

The management of uveal melanoma, a case report

Introduction

Le mélanome de l'uvée est la tumeur maligne intraoculaire la plus fréquente de l'adulte. Ces dernières années, des nouveaux concepts thérapeutiques sont apparus concernant le mélanome de la choroïde, du corps ciliaire et de l'iris. Des études récentes montrent la tendance à favoriser une approche conservatrice de cette pathologie au lieu de l'attitude radicale (qui est l'énucleation). Nous rapportons un cas typique de mélanome de l'iris et du corps ciliaire avec une extériorisation extra sclérale de l'œil droit comme exemple pour illustrer les différents types de traitements conservatifs pouvant être des choix alternatifs à l'énucleation chirurgicale.

Présentation du cas

Une découverte fortuite d'une lésion pigmentaire de l'iris avec une extériorisation extra sclérale a été faite lors d'un examen ophtalmologique de routine chez une femme de race caucasienne âgée de 49 ans. Après confirmation par l'anatomopathologie de la nature maligne de la biopsie à l'aiguille, la patiente a bénéficié d'une irradiation par plaque ¹²⁵I montrant d'excellents résultats concernant la lésion tumorale qui a progressivement diminué. Aucune métastase n'a été découverte lors du suivi. La patiente a développé une cataracte secondaire ainsi qu'un glaucome deux années après son traitement par plaque ¹²⁵I.

Conclusion

Bien que l'énucleation ait été le traitement de référence pour le mélanome de l'uvée dans le passé, il y a une tendance actuelle d'opter pour des approches thérapeutiques en vue de préserver la vision, telles que la thérapie transpupillaire, la radiothérapie par laser à protons, la radiothérapie par plaque, la thérapie par photocoagulation ou encore la résection locale de la lésion. Cette nouvelle approche a été largement investiguée, parmi d'autres, par l'étude COMS (*Collaborative Ocular Melanoma Study*), une étude randomisée prospective multicentrique aux Etats-Unis. Ceux-ci démontrent qu'il n'existe pas d'avantage statistiquement significatif en faveur de l'énucleation en comparaison avec les traitements conservatifs, telle la radiothérapie par plaque ¹²⁵I concernant le développement de métastases à distance, la récurrence tumorale ou les taux de survie.

MOTS-CLEFS

Intraocular melanoma, ciliary body melanoma, choroidal melanoma, uveal melanoma, transpupillary thermotherapy, radiotherapy, photocoagulation, ¹²⁵I plaque radiation therapy, enucleation

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INTRODUCTION

« Background »

Epidemiology

The most common primary malignant intraocular tumor in adults is the uveal melanoma. The current annual incidence of this neoplasia in Belgium is estimated to be 7 to 8 new cases per million population. This incidence is much greater in northern European descent than elsewhere in the world. For example, in the USA, the incidence is estimated to be 4.6 to 6 cases per million population. The incidence of uveal melanoma hasn't significantly changed for the past 20 years. Uveal melanoma is mostly seen in Caucasian races, more common in men for all age groups (however from age 20-39 years, a small predilection for women is noted). Its peak incidence is shown around 60 years. Risk factors include a fair skin, blue or grey iris color, increased number of cutaneous naevi, congenital ocular melanocytosis, and neurofibromatosis. Some evidence suggests that sun exposure contributes to the development of ocular melanoma, but this is not well established yet and is disputed in literature. The greater majority of uveal melanomas are malignant transformation of a localized naevus, but de novo cases have been reported. Bilateral uveal melanoma presentations are extremely rare (1-5).

Classification

Size Category	Basal Diameter (mm)	Thickness (mm)
Small	> 5-10	> 2-3
Medium	> 10-15	> 3-5
Large	> 15-20	> 5-10
Extra large	> 20	> 10

FIGURE 1

Categorization of Posterior Uveal Melanoma by Size [3]

They can be classified as anterior uveal melanomas when the tumor arises from the iris and as posterior uveal melanomas when it arises from either the choroid or the ciliary body. The most commonly affected region of the uvea is the choroid, 10 times more frequent than the ciliary body melanoma. Intraocular melanomas can involve more than one structure simultaneously, such as in this case report, a cilioiridial melanoma. Posterior Uveal Melanoma are categorized by size, each category implicates a different type of management (1, 3, 5, 6, 7).

Symptoms

Ciliary body melanomas are often discovered fortuitously and can remain asymptomatic until they grow enough to affect neighboring ocular structures. These symptoms



depend of the tumour's localization and are non specific. They can include blurred or distorted vision, floating specks, phosphene, hyphema, metamorphopsia, astigmatism, cataract development, painless loss of a visual field, severe ocular pain if secondary acute angle-closure glaucoma occurs due to impairment of the function of the affected ciliary body, and more general symptoms like fatigue, weight loss, cough, etc (1,8,9).

Diagnostics measures

Depending on the localization of the tumor, diagnostic measures include slit lamp examination, ophthalmoscopy, gonioscopy, scleral transillumination, fundus oculi, A Ultrasound scan, B Ultrasound scan, CT scan, MRI and different types of biopsy forms (3,5,7).

« Objective »

During the last years, new therapeutic concepts have immersed regarding the treatment of uveal melanoma. Recent studies show the tendency to prefer the conservative approach of the pathology instead of the radical one (enucleation surgery).

Through a classic case presentation, the main objective of this manuscript is to go through current knowledge sources in search of recent findings and actual recommendations regarding the treatment of uveal melanoma.

CASE REPORT

A 49-year-old Caucasian woman presented a fortuitous discovery of a pigmented iris lesion with extrascleral exteriorisation of the right eye during a routine ophthalmologic examination. Her medical history consisted of one single episode of pancreatitis of unknown origin. The patient's ophthalmologic history was spotless except for bilateral myopia (-1.25 OD ; -0.25 OS); with corrected visual acuity of 10/10 for both eyes. Intraocular pressure was measured at 16 mmHg (OD). Family history revealed probable open angle glaucoma on her mother's side.

Pathway through differential diagnoses

The ophthalmoscopy of the anterior segment of the right eye confirmed the presence of a highly pigmented lesion affecting the iris and the ciliary body. Basal dimensions of the iridial component were estimated to be 4.7 by 2.0 mm. There were no intrinsic vessels or nourishing vessels for the pigmented lesion. Consistent with the localisation of the intraocular lesion, a pigmentation plaque was found on the episcleral surface, measuring approximately 2.6 by 1.3 mm and was surimposed by a pingueculum. The conjunctiva didn't show signs of infiltration.

The gonioscopic examination confirmed the angular position of the melanocytic tumor with a highly pigmented trabeculum.

After dilating the pupil, an opaqueness of the cortex of the crystalline lens was seen behind the lesion. Through scleral transillumination the localisation of the tumor was confirmed and measured 6.7 by 5.0 mm, including the iridial portion of the tumor. The fundus oculi revealed that the lesion didn't affect the

choroid layer.

The thickness of the tumor was measured at 5.3 mm by a B-ultrasound scan.

The left eye was strictly normal.

Considering these results, the intermittent diagnosis was that of a melanocytic tumor of the ciliary body with secondary infiltration of the iris and extrascleral exteriorisation of the right eye.

A needle-biopsy needed to be performed to determine the nature of the tumor precisely due to the fact that at this point, differential diagnosis included naevus, melanocytoma, melanoma or adenoma of the pigmented epithelium. This histological approach was also required to make decisions regarding therapeutic actions on the tumor due to its difficult localisation.

The first analysis of the cellular components of the needle-biopsy confirmed the melanocytic nature of the tumor without showing major alteration of the nucleolus pleading towards a benign origin of the carried out biopsy. The cytologic specimen was sent to Professor Ralph Eagle of the Department of Pathology in Philadelphia (U.S.) to confirm the diagnosis. The final pathological report returning from Philadelphia leaned towards a malignant melanoma of the iris and the ciliary body.

Pathway through therapeutic options

Considering the difficult localisation of the tumor and its malignant nature, 3 therapeutic options were proposed to the patient. The choice of treatment could either have been a conservative one, like the surgical tumor resection in toto or ¹²⁵I plaque radiation therapy, or the radical one with complete eye enucleation.

The pros and cons for every therapeutic option were intensely discussed with the patient. The patient agreed to the most conservative option that was presented to her, a 5-day local cure of a 12 mm ¹²⁵I plaque delivering approximately 9500 cGy, placed in an episcleral and corneal position to include the iridial tumor of the ciliary body and the tumoral particles in the inferior angle.

After her ¹²⁵I plaque radiation therapy, the patient left the hospital with a compressive ocular bandage (for 48h) and 2 local treatments: a combined corticosteroid and antibiotic collyrium (Maxitrol) and cyclopentolate hydrochloride drops (Cyclopentol) (for 4 weeks).

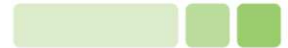
Metastatic assessment:

During her hospitalization, a systemic assessment was carried out and included the analysis of the hepatic enzymology, a hepatic ultrasound scan and a thoracic x-ray, all returning negative for distant metastases of the intraocular melanoma.

Results:

Immediate post-operative follow-up was considered normal.

The patient initially manifested intermittent episodes of superficial burning sensations to the right eye. The non-corrected visual acuity of the right eye three months post plaque radiation therapy was measured at 4/10, improvable at 9/10 with a steno-



peic hole. The intraocular pressure was measured at 10 mmHg.

The ophthalmoscopy of the anterior segment confirmed the progressive regression of the tumoral node of the iris and the pigmented episcleral portion corresponding to the exteriorization of the tumor. The plaque scar on the conjunctiva initially left a small paralimbal and inferior nasal conjunctival defect. There were no traces of post-radiation vasculopathy or secondary cataract development during follow-up.

The fundus oculi never revealed signs of retinal radiotoxicity.

The thickness of the tumor (measured with B-ultrasound scans), that initially measured 5.3 mm prior to plaque radiation therapy, shrank progressively, measuring 4.4 mm and 3.5 mm, respectively 3 and 9 months after plaque radiotherapy, until becoming so reduced that it became hard to distinguish the lesion from the normal ciliary body (approximately 2.5 years after plaque radiotherapy).

All post-radiotherapy results regarding the aspect of the lesion were very reassuring, showing no recurrence whatsoever of the lesion.

Metastatic assessments were realized at regular intervals of 6 months in search of hepatic metastases and intervals of 1 year in search of pulmonary metastases.

No signs of distant metastases of the intraocular melanoma were ever found.

Complications

1.5 years after her treatment, the patient developed a posterior subcapsular cataract in the superior-nasal region, secondary to the ^{125}I plaque radiation therapy. This was objectified during the biometrical examination after pupil dilatation. The cataract lesion spread progressively and rapidly affected the patient's visual acuity (1/20 improvable to 2/20 with a stenopeic hole). Her ophthalmologic history was not considered as a contraindication for cataract surgery, which was performed through phakoemulsification of the crystalline lens and the placement of a posterior chamber implant 2.5 years after her plaque irradiation.

A capsulotomy with YAG-laser needed to be performed 2 years after her cataract surgery because of posterior capsule opacification (PCO).

2 years after her plaque irradiation, the patient's intraocular pressure was increased to 20 mmHg in the right eye and betaxolol (Betoptic S) treatment was initialized. The diagnosis of open angle glaucoma (OAG) was made. Today, betaxolol treatment was replaced with dorzolamide 20mg/ml + timolol 5mg/ml collyrium (Cosopt), stabilizing the intraocular pressure around 18 mmHg.

DISCUSSION & CONCLUSION

« Synthesis »

A 49-year-old Caucasian woman presented a fortuitous discovery of a pigmented iridial lesion with extrascleral exteriorisation of the right eye during a routine ophthalmologic examination. The patient had some, but far from all predilecting

factors corresponding to known epidemiology for the development of an intraocular melanoma. She had an iridial naevus of the right eye, she has a fair skin, blue eyes and a relative amount of cutaneous naevi, she's from northern European descent, and her age matches the peak interval corresponding to the development of uveal melanoma. At the time the diagnosis was made, she was completely asymptomatic. The histological nature of the lesion was in this case impossible to determine on the simple basis of the patient's medical history, the biomicroscopical, gonioscopic and B-ultrasound scan characteristics and was a clear indication for the necessity to perform a biopsy. The results of the needle biopsy were ambiguous at first, but the final report from Professor R. Eagle of the pathology department in Philadelphia was clear cut, it was highly likely that the patient had a malignant melanoma of the iris and the ciliary body. Different alternative treatments suited for the case were explained to the patient and the most reasonable one, one of the conservative options, was chosen. The patient underwent a 5-day local cure of a 12 mm ^{125}I plaque delivering approximately 9500 cGy, which was placed in an episcleral and corneal position to include the iridial tumor of the ciliary body and the tumoral particles in the inferior angle. All post-radiotherapy results regarding the aspect of the lesion were very reassuring, showing shrinkage of the tumor without any recurrence whatsoever. The most frequent metastatic sites (liver & lungs) were carefully monitored, showing no signs of distant metastases of tumoral cells. Approximately 2 years after her treatment, the patient developed a secondary cataract and a secondary glaucoma due to the radiation therapy. The secondary cataract was treated by phakoemulsification of the crystalline lens with the placement of an intra ocular lens (IOL). Due to posterior capsule opacification, a YAG laser capsulotomy was performed approximately 2 years after the placement of the IOL. The secondary glaucoma was monitored and treated medically.

« Management »

Of the case in particular

Due to the difficult localisation of the tumor and its malignant nature, 3 options were plausible in this particular case. The choice of treatment could either have been a conservative one, like the surgical tumor resection in toto or ^{125}I plaque radiation therapy, or the radical one with complete eye enucleation.

The pros and cons for every therapeutic option were intensely discussed with the patient.

The patient agreed to the most conservative option that was presented to her, a 5-day local cure of a 12 mm ^{125}I plaque delivering approximately 9500 cGy, placed in an episcleral and corneal position to include the iridial tumor of the ciliary body and the tumoral particles in the inferior angle.

In literature

Although surgical enucleation was considered to be the treatment to refer to in the past, we can observe during these last years that tremendous progress has been made regarding the management of uveal melanoma, causing a trend towards the use of more focal conservative treatments preserving the integrity of the ocular organ. (5, 10-12).

The Collaborative Ocular Melanoma Study (COMS) (6), an enormous multicentric randomized study in the US, analyzed the foundations of this trend and confirmed its relevancy. This study

was divided in different parts. One of these parts compares mean survival rates after enucleation versus mean survival rates after Iodine-125 plaque radiation therapy. The results were clear-cut: *“Mortality rates following ¹²⁵I brachytherapy did not differ from mortality rates following enucleation for up to 12 years after treatment of patients with choroidal melanoma who enrolled in this COMS trial. The power of the study was sufficient to indicate that neither treatment is likely to increase nor decrease mortality rates by as much as 25% relative to the other”* (10).

The management of uveal melanoma is separated into 3 different types corresponding to the subdivisions of the uvea: the iris, the ciliary body and the choroid. Management recommendations also differ according to size of the melanoma. Choroidal melanomas represent 90% of uveal melanomas, iridial melanoma and ciliary body melanoma stand for the remaining 10%.

Radiation therapy is a well established treatment for uveal melanoma. Two types of radiation therapy are currently used: external radiation therapy and plaque brachytherapy (or « sandwich » therapy). Radiation therapy is a comfortable alternative to enucleation surgery. Different types of isotopes can be used for contact radiotherapy, such as Iodine-125 or Ruthenium-106 plaque radiation therapy. It has been established that Iodine-125 plaque radiation therapy has a better tissular penetration than Ruthenium-106 (10mm vs 5mm) and is therefore used more often, especially for thick lesions. Plaque radiation therapy or brachytherapy is known for its homogeneous distribution of the radiation on the basal surface of the tumor and also for causing

less post-radiotherapeutic complications in comparison with external radiotherapy with accelerated particles (proton beam radiotherapy). Plaque radiation therapy can be used when more than one uveal structure are involved simultaneously, such as cilioiridial or ciliochoroidal melanomas.

The most recent innovation in the therapeutic arsenal for uveal melanoma is the transpupillary thermotherapy (TTT), which consists of an ambulatory treatment by an infrared diode laser (810 nm) targeted directly onto the lesion, creating a local temperature of 45 to 60°C and generating a local lethal effect on the tumor cells. Increasingly popular, this method is used as a primary treatment or as a complementary treatment to radiotherapy or surgical resection for selected cases of posterior uveal melanoma (ciliary body & choroid layer), adding another comfortable therapeutic option to the weapon's arsenal against uveal melanoma.

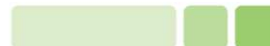
Tumor resection or « eye wall resection » is also a comfortable alternative to enucleation surgery, but should be reserved for small tumors located on the iris, the ciliary body or the anterior portion of the choroid to prevent possible loss of integrity to the ocular globe, causing major ocular and visual impairments.

Enucleation therapy should be considered as a last resort, an option to be considered only if every other therapeutic option fails or if they can't assure an adequate management of the tumor lesion. Indications for this type of intervention are: large tumors that cannot be treated by radiotherapy, transpupillary

	Iris	Ciliary body	Choroid
Observation	Close follow-up Small tumors	Close follow-up Small tumors	Slow growing tumor in an unique eye of a very elderly or chronically ill patient
Broad iridectomy	Small tumors	/	/
Iodine-125 or Ruthenium-106 plaque radiation therapy	Small tumors	Conservative treatment	Tumors < 20 mm in basal diameter. +/- TTT 5 mm thickness 10 mm thickness 106Rh plaque 125I plaque
Iridocyclectomy	Affected irido-corneal angle	Small or medium-sized tumors, affecting <1/3 of the iridocorneal angle.	/
Proton beam radiotherapy	Non-resectable tumors	Conservative treatment	Tumors not suited for plaque radiation therapy, i.e. large size or posterior location
Stereotactic Radiotherapy	/	/	A recently new technique, comparable to proton beam radiotherapy
Transpupillary Thermotherapy (TTT)	/	/	– Small, pigmented choroidal tumors when differentiation between naevus and melanoma is impossible and when radiotherapy is considered unsuitable. – Small chroidal melanoma when radiotherapy is inappropriate because of poor general health or reduced life expectancy – As an adjuvant treatment to radiotherapy as a treatment for exudation threatening vision.
Trans-scleral choroidectomy or tumoral resection of the ciliary body	/	– Carefully selected cases too thick for radiotherapy and usually less than 16mm diameter – Severe exudative retinal detachment and/or neovascular glaucoma	
Radical enucleation	Diffusely growing tumors	Large tumors and for those causing secondary glaucoma	Large tumor size, optic disc invasion, extensive involvement of ciliary body or angle, irreversible loss of useful vision, poor motivation for keeping the eye
Exenteration with palpebral preservation	/	/	Large tumor that cannot be controlled by lumpectomy and radiotherapy.
Metastases to the liver darken the prognosis of uveal melanoma. Therapeutic approaches are: systemic chemotherapy, radiotherapy or immunotherapy, partial hepatectomy, intra-arterial hepatic injection of fotemustine			

FIGURE 2

Synthesis of therapeutic options in uveal melanoma [5][7][9][12][14][15]



thermotherapy, tumor resection or laser photocoagulation, diffuse growing tumors, infiltration of the optic disc, neovascular glaucoma development, complete retinal detachment, irreversible loss of useful vision, extrascleral orbital extension of the tumor, or a poor motivation for keeping the eye. Recent development in prosthetics can nowadays assure remarkable results.

In case of liver metastases, vital prognosis is darkened. There are various therapeutic approaches in case of liver metastasis of a uveal melanoma. Systemic chemotherapy, radiotherapy and immunotherapy are equivalent in terms of inefficacy (Response in 10% of the patients with a survival gain of only 1 or 2 months). Partial hepatectomy is considered to be a more viable option. Promising results were shown using intra-arterial hepatic injection of fotemustine which tends to increase the local concentration of the drug near the metastasis. It is considered to be an effective and well-tolerated treatment against liver metastases from uveal melanoma with median survival rates among the longest reported so far (1 on 3 patients were still alive 2 years after the treatment) (5,7,9,12-15).

« Comparison »

The most logical and comfortable choice was indeed the plaque radiation therapy, which offered the possibility to treat the entire cilioiridial melanoma. Considering the size of the tumor, the simultaneous involvement of the iris and the ciliary body and its extrascleral exteriorisation, a tumor resection in toto would have been an « eye wall resection », causing a lot more visual and ocular impairment in comparison to ¹²⁵I plaque radiation therapy. Also, because tumoral particles were brought to light in the inferior angle, very distant from the principal tumor, the « eye wall resection » could also have been incomplete, needing therefore complementary ¹²⁵I plaque radiation therapy.

In case of a ¹²⁵I plaque radiation therapy, possible complications were carefully explained to the patient, these include the development of an iridial vasculopathy with neovascularization

and secondary hyphema, secondary cataract development, corneal decompensation and retinal retinopathy. All which usually appear within 3 years after the plaque radiation therapy.

A complete eye enucleation seemed to be too radical knowing that the systemic risks of metastasis development, tumor recurrence and survival rates have no association whatsoever with the type of treatment of uveal melanoma (5,6,10,12,14).

When the management of this patient was started (10 years ago), the effects of transpupillary thermotherapy were not well established yet, and therefore didn't partake in the management of her neoplasia.

« CONCLUSION & RECOMMENDATIONS »

Over the last years, it has been established in scientific literature that the systemic risks of metastasis development, tumor recurrence and survival rates have no association whatsoever with the type of treatment used for uveal melanoma. It is therefore recommended to choose as much as possible vision-sparing therapeutic options for the treatment of uveal melanoma and to push back enucleation to a "last resort" type of therapeutic approach.

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SUMMARY

Introduction

The most common malignant intraocular tumor in adults is the uveal melanoma. During the last years, new therapeutic concepts have emerged regarding choroidal, ciliary body and iridial melanoma. Recent studies show the tendency to prefer the conservative approach of the pathology instead of the radical one (enucleation).

We report a typical case of a melanoma of the iris and the ciliary body with extrascleral exteriorisation of the right eye as an example to illustrate the different types of conservative alternative treatments to surgical enucleation.

Case presentation

A 49-year-old Caucasian woman was presented with a fortuitous discovery of a pigmented lesion of the iris with extrascleral exteriorisation during a routine ophthalmologic examination. After confirmation of the malignant nature through the analysis of a needle biopsy from the pathology department, the patient underwent ¹²⁵I plaque radiation therapy with excellent results concerning the tumoral lesion that progressively shrank. No distant metastases were found during follow-up. The patient developed secondary cataract and glaucoma approximately 2 years post-radiation.

Conclusion

Although enucleation has been the treatment of choice for uveal melanoma in the past, the actual tendency is to choose vision-sparing therapeutic approaches, like transpupillary thermotherapy, proton beam radiotherapy, plaque radiation therapy, photocoagulation therapy or the local surgical removal of the lesion. This new approach has strongly been investigated, amongst others, by the Collaborative Ocular Melanoma Study (COMS), a prospective randomized multicentric study in the United States. These studies proved that there is no significant statistical benefit for enucleation in comparison with conservative treatment like ¹²⁵I plaque radiation therapy regarding secondary development of distance metastases, tumor recurrence or survival rates.