SCIENTIFIC REPORT

Iris ring melanoma: fine needle biopsy

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Aims: To delineate the diagnostic accuracy of fine needle biopsy in iris ring melanoma and determine the tumour related mortality of this neoplasm.

Methods: A retrospective analysis of 22 patients with iris melanomas that involve the entire 360 degrees of the anterior chamber angle.

Results: Iris ring melanomas were correctly diagnosed in all cases. In 11 of 16 cases (69%) a fine needle biopsy performed 180 degrees away from the main mass was positive for an iris ring melanoma. The tumour related mortality in iris ring melanoma cases was four of 22 patients (18%). Actuarial survival analysis showed a 10 year mortality (Kaplan-Meier) of 15%.

Conclusion: A fine needle aspiration biopsy can be used to diagnose an iris ring melanoma. Iris ring melanomas have significant mortality compared with focal tumours.

Iris ring melanomas are quite rare, usually misdiagnosed, and have higher tumour related mortality than focal iris tumours.¹ Most series have described an iris ring melanoma as a tumour that involves 360 degrees of the anterior chamber angle, although it can sometimes present as an apparently focal iris mass.¹ The first descriptions of this entity were by Vose and Solomon in 1882; Ewetzky originated the term “ring sarcoma” in 1898.^{2,3} In a case report in 1926, Murray noted 20 previous cases; over 60% presented with glaucoma.⁴ Rockwell summarised 32 cases of iris or ciliary body ring melanomas published before 1952.⁵ In a review of cases from the Wills Eye Hospital, 14 iris ring melanomas accounted for 0.2% of uveal melanomas managed at that institution.⁶ They noted a mean delay of diagnosis of approximately 8 months, and three of 12 patients with adequate follow up developed metastases.⁶ Similarly, a review of four cases from London observed that all patients were misdiagnosed, often had invasive glaucoma procedures, and two of four developed metastatic disease.⁷ In a report from Denmark, four of 10 iris ring melanomas developed metastatic disease.⁸

In 1989, we demonstrated that we could establish the correct diagnosis of an iris ring melanoma with fine needle aspiration biopsy (FNAB) of the anterior chamber angle 180 degrees away from a clinically solitary tumour mass with diffuse anterior chamber angle pigmentation.⁹ Subsequently, we and others have noted that while FNAB may often be useful in this setting its accuracy is not known.^{10–12}

We have reviewed iris ring melanoma cases to delineate the diagnostic accuracy of a fine needle biopsy and the tumour related mortality associated with this neoplasm.

METHODS

We reviewed the ophthalmic oncology database of the Tumori Foundation, and after obtaining human experimentation approval (CCPMC Human Experimentation Committee), retrieved all records in which either patients

were initially thought by us to have a possible iris ring melanoma on clinical examination, or developed one on subsequent follow up. All cases had histological confirmation of an iris ring melanoma that involved 360 degrees of the anterior chamber angle. All cytopathology and histopathology data were re-reviewed.

Twenty two patients had iris ring melanomas, although none was referred with that diagnosis. No patient had ultrasonographic evidence of ciliary body involvement. Eleven patients were studied with high frequency ultrasound; the others were analysed with emersion B-scan techniques before 1995. The mean age at diagnosis was 51.8 years (range 8.6–86.2 years) and the mean interval from onset of symptoms to first eye therapy was 4 years (range 2 weeks to 26 years). We portioned our cases into those in which a FNAB was performed and led to the correct diagnosis, those that had a false negative fine needle biopsy, and those four that did not have a fine needle biopsy in their initial evaluation. All fine needle biopsies were done with a 25 gauge needle going through a transcorneal route into the iris-corneal angle 180 degrees away from the main tumour mass. In cases of heterochromia without a distinct mass, an area of angle pigmentation was biopsied in this manner. In all cases the material was alcohol fixed and examined in the operating room using a toluidine blue “fast stain.” A typical positive cytopathological biopsy is shown in figure 1. Note it is paucicellular.

RESULTS

Our search identified 11 patients who were considered to have an iris ring melanoma on the basis of clinical and ancillary examinations. In 11 cases we initially thought, on the basis of clinical examination and ancillary studies, that the patient had an iris ring melanoma. All 11 had a 4+ pigment band 360 degrees in the anterior chamber angle. Seven had an apparently focal iris mass, and a 25 gauge FNAB was performed 180 degrees away from the main tumour mass. Four patients presented with only iris

Figure 1 Typical paucicellular specimen positive for melanoma at 60×.

Abbreviation: FNAB, fine needle aspiration biopsy

Table 1 Summary of results

	Total	True positive	False negative	True negative (excluded from further analysis)	FNAB not performed
FNAB results	–	11 (69%)	5 (31%)	4	6
Number of patients presenting with elevated intraocular pressure	14 (64%)	8	2	4	4
Number of patients who developed metastases	4 (18%)	1	1	0	2

heterochromia, and an FNAB was done in the inferior angle. All had a positive FNAB, and enucleation confirmed the diagnosis of a ring melanoma. Eight of these 11 patients had increased intraocular pressure at presentation. In two patients with diffuse heterochromia, a previous iris biopsy was read as benign. Four of the patients, two with an iris mass and two with heterochromia, had been treated with a trabeculectomy prior to referral. Long term follow up was available on all 11 cases, and one died of metastatic melanoma 12 years after enucleation (table 1).

In nine cases, negative fine needle biopsies were obtained in the setting of a mass and pigment in more than 270 degrees of the anterior chamber angle. Four cases were true negative FNABs; they had had iridocyclectomies with more than 5 years of follow up without recurrence. These latter cases were not included further in our analysis.

Five patients had false negative FNAB. All had focal iris tumours, but we suspected a ring melanoma because of suspicious pigment in the anterior chamber angle away from the mass. Two of these patients had elevated intraocular pressure at presentation. The needle biopsies were performed with a 25 gauge needle 180 degrees away from the mass lesion. All patients with an iris mass lesion and a negative needle biopsy underwent iridocyclectomies. They were informed of the possibility that they may have had a false negative fine needle biopsy and might require later enucleation if resection margins were positive. In all cases the resection margins were positive for tumour and the eye was later enucleated. On follow up, with a mean of over 6 years in this group, one patient with a mixed cell melanoma developed metastatic disease 2.5 years after enucleation.

We reviewed the predominant cell type in the histological specimens in which there was a false negative compared to true positive FNAB. Six of 11 positive FNAB cases had spindle cell tumours, and five were mixed cell melanomas. In the false negative group, one case had only epithelioid cells and four were mixed cell melanomas.

Six iris ring melanoma patients did not have FNAB. One case was previously reported.⁹ She developed heterochromia and increased pressure. A quadrant iridectomy was performed but did not demonstrate malignancy. She was

treated with topical anti-glaucoma medications, but when vision diminished and the eye became painful we were allowed to enucleate the eye, which contained a ring melanoma. She died of metastatic melanoma 13 years later. One patient refused enucleation and requested resection of the iris tumour. This was performed, but the eye was enucleated 2 years later because of pain; it contained a ring melanoma. One patient presented with a ring melanoma and a small area of extrascleral pigment. Biopsy of the nodule was positive for melanoma and the eye was enucleated. One patient requested enucleation when given the clinical diagnosis. Two patients presented with a focal iris lesion, normal pressures and no increased pigment band in the anterior chamber angle. In both cases, one of three margins of the iridocyclectomy specimens were positive, both recurred, and on enucleation a ring melanoma was diagnosed. One of these patients died of metastases. None developed focal extraocular extension.

Overall, four of 22 patients (18%) developed metastatic disease. Actuarial survival analysis is shown in table 2 and figure 2. The Kaplan-Meier 10 year tumour mortality estimate was 15%.

None developed localised extrascleral extension. One had a previous iris biopsy, one a primary enucleation, and two iridocyclectomies followed by prompt enucleation where positive margins were noted. None of the patients who had trabeculectomies developed metastatic disease. In living patients the mean follow up was 6 years (range 1 month to 20 years). One patient has died of non-malignant disease. No patient was lost to follow up.

DISCUSSION

Iris ring melanomas can be treacherous for several reasons. (1) They are often not initially diagnosed. The patient may present without a mass with either subtle heterochromia or marked pigmentation only visible in the trabecular meshwork and not the iris surface. (2) A number of these patients are initially misdiagnosed with either idiopathic or pigmentary

Table 2 Diffuse melanoma related mortality

Interval	Kaplan-Meier survival	
	Estimate	95% CI
5 year	93.30%	(61.3% to 99.0%)
10 year	84.80%	(51.2% to 96.0%)
15 year	70.70%	(30.6% to 90.3%)
20 year	70.70%	(30.6% to 90.3%)

Figure 2 Diffuse melanoma related mortality.

glaucoma. In two such cases in this series, trabeculectomies were performed. We have seen other such patients who have melanoma growing out of their filtering sites (unpublished data). (3) Probably because of the diagnostic confusion with treatment delay there is significantly higher tumour related mortality in patients with iris ring melanoma compared with those with solitary iris tumours.

Several different patterns and proposed mechanisms of iris ring melanoma development have been presented in the literature.¹⁻¹² Ring melanomas can involve the choroid, ciliary body, iris, or a combination of sites. Reese pointed out that these tumours could either grow within the confines of uveal tissue or disseminate by diffuse implantation.¹⁰ Manschot pointed out that probably both mechanisms occur in angle tumours, as our data demonstrate.¹¹

Usually ring melanomas are not initially correctly diagnosed, and Yanoff made the point that when glaucoma was present, uveal melanomas were undiagnosed much more frequently.¹² He delineated different glaucoma mechanisms that can occur in eyes containing uveal melanomas, including primary open angle, diffuse tumour infiltration into the angle, closure of the angle by tumour or effusion, and pigment laden macrophages clogging the outflow.¹² One case of neovascular glaucoma associated with a ring melanoma has been reported.¹³ Increased intraocular pressure and an angle mass is not always caused by a ring melanoma. While even rarer, benign naevi, angle haemosiderosis, lymphoma, and melanocytomas can present in this manner.¹⁴⁻¹⁷ Because of the diagnostic difficulty associated with ring melanoma, the latency between onset of patient awareness and correct diagnosis was delayed in this and other reports.⁶

How useful is FNAB in these atypical cases? In this series, 11 of 16 biopsies were positive. The major limitation is that even in an optimal setting the specimens are paucicellular. Therefore, the cytopathologist is faced with a difficult decision with relatively few cells to base a diagnosis on. Frankly, given the setting where we have deliberately biopsied away from the main tumour mass, we have been impressed that we obtained a positive biopsy in 69% of iris ring melanoma cases.

In cases with false negative biopsy, we recommend an open biopsy be performed. If there is a solitary mass we will do an iridocyclectomy and carefully assess the margins. If there is only heterochromia, an open biopsy is done in the most thickened area. The caveat in the latter setting is we have managed one patient in which quadrant iris biopsy was negative and yet several years later diffuse melanoma of the iris was confirmed histologically.

A major limitation of fine needle biopsy for iris ring melanoma diagnosis is the paucity of material obtained for cytopathological analysis. We have not used a vitrectomy instrumentation. In previous studies on ocular lymphomas, mechanical suction/cutting devices have degraded cytology.¹ In some cases where a liquid specimen is obtained (and we try to not aspirate anterior chamber fluid) we do an immediate cytocentrifuge preparation then analyse the cells in an alcohol fix toluidine blue stained preparation. A cytospin takes an additional 2-3 minutes, but usually there is insufficient fluid specimen for it to be useful.

The Kaplan-Meier estimate of 10 year tumour mortality was 15% overall; 18% of patients died of metastases. We are

uncertain why this is less than noted by several other investigators.⁷⁻⁸ Since no patient was lost to follow up and the mean follow up from our therapy was over 6 years, it is probably an accurate assessment.

The strengths of the study are that it is from a single institution with a relatively large number of patients. The obvious weaknesses of the study are several. (1) This is a very rare tumour and it is possible that we have selected a group of patients who are not representative of those that might be seen in other centres. (2) The FNAB technique is challenging both in terms of getting an adequate specimen and cytopathological analysis to make a decision based on a small number of cells. Fine needle biopsy is useful in patients with possible iris ring melanomas but, as above, it has limitations.

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