ADVANCED COATS’ DISEASE – CASE PRESENTATION

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ADVANCED COATS’ DISEASE – CASE PRESENTATION (Abstract): We present the histopathological features of an enucleated eye from a 4-years old boy admitted in Ophthalmology Department with leukocoria, nistagmus, and decreased visual acuity for six months. Clinical symptoms and signs, together with computertomographic features couldn’t make a clear cut up between a retinoblastoma and an advanced Coats’ disease. The microscopic examination revealed that retina was totally detached, folded, and pushed forward by massive hemorrhagic subretinal exudates. The exudate was composed of plasmoid material admixed with lipid-laden macrophages. Normal retinal architecture is almost completely destroyed especially on outer layers which presented a number of prominent intra-retinal rosettes comprising of photoreceptor type of cells. There was a striking diffuse proliferation of glial cells especially in the layer of optic nerve fibers. The pigment epithelium showed focal proliferative changes. Light microscopy showed the presence of many dilated and tortuous vessels with saccular or fusiform aneurysms, but also numerous newly formed capillary vessels. An intact endothelial lining was observed in some vessels, but others were partially devoid of endothelium and pericytes. They were either empty or contained plasmoid material inside their lumina. The more dilated aneurysmal and telangiectatic vessels showed an irregular wall invariably infiltrated with plasmoid material. Around these vessels there was a serofibrinous exudates which infiltrated into the surrounding tissue, too. The histopathological diagnosis was considered to be an advanced Coats’ disease. As histopathological features of an advanced Coats’ disease is not so often seen in medical literature since currently there are conservative ways to treat the disease, we considered that histopathological presentation of this entity will bring it into attention to ophthalmologists, radiologists and pathologists as the disease must to be differentiate from a retinoblastoma which was the clinical referral diagnostic in our case. Key words: COATS’ DISEASE, HISTOPATHOLOGICAL REPORT, LEUKOCORIA, RETINOBLASTOMA, TOXOCARIASIS

INTRODUCTION

In 1908, the Scottish ophthalmologist George Coats published his first report about forms of unilateral retinal diseases with massive intra- and subretinal exudation associated with numerous vascular retinal telangiectasias and occurrence in young males (1). Based on the clinical and histopathological features of six cases (aged between 7 years old and 37 years old), he defined three classes of retinal disease presenting with massive exudation: group I characterized by a massive exudative retinopa-
thy but without gross vascular disease; group II with gross angiomatous anomaly of retinal vessels and hemorrhage; and group III with large arterio-venous anastomoses but this group corresponds to Von Hippel disease as he described four years later (1). Four years later, Coats made a description of its clinical and pathological characteristics as follows: 1. Occurrence in infantile or juvenile male patients; 2. Unilaterality; 3. Absence of systemic diseases; 4. Exudates below the retinal vessels; 5. Retinal haemorrhages; 6. Slow progression to retinal detachment, cataract, atrophy, or glaucoma (2). As histological characteristics Coats enumerated: 1. Retinal haemorrhages penetrating into the subretinal space; 2. Subretinal fibrous tissue; 3. Cystic retinal degeneration; 4. Vascular anomalies, i.e. dilatation, hyaline thickening, endothelial proliferation, and thrombosis; 5. Proliferation of pigment epithelium; 6. Subretinal accumulation of foam cells (2).

In 1915, Leber published his own observations about multiple miliary aneurysms that characterized one form of retinal degeneration (3). These retinal entities receive the name of their authors and came to be known as Coats’ disease and Leber miliary aneurysms, respectively. In 1955, Reese observed that there were similarities between these two entities and considered them to be a spectrum of the same disease as he considered that Leber military aneurysms led to progressive exudation and retinal detachment. Since then Coats’ disease became a well-known ophthalmic entity (4).

In 1965, Morales distinguished a classification of the clinical progression into five major stages: I – focal yellow exudates; II – massive exudates; III – partial exudative retinal detachment; IV – total retinal detachment; V – apparition of secondary complications (iridocyclitis, cataracts, glaucoma) (5). The diagnosis “Coats’ disease” should be restricted to cases of exudative retinitis associated with vascular retinal anomalies in children. Some authors appreciate that exudative retinitis in adults should only be labelled with Coats’ name when the disorder has originated in childhood (6). The advanced form of Coats’ disease is defined by Haik as “an ocular condition characterized by total exudative retinal detachment secondary to leakage from congenital retinal telangiectasia“ (4). The disease may be extremely difficult to differentiate from retinoblastoma, inasmuch as both conditions may present in children with the triad of total retinal detachment, subretinal mass or exudation, and abnormal retinal vessels.

**CASE REPORT**

**Clinical presentation**

A 4 years – old boy presented with leukocoria, nystagmus, and decreased visual acuity which were noted at his left eye by his mother six months previously. Patient admitted into the hospital with the suspicion of retinoblastoma. Ophthalmologic examination disclosed leukocoria of the affected eye, transparent and smooth cornea, clear anterior chamber, two posterior synechias in the inferior sector of iris. Lens was in its position. Pigment mobilizations were seen on the anterior crystalloid. Left eye presented intermittent, variable esophoria, normal ocular motility in all directions. Digital normoton ocular pressure was measured in both eyes. Echocardiography showed tricuspid insufficiency of first/second degree and pulmonary insufficiency of first/second degree. Heart exam revealed rhythmic heart beats with cardiac frequency of 120 beats/minute. Blood pressure was 80/60 mm Hg.

The enucleation of the left eyeball was performed, with a good post-surgery health condition.

**Computer tomography**

At first glance, computer tomography showed intense contrast medium uptake into the posterior chamber, also visible in the sclera simulating an expansive process. The contrast medium uptake extended to the first part of the optic nerve without determining a significant size increase. The expansive process covered almost the entire vitreous body, determining a slight widening and flattening of the eyeball, but without penetrating its adjacent muscles. No pathological contrast medium uptake was noticed at the level of the optic chiasm or the pineal gland. Possible diagnosis, related to the age of the patient and to the computer tomographic features, was considered to be retinoblastoma in the left eyeball with clear invasion of the sclera and moderated contrast medium uptake in the first part of the optic nerve. However, a possible Coats’ disease couldn’t be excluded [figure nr. 1; a), b].
Histopathological report

A diagnosis of retinoblastoma was suspected and enucleation of the affected eye was done. The enucleated eye was submitted to histopathological examination. The eye was sectioned through the optic nerve and the two half fragments were fixed in 10% neutral buffered formaldehyde for 24 hours at 37°C, embedded in paraffin, and 4-μm sections were stained using hematoxylin-eosin, van Gieson and Gordon-Sweet methods.

The microscopic examination revealed that retina was totally detached, folded, and pushed forward by massive hemorrhagic subretinal exudates. There was marked disorganization and degeneration of all retinal layers [figures nr. 2; a), b), c)]. Although the structural disorganization involved the entire area of the retinal lesions studied microscopically, it was most marked in the anterior layers (i.e. nerve fibres, ganglion cell, and inner nuclear layers). Large amount of exudates existed in the subretinal space. The exudate was composed of plasmoid material admixed with lipid-laden macrophages [figure nr. 2; c) and d]).

There was a striking diffuse proliferation of glial cells especially in the layer of optic nerve fibers [figure nr. 3; a), b)]. The outer nuclear layer showed degenerative changes. A number of prominent intra-retinal rosettes comprising of photoreceptor type of cells were seen. Some of them enclosed a central lumen lined by an external limiting membrane [figure nr. 3; c), d)].

The pigment epithelium layer showed local areas of proliferation and formed subretinal nodules attached to the external surface of the neural retina or in some places were separated from the nervous components of the retina [figure nr. 4; a]). Some other areas presented subretinal nodular conjunctivo-vascular neof ormation made up of fibroblast and newly capillary vessels admixed with inflammatory cells [figure nr. 4; b)]. All sections showed severe pathological changes in the retinal vessels, many of which being dilated, thin-walled, and surrounded by proliferating glial cells. Light microscopy showed the presence of dilated and tortuous vessels with saccular or fusiform aneurysms, but also numerous newly formed capillary vessels [figure nr. 5; a), b)]. An intact endothelial lining was observed in some vessels, but others were partially devoid of endothelium and pericytes. They were either empty or contained plasmoid material inside their lumina. The more dilated aneurysmal and telangiectatic vessels showed an irregular wall invariably infiltrated with plasmoid material. Around these vessels there was a serofibrinous exudates which infiltrated into the surrounding tissue, too [figure nr. 5; c), d)]. In some instances, the existence of a blood vessel or aneurysm was recognized only by the presence of a space filled with plasma, red cells, and brown pigment-laden macrophages, and incompletely surrounded by a basement membrane of the adjacent glial cells. An infiltration of the retina with perivascularly macrophages filled with clumps of melanin pigment was seen particu-
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Fig. 2. a). Detached and thicken retina made folds around a fibrous branched stalk (H&E, x40); b). Using special stain we can determine the richness of reticulin fibers in the fibrous stalk that gathered together retinal folds. Reticulin fibers, being so numerous around the capillary walls, showed newly capillary formation in inner and middles layers of retina. (Gordon Sweet stain, x 40); c). Normal retinal architecture is almost completely destroyed especially on outer layers which presented dysplastic changes. The pigment epithelium showed focal proliferative changes and in places was separated from the nervous components of the retina. Beneath the detached retina there was a proteinaceous eosinophilic material with lipid-laden macrophages (H&E, x40); d). Subretinal exudates made up of proteinaceous material (plasmacitoid), red cells, and numerous lipid-laden macrophages (H&E, x200).

larly in the inner layers [figure nr. 4; d]). On the other hand, there were some mononuclear inflammatory cells around the abnormal vessels and within their walls. The disorganized retina was in close relationship with fibrous organized vitreous which presented diffuse infiltration with lymphocytes, but also a granular inflammation made up of a centrally placed area of coagulative necrosis surrounded by numerous mononuclear inflammatory cells. The anterior segment showed hypertrophied ciliary body and an irian chronic inflammatory infiltrate. There was visible a focally inflammatory mononuclear reaction at scleral level, too.

DISCUSSIONS

Coats’ disease is a sporadic nonhereditary condition that is not associated with identifiable systemic abnormalities and it is characterized by idiopathic retinal telangiectasia, retinal exudation, and retinal detachment (6, 7). It has a predilection for gender, with 76% of patients being males. Coats’ disease can occur at any age, but majority of patients are diagnosed in the first or second decades of life (8, 9). Some studies reported few older adults who had clinical, radiological, and histopathological findings identical to the children, and had no other underlying condition to predispose to exudative retinopathy (8, 10). Smithen et al. examined 13 patients being 35 year old who manifested findings typical of Coats’ disease, including the unilateral nature of the disease, male predominance, vascular telangiectasis, lipid exudation, macular edema, and areas of capillary nonperfusion with adjacent webs of
Fig. 3. a). Diffuse proliferation of glial cell in the layer of optic nerve fibers (H&E, x40); b). Higher magnification of the same region showed the thickened layer of optic fibers due to massive gliosis (H&E, x200); c). Outer nuclear layer presented marked disorganisation of its architecture (H&E, x100); d). Outer nuclear layer cells formed numerous rosettes-like structures around a lumina eventually delimited by a thin membrane (H&E, x200).

Fig. 4. a). In the area of retinal pigmented epithelium there was a nodular proliferation of fibroblasts admixed with scattered pigmented cell (H&E, x40); b). Subretinal nodular conjunctivo-vascular neof ormation made up of fibroblast and newly capillary vessels admixed with inflammatory cells (H&E, x40).

filigreelike capillaries. But they determined a number of important differences in disease manifestation in adults, including limited area of involvement, slower apparent progression of disease, and hemorrhage near larger vascular dilatations (11). Anyway, all the authors agreed that younger patients had more severe disease than older patients (12). Coats’ disease can present in very different ways. Though majority of investigators reported the disease to have
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unilateral predilection, bilateral disease is possible, even after several years (13). Ophthalmic pathologists rarely receive an enucleated eye because of Coats’ disease as the ophthalmologists usually diagnose the disease in its earlier stages, enabling them to save the globe and even useful vision in most of the cases (14). As a consequence, histopathological reports are not seen so often in the medical literature since currently there are conservative ways to treat the disease. So, an enucleation specimen that permits a histopathological study is rare.

Selected histopathologic sections obtained from our case reveal extensive structural eyeball distortion secondary to massive subretinal exudation. Retinal blood vessels presented marked thinning of their walls with irregular, telangiectatic distentions. Many of the distended retinal blood vessels were surrounded by proliferating glial cells, phagocytic cells, and eosinophils. Some of the dilated vessels, on the other hand, have thin walls devoid of endothelial cells and serofibrinous exudates which infiltrated into the surrounding tissue. The end result of the continuous leakage from abnormal blood vessels was the subretinal collection of exudates and hemorrhage, which lead to total disorganization of the retinal normal architecture. The retina is protected from any plasmatic exudation that can disrupt its architecture. It has two barrier systems, one located in the inner retina, apparently at the level of the vascular endothelium and the other in the outer retina at the level of the pigment epithelium. Breeching of either of these two barriers results in subretinal and/or retinal exudation. There is no doubt that Coats’ disease is an

Fig. 5. a). Retinal telangiectasia made up of numerous capillary vessels some of them being dilated and filled with a proteinaceous eosinophilic material (H&E, x100); b). Same image sowing retinal capillary telangiectasia made up of numerous capillary separated by retinal tissue (Gordon-Sweet stain, x100); c). Higher magnification showed a capillary retinal vessel with a tortuous contour and with discontinuity of its wall. Note the absence of endothelial cells in some areas and leakage of an eosinophilic material (plasmatic liquid) around the vessel. The vessel was surrounded by retinal gliosis (H&E, x200); d). Another capillary retinal vessel with the same morphological characteristics but also with numerous melanin - pigment- laden macrophages around it (H&E, x200).
example of such a barrier break-down, but the exact cause of this anomaly is still obscure (4, 6, 15). It is the widely accepted view that the sequence of structural changes in Coats’ disease is primarily triggered by a breakdown in the blood-retina barrier at the endothelial cell level, causing leakage of fluid into the vessel wall and perivascularly to weaken the vessel structure. This, in turn, leads to further distortion of the vascular structures with aneurismal dilatations and telangiectasis. The structural abnormalities cause further impairment of the endothelial barrier, and plasma leaks into the surrounding tissues to produce intraretinal and subretinal exudates and hemorrhages (4, 16).

The continuous leakage from abnormal blood vessels leads to extensive degeneration and detachment of the retina which may present as a nodular structure later in the disease, when the underlying lipid-rich exudate organizes and mixes with fibrous tissue (4). Chang et al. described some associated histologic findings: ruberosis iridis, cataract, vitreous and retinal neovascularization, and some fibrous macular nodules resulting from fibrous metaplasia of the retinal pigment epithelium (9). Coats speculated that the disorder represent “un unknown form of vascular disease, probably founded on a congenital vulnerability of the vessel wall” (1). Whether the abnormal vascular permeability is primarily due to a deficiency in structure or function, that is a failure to provide the normal blood-retinal barrier, is not at present clear (4, 15, 16).

An ultrastructural study of an early case of Coats’ disease suggested that the pathological changes may initially derive not from telangiectasis, but from a functional or structural breakdown of the blood-retinal barrier (vascular endothelium), giving rise to plasmatic vasculosis and mural disorganization, and that these result in aneurysmal dilatations and telangiectasis. Leakage of blood components then increases to form intraretinal and subretinal exudates, haemorrhages, lipid and fibrin deposits, with phagocytic proliferation, disorganization and destruction of the retinal elements, and eventually glial and fibrous tissue organization (15). Coats’ disease is initially painless and develops slowly and insidiously. Often, it is not discovered until well advanced (4) when the diagnosis is extremely difficult on clinical and radiological features and only histopathological findings can establish an accurate diagnosis. In a series of 62 histologically confirmed cases, Coats’ disease was the primary clinical diagno-

Coats’ disease may be difficult, some authors indicate eye enucleation in uncertain cases due
to the reduced visual prognosis and the risk of secondary complications in advanced Coats’ disease (22). In medical literature, Coats’ disease is responsible for approximately 7%-16% of the enucleations where the clinical diagnosis was retinoblastoma (23, 24). Thus, it is crucial for the pathologist to be familiar with the histopathological features of Coats’ disease in order to differentiate it from retinoblastoma. The prognosis differs considerably from one disease to the other and consequently, all the investigators suggest enucleation of such eyes if diagnostic uncertainty exists, since failure to treat retinoblastoma is a more serious error than enucleation of an eye with minimal function (22, 25). The patient with Coats’ disease is considered cured once the ocular manifestations are controlled and systemic treatment is unnecessary, but a misdiagnosis of retinoblastoma can submit a child to the potential risks and side effects of chemotherapy. On the other hand, retinoblastoma is a malignancy with a high mortality rate when not properly diagnosed and treated (14).

Persistent hyperplastic primary vitreous (PHPV), first described by Reese in 1955, presents more often with leukocoria (26). PHPV is a congenital malformation caused by the arrest of normal regression of the embryonic vascular connective tissue (hyaloid artery, vasa hyaloidea propria, tunica vasculosa lentis), regression that normally occurs after 4 months gestation (26, 27). It results from abnormal hypertrophy of fetal fibrovascular primitive stroma (hyaloid system) of the eye (28). Almost always unilateral, this condition often presents with moderate microphthalmia, retrolental white plaque of fibrovascular connective tissue, visible through the pupil, centrally dragged ciliary processes, an anteriorly shifted and (or) swollen lens, and varying degrees of lenticular opacification (26, 29).

Ocular toxocariasis is suspected by a history of contact with puppies and is confirmed by serologic testing. Toxocariasis is an infection by the nematode larvae of Toxocara canis. Ocular toxocariasis affects children at an average age of 7.5 years. Intermediate uveitis from Toxocara is almost always unilateral. The main ocular findings include peripheral retinoc choroiditis, posterior retinoc choroiditis, and vitreitis (29). Many investigators highlight the fact that even the most experienced observer may not be able to differentiate these entities on ophthalmoscopic findings alone (4) and so was the situation in our case. Our report illustrates the histopathological features of an advanced Coats’ disease in a four-year-old boy. When seeing the young boy, the ophthalmologist couldn’t exclude the existence of a retinoblastoma. Because the clinical diagnosis was uncertain, CT imaging was required, but the distinction between advanced Coats’ disease and retinoblastoma was difficult. Unfortunately, exceptions to the typical CT and MR features also exist in both Coats’ disease and retinoblastoma, still resulting in unnecessary enucleation for equivocal or conflicting findings (25, 30).

CONCLUSIONS

The diagnosis of Coats’ disease and the exclusion of unilateral retinoblastoma in this particular case were made on histopathological evaluation. All investigators agree that although there are more conservative treatments to Coats’ disease, enucleation is still indicated in cases with extensive exudative retinal detachment. The patient described in this article presented as an advanced Coat’s disease as his mother didn’t come as quickly as possible to the hospital when she observed leukocoria in her child’s eye. As severe morphological abnormalities appeared, treatments modalities other than enucleation couldn’t be effective. This case punctuates the importance of earlier presentation in case of leukocoria together with the need to establish the correct differential diagnosis in advanced Coats’ disease. When Coats’ disease is discovered in the advanced stage, clinical symptoms and imaging appearance can guide the diagnosis towards a form of retinoblastoma without calcification and only the pathological examination can establish the correct diagnosis.

REFERENCES