Complications of combined retinal and retinal pigment epithelium hamartoma involving the optic disc in a child, treated with Avastin - a review of the literature and case presentation

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Abstract
We present a case of a 9 years old boy, followed up for 4 years, with bilateral combined pigmented epithelial and retinal hamartoma, complicated with recurrent vitreous hemorrhages in one eye and neovascular glaucoma and cataract in the other eye, treated with repeated intravitreal injections of Bevacizumab. A review of the literature suggested that such lesions may be symptomatic because of decreased vision, macular pucker, strabismus and vitreous hemorrhages. This particular compressive, bilateral form of hamartoma of the optic nerve has not previously been reported as a cause for such an ischemic syndrome, complicated with neovascular glaucoma and cataract.

Key words: hamartoma, leukocoria, neovascular glaucoma, vitreous hemorrhage, Bevacizumab.

Introduction

According to Gass, citing Stedman’s Medical Dictionary, a hamartoma is a focal malformation that resembles a neoplasm grossly and even microscopically [1] but results from faulty development in an organ; it is composed of abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present at that site, which develops and grows virtually at the same rate as normal components, and it is not likely to result in compression of the adjacent tissue (in contrast with neoplastic tissue).

Retinal hamartomas are included in the developmental tumors of the retinal pigment epithelium RPE and retina, along with retinal choristomas, phacomas and nevi.

Biomicroscopic examinations reveals an ill-defined, slightly elevated, partly pigmented tumor involving part of the optic nerve head and adjacent retina. The presence of many fine capillaries within the tumor may be partly obscured from view by a semitranslucent gray membrane that is always present on the inner retinal surface. Patients become symptomatic either because of metamorphosis caused by contraction of this membrane that produces traction folds in the retina that extend into the central macular area, or less frequently because of subretinal and intraretinal exudation derived from the capillary component of the tumor. This exudation may reabsorb spontaneously and
leave atrophic changes in the RPE surrounding the tumor. Other complications that may occur infrequently include choroidal neovascularization, retinal hemorrhages and vitreous hemorrhages [2]. Most cases are isolated ocular findings, though an association with neurofibromatosis types 1 and 2 has been found, especially for those with bilateral lesions [3].

The early phases of angiography demonstrate dilated, multiple, fine blood vessels within the tumor, and later phases show evidence of leakage of dye from these vessels [1].

Histopathologically, the optic disc tumors show evidence of a hamartomatous malformation involving hyperplasia of the RPE, glial cells, and blood vessels.

Many of these lesions remain stable. Some may develop exudative changes and show an increase in opacificiation of the glial component of the tumor. The surface glial membrane causing the retinal folding is an integral part of the tumor and accounts for the fact that surgical stripping of the membrane is difficult and has limited chance of restoring central vision [1].

Case presentation

History: The child had his first ocular examination at 4 years old, when mother noticed the misalignment of the eyes. She reported the appearance of an inconstant white reflex of the left pupil in photographs from the age of 1 month (intermittent photoleukocoria), without worrying her though.

The child was clinically healthy, with healthy parents. He has an older sister with an atypical form of epilepsy.

At first presentation on March 2011, at the age of four, the vision was OD - 20/20, OS - light perception.

The ocular fundus examination revealed:

OD - abnormal vessels on the surface of the optic nerve, tortuosity of the arteries, hard intraretinal exudates in the intermaculo-papilar area

OS - white mass at the optic nerve head covered by extensive exudates protruding into the vitreous cavity, tortuous vessels and hemorrhages at the surface of the lesion (Fig. 1), sheathing of the vessels in the periphery, hard intraretinal exudates at the mid periphery, visible with the blue filter (Fig. 2).

There were no inflammatory cells, neither in the vitreous cavity, nor in the aqueous.
The early phases of angiography demonstrated hyperfluorescence of the optic nerve head. The late phase revealed:

OD - staining of the optic nerve and normal filling of the retinal and choroidal vessels

OS - leakage of the optic nerve head, staining of a strong vascular branch sticking out into the vitreous, hypofluorescence of the retinal and choroidal vessels.

An extensive evaluation was performed. The erythrocyte sedimentation rate was 10 mm/hour (Westergren). The absolute leucocyte count was 10,000 / mm³ with 7% eosinophils. The angiotensin converting enzyme level was normal.

Titters of antibodies for Toxoplasma, Borrelia, Treponema, Cytomegalovirus, Leptospira, HSV, HZV, were normal. A PPD skin test was negative. He was found positive for Toxocara Canis (IgG 5.21 UI/ml) and received treatment with Albendazole.

The testing of the anterior chamber aqueous for antibodies against Toxocara was negative. The mother was found negative for Toxocara, but his older sister was also positive. The presence of leukocoria at one month of age, the absence of the antibodies in his mother’s blood or in the child’s aqueous, the absence of inflammatory cells and the normal ESR, excluded the hypothesis, theoretically possible, but very unlikely, of a congenital bilateral toxocariasis as a cause for those lesions. It is more likely that the infestation occurred after the age of one month, when the leukocoria was first noticed.

A differential diagnostic of leukocoria was made:

- Retinoblastoma – is a retinal growing tumor, with normal optic disc
- Coats disease- exudates from peripheral vascular telangiectasia and aneurysmal dilations of the retinal vessels
- Toxocara Canis - excluded as mentioned above
- Familial exudative vitreoretinopathy FEVR - has a family history, peripheral ischemia resembling ROP, due to arrest of normal vasculogenesis
- Retinal or vitreoretinal dysplasia (Norrie's disease, Patau Sdr - trisomia 13, Edward Sdr) - are maldevelopments of the retina and vitreous
- Other posterior segment tumors (eg. Combined hamartoma of the retina and pigment epithelium – CHR-RPE, affecting the optic nerve) - could not be excluded

The presumptive diagnosis of hamartoma was made based on leukocoria, the abnormal vessels of the optic disc, the presence of exudates and the glial proliferation. The child did an Angio MRI of the head and an abdominal ultrasound which were within normal limits. Knowing that combined hamartoma of the retina and pigment epithelium is a relatively common feature of the neurofibromatosis type 1 and 2 [3], he was tested for neurofibromatosis in a specialized
The mother asked for other opinions in Bucharest, Antwerp and Brussels, with no change in diagnostic and no therapeutic suggestions.

In Brussels he was tested for PAX2 gene, which was found normal.

The mother returned with the child in our service in July 2012. The vision was OD - 20/20, OS - no light perception. The fundus examination revealed (Fig. 4):

- OD - hemorrhages of the optic nerve head, sheathing of the vessels at the emergence from the optic nerve, arterio-arterial anastomoses, retinal hemorrhages at the inferior-temporal periphery. The hard exudates disappeared, being replaced by a translucent membrane with folds between the optic nerve head and macula.
- OS - ghost retinal vessels, an avascular funnel sticking out from the optic nerve into the vitreous, optic nerve discoloration, retinal pigmentary changes and a translucent membrane at the vitreoretinal interface.

The fluorescein angiography is showed in (Fig. 5).

The late phase revealed:
- OD – leakage from the optic disc vessels, normal filling of the retinal and choroidal vessels
OS – peripheral nonperfusion of the retina and choroid, absence of filling of the optic disc and retinal vessels, pigmentary changes in the mid periphery.

A peripheral indirect laser photocoagulation was attempted on OS, with no results, because of the thick epiretinal membrane.

Knowing that neurofibromatosis-like tumors could benefit from anti VEGF injections [4], we decided to use Avastin injected intravitreal.

The first Avastin injection was performed in OD (0.1 mg/0.04 ml), followed by the remission of the hemorrhages both at the optic nerve and in the periphery. After that, the child had monthly follow-ups, with monthly photographs of the fundus, monthly IOP measurements (which were always 20/20 mm Hg), FAG as needed and gonioscopy at three months interval.

In May 2013, after 10 months from the first injection, there was a new hemorrhage at the optic disc in OD. A second injection with Avastin was performed, followed by the remission of the hemorrhage. The vision remained 20/20 in OD. The fundus photographs show the sheathing of the retinal vessels at the emergence from the optic disc (Fig.6).

Fig. 6. OD before Avastin

In November 2013 the child developed white cataract in the left eye.

In January 2014, after two injections of Avastin in OD, the child was accidentally found with high blood pressure. At that time we couldn’t find any evidence of a prior blood pressure measurement in his history. He was tested for the renal causes of secondary hypertension, but all the tests (blood tests, abdominal ultrasound, abdominal angio CT) were normal. The final diagnosis was essential hypertension stage II, with left ventricle hypertrophy. He received treatment with amlodipine (Norvasc) 2.5 mg/day.

In March 2014 he presented with pain in the OS and high intraocular pressure (OD 20 mm Hg, OS 90 mmHg) measured with Icare tonometer, and rubeosis iridis. A diagnostic of neovascular glaucoma OS was made. The pressure was lowered with hyperosmotic agents (Manitol i.v.), after which he received one intravitreal injection of Avastin in OS, followed by the normalization of the IOP. The intraocular pressure was stable at a level of 0.6 mmHg for 11 months from that injection, with no other treatment. A second peak of IOP was noticed in February 2015 (OS 68 mm Hg), and he received the second injection in OS. At the present moment (July 2015) the IOP is stable, 0.7 mm Hg (Chart 1).
In February 2015 the child presented a vitreous hemorrhage in the right eye (Fig 7). He received the third Avastin injection in OD, followed by a fluorescein angiography which showed minimal staining of the optic disc and normal perfusion in the periphery in all quadrants (Fig 8).

In February 2015, at the age of 8.5 years, he did a visual field at the right eye (Fig.9), showing a horizontal hemianopsia and some relative scotomas in the superior hemifield.

Chart 1. The normalization of IOP after the first (March 2014) and the second Avastin injection (Feb 2015) in OS

Fig. 7. OD before Avastin

Fig. 8. FAG OD – normal perfusion in all quadrants

Fig. 9. Visual field in the right eye at the age of 8.5 years old.
Discussions

This dramatic case is uncommon for a number of reasons. First, CHR-RPE was believed to be a unilateral disease. In 1984, Schachat et al. revised 60 cases of CHR-RPE [5], stated that there wasn’t any bilaterally in those cases. Since then, there have been only two other reports of bilaterally, one in 1979[6] and other in 1996[7].

Second, the definition of hamartoma that “it is not likely to result in compression of the adjacent tissue” is not applicable here, since the compression within the optic nerve determined ischemic manifestations in both eyes: vitreous hemorrhages in one eye and neovascular glaucoma and cataract in the other eye. To our knowledge, there wasn’t any case presented before with neovascular glaucoma secondary to the CHR-RPE, nor was presented an FAG examination of this disease at such an early age.

Third, the use of Avastin in such lesions was only speculated until now [4], and this surprisingly long effect of the Avastin upon the IOP could be a starting point for further discussions about the pathophysiology of this disease.

While hypertension appears to be one of the most common side effects of VEGF inhibitors[9], in our case the causal relationship between intravitreal Avastin injections and the high blood pressure could not be precisely demonstrated, since we didn’t have any evidence of BP measurements prior to the injections. On the other hand, the high blood pressure could be itself a risk factor for further vitreous hemorrhages, therefore close monitoring the blood pressure is mandatory in our case.

The future of the child’s vision could be questioned also. In 1984, the Macular Society reported on a series of 60 patients affected by CHR-RPE, of whom only three underwent epiretinal membrane peeling [10]. All of these subjects obtained relief from macular distortion, although only one showed improved visual acuity postoperatively, from 20/200 to 20/40. The authors hypothesized that if the membranes were linked tightly to the tumor vitreous, then surgery would fail to recover the lesion [10]. Indeed, peeling of a membrane intrinsic to the dysplastic retina can damage the retinal fiber layer and Muller cells. Gass [11] indicated that the surface glial membrane causing the retinal distortion is often an integral part of the tumor, which can mean that it is difficult or impossible to strip the membrane and that there is little chance of recovering central vision [10]. Stallman [12] described a 10-year-old girl who underwent successful vitrectomy and epiretinal membrane peeling, with histopathological examination of the specimen. The glistening membrane did not show any hallmarks that characterized this membrane as having components intrinsic to the retina, and the ultrastructural composition was analogous to an idiopathic epiretinal membrane. He speculated that the membrane is not interwoven within the dysplastic retina, and that this lesion could be a combined hamartoma of the retina, retinal pigment epithelium, and vitreous. There are no established criteria to determine how intrinsic the membrane is to the retina or to the cortical vitreous. An important role in this regard can be played by SD-OCT. In all cases, SD-OCT demonstrated deep shadowing with a normal adjacent retina and a hyper-reflective line overlying the lesion. This suggests that the membrane is extrinsic to the retina. SD-OCT was useful for defining the exact location of the membrane and its cleavage plane [13].

In our case, the intravitreal injection of Avastin determined a decrease of vessels permeability for fluorescein, evidenced by FAG, and therefore lowered the risk of further vitreal hemorrhages. At the same time it decreased significantly and for a relative long period of time the intraocular pressure in the neovascular glaucoma, temporizing the use of a more invasive surgical method.

The high blood pressure evidenced after the Avastin injections could not be related directly with the use of the anti-VEGF agents, because we couldn’t find any evidence of a prior blood pressure measurement in the child’s history, but it can generate some concerns about the safety of the use of anti-VEGF agents in children.

Conclusions

-Bevacizumab therapy could be considered as a novel therapeutic approach for treating complications of combined hamartoma of the
retina and retinal pigment epithelium, temporizing other more invasive procedures, like vitrectomy with or without peeling of the epiretinal membrane, or surgical alternatives for neovascular glaucoma.

-A long term survey should be done in order to establish the safety of the administration of anti-VEGF agents in children.

References