

Ocular malignant melanoma in pregnancy: is a happy ending possible?

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SUMMARY

Uveal, especially choroidal melanoma is the most common ocular melanoma. There is no clear evidence that pregnancy impacts its development. Enucleation is generally indicated for advanced tumors. Five-year mortality rate is 53% in patients with large melanomas (>8 mm).

Key words: Eye Neoplasms; Melanoma; Pregnancy

INTRODUCTION

Melanocytic lesions, malignant melanoma, and nevi, can often be found in ocular structures. Four tissues in the ocular region can give rise to primary melanoma, including the uveal tract (uvea), conjunctiva, eyelid, and orbit. Each manifests with different clinical features and symptoms. The management strategy varies depending on the tumor location, size, and other factors. Uveal, especially choroidal melanoma is the most common ocular melanoma and accounts for about 90% of all intraocular melanomas (1).

In addition to primary ocular melanoma, the ocular region can serve as a site for metastatic cutaneous, breast, lung, kidney, and prostatic melanoma. Metastases most often manifest in the highly vascular uvea, particularly the choroid (2).

Pregnant women more often note a change in pigmented lesions during pregnancy. Most of these lesions were not malignant but other benign neoplasms with a slightly higher atypia score which could be considered minor (3).

CASE REPORT

A 30-year-old pregnant woman was admitted at the Clinic of Ophthalmology, during the 23rd week of gestation. Her symptoms were fatigue and a shadow in front of her right eye, in the upper part of the visual field. Symptoms started a week before and they got more intense during the next few days. This was her third pregnancy and she was expecting her second child. Her first pregnancy was finished as an involuntary abortion, while the second was regular and ended in the 36th week of gestation with giving birth to a healthy infant. Current pregnancy was regularly controlled and amniocentesis findings did not show any irregularities. Gynecological ultrasound showed only compartments of the womb.

were regular. But, on the fundus of the right eye a solid, globular mass could have been observed. The mass was spreading towards the vitreous body, down and partially nasal. Around this mass was a shallow ablation (Figure 1). The ultrasound of the right eye verified prominent solid mass, 11 mm thick, mildly high, and partly diluted reflection, with intense reflex of the surface. Translucency was seen towards the base, which was narrower. A shadow in the orbit was partly seen in the projection of the basis of the lesion (Figure 2).



Figure 1. Fundus of the right eye



Figure 2. Ultrasound of the right eye

Ophthalmological status: visual acuity was 1.0 (20/20) bilaterally; findings of the anterior segment of both and of the posterior segment of the left eye

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The ultrasound of the liver and upper abdomen, as well as alkaline phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase and melanin in the urine were normal.

Considering general status of the patient, her late pregnancy, size of the tumor and limited possibilities of radiotherapy, we have assumed that the only way of treatment in this case was enucleation. The enucleation was performed in the 26th week of gestation in the other center. Histopathological findings have shown that it was B cell malignant melanoma. Bruch's membrane was ruptured.

Patient did not go to the advised prenatal consultations, which could show eventual risk for the fetus. The labor was on time, two and a half months after the enucleation, and she gave birth to a, so far, healthy child.

DISCUSSION

Intraocular melanoma includes tumors originating in the iris, ciliary body, and choroid. Some patients with intraocular melanoma have no symptoms, and the malignancy is discovered on routine eye examination.

Iris melanoma is usually small at discovery, measuring 3 to 4 mm or less. It generally produces no symptoms, but the patient notices a brown or yellow spot on the iris that enlarges slowly over months or years. In some cases, this tumor can produce elevated intraocular pressure. Melanoma-related glaucoma can cause eye pain (4).

Ciliary body melanoma is typically large at discovery, measuring 8 mm or larger, because it hides behind the normal iris in an area of the eye that does not interfere with vision until late and is difficult to visualize by the ophthalmologist. When symptoms are experienced, the patient notes unilateral loss of vision or pain caused by the elevated intraocular pressure.

Our patient had choroidal melanoma, which is the most common location of uveal melanoma, representing more than 90% of intraocular melanoma. Many patients experience no symptoms, and the mass is discovered on routine eye examination. Those with symptoms note visual loss, flashing lights, floaters, or visual field defect. Pain is rarely a symptom but, when it appears, it is a sign of an enlargement of the tumor with a necrosis in it, which causes secondary glaucoma. Tumors nearer the macula produce symptoms earlier and tend to be detected when they are smaller than tumors near the ora serrata (5). The tumor in our patient was located down and partially nasal on the fundus, which represents upper and temporal part of the visual field. The patient had such visual field defects, but the tumor was so periphery so she could notice the defects only in the late phase of the disease when the lesion was inadmissibly large.

Melanoma of the uvea classically appears as a brown-pigmented mass. In less than 20% of cases, the mass is yellow and nonpigmented. Ablation of the retina is always present. It can appear in one of three configurations including dome, mushroom, and diffuse. Most melanomas are dome-shaped, with the tumor thickness approximately 50% the basal dimension. Mushroom-shaped choroidal melanoma, which was verified in this case, occurs when the tumor breaks through the overlying Bruch membrane and herniates into the subretinal space. Diffuse melanoma configuration is found in only 4% of cases and appears as a flat, minimally thickened mass that grows horizontally in base rather than thickness and is often mistaken for a nevus. Choroidal melanoma is classified by tumor thickness as small (0–3.0 mm), medium (3.1–8.0 mm), and large (≥ 8.1) (6).

The most important factor in the development of uveal melanoma is the presence of congenital ocular melanocytosis, called oculodermal melanocytosis or Ota's nevus when the eyelid skin is affected. Another risk for the development of uveal melanoma is the presence of uveal nevus. Choroidal nevus tends to appear in the teenage years as a brown stable mass with chronic overlying drusen. A further investigation of the risk for transformation of choroidal nevus into melanoma identified five clinical features that predict growth, including thickness exceeding 2 mm, subretinal fluid, symptoms, orange pigment, and lesions within 3 mm of the optic disc (7). It is unknown if our patient has had a choroidal nevus before. She did not have such documentation but it is reasonable to suppose that her pregnancy could have influenced the course of the disease if the nevus was present.

There is no clear evidence if the pregnancy, oral contraceptive pills, and hormonal replacement therapy influence the development of malignant melanoma. Estrogen receptors were not found, suggesting that estrogen receptor activity may not be involved in the presentation or growth of ocular melanomas.

The absence of estrogen receptor, however, does not rule out the possibility that estrogens may influence tissue by a mechanism not involving the receptor, or that they may exert an indirect effect via the regulation of other hormones or factors that directly affect the melanoma. Other possibilities for hormone control other than estrogens include a direct effect of melanocyte stimulating hormone, androgens, or other trophic factors. Another possible mechanism is that pregnancy may be associated with decrease of a systemic inhibitor allowing stimulation of growth. Changes in cellular and humoral immunity occur during pregnancy. An increase in immunosuppression-related problems could occur which would allow development or growth of a pre-existing slow growing melanoma in the eye (8).

The most reliable way to make the diagnosis of choroidal melanoma is with the use of indirect ophthalmoscopy. In addition to that, we made an ultrasonography of the eye in the atypical cases. Fluorescent angiography, indocyanine green angiography, optical coherence tomography, auto-fluorescence, and fine needle aspiration biopsy can be helpful ancillary procedures, too.

Management of choroidal melanoma includes: photocoagulation, transpupillary thermotherapy, plaque radiotherapy, charged particle irradiation, local resection, enucleation, orbital exenteration, chemotherapy, and immunotherapy (1).

Photocoagulation is an acceptable method for treating selected choroidal melanomas that are less than 3 mm thick.

Transpupillary thermotherapy is a method of treating selected small choroidal melanomas using a modified diode laser system directed through the pupil into the tumor. The tumors most suitable for transpupillary thermotherapy are small, heavily pigmented melanoma (<3 mm thick) with minimal or no subretinal fluid, and located in the extramacular region, not touching the optic disc (9).

Radiotherapy is still the most widely used treatment for posterior uveal melanoma. The most commonly form of radiotherapy is brachytherapy using a radioactive plaque. Iodine 125 and ruthenium 106 plaques are used. Another method of radiotherapy is charged particle irradiation. Radiotherapy in pregnancy is not the recommended method so it was not performed.

Local resection of melanomas can be performed using a partial lamellar sclerouvectomy technique. Many complications can be expected when larger

post-equatorial tumors are managed in this manner. This is the reason why we did not perform such intervention.

Enucleation is generally indicated for advanced melanomas that occupy most of the intraocular structures and for those that have produced secondary glaucoma. There have been no clinical trials evaluating the effectiveness of therapies other than enucleation for large melanomas (10). We have consulted several European centers which treat malignant melanoma and they have confirmed that the only way to treat malignant melanoma in our patient is enucleation. Their opinion was that the tumor was too big for brachytherapy. Possible access with cyclotron in this case makes great risk for both, mother and the child (1-11).

The 5-year mortality rate is 16% for patients with small tumors (<3 mm), 32% for medium tumors (3–8 mm), and 53% for large tumors (>8 mm). It is unclear at what size choroidal melanoma becomes risky for formation of metastases. Clinical studies indicate that small melanoma at approximately 1 mm in thickness have metastasized. The average volume of an intraocular melanoma at the time that tumor metastasis occurs in other organs is approximately 7 mm³. This tumor volume could represent a dome-shaped melanoma of 3 mm in the base and 1.5 mm in thickness. Metastases from choroidal melanoma thus generally occur early in the course of the visible tumor, when it is small and easily confused with a benign choroidal nevus. This information underscores the need for early detection of choroidal melanoma, ideally when the tumor thickness is less than 1.5 mm, in an effort to prevent metastatic disease. The procedure that was performed in this case showed no visible metastases at that time, even though she was in the high-risk (53%) group. Systemic monitoring twice yearly with physical examination and liver function tests and annually with liver imaging and a chest radiograph is advised. In contrast to cutaneous melanoma, uveal melanoma does not metastasize to lymph nodes (6-7).

The evaluation of the pregnant woman with a suspicious pigmented lesion or confirmed melanoma is similar to that for the nonpregnant patient. Melanocytic nevi may enlarge and darken in color during pregnancy, possibly related to the influence of pregnancy-related hormones, but pregnancy does not appear to adversely affect survival in those women diagnosed with localized melanoma before, during, or after the pregnancy (3).

The management is based upon the degree of histologic atypia for the malignant melanoma, or a stage of the disease for confirmed melanoma. Little is known about the safety of chemotherapy or interferon- α -2b as a treatment for pregnant women with more advanced disease, although one center has not observed specific birth defects in children born to women treated with interferon- α -2b during pregnancy (12). It was proved that interferon- α -2a has no material influence on survival in patients with choroidal melanoma as an adjuvant therapy (13). Taking all of the previously stated in the account, adjuvant therapy was not recommendable in our case.

Conflict of interest

We declare no conflicts of interest.

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