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RETINAL HEMANGIOBLASTOMA ASSOCIATED WITH VON HIPPEL-LINDAU SYNDROME.

Francesc Tresserra (1), Sandra Planella (2),María Ángeles Martínez-Lanao (1),Rafael Ollero (2), Melissa Fernández-Acevedo (1).

Servicio de Anatomía Patológica. Hospital Universitario Dexeus (1). Oculoplastics Department, Centro de Oftalmología Barraquer, Barcelona, Spain (2).
Servicio de Anatomía Patológica. Hospital Universitario Dexeus (1). Centro de Oftalmología Barraquer (2). Barcelona. Spain.

Correspondence:
Francesc Tresserra
Servicio de Anatomía Patológica
Hospital Universitario Dexeus
Sabino Arana 19
08022 Bacelona, Spain.
francesc.tresserra@quironsalud.es

Introduction:

Retinal hemangioblastoma (RHB) is a rare tumor that can occur spontaneously or in association with von Hippel-Lindau syndrome (VHLS) (1–9).
We present a case of a retinal lesion diagnosed as RHB in an enucleated eye due to blindness and pain in a patient with VHLS.

Clinical case:

We present the case of a 26-year-old male with VHLS and a maternal history of the same disease with a 6-year history of decreased visual acuity (VA) (20/200 on the Snellen Eye Chart) in his left eye. The ocular fundus exam revealed a vascular tumor causing retinal detachment (RD). Ultrasound showed vitreous haze, inferior RD and an intraocular mass (basal diameter: 8,23mm; height: 3,21mm) with high internal reflectivity located in the temporal quadrant. Retinal surgery including intraocular silicone oil and two sessions of laser photocoagulation were performed.
He did not have any other clinical manifestations of VHLS.
In the last ophthalmic check-up the patient complained of total vision loss and severe persistent pain in his left eye. He also presented with exophthalmos and a large nodular vascular epibulbar lesion located in the upper eyelid with secondary mechanical ptosis. The sclera was thin in many areas. Magnetic resonance imaging showed a polylobulated tumor affecting entirely the left eyeball, which was very vascularized. Extraocular involvement was ruled out. Ultrasound revealed multiple intraocular hyperechoic masses.
An evisceration surgery with a 20mm orbital implant and a covering donor sclera was performed. An ovoid specimen of dark brown color and enlarged consistency measuring 3 cm was obtained. In addition, a whitish lenticule measuring 1 cm was received.
Microscopically the eyeball showed a distorted architecture with extensive calcification and hemorrhagic necrosis in the center. At the periphery there was a lobular proliferation of cells with round, hyperchromatic nuclei and slightly eosinophilic cytoplasm. In addition, interspersed clusters of cells with foamy or vacuolated cytoplasm were found in the tumor. There was an abundant vascular network with vessels of very varied caliber. Immunohistochemically the cells were positive for: CD31, CD34, neuronal specific enolase (NSE), alpha-inhibin and vimentin. Focal positivity for: glial fibrillary acidic protein (GFAP), S-100 protein and PAX-8. And negativity for: Cytokeratins (AE1/AE3, CAM 5.2, CK5/6), Factor XIIIa, Actin, epithelial membrane antigen (EMA), CD45, chromogranin, and synaptophysin. The proliferative index measured with Ki67 was 20% of cells.

The differential diagnosis was established between epithelial metastasis of neuroendocrine pattern and lymphoproliferative process.
Based on the morphologic features and the immunohistochemical panel, the lesion was diagnosed as a retinal hemangioblastoma. In addition, there were changes secondary to silicone oil treatment of the retinal detachment.
The postsurgical cosmetic result through the implantation of an ocular prosthesis was satisfactory and the patient remained asymptomatic after six months of treatment.

Discussion:
Hemangioblastoma is a benign, highly vascularized tumor containing neoplastic stromal cells with clear or vacuolatedcytoplasm and immunohischemical expression of alpha-inhibin(1). Although frequently occurring in the cerebellum, hemangioblastoma can also be found in the spinal cord, brain, retina, peripheral nerves and in locations outside the CNS such as bone, soft tissue, liver, lung, pancreas, kidney, intestine and skin(1,6). RHBdisplays similar characteristics to that of the cerebellum(2).
Hemangioblastoma can occur sporadically or in association with VHLS(1–9). This syndrome is a phakomatosis that can be sporadic or by autosomal dominant inherited and is associated with multiple angiomas in retina, CNS and visceral organs. In addition, patients present renal or pancreatic cysts, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, paragangliomas, and other visceral tumors(2,6). The presence of RHB in patients with VHLS has been described in 25-60% of cases depending on the series(6).
Clinically, RHB is the form of presentation in 77% of patients with VHLS and in many occasions it is the only manifestation of the disease(4,6). It appears as a small but rapidly growing lesion leading to multiple ocular complications such as exudative retinal detachment, lipid exudation and neovascular glaucoma(3), sometimes can be highly aggressive, with extraocular extension and requiring enucleation(6). It usually occurs in the peripheral region of the retina, especially in the superotemporal or inferotemporal quadrants. Occasionally it can affect the juxtapapillary area(3,5).
The age of presentation is usually around 25 years, more frequently between 10 and 40 years, and it is extremely rare after 60 years(6), although cases have also been described in pediatric age(5,10).
The age of patients with RHB and VHLS is younger than that of patients with sporadic RHB and more frequently (80% of cases) they are asymptomatic. In addition, 76% of these patients have a family history of VHLS(4). In patients with RHB and VHLS, cerebellar hemangioblastoma has also been described in 5% of cases(3).
Microscopically it is characterized by two main components: stromal neoplastic cells that are characteristically large and with clear or vacuolated cytoplasm, and another component of abundant vascular cells (endothelial and pericytes) that form numerous vascular channels. The amount of both components is variable depending on the tumor(1,2). Sometimes the stromal component has a solid pattern forming epithelioid aggregates with extramedullary hematopoiesis(11). Mitosis figures and necrosis are rare(8). In our case the presence of necrosis and calcification were attributed to the long evolution of the lesion. Tumor cells express immunohistochemically: Neuronal specific enolase (NSE), S-100 protein and characteristically alpha-inhibin(1,2,8,12). On rare occasions positivity for PAX-8 has been described in cases of HB, one of them in orbital location and another in the kidney(13).
The differential diagnosis must be established basically with a metastasis of clear cell renal carcinoma that usually expresses PAX-8, CD10, EMA, CAM5.2 cytokeratin and not alpha-inhibin(1,12,13). In our case the homogeneous pattern of cellularity raised the differential diagnosis with a neuroendocrine tumor or lymphoma.In pediatric patients the clinical differential diagnosis with retinoblastoma can be considered(5).
Regarding the origin of the tumor, it has been suggested that the stromal cells shown may have their origin in reticuloendothelial, astrocytic, neural, pericytic or endothelial cells(2), although it seems more likely that they have a glial origin(7), although the expression of glial fibrillary acidic protein in stromal cells has been attributed to protein phagocytosis of retinal glial debris by these cells(2).

Photocoagulation, cryotherapy, radiotherapy, photodynamic therapy, transpapillary thermotherapy can be used as treatment, reserving enucleation for extreme cases(6,8,9). The success of the treatment will depend on factors such as: tumor size, location, presence of exudates, retinal detachment, fibrosis, or hemorrhage(9).
The visual prognosis of RHB is significantly better when diagnosed in the asymptomatic phase. Patients with sporadic hemangioblastoma do not show any increased risk for other tumors(4). Advanced lesions with aggressive behavior significantly compromise visual capacity(6). The prognosis with respect to survival will be conditioned by the prognosis of tumors associated with VHLS.

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