Uveal melanomas presenting during pregnancy and the investigation of oestrogen receptors in melanomas

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SUMMARY We observed a young woman who showed growth of a choroidal melanoma over the course of 2 pregnancies, with subsequent enucleation of the eye. This is the first such documented case. In addition 4 other women with uveal malignant melanomas presented during pregnancy. This observed number of pregnancies (5) was greater than the expected number (2.1) among women of childbearing age who underwent enucleation with subsequent analysis in our pathology laboratory. However, this difference was not statistically significant. Further, more females 44 years of age or younger underwent enucleation for malignant melanoma than men of comparable age. Evaluation of these cases led us to propose that there is a subset of patients whose ocular melanomas are hormonally responsive. We therefore analysed uveal melanoma and choroidal tissue from 7 patients, including one of the pregnant women, for the presence of oestrogen receptors. No specific oestrogen binding was found. The possibilities that other hormones are involved or an immunological mechanism is operative are discussed.

Endocrine influences on cutaneous malignant melanoma have been explored for many years.1-16 In contrast, the effect of endocrine factors on ocular melanomas has received little attention. A few anecdotal references13 17 18 and case reports19-22 of uveal melanomas occurring during pregnancy could be found in the literature. However, no one has reported whether or not growth of a uveal melanoma occurs during pregnancy or explored hormonal aspects of ocular melanomas or uveal tissue.

Studies of cutaneous melanoma on differences in incidence and mortality according to sex yield contradictory results.1-4 The association between cutaneous melanoma and pregnancy or hormonal status among women is also equivocal.17-16 Some report a better prognosis in women than in men3 or in pregnant than in nonpregnant women.4 However, a few find no significant differences in outcome according to sex,4 pregnancy,15-17 marriage status,8 9 or use of oral contraceptives.10

On the other hand some epidemiological studies reveal a higher incidence and mortality for cutaneous melanoma in women of reproductive and menopausal age than in men.11 12 Similarly, other reports suggest an unfavourable effect on prognosis when melanomas are exacerbated during pregnancy13 or when stage II melanomas are related to pregnancy.14 Activation of naevi or melanomas with use of birth control pills,15 during pregnancy,16 and after oestrogen administration12 has been observed. Furthermore some animal studies imply changing growth patterns of skin melanoma in animals of differing hormonal status.13 23 24

Such clinical findings arouse the suspicion that some patients with cutaneous melanoma may respond to hormonal stimuli. Since uveal and skin melanocytes both derive from the neural crest, it is reasonable to propose that similar mechanisms may play a role in ocular melanoma.

Steroid hormone receptors have also been studied in an effort to understand hormonal influences on malignancies. The presence of steroid receptors in the cytoplasm of cells is characteristic of endocrine responsive tissue. Oestrogen binding activity has been
found in 12 to 46% of cutaneous melanomas independent of the patient's sex or age.\textsuperscript{25-28} Since steroid hormones may be involved in the pathophysiology of various human malignancies or may be useful as therapeutic regimens, as in breast cancer, looking for receptors in cancer tissue makes good biochemical sense.\textsuperscript{29}

We herein report 5 cases of young women who presented with uveal malignant melanomas during pregnancy, one of whom is the only well documented case in the literature of growth of ocular melanoma associated with pregnancy. The possibility that there might be a subset of patients whose ocular melanomas are hormonally responsive was raised. Since oestrogens are the major trophic hormone of pregnancy, a biological response of uveal tissue to oestrogens was proposed. To test this hypothesis, we analysed uveal melanomas and adjacent uveal tissue after enucleation for the presence of oestrogen receptors, and, as will be discussed, none were found.

**Subjects and methods**

**CASES**

We recently observed 2 patients with ocular melanoma presenting during pregnancy. This led us to review our series of melanomas in the Pathology Laboratory at the Massachusetts Eye and Ear Infirmary (MEEI) from 1953 through 1973 and we identified specimens from 3 other pregnant women with ocular melanoma. Paraffin embedded, formalin fixed tissue was processed for light microscopy. Slides were stained with haematoxylin and eosin or periodic acid-Schiff, and potassium permanganate treated (bleached) sections, when indicated, were obtained. We examined the slides, verified the diagnosis, and described characteristics of the tumours in each case. A specimen from the tumour which grew during 2 pregnancies (case 1) was studied by electron microscopy by techniques previously described.\textsuperscript{30,31}

Follow-up procedures on the 4 living patients involved personal contact with the patients as well as documentation of their status from their ophthalmologists and interns. Two patients died, and discharge summaries and slides of biopsies were examined to confirm the cause of death.

The age and sex distributions of patients who had an enucleation for uveal malignant melanoma with subsequent pathology analysis at the MEEI over the same time period as the 5 cases were evaluated. Female and male ratios for patients 44 years of age or younger were calculated. Birth rates for all women in the United States adjusted for age and year of birth\textsuperscript{32} were then used to calculate the cumulative probability of being pregnant for each woman 44 years of age or younger. These probabilities were then added to obtain the expected number of pregnancies among women in this age group. The significance of the difference between the observed and expected number of pregnancies was then determined by the Poisson distribution.

**OESTROGEN RECEPTOR ANALYSIS**

Uveal melanoma tissue (at least 2 mm\textsuperscript{3}) was collected under sterile conditions from 5 cases as soon as possible after enucleation and frozen in liquid nitrogen. One of these specimens was from the eye of a pregnant young woman discussed in this report (case 1). At the same time normal choroid was collected from an area adjacent to the tumours to serve as control tissue. Delays of 4 and 7 hours in processing tissue were encountered in two other cases (one necropsy and one from a distant institution), and these cases were analysed as negative controls.

Oestrogen receptor assays were carried out on the tumour and choroidal tissue cytosols according to methods used for the analysis of oestrogen receptors in human breast cancers in the laboratory performing breast receptor assays for the Massachusetts General

<table>
<thead>
<tr>
<th>Patient (accession number)</th>
<th>Age</th>
<th>Month of pregnancy</th>
<th>Presenting complaint</th>
<th>Melanoma Location</th>
<th>Melanoma Size</th>
<th>Cell type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (E80–923)</td>
<td>27</td>
<td>7 (1st)</td>
<td>Ocular pain OS for 2 days</td>
<td>Choroid</td>
<td>Medium</td>
<td>Mixed</td>
<td>Normal delivery dead due to metastatic melanoma</td>
</tr>
<tr>
<td>2 (E80–1275)</td>
<td>33</td>
<td>6 (2nd)</td>
<td>Blurred vision OD for 2 days</td>
<td>Choroid</td>
<td>Small</td>
<td>Spindle B</td>
<td>Normal delivery alive and well</td>
</tr>
<tr>
<td>3 (E56–341)</td>
<td>35</td>
<td>3</td>
<td>Blurred vision OD for 2 weeks</td>
<td>Choroid</td>
<td>Small</td>
<td>Spindle B</td>
<td>Normal delivery alive and well</td>
</tr>
<tr>
<td>4 (E69–746)</td>
<td>22</td>
<td>5</td>
<td>Blurred vision OS for 4 days</td>
<td>Choroid</td>
<td>Large</td>
<td>Spindle B</td>
<td>Normal delivery dead due to metastatic melanoma</td>
</tr>
<tr>
<td>5 (E61–497)</td>
<td>29</td>
<td>4</td>
<td>Injection OS, history of glaucoma and 'cyst' OS</td>
<td>Iris, ciliary body</td>
<td>Small</td>
<td>Spindle B</td>
<td>C-section alive and well</td>
</tr>
</tbody>
</table>
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Since the tumour samples were small (tumour average net weight 98 mg, choroid average weight 61 mg), duplicate single saturating dose assays at 2 nM^3H oestradiol in the absence and presence of 250-fold molar excess of unlabelled diethylstilbestrol were performed.

Results

Five white women ranging in age from 22 to 35 presented during their fourth to seventh months of pregnancy with uveal malignant melanoma (Table 1). All delivered full-term normal infants. Two of them subsequently died of metastatic malignant melanoma.

CASE 1

This 27-year-old white female was first seen on 30 October 1978, with the complaint of pain in the left eye of 2 days' duration followed by oedema and redness of the eyelids and decreased vision. At this time she was 7 months pregnant. There was no significant past ocular history. She had been on birth control pills from about March 1977 to March 1978. Family history revealed that her mother died of stomach cancer. Her last ocular examination, in April 1973 by an optometrist, revealed normal visual acuity in both eyes.
Ocular examination of the right eye was normal. Visual acuity OS was counting fingers at 1 foot (30 cm). Visual field examination revealed a central scotoma, almost complete loss of the superonasal quadrant, with marked constriction superotemporally. She had moderate oedema and erythema of the lids, with minimal conjunctival injection and chemosis. There was an afferent pupillary defect. Ocular motility was normal. Slit-lamp examination of the cornea and anterior chamber was unremarkable. Appplanation tonometric pressures were 15 mmHg, 10 mmHg OS.

In the fundus of the left eye was a dark lesion measuring about 3×4 disc diameters located 1½ disc diameters temporal to the disc involving the macula (Fig. 1A). There was some pigment proliferation and mottling at the temporal border of the lesion. A large serous detachment extended from 2.30 to 8.00 o'clock. Ultrasonography revealed a lesion 2 mm in height with no choroidal excavation.

The differential diagnosis at this time was subretinal pigment epithelial haemorrhage or malignant melanoma. It was decided that because of her pregnancy, further testing would be delayed. The lesion remained stable during the latter part of her pregnancy.

She was then delivered of a normal daughter on 29 January 1979. She did not resume birth control pills and again became pregnant in August 1979. During this interval between pregnancies the subretinal fluid decreased (Figs. 1B,C).

Suddenly on 1 February 1980, 6 months into her second pregnancy, she had a recurrence of the ocular pain and irritation OS similar to her experience during her first pregnancy. Her visual acuity had not changed.

There was minimal conjunctival injection and the globe was tender to palpation. There were a moderate number of cells in the anterior vitreous OS. The pigmented lesion in the left eye was slightly larger, extending superior and inferior to the disc with irregular margins. There was a bullous retinal detachment extending from 2.00 to 9.00. There did not appear to be an increase in height. Again, because of her pregnancy, further testing was not performed.

She was delivered of a normal son at term on 27 May 1980. In June her visual acuity was counting fingers at 5 feet (150 cm) OS. Fundus examination revealed that the pigmented tumour was even larger than before, and it surrounded the optic disc (Fig. 1D).

Fluorescein angiography was performed and revealed several hyperfluorescent areas in the early and middle phases of the angiogram which progressed during the transit and leaked, consistent with vascular areas seen in melanomas (Fig. 2). Ultrasonography revealed a solid lesion with some suggestion of acoustic shadowing in the orbit. Choroidal excavation was not definitely seen.

A clinical diagnosis of malignant melanoma was made. Because the lesion had grown and her visual acuity was poor, enucleation was advised. Liver function tests including bilirubin, alkaline phosphatase, and SGOT were normal. Enucleation of the left eye was performed on 28 July 1980.

She remained well until January 1982, when biopsy-proved liver metastases developed. Chemotherapy was initiated, but she died in April 1982 of widespread metastases.

Pathological examination. On gross examination of the eye a pigmented choroidal tumour was seen surrounding the optic nerve. It extended 10 mm temporally from the disc and 2 mm nasally. The temporal aspect of the tumour was a circumscribed mass elevated 3 mm, while the remainder of the tumour had a more flat, diffuse configuration with an elevation of 1–2 mm (Fig. 3A). The retina was totally detached.

Histologically the tumour contained areas of dense connective tissue (Fig. 3B). Spindle A, spindle B, and epithelioid cells were present, with a diagnosis of mixed cell type. There were nests of naevus-like cells at the edge of the tumour adjacent to the optic nerve. Tumour cells were seen invading the optic nerve anterior to the lamina cribrosa and scleral emissary canals (Fig. 3C). Bruch's membrane was not ruptured. A moderate amount of chronic non-granulomatous inflammation was present within the tumour. The retina was detached, and areas of associated retinal pigment epithelium had undergone fibrous metaplasia. The cornea, anterior chamber, lens, iris, and ciliary body appeared normal. Electron microscopy of this melanoma revealed bundles of collagen.

Fig. 2  Case 1. Fluorescein angiogram of the mass OS during arteriovenous phase showing hyperfluorescent areas.
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Fig. 3 Case 1. (A) Choroidal tumour with diffuse configuration. (Haematoxylin and eosin, ×5-8). (B) Dense connective tissue within the tumour. (Haematoxylin and eosin, ×42). (C) Peripapillary tumour with invasion of the optic nerve (arrow). (Haematoxylin and eosin, ×26-5).
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Fibris amid tumour cells in areas of connective tissue seen on light microscopy.

case 2

This 33-year-old woman presented in her seventh month of pregnancy with a 2-day history of her vision being obstructed by a 'veil' OD. Her last reported visual acuity was 20/20 OU in November 1977, when she was treated for an allergic conjunctivitis. There was no other significant past ocular history.

Her visual acuity was 20/100 OD and 20/20 OS. External and anterior segment examination was entirely within normal limits OU. Applanation intraocular pressures were 18 mmHg OU. Fundus examination of the right eye revealed a pigmented lesion 5 mm in diameter, 2 mm elevated located 3 to 4 disc diameters superior to the disc OD (Fig. 4). A secondary serous detachment involving the macula was present. The fundus of the left eye was normal.

A number of consultants agreed that the lesion was a malignant melanoma. Various treatment possibilities including observation for evidence of growth, enucleation, and alternative methods, such as proton beam irradiation, were discussed. When the patient learned that she had a tumour in her eye she insisted on prompt enucleation and would not consider alternative therapies. Her alkaline phosphatase level was normal. Enucleation was then performed on 14 October 1980. The size of the tumour was too small to warrant sampling for oestrogen-receptor analysis.

The patient did well subsequent to her enucleation and was delivered of a normal son on 12 December 1980. Thus far she and her son have remained in good health with no systemic medical problems.
**Pathological examination.** A small pigmented tumour was present arising from the choroid in the posterior pole above the optic disc. It measured 4½ mm in largest diameter and 3 mm in elevation (Fig. 5A). The surrounding retina was detached. There was no gross extrasceral or optic nerve extension.

Histologically the tumour was composed of a mixture of spindle A and spindle B type cells (Fig. 5B). No epithelioid cells were seen and Bruch's membrane was not ruptured. There were a minimal number of chronic inflammatory cells. A shallow detachment involving the macula was present. Degeneration of photoreceptors and outer nuclear layer of the retina was seen overlying the tumour. There was superficial involvement of sclera by tumour cells. The anterior segment was normal.

**CASE 3**

This 35-year-old woman presented in her fifth month of pregnancy in July 1956 with a history of blurred vision OD for 2 weeks. She had no previous ocular problems. Her best corrected visual acuity was 20/70–2 OD and 20/20 OS. Applanation intraocular pressures were 17 mmHg OU. Fundus examination revealed an elevated mass inferior to the macula 3 to 4 disc diameters in its widest dimension. There was macular oedema and a retinal detachment overlying the mass. The left eye was normal. She was seen at the MEEI and consultants agreed that the lesion was a malignant melanoma. The right eye was enucleated on 21 August 1956.

She was delivered of a normal daughter on 17 November 1956. Since then she and her daughter have remained in good health with no systemic problems.

**Pathological examination.** A minimally pigmented choroidal tumour 6 mm in largest diameter and 2 mm in height was located in the posterior pole involving the macula. The cell type was classified as spindle B in a fascicular arrangement. Compact spindle cells were present at the base of the tumour. Bruch's membrane was not ruptured. There was minimal invasion of the inner aspect of the sclera.

**CASE 4**

This 22-year-old woman presented in September 1969 when she was 6 months pregnant with a 4-day history of blurred vision OS. She had no significant past ocular history. Her family history was significant for cancer; her sister died from a central nervous system malignancy at age 16 and a paternal uncle was treated for cutaneous malignant melanoma. Her visual acuity was 20/15 OD and 20/400 OS. Applanation intraocular pressures were 16 mmHg OU. A choroidal tumour was seen inferotemporally in the left eye extending from the ora to posterior to the equator with a retinal detachment at the edges of the tumour. Examination of the fundus OD was normal. Consultants agreed that this was a malignant melanoma OS. The left eye was enucleated on 22 September 1969.

She was delivered of a full-term baby in December 1969. Three and a half years later she developed a carcinoma in situ of the cervix and underwent a total hysterectomy in May 1973. Slides of the cervical lesion have been reviewed and the diagnosis has been confirmed by the authors. In November 1974, she noticed multiple nodules in her right breast which were biopsied and subsequently verified by the authors as metastatic malignant melanoma of mixed cell type. Chemotherapy and BCG therapy were started in June 1975. A liver scan was suspicious for early metastatic disease. In September 1976 she developed multiple bone metastases, which were treated with radiotherapy. She later developed extensive subcutaneous melanotic nodules. Bone marrow failure developed due to extensive chemotherapy. She died on 30 April 1977 of metastatic malignant melanoma and bone marrow failure.

**Pathological examination.** A tumour 14 mm in largest diameter and 7 mm in elevation was present arising from the choroid. Histologically the tumour consisted almost exclusively of spindle B cells arranged in a fascicular pattern. It was lightly pigmented with minimal chronic inflammation. A retinal detachment was present overlying and surrounding the tumour. The pigment epithelium over the lesion had undergone fibrous metaplasia. Bruch's membrane was ruptured and there was invasion of the overlying retina. No tumour cells were seen in the vitreous. There was invasion of the inner aspect of the sclera but no invasion into the scleral emissary canals.

**CASE 5**

This 29-year-old nurse presented at the MEEI when 4 months pregnant on 25 July 1961. Her visual acuity was 20/20 OD and no light perception OS. Her right
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eye was normal. Her left eye had minimal conjunctival injection. She had a superior peripheral iridectomy OS. A pale vascularised mass was present on the anterior surface of the iris inferiorly (Fig. 6). There was also a subconjunctival mass at the limbus inferiorly. The pupil OS was irregular, and the anterior chamber was normal in depth. The lens OS had pigment on the capsule. Intraocular pressures were 16 mmHg OD and 38 mmHg OS. The disc OS was atrophic. No masses were seen on dilated fundus examination.

The patient's previous ocular history according to notes obtained in 1961 from her ophthalmologist revealed a normal examination in November 1948, when she was 17 years old. Examination one year later revealed advanced glaucoma OS with optic atrophy and 'marked nasal field loss.' She had an 'iridectomy and sclerectomy' for control of the pressure on 24 April 1950. We were unable to obtain slides of material removed at that time. A cystic, vascularised subconjunctival nodule below the limbus was noted prior to the surgery but not biopsied or resected. No iris lesion was noted at that time. She was followed up by her ophthalmologist over the following years, but these records could not be obtained. An iris lesion had never been mentioned to the patient. Because of the presence of a tumour in her blind eye when seen at MEEI, an enucleation was performed on 11 October 1961.

She was delivered of her child by caesarian section on 26 December 1961. Since then she has had two more caesarian sections and a hysterectomy. During abdominal surgery, exploration for metastases was done which was negative. She has had no further medical problems.

**Pathological examination.** A tumour consisting mostly of spindle B cells was present, replacing the inferior aspect of the iris and involving the ciliary body and the trabecular meshwork. It extended through the sclera into the subconjunctival space. Tumour cells were present within the inner layers of the corneal periphery and beneath the corneal epithelium at the limbus. Many large vascular channels were present in the tumour. Pigment clumps were scattered among the tumour cells. The angle was closed inferiorly. The choroid showed no evidence of tumour. Diagnosis was malignant melanoma of the spindle B cell type, involving the iris and ciliary body with extracocular extension.

**STATISTICAL ANALYSIS**

From 1953 to 1973 there were 27 females and 18 males 44 years of age or younger who had an enucleation for uveal melanoma and pathology examination at the Massachusetts Eye and Ear Infirmary with adequate follow-up. In 1980 there were 6 females and 2 males in the same age range. The female to male ratios were 1:5:1 and 3:1 respectively.

The expected number of pregnancies among women 44 years of age or younger in our sample was 2·1. Although the observed number (5) was greater than the expected (2·1), this difference was not statistically significant (one sided p value = 0·06).

**OESTROGEN RECEPTOR ANALYSIS**

A summary of the findings can be found in Table 2.
One of the specimens studied was a melanoma from a pregnant woman (case 1) in which no oestrogen receptor was detected. The remaining uveal melanomas and normal choroidal tissues that were studied were also negative.

Discussion

It is difficult to ascertain the natural history of melanomas prior to their discovery. In case 1, however, there is no question that her symptoms of discomfort and injection began during the latter half of each of her two pregnancies and that the melanoma grew to ultimately surround the optic nerve while she was pregnant. Reasons for her ocular pain and oedema at similar times during her pregnancy remain speculative but may be related to growth of the melanoma. The decrease in sub-retinal fluid and change in the appearance of the edges of the mass suggested a remission or regression between pregnancies. This case and the others discussed in this report led us to question a possible influence of hormones or other mechanisms involved in pregnancy and the premenopausal period. This hypothesis is corroborated by our finding of an increased female to male ratio in cases 44 years of age or younger. We also found a higher than expected number of pregnancies among women of childbearing age in our sample; however, this was not statistically significant. Since our patients are not necessarily representative of all cases of uveal melanoma in the source population, and the sample size is small, results are suggestive and warrant further investigation.

The present study represents the first investigation in the literature for the presence of oestrogen receptors in uveal melanoma and choroidal tissue. Oestrogen receptors were not found, suggesting that oestrogen receptor activity may not be involved in the presentation or growth of uveal melanomas. This assumption is consistent with the finding that cutaneous melanomas show a poor response to endocrine therapy and that the putative responses to hormone therapy in cutaneous melanoma have no correlation with the presence of receptor. Our receptor test group was small, with only one a melanoma of pregnancy, so a larger number of this relatively rare condition needs to be examined before the statistical significance of the findings can be established. Questions that remain unanswered include: are uveal melanomas of pregnancy different from tumours in nonpregnant age-matched cases with respect to receptor frequency and concentration? Are there significant receptor differences between males and females, and do values change with age?

The absence of oestrogen receptor, however, does not rule out the possibility that oestrogens may influence tissue by a mechanism not involving a 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 oestrogens 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. An immunological rather than hormonal mechanism consistent with this theory is the recent evidence that fetal suppressor cells are present which affect maternal adult lymphocytes and alter the mother's immunological reactivity, preventing rejection of the fetal allograft. Moreover proteins produced by the mother or a reduction in levels of maternal helper T cells may partly explain survival of the fetus. Changes in cellular and humoral immunity may occur during pregnancy and are thought to be responsible for the diminution during pregnancy of such autoimmune diseases as systemic lupus erythematosus or rheumatoid arthritis. Pregnancy has also been found to exert a beneficial effect on the Vogt-Koyanagi-Harada syndrome. Similarly, perhaps an increase in immunosuppression-related problems could occur which, for example, would allow development or growth of a pre-existing slow growing melanoma in the eye. Immunodeficiency states are associated with an increased incidence of neoplasia, but this has not been explored in the pregnant state.

To evoke an immunological mechanism there should be evidence that melanoma is an antigenic tumour. Virus-induced tumours are almost always antigenic, and there is suggestive evidence that at least some ocular melanomas contain virus. Moreover, evidence of immunological effects in melanoma patients has been demonstrated.

Our clinical observations pose the following questions: (1) Do pregnancy and other hormonal changes influence the occurrence of uveal melanomas? (2) Does pregnancy affect the course and prognosis of uveal melanomas, and if so, by what mechanism? A case control study would be helpful in answering these questions. Ideally, a prospective follow-up of melanoma patients in a national registry would be established to determine differences in occurrence as well as outcome in women of differing hormonal status controlling for histological and other prognostic factors. Such investigations may provide insight into the patho-physiology or therapeutic management of a subset of patients with ocular melanoma.

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