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UVEAL MELANOMA: A REVIEW

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Abstract: Goal: To understand the relevant aspects regarding Uveal Melanoma. Methods: This is a literature review using the terms: "uveal melanoma", "choroidal melanoma", "ciliary body melanoma" and "iris melanoma" in the PubMed and Medline databases, with articles selected from among 2017 and 2023 that best relate to the objectives of this work, which is to review the most relevant aspects of this important disease. **Literature Review:** Melanoma is a serious cancer originating in melanin-producing cells, predominantly found in the skin and mucous membranes, but occasionally affecting the eyes. Representing around 5% of ocular cases, uveal melanoma, especially in the choroid, is the most common in adults. Risk factors include fair skin, advanced age and genetic predisposition. Symptoms vary depending on the size and location of the tumor, making diagnosis challenging. Treatments such as Thermotherapy and Brachytherapy depend on the specific characteristics of the lesion and delays in diagnosis result in a worse prognosis, with the size of the tumor being a critical indicator. Understanding clinical, molecular and genetic aspects is crucial to stratify risks and guide therapies, highlighting the need for personalized approaches to improve outcomes and reduce mortality rates.
Keywords: Uveal Melanoma, Choroidal Melanoma, Iris Melanoma, Ciliary Body Melanoma.

INTRODUCTION

Melanoma is a serious form of cancer that originates in melanin-producing cells. It is most commonly found on skin and mucous membranes, but in about 5% of cases it can also be found in the eyes. In around 80% of cases, primary ocular melanomas arise in internal structures of the eye, notably in the uvea. To a lesser extent, they can be found in the conjunctiva, eyelids and orbits.

Melanoma that affects the ocular structures is similar to skin melanoma in terms of the cell that gives rise to the tumor and immunohistochemical characteristics, but it differs in terms of classification, treatment and prognosis.

Uveal melanoma can originate in several parts, including the iris, the ciliary body and the choroid, which accounts for the majority of cases (around 90%). Although relatively rare, uveal melanoma is the most common primary intraocular malignant tumor in adults. Despite its aggressiveness, recent scientific advances in ophthalmic oncology allow for increasingly earlier diagnoses and better treatment options, which can prevent the occurrence of metastases.

LITERATURE REVIEW

EPIDEMIOLOGY

Uveal melanoma has an incidence of 7.9 cases per million inhabitants, being a relatively common condition in ocular tumor clinics. Iris melanomas represent approximately 3 to 5% of uveal melanomas. Tumors that reach the anterior chamber angle are most commonly associated with metastases as well as glaucoma. At first, when they are still small in size, differentiation from iris nevus can be difficult, which is why this disease can often be underdiagnosed in the early stages.

Choroidal and ciliary body melanomas are the most common malignant intraocular tumors in adults. Most cases occur in Caucasian adults living in high latitude regions. Approximately 80% of cases occur after 45 years of age, with an average age of diagnosis around 60 years.

RISK FACTORS

There are several risk factors described for the development of uveal melanomas, whether environmental or related to the patient. Identifying these factors in predisposed patients is essential to optimize surveillance and allow for early diagnosis and therapy. Among the best-established factors we can mention white skin (especially patients with light eyes and blond hair), difficulty in tanning and propensity for sunburn, advanced age, presence of choroidal nevus/ciliary body (risk of 1:500 per lifetime), ocular and oculodermal congenital melanocytosis (lifetime risk of 1:400), dysplastic nevus syndrome (about 3-fold increase in risk), BAP1-related tumor predisposition syndrome (BAP1-TPDS). Although most uveal melanomas occur sporadically, in approximately 1% of cases there is a prior family history. The relationship between sun exposure and the appearance of uveal melanomas has been frequently studied, presenting contradictory results.

CLINICAL FEATURES

The symptomatological characteristics of uveal melanoma will vary depending on the location of the tumor. In a considerable percentage (above 13%) it is asymptomatic, which is why routine ophthalmological examination must be so valued. Iris melanomas range from brownish lesions to amelanotic tumors with little pigmentation. Most cases affect the lower hemisphere of the iris and rarely involve a diffuse pattern of growth.

When ciliary body melanoma is located, it will often be asymptomatic until it reaches a size sufficient to disrupt the architecture of the anterior chamber. Adequate dilation is essential for observation. There are some changes in biomicroscopy that are important signs in the diagnosis of this tumor, such as: episcleral vascular congestion ("medusa head vessels"), lens displacement, retinal detachment, etc. Ciliary body melanoma can extend into the circumferential aqueous canals, receiving the name ring melanoma.

Choroidal melanoma consists of a subretinal lesion with significant elevation (normally above 2mm), pigmented, and may present symptoms such as photopsies, metamorphopsia and loss of visual field depending on the stage at which it is found. The presence of orange pigmentation at the level of the RPE is frequently found and helps to differentiate it from choroidal nevus. Approximately half of cases cross Bruch's membrane and take on a dome shape, which can cause associated vitreous hemorrhage. Naturally advanced cases can cause retinal detachments, anteriorization of the iridocrystalline diaphragm and neovascular glaucoma.

DIAGNOSIS

This neoplasm presents a diagnostic challenge, given the difficulty of performing invasive procedures for its direct assessment. For this reason, the clinical history accompanied by the evaluation of the lesion with a complete ophthalmological examination is very important, which includes retinal mapping, detailed anterior biomicroscopy and gonioscopy. It is also mandatory to carry out complementary imaging tests, such as retinography, optical coherence tomography (OCT), retinal autofluorescence, angiography and diagnostic ultrasound. Despite the intrinsic difficulty of this condition, with the use of these complementary methods, the diagnosis is obtained in almost all cases.

In addition to its importance in diagnosing the primary tumor, carrying out this workup allows longitudinal monitoring of the patient, helping to exclude differential diagnoses, evaluate the ocular structure as a whole and evaluate the therapeutic

response and recurrence of the lesion. When evaluating a choroidal nevus, for example, documenting and monitoring the lesion with the aforementioned exams makes it possible to assess its eventual growth or emergence of malignant characteristics.

Optical coherence tomography (OCT) came to assist in the diagnosis and monitoring of uveal melanoma, particularly the most recent technologies that have high definition such as Swept Source. The images demonstrate lesions with dome formation, disruption of the photoreceptor layer and compression of the choriocapillaris, in addition to the classic intraretinal fluid close to the lesion.

Diagnostic ultrasound consists of an imaging test that is of great assistance in the diagnosis and monitoring of choroidal melanomas. Through ocular ultrasound, it is possible to obtain the location, size, morphology and extent of intraocular tumors. This diagnostic modality also serves as a guide for carrying out therapeutic interventions and monitoring tumor growth.

Some ultrasound characteristics are typically found in choroidal melanomas and help to strengthen the diagnostic hypothesis in inconclusive cases. In mode A ultrasound, medium to low internal reflectivity is observed with a homogeneous structure, in addition to an initial peak followed by a decreasing attenuation called the Kappa angle. On B-mode ultrasound, we can observe a lesion with internal vascularization, choroidal excavation, which may take on a dome or mushroom shape, with acoustic void and posterior acoustic shadow.

When it comes to evaluating melanoma located in the iris and ciliary body, the most relevant exam is ultrabiomicroscopy (UBM), which consists of a high-resolution ultrasound with detailed images of the anterior segment. An alternative option is the use of anterior segment optical coherence tomography (OCT-A), which has greater resolution when compared to UBM, in addition to greater comfort for the patient examined. However, UBM persists as a superior imaging method due to its ability to penetrate tissue as well as pigmented lesions.

Another imaging test that can be used in propaedeutics is fundus autofluorescence. It also consists of a non-invasive method that evaluates the distribution of lipofuscin, notably in the RPE. In melanoma, there is an accumulation of subretinal fluid and lipofuscin, with associated hyper autofluorescence. Fluorescein angiography, a contrast exam that evaluates choroidal retinal vascularization, is especially important in choroidal melanoma because it demonstrates the phenomenon of double circulation, that is, the observation of retinal vessels in parallel with the vessels of the tumor lesion.

NEVUS X MELANOMA

One of the major challenges in evaluating retinal pigmented lesions is differentiating the nevus from melanoma. This differentiation is not simple and requires enormous care on the part of ophthalmologists. One of the most important factors in this differentiation is the thickness of the tumor. Approximately 20% of melanocytic tumors more than 3.0 mm thick are melanomas, while less than 1% of tumors less than 1.0 mm are malignant. The presence of intraretinal fluid is more commonly associated with melanomas than nevi, and is an important factor to consider. Lesions with a diameter greater than 6.0 mm have an increased risk of malignancy when compared to smaller lesions. The presence of symptoms such as low vision, loss of visual field, metamorphopsia and photopsia is also more frequently found in malignant tumors, as is the presence of lipofuchsin (orange pigment). Choroidal nevi often present with drusen, which are lesions more commonly

seen in chronic retinal changes, with slow growth. Likewise, nevi usually have halos around them, unlike melanomas. Imaging exams help a lot by revealing changes that are more typical of malignant tumors, helping to differentiate them, such as the presence of ultrasound acoustic void, double retinal circulation, kappa angle, among others.

THERAPEUTIC APPROACH

Given the variety of shapes, sizes and possible locations for uveal melanoma, the choice of treatment must be individualized, taking into consideration, the patient's visual function, age, performance status and other personal characteristics.

In general, it is accepted that lesions with a thickness of less than 2.0 mm, asymptomatic, distant from the optic nerve and without subretinal fluid or nearby orange pigments can be observed longitudinally with documented clinical and imaging examination. In case of growth, specific treatment is indicated.

One modality of approach for small lesions is Transpupillary Thermotherapy (TTT), which uses a low-energy, long-lasting infrared diode laser, which can be considered for tumors smaller than 3.0 mm thick, without subretinal fluid and far from the optic disc and of the macula. Brachytherapy consists of the use of radioisotopes such as Iodine-125 and Ruthenium-106 through a plate adjacent to the sclera. This therapy allows the delivery of high doses to the base of the tumor, reaching up to 1000gy and, as a side effect, it can induce radiation retinopathy, neuropathy and crystal opacity. Brachytherapy is indicated for small to medium-sized tumors, up to 10mm thick and 16mm in basal diameter. One of the biggest technical difficulties is the appropriate positioning of the scleral plate to the topography of the tumor that is to be irradiated. Unfortunately, like transpupillary thermotherapy, it is a treatment with little availability in our country.

External beam radiotherapy is a modality often seen in the past. Its isolated use is not effective in the treatment of uveal melanoma. Carrying out external radiotherapy prior to enucleation, in addition to not increasing patient survival compared to isolated enucleation, makes the tissues friable and can make the procedure difficult to perform intraoperatively.

Enucleation is the most feasible treatment for the majority of patients, either due to late diagnosis with lesions that do not allow other forms of treatment, or due to the difficulty of obtaining brachytherapy in a large part of the country. It is indicated for the treatment of large lesions (more than 10mm thick and 16mm in basal diameter), as well as tumors that invade the optic nerve, anterior segment, with secondary glaucoma or extrascleral extension. The presence of a small extrascleral extension does not indicate the need for exenteration, which will only be performed in cases of massive orbital invasion.

In the management of metastatic diseases, chemotherapy comes into play, both systemic and hepatic intra-arterial, and may be accompanied by surgical resection of metastases in some cases. Other options at this stage are immunotherapy and radioembolization. It is important to highlight that a case of uveal melanoma must be monitored by a multidisciplinary team that is capable of offering available solutions in light of modern knowledge about ocular oncology, associated with psychological support that places the patient at the center of care.

PROGNOSIS

Many advances in diagnosis and treatment have occurred in recent decades, but despite this, the mortality rate remains unchanged. A significant number of patients are diagnosed late and develop metastases, the treatment of which cannot yet be achieved. Survival time after diagnosis of metastatic disease is generally short, with mortality rates above 80% after one year of illness. Dividing patients based on prognosis is crucial for determining the approach to treatment, including specific therapies and follow-up. Furthermore, identifying patients at higher risk of metastasis can guide the application of more aggressive treatments.

The prognosis is influenced by clinical characteristics, including the patient's age and sex, as well as tumor characteristics, such as size, location, and extent. The size of the primary tumor is one of the main predictors of metastasis and mortality, with studies showing an increase in metastasis rates with increasing tumor dimensions. In addition to large tumors, other factors with a worse prognosis are extrascleral extension, extension to the ciliary body, oculodermal melanocytosis, rapidly growing tumors, recurrence after conservative treatment, presence of epithelioid cells and a high mitotic index. Ciliary body melanoma is associated with a worse prognosis, possibly due to late detection and intense vascularization, facilitating hematogenous spread. Iris melanoma, on the other hand, has a more favorable prognosis, whether due to early detection or intrinsic cellular characteristics.

In addition to clinical factors, histological, cytogenetic and molecular features also play an important role in prognosis. The deletion of chromosome 3 is particularly relevant, associated with more aggressive melanomas and high rates of metastasis. Gene expression profile analysis allows classifying uveal melanomas into molecular classes with distinct prognoses, providing valuable information for risk stratification and therapeutic decision-making.

In summary, understanding and evaluating multiple clinical and molecular aspects is essential to determine the prognosis of uveal melanoma. Developing more effective therapies, early identification of the disease, and applying individualized approaches based on specific patient and tumor characteristics are essential to improving clinical outcomes and reducing the mortality rate.

FINAL CONSIDERATIONS

Uveal melanoma is a serious and complex disease that is difficult to diagnose and requires a thorough investigation. The different anatomical sites that can be affected and the degree of cellular variability of the tumors make the clinical presentation unpredictable, as does the prognosis, which in most cases is dismal.

When faced with a melanocytic lesion during the physical examination, the ophthalmologist must carry out a serial clinical and imaging investigation to document any changes in the characteristics of the lesion. Risk factors must be investigated and, if the diagnosis of uveal melanoma is confirmed, therapy must be proposed and carried out as quickly as possible.

Therefore, diagnosing and treating uveal melanoma early is essential to improve the prognosis and overall survival of the affected patient. Furthermore, part of the new strategies for combating the tumor is a more in-depth understanding of the genetic changes and the signaling pathways involved. With this, it will possibly be possible to develop targeted therapies with the aim of preventing the development of metastases and thus achieving a cure for the patient.

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