



Cavernous hemangioma of the retina – case report

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ABSTRACT

Cavernous hemangioma of the retina is a rare, congenital, benign, typically unilateral retinal vascular tumor, occurring predominantly in children and young adults.

The aim of this paper is to present the case of a 36-year-old patient with macular cavernous hemangioma of the retina complicated by hemorrhage and deterioration in visual acuity.

Treatment involved intravitreal injections of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, used off-label,

which resulted in both functional and morphological improvement.

The case discussed highlights the importance of differential diagnosis of cavernous hemangioma of the retina with other vascular anomalies of the fundus as well as diagnostic evaluations including central nervous system or genetic examinations.

KEY WORDS: cavernous hemangioma of the retina, optical coherence tomography, bevacizumab.

INTRODUCTION

Primary retinal vascular abnormalities, which include vascular tumors and telangiectasias, are benign in nature. Vascular tumors of the retina include retinal capillary hemangioma, cavernous hemangioma of the retina, racemose hemangioma, and retinal vasoproliferative tumor. Primary retinal telangiectasias include Coats' disease, Leber's miliary aneurysms, and idiopathic parafoveal telangiectasias [1]. In most cases, these diseases cause significant visual impairment due to macular exudation resulting from structural abnormalities of the retinal vascular system [1].

Cavernous hemangioma of the retina (CHR) is a rare, congenital, benign retinal vascular tumor occurring predominantly in children and young adults. CHR was first described in 1934 by Niccol and Moore [2]. The condition was originally referred to as "angiomatosis retinae". It was not until 1971 that CHR was recognized as a distinct clinical entity [3].

The majority of documented cases of CHR are episodic, but the condition may also have a familial presentation (autosomal dominant inheritance with varying gene penetration rates). Such cases present with additional vascular anomalies of the hamartoma type involving the skin and/or the central nervous system (CNS). They are diagnosed as neurooculocutaneous phakomatosis [3-5]. The coexis-

tence of cavernous hemangioma of the retina with neurocutaneous abnormalities is relatively rare (6%), and the relationship between them is uncertain. Consequently, some authors consider coexisting cutaneous lesions to be coincidental [6]. Patients diagnosed with both CHR and cavernous vascular lesions in the CNS have a mutation in the KRIT1/CCM1 gene [7, 8]. CHR may coexist with choroidal hemangiomas and ocular melanocytosis [9]. Retinal cavernous hemangiomas vary both in size and location. They are typically located along the course of major retinal veins [10]. In most cases (over 70%), CHR affects the peripheral retina, with a predilection for temporal location. Other possible locations include the macula and the optic disc [1]. The tumor typically presents as a single lesion, one to two optic disc diameters in size.

The aim of this paper is to present the case of a patient with macular retinal cavernous hemangioma complicated by hemorrhage and deterioration of visual acuity. The patient was treated with intravitreal injections of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, used on an off-label basis.

CASE REPORT

In December 2018, a 36-year-old man presented to the admission room of the Department of Ophthalmology at the Military Medical Institute in Warsaw with transient

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visual disturbances manifested as blurred vision in the right eye. The symptoms had been occurring intermittently for approximately a year. Previously, the patient had underwent ophthalmological consultation in another medical center, where a retinal hemangiomatous lesion accompanied by bleeding was diagnosed. Follow-up examination and vessel-sealing agents were prescribed. The man's prior medical history was incomplete. Based on information obtained from the patient, a retinal vascular abnormality had been found 15 years previously, during a routine ophthalmic check-up. At the time, further diagnostic work-up was indicated. However, detailed medical records from that period were unavailable. During the subsequent years, the patient experienced no ophthalmic symptoms until 2018. The man had no remarkable family history of ophthalmic or neurological diseases. In 2015, the patient also underwent diagnostic imaging and genetic testing for von Hippel-Lindau disease. No abnormalities were found in the CNS, and genetic tests did not confirm the diagnosis.

On admission, the patient's best corrected visual acuity (BCVA) was 0.7 in the right eye and 1.0 in the left eye (based on Snellen chart). Slit-lamp examination showed no pathological findings in the anterior segment of both eyes. In the fundus of the right eye, a well-demarcated lesion was found in the inferior temporal region of the macula. It was composed of clusters of red saccular dilated blood vessels resembling grapes, filled with dark red venous blood. The lesion was slightly raised above the retinal surface. It was accompanied by dense fibrous tissue, and grey and white gliosis zones on the surface, partially covering the lesion. Along the periphery, there were yellowish deposits likely



Figure 1. In the biomicroscopic examination of the right eye, a lesion consisting of clusters of red and dilated sac-like aneurysms filled with dark red venous blood. On the surface, gray-white gliosis partially covers the area of the lesion located in the temporo-lower macular area. Hard exudates on the periphery, fresh hemorrhage at the nasal border

corresponding to hard exudates. Also, a fresh retinal hemorrhage was found at the margin of the lesion on the nasal side. The caliber of the arterial and venous vessels adjacent to the lesion was unchanged (Figure 1). On MultiColor imaging (Heidelberg Spectralis HRA OCT, Heidelberg Engineering, Heidelberg, Germany), the lesion was visualized in green pseudo-color corresponding to the white fibrous tissue detected by color fundus photography, with distinctly irregular margins (Figure 2). Pseudo-3D MultiColor visualization revealed irregular surface of the lesion and its elevation above the surface. Fundus examination of the left eye found no abnormalities. On fluorescein angiography (FA), extensive hypofluorescence was seen in the center of the lesion in the early phases of the examination, followed by delayed incomplete perfusion over the subsequent phases. There was no diffusion of dye from the blood vessels. Blood circulation within the retina was normal (Figure 3). Aneurysmal vessels were filled in the late venous and recirculation phases, some in a non-uniform manner, while others remained unfilled. Vesicular dilatations with blood components inside showed characteristic “capped fluorescence” (fluorescein stasis in the superior portion of the lesion; the so-called “capping” is caused by gravitational separation of plasma from erythrocytes within larger aneurysms and slow blood flow; Figure 4). There were no significant differences in lesion size when comparing FA results obtained in August 2018 and December 2018. The only difference was hypofluorescence detected by FA at the more recent examination at the border of the lesion on the nasal side, attributed to hemorrhage. Optical coherence tomography (OCT) of the right eye revealed prominent irregularities on the inner retinal surface. Hyporeflective vesicular formations corresponding to thin-walled vascular structures were identified. They were located in the inner layers of the retina and

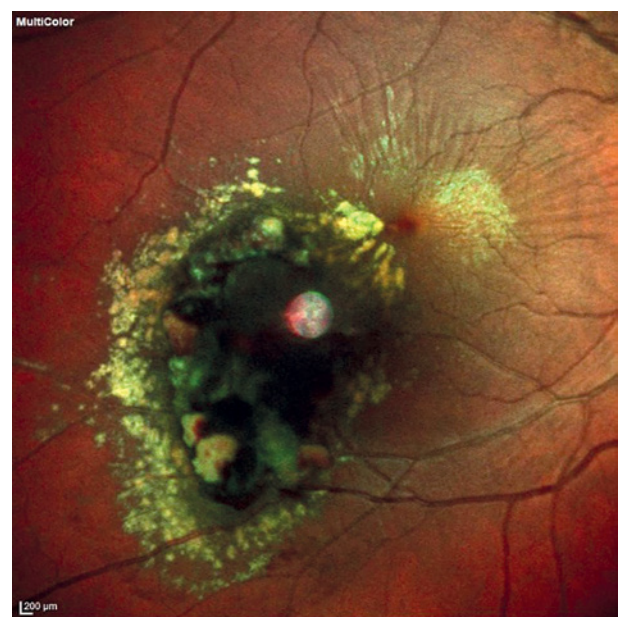


Figure 2. MultiColor imaging (Heidelberg Spectralis HRA OCT)

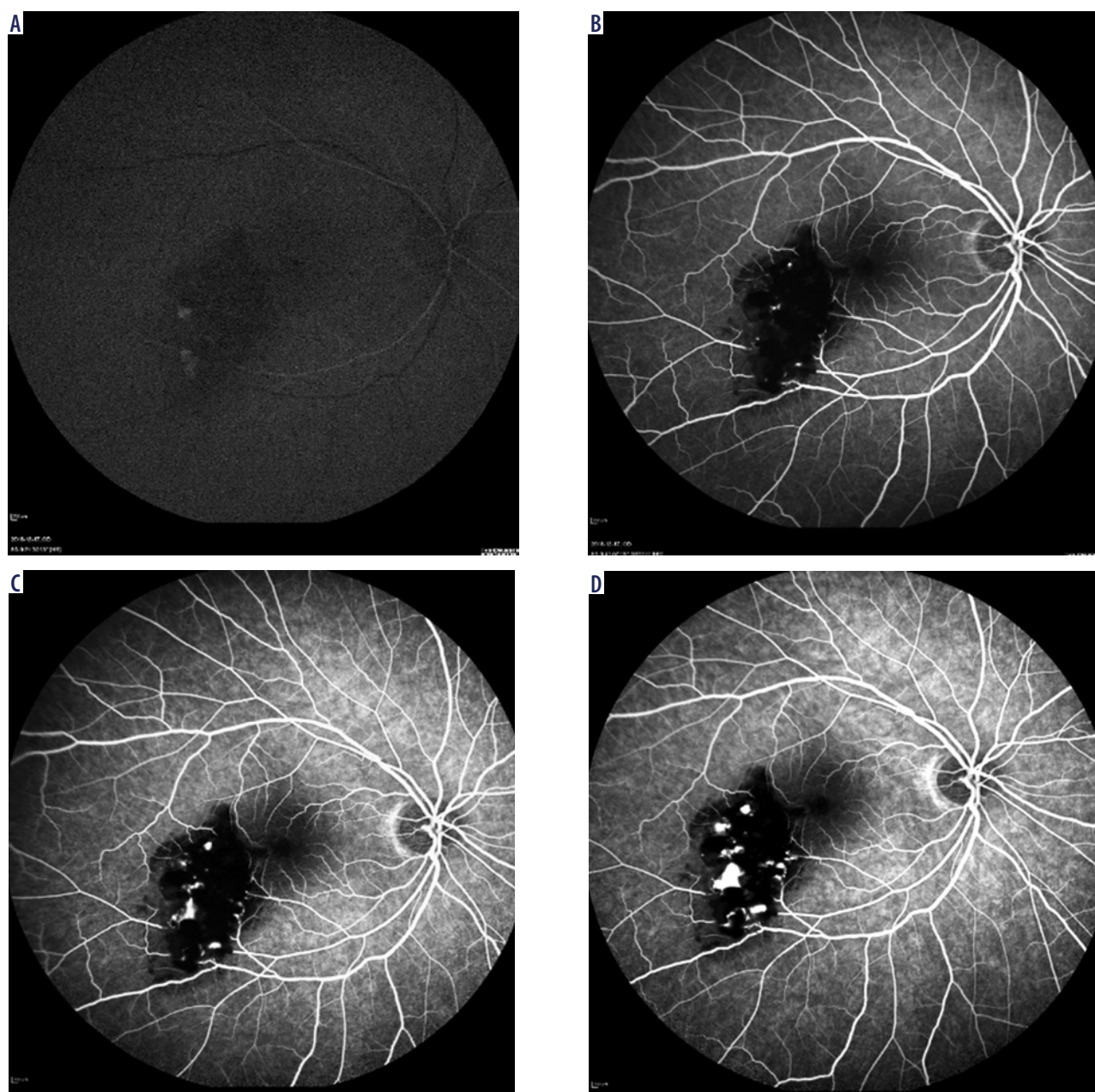


Figure 3. Extensive hypofluorescence from the early stages of the study, delayed incomplete perfusion of changes in the later phases, normal retinal circulation perfusion, no specific sites for dye diffusion from blood vessels

contained moderately hyperreflective material, consistent with blood, and were covered with preretinal membrane (Figure 5). An accumulation of subretinal fluid was identified in the foveal region. Overall, retinal morphology was abnormal as a result of compression caused by the detected tumorous lesion. Macular OCT findings in the left eye revealed no abnormalities. A visual field test showed a paracentral scotoma in the right eye, consistent with the tumor site in the fundus.

Based on the clinical findings and the results of additional diagnostic examinations, the diagnosis of retinal cavernous hemangioma in the fundus of the right eye, complicated by hemorrhage, was made. The diagnosis was aided

by the patient's medical history, spanning many years, and the results of previous diagnostic evaluations of the CNS and genetic tests.

Because of vision-threatening bleeding (macular location of the lesion) and the presence of subretinal fluid in the fovea of the right eye, it was decided to administer an intravitreal injection of bevacizumab (Avastin) at a dose of 1.25 mg/0.05 ml. Following drug administration, an improvement in BCVA to 0.8 and a decrease in the volume of subretinal fluid in the fovea were observed. A decision was made to administer another dose of bevacizumab. Follow-up OCT showed normalization of the foveal region and absorption of subretinal fluid. Within two months, all blood had been resorbed,

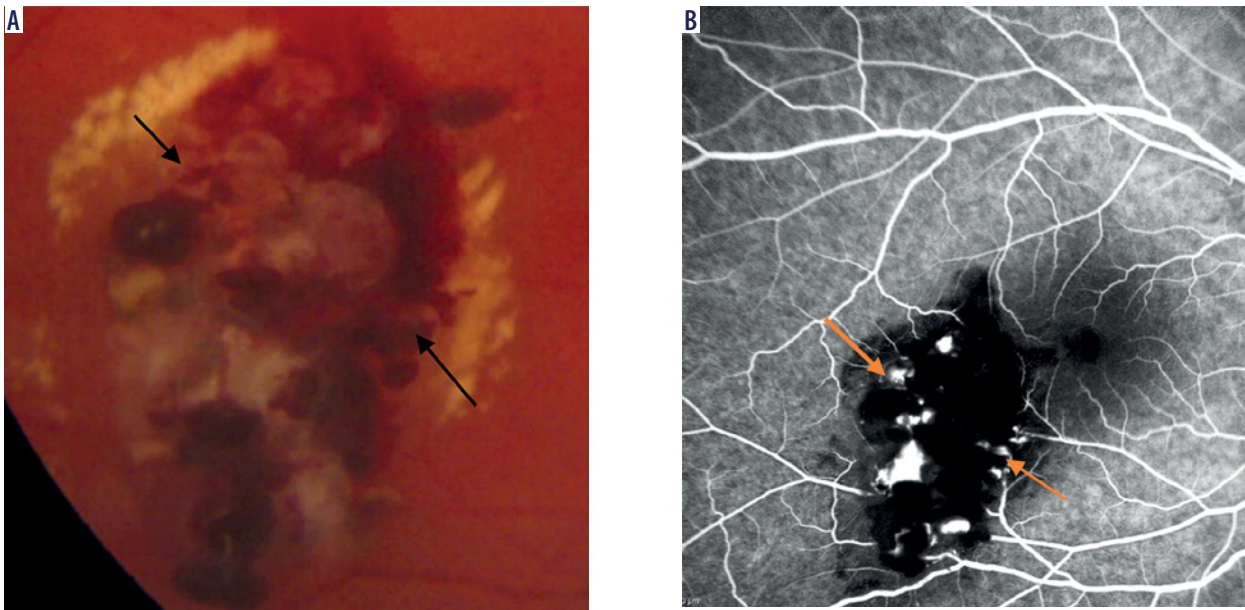


Figure 4. **A)** Fundus colour photography: gravitational sedimentation of plasma/red blood cells within the aneurysm (arrows); **B)** FA – characteristic image of “capping” marked with arrows

exposing a ring of hard exudates (Figure 6). The anti-VEGF therapy used most likely had no direct effect on the absorption of the small amount of blood.

The patient remains under ongoing follow-up. In July 2020, i.e. almost two years later, the BCVA of the right eye was found to have deteriorated to 0.63 on the Snellen chart. The fundus image of the right eye showed no significant differences from previous findings, except for an increased amount of hard exudates near the temporal border of the lesion (Figure 7). In addition, OCT demonstrated increased preretinal gliosis (Figure 8).

DISCUSSION

The diagnosis of CHR can be made based on the distinctive appearance of the fundus, combined with imaging findings [11]. Ophthalmoscopically, the tumor presents as a cluster of dark red, blood-filled saccular channels (characteristic “bunch-of-grapes” appearance) involving the inner layers of the retina, accompanied by superficial fibrous tissue and macular hemorrhages, as observed in our case [12].

CHR originates from the venous bed, and it is usually unilateral (as in our reported case). On microscopic examination, cavernous hemangioma of the retina presents as multiple interconnected thin-walled vascular spaces lined by flat, non-fenestrated endothelium accompanied by foci of partially organized intravascular thrombus. The vascular spaces are separated by a thin fibrous septum [13]. Aneurysms may be connected with the branches of the central retinal vein, but not with the choroid [14]. The inner preretinal membrane covering CHR shows locally thinned sections and breaks [14]. The whitish gray preretinal membrane can be a major component of the entire lesion and cause traction with the adjacent retina. It has been hypothesized that this superficial membrane causes multiple adhesions leading

to tortuosity and dilatation of the retinal vessels, and even hemorrhagic complications, as observed in the reported case [15]. Increased surface gliosis may be due to spontaneous thrombosis of the lesion [6]. In the reported case, surface gliosis was seen as moderate hyperautofluorescence in FA images and as a pseudo-colored green structure on MultiColor imaging.

The presence of hard exudates is a very rare finding in patients with cavernous hemangioma, both at the stage of CHR diagnosis and over long-term follow-up. In the reported case, hard exudates were found along the periphery of the lesion. Possibly, their presence can be attributed to concomitant vascular anomalies (macroaneurysm, retinal macrovessel). Being a slow-flow vascular anomaly, CHR is not generally associated with increased vascular permeability (edema, hard exudates). Abnormal retinal vasculature may accompany other pathologies as asymptomatic lesions. Consequently, the possibility of coexisting pathologies cannot be excluded with absolute certainty, which highlights the potential role of abnormal vascular development in the emergence of each of them separately. Since the authors of this paper are unable to trace back the morphology of the lesion to its onset, the coexistence of additional vascular anomalies in the reported case cannot be ruled out.

FA is the most common imaging examination supporting the diagnosis of CHR. In the late phases, the “capping” sign (also found in the present case) is seen, attributable to blood stasis and erythrocyte sedimentation [16]. As confirmed by FA, CHR is relatively well isolated from the retinal circulation [16, 17]. No dye leakage is observed within the hemangioma itself. Our own observation confirmed typical CHR features on FA. The absence of vascular leakage of fluorescein is helpful in differentiating CHR from

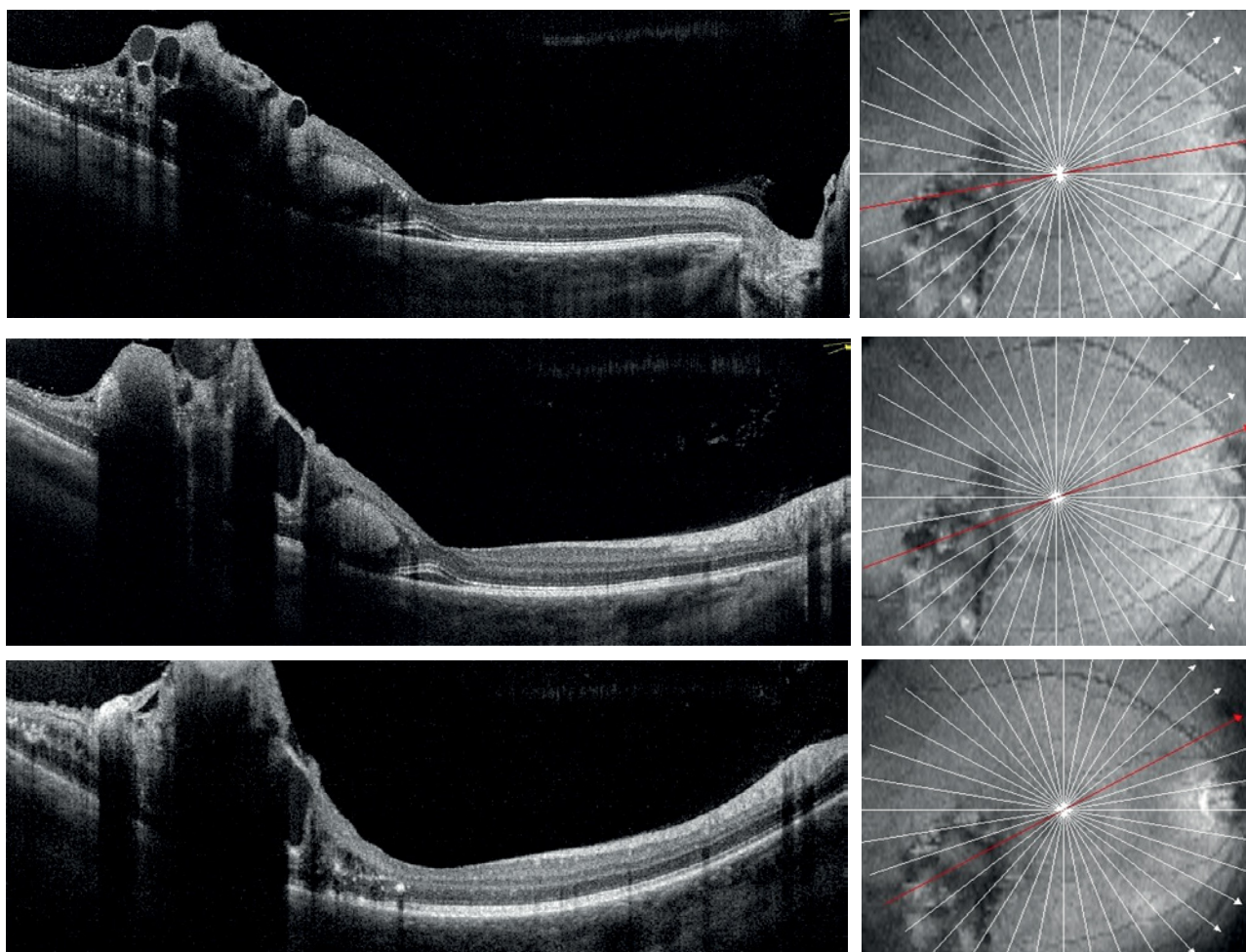


Figure 5. OCT images: Hyporeflective vesicular formations located in the inner retina, with an inner material of medium hyperreflectivity corresponding to the presence of blood, subretinal fluid in the subfoveal area. Preretinal membrane on the surface of the lesion. Minor hyperreflective lesions may correspond to hard exudates

other retinal vascular abnormalities, i.e. telangiectasia, Coats' disease, and von Hippel angiomas. Coats' disease and Leber's miliary aneurysms represent the greatest challenges in differential diagnosis. CHR shares few features with the clinical entities listed above, mainly due to venous malformation without vascular decompensation. The histological features of these entities vary considerably. Cavernous hemangioma is composed of multiple interconnected thin-walled vascular spaces lined by flat endothelial cells [13]. In telangiectasias, the cell membrane is multilayered, while the endothelium may be degenerate or absent [18]. Coats' disease and Leber's miliary aneurysms present as progressive dilatations of blood vessels accompanied by massive intra- and subretinal exudation [19]. Unlike in CHR, FA reveals vascular lesions located in the main bloodstream, as well as zones of non-perfusion and exudates. Leakage of dye from the capillaries is commonly seen in telangiectasias even in the early stages [17]. Aneurysms associated with telangiectasias present as single lesions located along the retinal vessels, at the border with areas of non-perfusion, whereas in CHR they form clusters

that are relatively isolated from the vascular tree and not associated with ischemia [20].

OCT is a modality that delivers cross-sectional imaging of CHR. The case described here revealed characteristic features of CHR including hyporeflective vesicular formations in the inner retina, covered by hyperreflective fibrous membrane.

CHR is a rare, benign, non-progressive tumor, usually isolated, as in the case reported in this paper [3]. The clinical history collected from the patient ruled out seizures, transient visual disturbances or headaches as the initial symptoms of hemangioma of the CNS. Examination findings excluded associated CNS lesions. It is important to note that cerebrovascular disorders potentially coexisting with CHR can lead to serious complications and premature death, if left untreated [11].

CHR located peripherally is usually asymptomatic. Hewick *et al.* described two patients with unilateral retinal cavernous hemangioma extending circumferentially and involving 360° of the mid-peripheral retina [21]. Messmer *et al.* reported on a case of cavernous hemangioma as a pe-

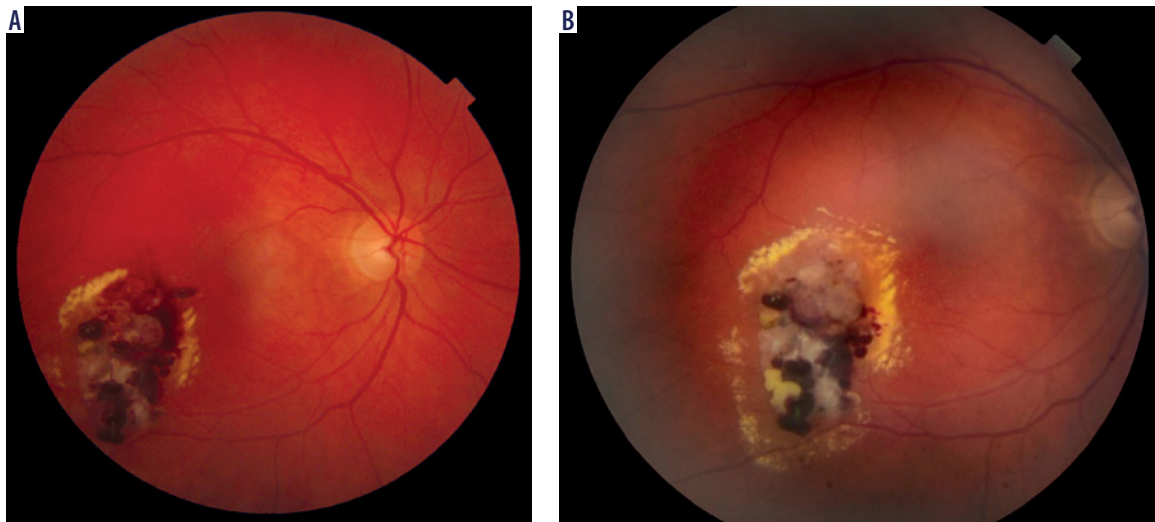


Figure 6. Fundus image of the right eye after anti-VEGF injections: **A)** pre-injection image; **B)** image after 2 anti-VEGF injections. Blood resorption is visible mainly from the area near the nasal edge of the lesion. The size of the lesion is similar, photo B shows a circular ring of hard exudates

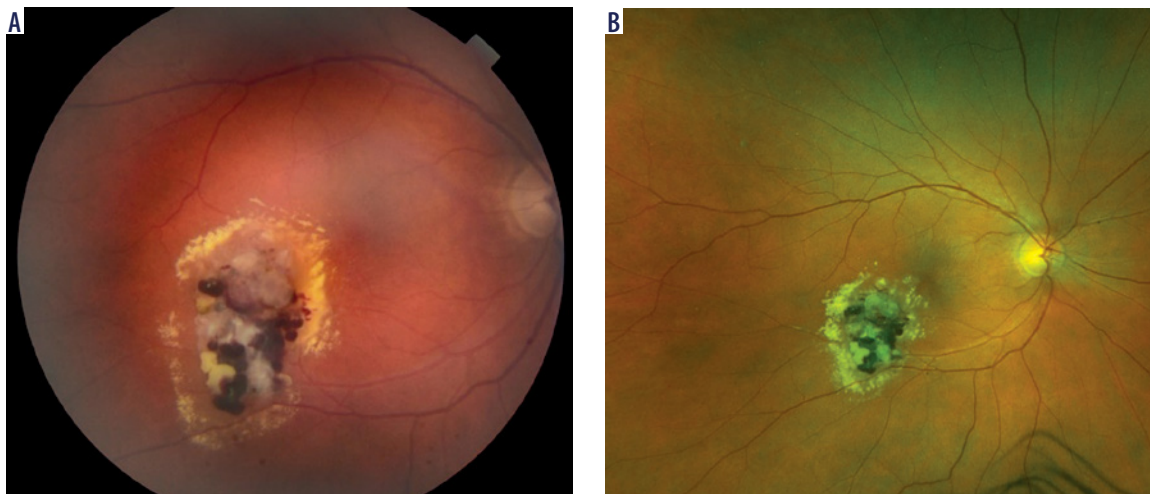


Figure 7. Fundus images of the right eye: **A)** January 2019; **B)** July 2020

ripheral dilated shunt vessel connecting the superior and inferior temporal vascular arcades [22]. In addition, there are two documented unique cases of cavernous hemangioma of the retina coexisting with retinal venous macrovessel [8].

In the case of macular CHR reported here, the lesion was complicated by retinal hemorrhage and the accumulation of subretinal fluid in the foveal area, resulting in visual impairment. The majority of retinal cavernous hemangiomas remain stable over a long period of follow-up [22]. Apart from minor changes in tumor morphology, in most cases lesions are not progressive either in size or extent [23]. Some of these may undergo spontaneous thrombosis, with secondary progression of preretinal gliosis potentially leading to deterioration of visual acuity [24]. A similar finding of progressive organization of hemangioma is currently observed in our reported case. The risk of spontaneous massive

bleeding in this type of tumor is relatively low. However, multiple minor bleeding episodes may lead to chronic glaucoma and, possibly, vision loss. These secondary changes are currently believed to be an effect of compression caused either by the tumor itself or the presence of fibrous membranes between the tumor surface and the tumor. Furthermore, follow-up studies have shown a good prognosis for visual acuity in eyes with cavernous hemangioma, except for cases where the macula is involved [11].

Currently available strategies for the treatment of CHR aim to minimize the occurrence of bleeding events and exudation and, if these occur, to prevent vision loss. Standard therapeutic management includes routine patient follow-up. Treatment is only considered in patients with severe vitreous bleeding or retinal hemorrhage. Cryotherapy and laser photocoagulation may be associated with the occurrence of secondary hemorrhage into the vitreous [11]. In

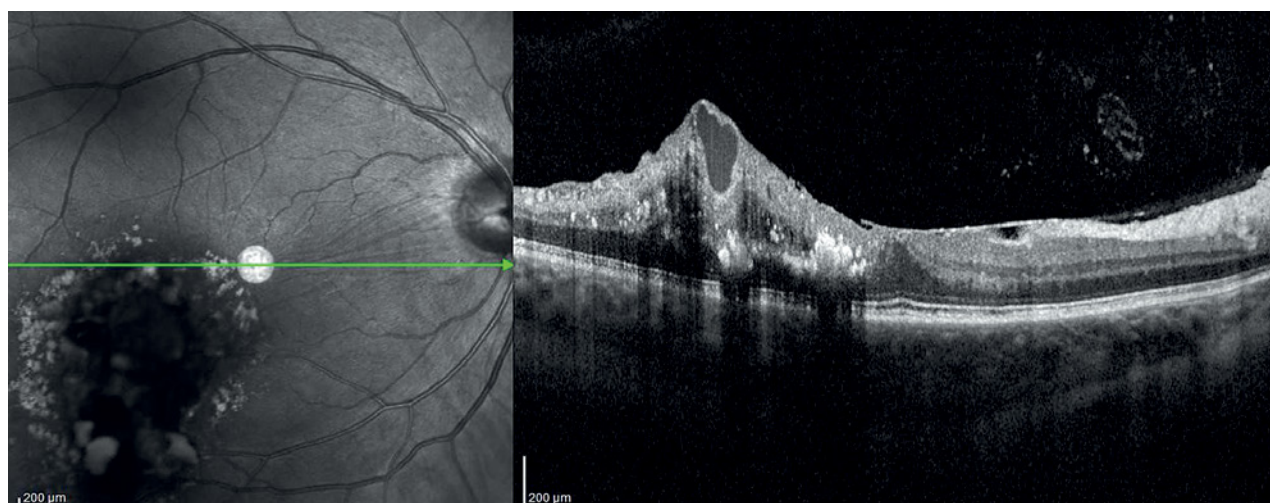


Figure 8. OCT image (Heidelberg Spectralis HRA OCT)

most cases, vitrectomy is not required, as vitreous or retinal hemorrhage is usually mild and absorbed spontaneously [11]. Japiassú *et al.* reported regression of macular cavernous hemangioma following treatment with systemic infliximab. However, Alsulaiman *et al.* did not achieve a similar outcome [25]. The available literature includes just one report of anti-VEGF therapy consisting of three monthly injections for the treatment of cavernous hemangioma complicated by recurrent bleeding into the vitreous chamber. The decision to treat the lesion with intravitreal injections of bevacizumab was made based on the presence of leakage on FA and the risk of recurrent vitreous hemorrhage. Two-year follow-up showed a marked reduction in hemangioma size, no features of leakage seen on FA, and no episodes of bleeding into the vitreous [26]. Intravitreal administration of anti-VEGF drugs had previously yielded encouraging results in cases of other retinal vascular tumors e.g. retinal capillary hemangioma, vasoproliferative tumor or primary telangiectasias. This treatment modality may be considered particularly in patients with retinal hemangiomas involving the center of the macula [27-30]. However, prospective clinical trials are needed to fully evaluate the effects of these therapies.

CONCLUSIONS

The manuscript presents a case of previously undiagnosed cavernous hemangioma of the retina causing episodes of macular hemorrhage with visual impairment. Intermittent anti-VEGF intravitreal therapy resulted in the regression of fluid spaces confirmed by OCT, with functional improvement and further stabilization over a longer period. After a follow-up of more than two years, morphological remodeling typical of cavernous hemangioma of the retina is seen, without progression of lesion size. The patient remains under ongoing follow-up. Although no extraocular abnormalities were found in our reported case, it is important to bear in mind that pathologies may also involve other body organs and systems. In each case of cavernous hemangioma of the retina, it is necessary to perform an imaging examination of the CNS to exclude vascular pathologies that may be asymptomatic but potentially life-threatening. While new diagnostic modalities for the fundus, such as OCT, contribute to better understanding of the physiopathology of CHR, present-day knowledge of this rare disease is still limited.

DISCLOSURE

The authors declare no conflict of interest.

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