover, OCT-A techniques are based on macular area, and software still has difficulties with segmenting the retinal layers in the juxtapapillary area properly. Therefore, segmentation had to be adjusted manually, which could cause slight differences in *en-face* representations.

Besides these small limitations of this technique possibly leading to slight flow deviations on *en-face* images of the JRH at week 1, 4 and 6, we believe we were overall well able to subjectively distinguish growth and stabilization of the lesion during this follow-up period. However, for future studies, when segmentation has been improved for the juxtapapillary area, we would recommend a quantitative analysis of the extent of the lesion.

We are not able to provide a sufficient general comparison between the two used OCT-A systems, since we report on one case only and Spectralis OCT-A was not available during the whole follow-up period. An important drawback of our experimental Doppler OCT, was the lack of an eye tracker, which makes acquisition more prone to movement artifacts (Fig. 4).

#### 4. Conclusions

In conclusion, OCT-A seems valuable in classifying the growth type of JRH located in the posterior pole by determining its location in depth, which is not possible using conventional imaging techniques. Information on growth type of a JRH is of great importance when making decisions regarding the treatment, especially when surgery is considered. Furthermore, OCT-A is an easy, relatively quick and non-invasive technique to use for follow-up of the treatment outcome. However, the images should be interpreted carefully, due to the possibility of imaging, segmentation and motion artifacts.

Although this case report shows that OCT-A seems a promising additional diagnostic and follow-up technique in the management of JRHs, we have imaged only one growth type and treatment path. Therefore, more research is needed to expand the knowledge on usability and ability of OCT-A in classifying all existing growth types, as well as its use in follow-up of different treatment strategies.

#### 5. Patient consent

The patient signed an informed consent of the Exploratory flow-OCT study. The study was approved by the local internal review board of the Rotterdam Eye Hospital and the Medical Ethical Committee of the Erasmus University Hospital (Rotterdam, the Netherlands).

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#### Conflicts of interest

- LS, VD, JdB and KV: Financial support (Heidelberg Engineering);
- JdB: Patent (Massachusetts General Hospital);
- MvV: Recipient (Bayer NL, Abbvie NL, Novartis NL, Allergan NL);
- KvO and JdJ: no financial disclosures.

#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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