Retinal vasoproliferative tumor
Tumor vasoproliferativo da retina

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ABSTRACT
Retinal vasoproliferative tumor is a rare disease that has capillary hemangioma as the most frequent differential diagnosis. The tumor is considered to be of reactive nature. It can be idiopathic or secondary to other ocular diseases such as: uveitis, retinitis pigmentosa, sickle cell disease, previous surgery and retinopathy of prematurity. Lesions with no exsudation or visual decrease can be observed. Lesions that need treatment can be managed by on or more modalities such as cryotherapy, a variety of lasers, surgical excision, radiation, and antiangiogenic intravitreal injections.

Keywords: Retina/pathology; Retinal neoplasms/diagnosis; Retinal neoplasms/pathology; Retinal neoplasms/therapy

INTRODUCTION
The histopathological description of what we now know as retinal vasoproliferative tumor (RVPT) was first done by Henkind and Morgan back to 1966, based in findings that they quoted as "Coat's like" appearance in eyes enucleated due to other diseases. From that starting point, eventual case reports and small case series describing the clinical aspects of primary and secondary peripheral vascular retinal tumors posing a diagnostic dilemma with uveal melanoma and retinal capillary hemangioma started to came out. In 1995, Shields et al. reported 103 cases of peripheral acquired retinal vascular tumor (PVRV) and proposed the term RVPT.

Our goal is to review the clinical picture, differential diagnosis, etiology, histopathological aspect and management of RVPT, based on major publications about the topic and on our personal experience with this rare disease at the Federal University of Bahia and Hospital São Rafael, two major regional referral centers for eye tumors in Bahia - Brazil.

CLINICAL PICTURE AND DIFFERENTIAL DIAGNOSIS
RVPT can be primary (idiopathic) or secondary (associated) to other ocular diseases like retinitis pigmentosa, sickle cell retinopathy, Coat's disease, retinopathy of prematurity, toxoplasmosis, toxocarasis, tuberculosis, other uveits, ocular trauma, retinocchoroidal coloboma and retinal detachment. Primary tumors correspond from 53 to 80% of the cases in the major reported series.

RVPT usually presents as a solitary mass in the retinal periphery. The inferior retina is affected in 60 to 90% of cases and the temporal retina in 42 to 75% of cases. The tumor is usually a red or orange mass and can present with some cases are discovered on routine evaluation. Floaters, photopsias and metamorphopsia are other common complaints.

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uveolar tuberculoma and granuloma due to sarcoidosis - lesions that frequently are located in the periphery and frequently exhibit vitreous cells, just like a RVPT, but lack the typical vascular component and usually have a pale aspect(12,14).

Complementary tests include echography, fluorescein angiography (FA) and optical coherence tomography (OCT). Echography shows a solid tumor with medium to high internal reflectivity and lacking choroidal shadowing (Figure 2 B and C). Echography is also useful to measure (most of RVPTs are less than 3 mm high) and follow RVPTs' response to treatment(7,10,13). FA is usually of limited value due to the preferred peripheral location of RVPTs. When feasible RVPTs' AF reveals early filling in the arterial phase with increasing hyperfluorescence and late leakage(7,10,15). OCT also has a limited role for the same reason as AF, but is frequently used to document and follow the secondary retinal findings like edema and membrane formation (Figure 3)(15).

Despite its benign nature, RVPT can cause severe visual loss due to the secondary compromise of the vitrous and retina (epiretinal and subretinal membranes, vitreous hemorrhage, subretinal fluid and exsudation) or, less frequently, neovascular glaucoma the can result in a blind painful eye and may prompt removal of the globe(16).

ETIOLOGY AND HISTOPATHOLOGY

The etiology of RVPT is yet to be completely understood. Although most RVPTs are supposedly of idiopathic nature, the study of lesions obtained by enucleation or from eyes enucleated due to neovascular glaucoma suggests a reactive, rather than neoplastic nature. The microscopic study reveals a mix of vascular and glial proliferation. The glial component usually exhibits fusiform and rather uniform cells. Vascular component show dilated vessels with mural hyalinization and occasional thrombosis (Figure 4). Proliferative index is low. RPE cells can permeate the tumor mass, exhibiting a variety of phenotypes like macrophages, fibroblasts, cuboidal and pseudoadenomatous with tubuloacinar aspect(16-18). The preferential location of RPE cells around blood vessels or in areas of previous hemorrhage in RVPTs, highlights the reactive nature of those cells(18).

The reactive nature of RVPTs is questioned to be a variant of proliferative retinopathy(18). Hiscott and Mudhar, studied 6 enucleated eyes harboring RVPT. They found epiretinal and subretinal membranes containing RPE cells in association with RVPTs in all eyes(18). While Shankar et al. highlighted the vascular content of a surgical excised epiretinal membrane associated to RVPT, calling attention to the resemblance to epiretinal membranes from diabetic patients and questioning the role of RVPTs as a source of vasoactive citokyns(19).

TREATMENT AND PROGNOSIS

The ideal treatment scheme for RVPTs is yet to be determined. A number of different treatment approaches have been described with variable success rates, usually on case reports or small case series(18,19).
In the largest published series on RVPTs, Shields et al. used the presence of subretinal fluid, macular edema, epiretinal membrane close to the macula or exudates close to the macula as criteria to treat or observe RVPTs’ patients. Based on these criteria 51% of the eyes needed treatment in their series.

Various treatment modalities are available including cryotherapy, laser photocoagulation, photodynamic therapy (PDT), brachytherapy, surgical resection, intravitreal injections and immunomodulators. All of them can be used alone or in combination, as we will discuss in the following sections.

**CRYOTHERAPY**

It seems to be the most frequently employed treatment modality for RVPTs. As RVPTs are usually located in the periphery, cryotherapy can be applied in a transconjunctival way, under observation through binocular indirect ophthalmoscopy. The treatment goal is to freeze all tumor, allowing slow thawing and repeating the whole process 2 or 3 times. More than one cryotherapy section can be necessary to achieve complete tumor involution specially in thick tumors. Figure 1 shows a large RVPT measuring 4.04 mm thick that was successfully treated by cryotherapy followed by one anti VEGF injection for macular edema after the tumor has regressed. A similar approach was successfully employed by Rodrigues et al. who treated a 2.25 mm RVPT with cryotherapy, associated to triamcinolone intravitreal injection.

Cryotherapy can cause some adverse effects like the persistence of macular edema and the occurrence of retinal detachment arising in a retinal tear adjacent to the scared area.

**LASER PHOTOCOAGULATION**

Although its use has been reported in RVPTs, it has a limited role. Probably laser photocoagulation should be reserved for small tumors and, most often, as a complement to other treatment modalities, since it is incapable to destruct thick tumors.

**PHOTODYNAMIC THERAPY (PDT)**

PDT has been reported as an effective treatment in retinal and choroidal vascular tumors. There are a few reports of its successful use in RVPT even for larger tumors, like the ones reported by Blasi et al., with a thickness varying from 2.03 to 4.45 mm. Its major limitation is the technical difficulties to reach the typical peripheral location of RVPTs.

**BRACHYTHERAPY**

Its major indication in RVPTs is for large lesions (more than 2.5 mm thick) and lesions associated to retinal detachment. In these clinical situations, cryotherapy is prone to wide tissue destruction, intense inflammatory reaction, vitreous hemorrhage and an increase in subretinal fluid. There are reports of well successful brachytherapy for RVPTs using either Ruthenium or Iode, reaching total tumor remission in 88 and 97% of the cases respectively. However, when there is associated neovascular glaucoma, brachytherapy failed to achieve disease control. It is also important to remember the risk of developing some adverse effects of eye irradiation: dry eyes, cataracts, actinic optic neuropathy, actinic retinopathy and neovascular glaucoma.

**SURGICAL RESECTION**

It is seldom indicated. There are reports of surgical resection for RVPTs that failed to respond to cryotherapy in association to intravitreal injections of antiangiogenics or as a primary treatment in an eye harboring multiple RVPTs and vitreous hemorrhage. The surgery can be performed through pars plana vitrectomy or by a transcleral route. Cataract is a common complication after vitrectomy in phakic eyes, specially when silicone oil or gas is used to seal the retinotomies necessary to perform tumor’s endoresection.

**INTRAVITREAL INJECTIONS**

There are a few reports of antiangiogenic intravitreal injections for RVPTs, like bevacizumab, ranitumab and triamcinolone. Although the exact effect of these substances on RVPTs is lacking, it seems reasonable to consider their use in association to or after other
The treatment options available is lacking. From our personal perspective, faced to a new RVPT case the first point to be addressed is the decision to treat or observe. It seems reasonable that patients with good visual acuity, small and stable tumors, no subretinal fluid (or very limited and non progressive) and lacking exudation can be securely observed on a 3 to 4 months basis. These patients should be oriented to frequently perform self visual acuity test with immediate return if any visual acuity drop or initiation of other symptoms like photopsias or floaters are noted. For symptomatic patients, and even for patients with good vision but exhibiting signs of impending visual acuity risk (like growing tumors with progressive subretinal fluid or exsudates) we advocate immediate treatment. After the decision to treat is taken, one should decide which treatment modality to use. Some authors recommend that tumors thicker than 2.5mm should be treated with brachytherapy as an initial approach. Nevertheless, brachytherapy is an expensive treatment that is not easy available in most centers. On the other way, successful treatment of thicker RVPT with multiple sessions of cryotherapy, PDT, photocoagulation or the association of cryotherapy with intravitreal injections of antiangiogenic for the secondary retinal changes were reported. Such approaches are probably more much commonly employed in the treatment of RVPTs than brachytherapy worldwide. From our personal perspective, treatment decision should be based on specific tumors characteristics, but also on local availability. For instance, brachytherapy can be considered an indication in thicker tumors, but it should not be considered as the only possible treatment option specially when considered its costs and the fact that it is not available in most referral centers and that other modalities have been successfully employed, even for thicker tumors. Probably a tumor located on a PDT amenable position, in a center where PDT is available, will be suitable for PDT treatment, whereas successive gentle cryotherapy sections can be successfully employed in thicker tumors specially if combined to intravitreal injections of triamcinolone or anti VEGF agents (Figure 1). It is also important to note that immediately after treatment and for at least a few weeks after, it is common to find an increase in tumor dimensions that is probably caused by intraretinal inflammation or hemorrhage. So the decision to give more treatment or to change the treatment modality should not be done in a precipitated fashion.

REFERENCES