Proliferative Hypertensive Retinopathy in Secondary Arterial Hypertension

Retinopatia Proliferativa e Hipertensão Arterial Secundária

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ABSTRACT

A 48-year-old Caucasian male presented in the emergency department complaining of right eye floaters. Ophthalmologic evaluation suggested bilateral proliferative retinopathy with vitreous hemorrhage in the right eye. Blood pressure was found to be 210/110 mmHg and severe hypertensive retinopathy was suspected. A fluorescein angiography revealed bilateral areas of macular and peripheral retinal ischemia and retinal neovascularization in the right eye. On spectral domain optical coherence tomography, bilateral macular edema was present. Management included bilateral targeted retinal photocoagulation in non-perfused areas and intravitreal bevacizumab injections in the right eye. A diagnosis of primary hyperaldosteronism was made after systemic investigation. During follow-up, both clinical and angiographic improvement were observed. Retinal neovascularization is a rare complication of severe hypertensive retinopathy, for which treatment with laser photocoagulation and intravitreal anti-angiogenic agents can be undertaken. The potentially devastating effects of retinal neovascularization highlight the need for prompt ophthalmologic evaluation along with extensive multidisciplinary investigation.

KEYWORDS: Hypertension/complications; Hypertensive Retinopathy/diagnosis; Hypertensive Retinopathy/drug therapy; Retinal Neovascularization.

RESUMO

Um homem caucasiano de 48 anos recorreu ao serviço de urgência por miodesópsias do olho direito. À avaliação oftalmológica apresentava sinais de retinopatia proliferativa bilateral com hemorragia vítrea no olho direito. A pressão arterial era 210/110 mmHg. Neste contexto, considerou-se a hipótese de retinopatia hipertensiva. A angiografia fluoresceínica revelou áreas de isquemia macular e retiniana periférica bilateral e neovascularização retiniana no olho

direito. A tomografia de coerência ótica revelou edema macular bilateral. O tratamento incluiu fotocoagulação retiniana nas áreas isquémicas e injeções intravítreas de bevacizumab no olho direito. Após investigação sistémica, foi feito o diagnóstico de hiperaldosteronismo primário. Durante o seguimento, houve melhora clínica e angiográfica. A neovascularização retiniana, uma complicação rara da retinopatia hipertensiva grave, pode ser tratada com fotocoagulação laser e fármacos antiangiogénicos intravítreos. Os efeitos potencialmente devastadores da neovascularização retiniana destacam a necessidade de uma completa avaliação oftalmológica e em contexto multidisciplinar.

PALAVRAS-CHAVE: Hipertensão; Neovascularização Retiniana; Retinopatia Hipertensiva/diagnóstico; Retinopatia Hipertensiva/tratamento farmacológico.

INTRODUCTION

The most common ocular presentation of systemic hypertension is hypertensive retinopathy, a condition that primarily affects the microvasculature of the retina.[1] Additional damage in the eye may occur in the form of choroidopathy, optic neuropathy and major retinal vessel occlusion. The ocular changes induced by increased blood pressure may be transient or permanent and can cause blurred vision, floaters and mild to severe vision loss.[1] Retinal neovascularization is a known severe but rare complication of hypertensive retinopathy, for which there has been recently coined the term "proliferative hypertensive retinopathy".[2] This serious complication requires timely diagnosis and targeted management to prevent further organ damage.

CASE REPORT

We report the case of a 48-year-old Caucasian male, with no previous ophthalmic history, who presented in the emergency department (ED) complaining of isolated right eye (RE) floaters with one one-week duration. Past medical history included 10 years of untreated systemic hypertension, long-term cigarette smoking and occasional cannabinoid use. Family history was notable for systemic hypertension in one first-degree relative. Baseline best corrected visual acuity (BCVA) was 20/40 on both eyes. There was no relative afferent pupillary defect. Anterior segment examination was unremarkable and intraocular pressure was 15 mmHg bilaterally. Dilated fundus examination revealed bilateral foci of retinal neovascularization with RE vitreous hemorrhage. Systemic evalua-

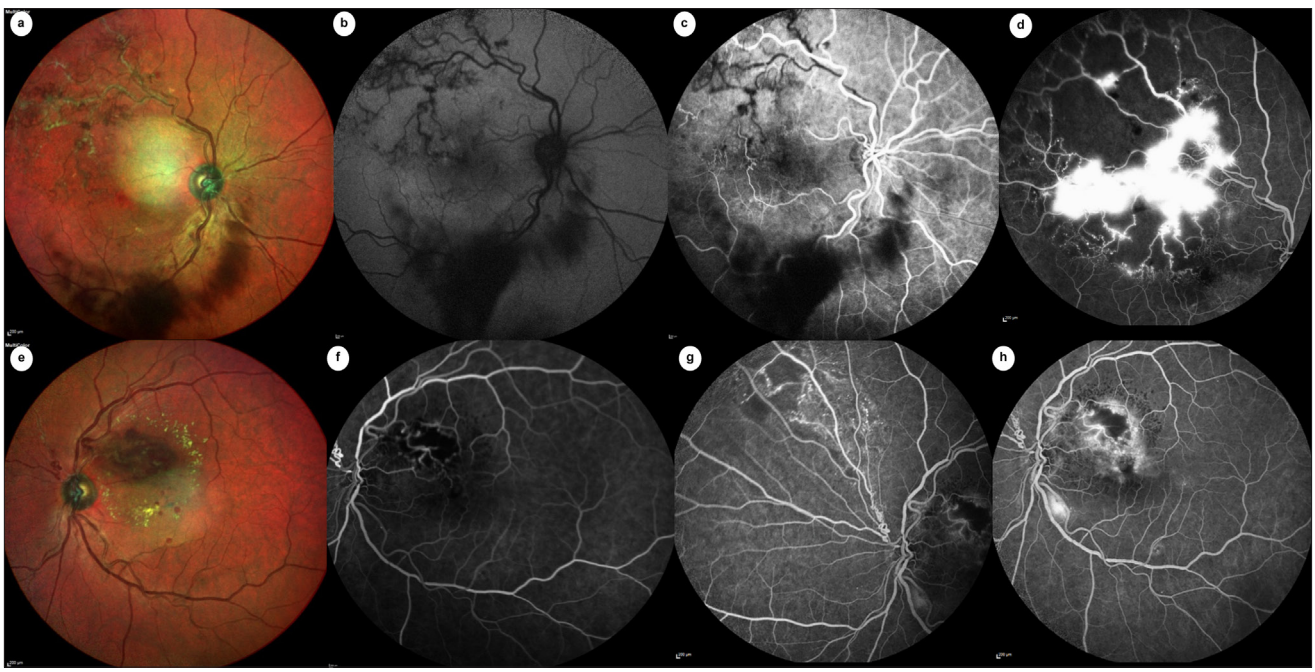

Figure 1. Multicolor fundus photography of the right eye (a) and left eye (e) and fluorescein angiography of the right eye (b: choroidal phase; c: arteriovenous phase and d: venous phase) and left eye (lower row f,g,h: early, mid and late venous phase) at presentation. In the RE there is macular ischemia with extensive microvascular changes and peripheral areas of ischemia and posterior pole retinal neovascularization with dye leakage. In the LE, areas of macular and peripheral retina ischemia and macular dye leakage with a small neovascularization focus inferior to the optic disc.

tion revealed a serum fasting glucose of 105 mg/dL and blood pressure of 210/110 mmHg. On fluorescein angiography, the RE exhibited filling delay of the superior temporal vessels with extensive capillary dropout, temporal superior peripheral retina and macular ischemia with a large retinal neovascular lesion. The left eye (LE) exhibited superior macular ischemia with significant capillary occlusion, superior nasal peripheral retina ischemia, microaneurysms, vessel wall staining and a small peripapillary neovascularization spot (Fig. 1). No optic disc edema was observed.

Following treatment with intravenous labetalol in the ED, the patient was admitted into the Internal Medicine Care Unit for investigation. Evidence of additional hypertension end-organ damage was detected in echocardiography, with mild concentric left ventricle hypertrophy with normal ejection fraction. No abnormalities were found in kidney and liver function tests. Complete blood cell count revealed normal white blood cell count and mild anemia (hemoglobin concentration: 12.6 g/dL). Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were normal. Rheumatoid factor was positive. Work-up for secondary causes of hypertension found no abnormalities in thyroid function, phosphate-calcium metabolism, urinary catecholamines and metanephrines, blood and urinary cortisol and dexamethasone suppression test. Renal artery stenosis was excluded with an ultrasound-Doppler directed study. The patient was discharged on four oral antihypertensive drugs. To exclude primary hyperaldosteronism, an aldosterone/renin ratio (ARR) was performed after withdrawal of all antihypertensive agents that affect the renin-aldosterone axis for 4 weeks, and replacing them with drugs without influence in this hormonal test. A positive ratio of 64.7 was found (aldosterone 414 pg/mL; renin 6.4 pg/mL; normal ARR <57) and a salt-loading test showed no suppression on plasma aldosterone concentration, confirming the diagnosis of primary hyperaldosteronism. Adrenal glands computed tomography (CT) showed bilateral mild adrenal gland hyperplasia, with absence of nodules. Adrenal vein sampling was done but could not be used to confirm lateralization since criteria for bilateral selectivity were not met. Approximately one month after discharge, bilateral retinal photocoagulation targeting non-perfused areas was performed in the peripheral retina as well as in the macular area with adjusted laser parameters. During follow-up, considering the presence of RE macular edema on spectral-domain optical coherence tomography (SD-OCT), three bevacizumab intravitreal injections were performed, with a four-week interval. Patient compliance to consultations, intravitreal injections and laser appointments was poor throughout the follow-up period. Twenty-four months after presentation in the ED, BCVA improved to 20/32 in the RE and to 20/25 in the LE. At this time, FA in the RE revealed persistent areas of non-perfusion in the superotemporal macular area and laser scars in the previously ischemic peripheral retina, with NVE regression confirmed with fluorescein angiography (Fig. 2). The LE exhibited laser scars and there was no evidence of increasing or new ischemic areas in both eyes (Fig. 2). On follow-up, obstructive sleep apnea was diagnosed and appropriate treatment started. For complaints of intermittent claudication in the right calf and absence of right popliteal and distal pulses, right and left ankle-brachial indexes were assessed and found to be 0.71 and 1.06, respectively. Doppler ultrasonography of the lower limbs exhibited right atherosclerotic femoro-popliteal disease. Treatment with acetylsalicylic acid and statins was initiated. A computed tomographic angiography (CTA) showed significant right superficial femoral artery stenosis (Fig. 3). A diagnosis of type 2 diabetes mellitus was made in the 1-year Endocrinology follow-up visit, after which metformin was initiated.

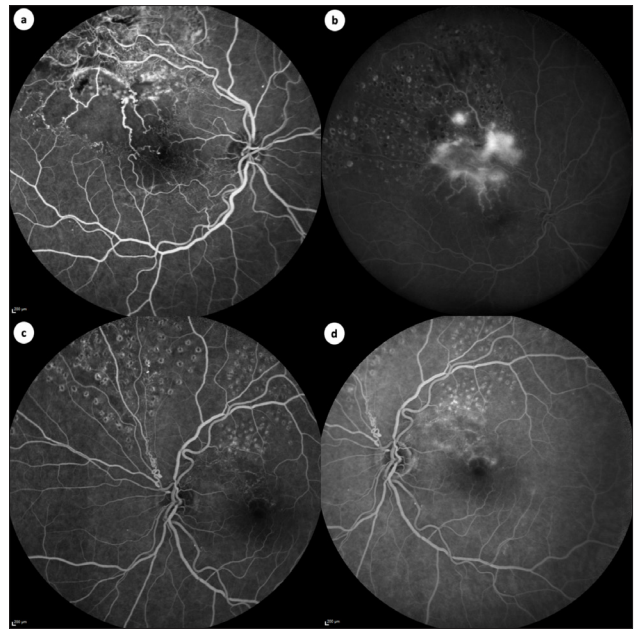

Figure 2. Early (a and c) and late (b and d) venous phase fluorescein angiography at the 24-month follow-up demonstrating maintenance of macular ischemic areas with microvascular changes (a) and peripheral TRP laser scars without new ischemic areas (b) in the right eye. In the left eye, there are laser scars in the superior nasal peripheral retina (c) and superior temporal macula (d).

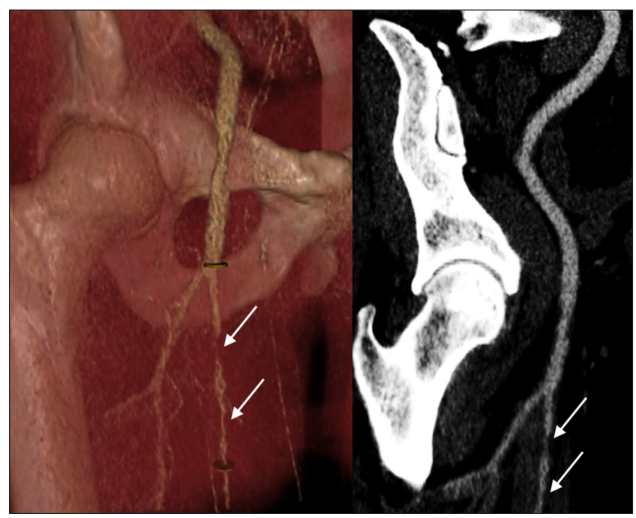

Figure 5. Computed tomographic angiography scan reconstruction showing atherosclerotic involvement with significant morphologic stenosis of right superficial femoral artery (arrows).

DISCUSSION

Systemic arterial hypertension is the leading risk factor for cardiovascular disease and chronic kidney failure.[1] Although essential/idiopathic hypertension is the most common etiology, a secondary cause should be suspected when in face of suggestive symptoms, young onset (<40 years old) of grade 2 or 3 hypertension, sudden development of hypertension or rapidly increasing blood pressure (BP) in older patients.[1] In non-diabetic patients, hypertensive retinopathy is thought to occur in 2% to 17%[3] and has well-documented prognostic significance.[1] Namely, hypertensive retinopathy is known to predict the long-term risk of stroke.4 Recent guidelines recommend fundoscopy as a standard practice in grade 2 and 3 hypertensive patients and in those with concomitant diabetes, due to the increased likelihood of retinal disease.[1] Fundoscopy findings associated with hypertensive retinopathy include arteriolar narrowing, arteriovenous nicking, cotton wool spots, intraretinal hemorrhages, hard exudates and optic disc swelling. Hypertensive emergencies correspond to situations in which grade 3 hypertension (BP ≥ 180/110 mmHg) is associated with hypertension-mediated organ damage, including fundoscopic changes, such as flame hemorrhages and/or papilledema.[1] Emergent treatment usually requires intravenous beta-blockers. Our patient exhibited high BP associated with signs of grade 3 hypertensive retinopathy, according to the Keith-Wagner-Barker classification proposed in 1939. Although infrequently seen in the context of hypertensive retinopathy, our patient presented with bilateral proliferative retinopathy. Retinal neovascularization, ultimately attributed to hypertension, is a rare event reported in the literature. Neovascularization is known to develop in response to hypoxia in retinal ischemic areas, mediated by up-regulation of growth factors such as vascular-endothelial growth factor (VEGF),[5] a mechanism already well established in the pathophysiology of proliferative diabetic retinopathy and retinal vein occlusion. Hence, proliferative retinopathy may be a common endpoint to several retinal vascular diseases. Before ascertaining proliferative changes to systemic hypertension, pathologies such as diabetic retinopathy, retinal vein occlusion, ocular ischemic syndrome, hyperviscosity syndromes, hemoglobinopathies, systemic lupus erythematosus, vasculitis, among others, should be excluded. In the existing literature, case reports on the association between retinal neovascularization and systemic hypertension include mostly young adults who were found to have high BP readings after ophthalmological observation for visual complaints. Georgiadis *et al*[6] reported the case of a 33-year-old male patient with gradual bilateral visual loss whose fundus findings included extensive areas of bilateral retinal neovascularization with macular and peripheral retinal ischemia. No macular or optic disc edema were observed. Subsequent investigations led to the diagnosis of primary hyperreninemia leading to secondary hyperaldosteronism and hypertension. Two ranibizumab intravitreal injections with 2 2-month interval were administered in the right eye, which had worse central vision and macular ischemia, and panretinal photocoagulation was performed in the left eye. Follow-up examination, 12 months after presentation and after treatment with ranibizumab intravitreal injections and panretinal photocoagulation (PRP), documented the regression of retinal neovascularization on FA in the RE and reperfusion in the LE. Golshani *et al*[7] reported the FA abnormalities of a 30-year-old female patient who presented with new-onset visual complaints in the setting of hypertensive crisis. The patient was known to be non-compliant with anti-hypertensive drugs and hemodialysis sessions for end-stage renal disease due to suspected IgA-nephropathy. In this case, bilateral optic disc edema was present along with diffuse retinal hemorrhages. FA showed optic disc neovascularization (NVD) in both eyes, complete loss of retinal capillaries and severe venous beading. A single anti-VEGF intravitreal injection and PRP were performed in both eyes. After being lost to follow-up for several months, the patient returned for observation due to RE pain, secondary to neovascular glaucoma, which ultimately led to enucleation and confirmation of IgA nephropathy on tissue biopsy.[8] Stryjewski *et al*[2] reported on a 40-year-old male patient with an 8-month history of progressive bilateral visual loss. The patient exhibited bilateral vitreous hemorrhage and a macular tractional retinal detachment in the LE due to fibrovascular proliferation along the temporal vascular arcades. BP was 270/160 mm Hg. Another recently reported case by Abu Sbeit *et al*[9] described bilateral severe retinal ischemia with active, leaking, neovascularization on the FA of a 34-year-old female patient. She had a known history of hypertension, although non-compliant with appointments and anti-hypertensive medication. She presented with complaints of blurred vision and headache and was diagnosed with a hypertensive crisis. Optic disc edema, along with vitreous hemorrhage in the RE were observed among other features of hypertensive retinopathy. Bilateral PRP was conducted. Six months later, bilateral regression of NVE was documented.

In all the above reported cases, patients were young adults with either previous or newly diagnosed systemic arterial hypertension. Abu Sbeit *et al*[9] suggested that the young are more likely to develop retinal proliferative changes in the context of hypertension due to non-sclerotic blood vessels in the retina. Younger patients also seem to be more susceptible to hypertensive choroidopathy for the same reason.[10] An extensive investigation should be undertaken before establishing hypertension as the potential cause of retinal findings. Blood pressure control and exclusion of secondary causes is paramount in the management and follow-up of these patients. If a previously unknown proliferative retinopathy is diagnosed, emphasis should be put on BP measurement by the attending ophthalmologist. Regarding patients with known hypertension, ophthalmological evaluation is essential to stratify hypertension-related disease and to act timely, if justified, to prevent further visual deterioration. Along with intravitreal anti-VEGF injections, targeted retinal photocoagulation is known to be effective in the management of peripheral retinal ischemia

complicated with retinal neovascularization. This case report thus acknowledges proliferative retinopathy has an end-stage phase in the natural history of severe arterial hypertension and underscores the need for blood pressure measurement by the attending ophthalmologist when in face of a patient with new onset visual complaints whose fundus exhibits suspicious vascular signs.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

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

Todos os autores atestam que cumprem os critérios atuais do ICMJE para a autoria.

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