Characterization, treatment, and outcome of uveal melanoma in the first two years of life

Yacoub A Yousef *, Mais Alkilany

Department of Surgery/Ophthalmology, King Hussein Cancer Centre, Amman, Jordan

* Corresponding author at: Department of Surgery/Ophthalmology, King Hussein Cancer Centre, Queen Rania Al-Abdullah Street, P.O. Box 1269, Amman 11941, Jordan. Tel.: +962 5300460; fax: +962 5300460/1552. yyousef@khcc.jo

BACKGROUND AND OBJECTIVES: Features and characteristics of uveal melanoma are well described in adults, but little is known about the presentation of uveal melanoma in infancy.

DESIGN: Systematic literature review.

METHODS: A review of published, peer-reviewed literature reporting on uveal melanoma presenting during the first two years of life. Outcome measures included demographics, clinical features, histopathological findings, extent of the disease, therapeutic interventions, management outcomes, association with skin lesions or systemic diseases, and survival data.

RESULTS: This review revealed 13 reported cases (seven boys and six girls) of uveal melanoma diagnosed within the first two years of life. The median age at diagnosis was seven months. Orbital mass and proptosis were the most common presentations (38%); only one tumor (8%) was melanotic, and pathologically 10 tumors (77%) had epithelioid component. Associated pigmented skin lesions (cutaneous disease) were seen in six cases (46%). All affected eyes were surgically removed; three patients received chemotherapy, and one received radiotherapy. At a median follow-up of 25 months, two patients (15%) had metastasis, and one of them (8%) was dead at six months’ follow-up with liver and multi-organ metastasis.

CONCLUSIONS: Uveal melanoma can present within the first two years of life. In very rare cases, it can present as an intraocular tumor that simulates retinoblastoma, but it can also present as an orbital tumor. It has a tendency to affect patients with cutaneous diseases like familial atypical mole, melanoma syndrome, and dysplastic nevus syndrome. Despite this, uveal melanoma in this group has a more favorable prognosis than adult melanoma.

KEYWORDS: Choroid; Ciliary body; Iris; Melanoma; Tumor

Uveal melanoma, the most common primary intraocular malignant tumor in adults, is very rare in childhood. In a series of 8000 patients with uveal melanoma; 0.12% were diagnosed at age 10 years or younger, and no patient in that series was two years old or younger.

The literature contains a large body of data regarding the clinical features, management, outcome, and prognostic factors of uveal melanoma in adults, including histopathologic features and cytogenetic factors. However, little information is available on the specific clinical characteristics, pathologic features, survival, and late effects of uveal melanoma diagnosed in the first few months of life. This information may serve to advance treatment, educate healthcare providers, and improve monitoring and rehabilitation efforts for this specific entity of patients. We therefore present a literary review of the reported cases of uveal melanoma diagnosed in the first 24 months of life.

PATIENTS AND METHODS

A search for published, peer-reviewed literature reporting on uveal melanoma diagnosed during the first two years of life by MEDLINE search with key words “uveal melanoma, choroid melanoma, ciliary
body melanoma, iris melanoma, and uveal tumors” was conducted up to March 2014. We also examined reference lists of the reports. We analyzed in detail all case series and case reports describing uveal melanoma diagnosed in children aged two years or younger. We excluded cases with any diagnosis other than melanoma, and reports in languages other than English for which translation was not available.

Outcome measures included: demographics, clinical features, radiologic features, histopathologic findings, extent of the disease, therapeutic interventions, and management outcomes, as well as association with skin lesions or systemic diseases, and survival data.

RESULTS

Our review of Medline literature before March 2014 identified 13 cases of uveal melanoma diagnosed before 24 months of age between 1966 and 2013 (Table 1).

Patients and clinical characteristics

There were seven males (54%) and six females (46%). The affected eye was known in nine cases: in the right eye in four cases (44%), and in the left eye in five cases (56%). The median age at time of diagnosis was seven months (range: 0–19 months) (Table 1).

Table 1. Review of the literature: published case reports of uveal melanoma diagnosed within the first two years of life, and their demographics.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greer</td>
<td>1966</td>
<td>Australia</td>
<td>Birth</td>
<td>Male</td>
</tr>
<tr>
<td>Scheffer</td>
<td>1972</td>
<td>Utrecht</td>
<td>8 months</td>
<td>Female</td>
</tr>
<tr>
<td>Fledelius</td>
<td>1975</td>
<td>Denmark</td>
<td>11 months</td>
<td>Male</td>
</tr>
<tr>
<td>Jensen</td>
<td>1987</td>
<td>NA</td>
<td>3 months</td>
<td>Male</td>
</tr>
<tr>
<td>Broadway</td>
<td>1991</td>
<td>UK</td>
<td>Birth</td>
<td>Female</td>
</tr>
<tr>
<td>Posnick</td>
<td>1993</td>
<td>USA</td>
<td>Birth</td>
<td>Female</td>
</tr>
<tr>
<td>Joo</td>
<td>1993</td>
<td>NA</td>
<td>10 months</td>
<td>Female</td>
</tr>
<tr>
<td>Pallazi</td>
<td>2005</td>
<td>Brazil</td>
<td>Birth</td>
<td>Male</td>
</tr>
<tr>
<td>Thiagarajan</td>
<td>2011</td>
<td>India</td>
<td>Birth</td>
<td>Female</td>
</tr>
<tr>
<td>Rai</td>
<td>2011</td>
<td>NA</td>
<td>7 months</td>
<td>Male</td>
</tr>
<tr>
<td>Grabowska</td>
<td>2011</td>
<td>Spain</td>
<td>19 months</td>
<td>Male</td>
</tr>
<tr>
<td>Kumar</td>
<td>2011</td>
<td>Nepal</td>
<td>18 months</td>
<td>Male</td>
</tr>
<tr>
<td>Nawaiseh</td>
<td>2013</td>
<td>Jordan</td>
<td>16 months</td>
<td>Female</td>
</tr>
</tbody>
</table>

The presentation was variable between reported cases. Five patients (38%) presented with orbital mass (of variable sizes and extensions) and proptosis; two patients (15%) presented with glaucoma; two patients (15%) presented with facial mass; one patient (8%) presented with leukocoria; and one patient (8%) presented with strabismus. In two patients the presentation was not mentioned.

In five cases (38%), the tumor was from the choroid; in one case (8%) it was from the ciliary body; in one case (8%) it was mixed choroid and ciliary body; and in one case (8%) it was mixed iris and ciliary body. The tumor was not mentioned in the remaining five reports (Table 2).

Of the 13 cases, four (31%) had no extra uveal tumor extension; one (8%) had scleral invasion; two (15%) had extrascleral extension; three (23%) had orbital invasion (including extraocular muscles and orbital fat); and one case (8%) had maxillary as well as zygomatic bone invasion (Table 2).

Regarding tumor features, 10 patients (77%) had melanotic tumor; one (8%) had amelanotic tumor; while tumor features were not known in two patients (15%). Pathologically; seven cases (54%) were mixed-cell-type malignant melanoma; three cases (23%) were epithelioid type; one case (8%) was spindle cell type; and the pathology was not known in two cases. Chromosome 13 loss was reported in one case (8%) only.

Associated pigmented skin lesions were seen in six cases (46%), as follows: Familial atypical multiple mole melanoma (FAMMM) syndrome in four cases (31%); dysplastic nevus syndrome in one case (8%); and cafe au lait spots in one case (8%). Tumor characteristics are summarized in Table 2.

Not one of the patients in this review had a family history of melanomas or other malignancies.

Treatment and survival

The eyes of all reported cases of uveal melanoma diagnosed before the age of two years were surgically removed; 11 eyes (85%) by enucleation, and two eyes (15%) by exenteration. Systemic chemotherapy was given in two (15%) cases as adjuvant therapy after enucleation. In one case (8%), neoadjuvant chemotherapy was given, but since no tumor response was seen, exenteration was done.

One eye (8%) received external beam radiation therapy after exenteration (Table 2).

At a median follow-up of 25 months (range 6–120 months), two cases (15%) were reported to have metastasis. One patient (8%) who had chromosome 3 losses, and had trans-scleral invasion of epithelioid-type
Table 2. Clinical and pathological features, management and outcome of uveal melanomas diagnosed within the first two years.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Affected eye</th>
<th>Extension</th>
<th>Type</th>
<th>Pathology</th>
<th>Systemic association</th>
<th>Treatment</th>
<th>Metastasis</th>
<th>Genetics</th>
<th>Last follow up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green 6</td>
<td>1966</td>
<td>Ciliary body + iris</td>
<td>Left</td>
<td>Intraocular</td>
<td>Melanotic</td>
<td>Mixed cell</td>
<td>Multiple melanocytic nevus</td>
<td>Enucleation</td>
<td>No</td>
<td>None</td>
<td>2 years</td>
<td>Alive</td>
</tr>
<tr>
<td>Scheffer 7</td>
<td>1972</td>
<td>Uveal</td>
<td>Left</td>
<td>Intraocular</td>
<td>Melanotic</td>
<td>Epithelioid</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fledelus 8</td>
<td>1975</td>
<td>Choroid</td>
<td>NA</td>
<td>Intraocular</td>
<td>Mixed cell</td>
<td>Mixed cell</td>
<td>Dysplastic melanocytic nevi</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>6 months</td>
<td>Dead</td>
</tr>
<tr>
<td>Jensen 9</td>
<td>1987</td>
<td>Anterior Uveal</td>
<td>Left</td>
<td>Intraocular</td>
<td>Uveal</td>
<td>Uveal</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>2 years</td>
<td>Alive</td>
</tr>
<tr>
<td>Broadway 10</td>
<td>1991</td>
<td>Uveal</td>
<td>NA</td>
<td>Extraocular muscles and fat</td>
<td>Melanotic</td>
<td>Melanotic</td>
<td>Multiple melanocytic nevi</td>
<td>Extensive exenteration and CTX</td>
<td>No</td>
<td>No</td>
<td>25 months</td>
<td>Alive</td>
</tr>
<tr>
<td>Posnick 11</td>
<td>1993</td>
<td>Choroid</td>
<td>Left</td>
<td>Maxillary and zygomatic bones</td>
<td>Melanotic</td>
<td>Spindle cell</td>
<td>Café au lait spots</td>
<td>Enucleation followed by CTX</td>
<td>No</td>
<td>No</td>
<td>34 months</td>
<td>Alive</td>
</tr>
<tr>
<td>Joo 12</td>
<td>1993</td>
<td>Choroid + Ciliary body</td>
<td>Right</td>
<td>Sclera, optic nerve, extraocular muscles</td>
<td>Melanotic</td>
<td>Mixed cell</td>
<td>Multiple pigmented skin lesions</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>10 years</td>
<td>Alive</td>
</tr>
<tr>
<td>Palazzi 13</td>
<td>2005</td>
<td>Uveal</td>
<td>NA</td>
<td>Sclera</td>
<td>Melanotic</td>
<td>Epithelioid</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>Chromosome 3 loss</td>
<td>6 months</td>
<td>Dead</td>
</tr>
<tr>
<td>Rai 15</td>
<td>2011</td>
<td>Choroid</td>
<td>Right</td>
<td>Filling orbit up to orbital apex</td>
<td>Melanotic</td>
<td>Mixed cell</td>
<td>Multiple</td>
<td>Exenteration followed by XRT</td>
<td>No</td>
<td>No</td>
<td>34 months</td>
<td>Alive</td>
</tr>
<tr>
<td>Grabowska 15</td>
<td>2011</td>
<td>Uveal</td>
<td>Left</td>
<td>Intraocular</td>
<td>Melanotic</td>
<td>Mixed cell</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>3 years</td>
<td>Alive</td>
</tr>
<tr>
<td>Thiagarajan 14</td>
<td>2011</td>
<td>Ciliary body</td>
<td>Right</td>
<td>Extrascleral</td>
<td>Melanotic</td>
<td>Epithelioid</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kumar 7</td>
<td>2011</td>
<td>Choroid</td>
<td>Left</td>
<td>NA</td>
<td>Amelanotic</td>
<td>Mixed</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nawaiseh 18</td>
<td>2013</td>
<td>Choroid</td>
<td>Right</td>
<td>NA</td>
<td>Mix melanotic</td>
<td>Mixed</td>
<td>None</td>
<td>Enucleation</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: Data not available.
CTX: Chemotherapy, XRT: Radiotherapy.
tumor died with orbital recurrence and multiple metastasis six months after enucleation, and one patient (8%) who had extraocular invasion by epithelioid type tumor had liver metastasis at his last follow-up 34 months after enucleation and adjuvant chemotherapy (Table 2).

DISCUSSION

In a series of 8000 patients with uveal melanoma, 0.12% of patients were diagnosed between two and 10 years of age, while no patient in that series was two years or younger.3 In our review of the literature, only 10 patients were diagnosed with uveal melanoma within the first 24 months of life.

Familial atypical mole and melanoma syndrome (FAM-M), previously described as B K mole syndrome,19 dysplastic nevus syndrome,20 and familial atypical multiple mole-melanoma syndrome (FAMMM),21 are characterized by a hereditary predisposition to cutaneous melanoma.22 Singh et al.23 tried to study the possible correlation between these cutaneous diseases and uveal melanoma by running a retrospective review of 4600 consecutive patients with diagnosis of primary uveal melanoma. They found eight patients (0.2%) who had uveal melanoma and biopsy-proven FAM-M syndrome at the same time.23 In addition, they found that in patients with FAM-M syndrome, the uveal melanoma occurred at a relatively young age (mean 40 years).23 Of the total 13 cases of uveal melanoma diagnosed in the first 24 months of life in our review, we found five cases (38%) of congenital choroidal melanoma, four of them associated with systemic features of FAMMM, or dysplastic nevus syndrome, and one more case diagnosed with choroidal melanoma at age three months had dysplastic nevus syndrome. Since atypical cutaneous nevi in the FAM-M syndrome are the precursors of cutaneous melanoma,24 and due to evidence of an increased number of uveal nevi in patients with FAM-M syndrome,25 and in addition to the reported case of uveal nevi that showed transformation to uveal melanoma in a patient with iris melanoma,26 we expect that the five cases (38%) in our review who had associated FAMMM or dysplastic nevus syndrome evolved from precursor lesions in the uveal tissues.

The survival time observed for most uveal melanoma that extended outside the eye in adults was brief, with death occurring within months or, exceptionally, a few years.27 In younger patients in this review, seven had scleral, extrascleral, or orbital invasion and only two (28%) had metastasis. Two patients with extraocular disease and without metastasis had received chemotherapy, and one had received radiation therapy. It is possible that ocular melanomas in children may have a more favorable response to chemotherapy than those in adults, but given the small sample size, it becomes impossible to draw an accurate conclusion.

The cellular composition of melanoma is important because mixed-cell-type tumors have been associated with more tumor growth and mortality than spindle-cell-type tumors.3 Spindle-cell type may be more commonly found in uveal melanoma in children (46%) than in adults,27 and that partially explains why uveal melanoma in young patients (20 years or less) was associated with a lower rate of metastasis than in mid-adults and older adults.26,27 In contrast, 77% of cases in this review were of mixed-cell-type tumors or of epithelioid-cell-type, and despite that, metastasis was seen only in 1% of cases. Of more interest, seven cases (54%) in our review had extraocular tumor invasion, and only two cases (15%) had metastasis. The unexpected low rate of metastasis with these poor prognostic pathologic and clinical features may be due to the short follow-up time for the cases in this review, or to different behavior between uveal melanoma presenting at a very young age and melanoma in adults. Only one case in this review had genetic analysis which showed monosomy 3: the patient who had metastasis and who subsequently died. Therefore, genetics in pediatric uveal melanoma may have a more important prognostication role than clinical and pathologic features. This is, however, a premature conclusion because of the small sample size and short follow-up.

The differential diagnosis of pediatric uveal melanoma includes medulloepithelioma, melanocytoma, neuroepithelial cysts, hemangiomas and hematomas, and acquired inflammatory masses. Even uveal melanoma in children is very rare, and should be considered in the differential diagnosis of intraocular mass in children, mainly when associated with predisposing factors such as neurofibromatosis type 1, ocular or oculodermal melanocytosis, and dysplastic nevus syndrome.

In conclusion, this review illustrates that uveal melanoma can present within the first 24 months of life in very rare cases. It can present as intraocular tumor that simulates retinoblastoma, but it can also present as orbital tumor. It has a tendency to affect patients with cutaneous diseases like familial atypical
UVEAL MELANOMA IN INFANTS

mole and melanoma syndrome and dysplastic nevus syndrome. Despite these facts, uveal melanoma in this patient group has a more favorable prognosis than adult melanoma.

REFERENCES

15. Barr CC, McLean NW, Zimmerman LE. Uveal melanoma of the choroid in an infant with the dysplastic naevus syndrome and melanoma syndrome and dysplastic nevus syndrome. Despite these facts, uveal melanoma in this patient group has a more favorable prognosis than adult melanoma.