DIAGNOSTIC TRANSVITREAL FINE-NEEDLE ASPIRATION BIOPSY OF SMALL MELANOCYTIC CHOROIDAL TUMORS IN NEVUS VERSUS MELANOMA CATEGORY

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ABSTRACT

Purpose: To report an experience with fine-needle aspiration biopsy of selected small melanocytic choroidal tumors during the interval from April 13, 1983, through January 19, 2001.

Methods: Retrospective descriptive case series report of 34 patients with a small melanocytic choroidal tumor (maximal diameter, ≤10 mm; thickness, ≥1.5 mm but ≤3 mm) evaluated diagnostically by transvitreal fine-needle aspiration biopsy prior to treatment. None of the tumors had invasive features at the time of biopsy.

Results: Patients ranged in age from 26 to 73 years (mean, 50.9 years). The evaluated choroidal tumors had a mean maximal basal diameter of 8.0 mm and a mean maximal thickness of 2.4 mm. Eighteen of the 34 tumors (52.9%) had been documented to enlarge prior to biopsy. Biopsy was performed in all cases using a 25-gauge hollow lumen needle and a transvitreal approach via a pars plana puncture site. The biopsy yielded a sufficient aspirate for cytodiagnosis in 22 of 34 cases (64.7%). In these cases, the tumor was classified as malignant melanoma in 16 (47.1% of total), intermediate lesion in 4 (11.8%), and benign nevus in 2 (5.9%). The 12 tumors that yielded an insufficient aspirate and the four lesions that yielded intermediate cells continued to be classified as "nevus versus melanoma" and were monitored periodically for growth or other changes. Four of the 12 tumors that yielded an insufficient aspirate for cytodiagnosis and all four lesions that yielded intermediate cells were eventually reclassified as small choroidal melanomas and treated. The remaining eight tumors that yielded an insufficient aspirate and the two tumors that yielded benign nevus cells were classified as benign nevi at the most recent follow-up evaluation.

Conclusions: Fine-needle aspiration biopsy showed that a substantial proportion of small melanocytic choroidal tumors likely to be classified clinically as small choroidal melanomas in many centers were in fact benign nevi or intermediate lesions.

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INTRODUCTION

Several years ago, I (J.J.A.) spoke to the American Ophthalmological Society about whether observation is really appropriate management for suspected small choroidal melanomas.[1] In that presentation, I indicated that there were significant potential benefits as well as significant potential risks of observing versus promptly treating such tumors. I concluded that "observation as management for patients with such tumors . . . appears to be an acceptable management approach for the time being in the absence of convincing evidence to the contrary." I went on to indicate that the prospects for resolving the question of the preferred management of a small suspected choroidal melanoma appeared bleak.

Today I would like to present evidence I have accumulated regarding the role of transvitreal fine-needle aspiration biopsy for differential diagnosis of small suspected choroidal melanomas in the nevus versus melanoma category. On the basis of my experience, I believe that diagnostic transvitreal fine-needle aspiration biopsy has an important role in distinguishing between small suspected choroidal melanomas that need to be treated promptly and those that can and probably should be managed by observation, at least initially.

For the purposes of this study, a small melanocytic

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choroidal tumor was defined as a choroidal tumor classified as probably melanocytic on the basis of its ophthalmoscopic appearance and measuring ≤10 mm in maximal basal diameter and ≤3 mm in maximal thickness, as determined by ophthalmoscopic fundus mapping and B/A-scan ultrasonography. A small melanocytic choroidal tumor was subclassified as a "nevus versus melanoma" if it did not exhibit clearly invasive clinical features such as focal nodular eruption through Bruch's membrane, retinal invasion, scleral invasion (by B-scan ultrasonography), and transcleral tumor extension (by B-scan ultrasonography). Any small melanocytic choroidal tumor that exhibited one or more of these invasive features was categorized as an unequivocal small melanoma and not a nevus versus melanoma. Similarly, a suspected melanocytic choroidal tumor that was larger than 10 mm in diameter, larger than 3 mm in thickness, or both, but exhibited no clearly invasive clinical features was subcategorized as an atypical probable melanoma and not a nevus versus melanoma. Unequivocal small choroidal melanomas and atypical probable choroidal melanomas were not evaluated in this study.

The purposes of this study were (1) to summarize the cytopathologic findings in a series of patients who underwent transvitreal fine-needle aspiration biopsy of a small melanocytic choroidal tumor in the nevus versus melanoma category and (2) to evaluate the accuracy of cytopathologic diagnosis in these cases using final diagnosis through available follow-up as our standard.

METHODS

PATIENTS

With the aid of my coauthors, I have developed and currently maintain a computerized database of all fine-needle aspiration biopsies performed by me personally since my initial case in 1981. As of January 31, 2001, this database contained 385 patients. Some of the early cases in this database have been reported.[2-7] Using a computerized records search, my coauthors and I identified 34 patients on whom a diagnostic fine-needle aspiration biopsy was performed to evaluate a small melanocytic choroidal tumor in the nevus versus melanoma category. To be categorized as a nevus versus melanoma, the tumor had to appear at least partially melanotic, measure ≤10 mm in maximal basal diameter, measure ≥1.5 mm but ≤3.0 mm in thickness, and exhibit no invasive ophthalmoscopic features (retinal invasion, optic disc invasion, eruption of the tumor through Bruch's membrane) or ultrasonographic features (scleral invasion, transcleral tumor extension). Presence or absence of overlying or surrounding serous subretinal fluid, surface clumps of orange pigment (lipofuscin), and documented lesion enlargement were recorded in each case but were not used as classification factors in this study. The first of these biopsies was performed April 13, 1983, and the last was performed January 19, 2001. Table I contains data on demographic and ophthalmic variables in the 34 patients.

CLINICAL DIAGNOSTIC METHODS

All patients in the database underwent comprehensive baseline prebiopsy ophthalmic evaluation by me personally. Components of the evaluation included assessment of best corrected visual acuity in each eye, evaluation of the external appearance of each eye in diffuse light, evaluation of the anterior segment features of each eye by slit-lamp biomicroscopy, measurement of the intraocular pressure in each eye by applanation tonometry, evaluation of the fundus features of each eye by non–contact lens fundus biomicroscopy and indirect ophthalmoscopy, preparation of a detailed fundus drawing of the affected eye, and performance of B/A-scan ultrasonography of the affected eye. The appearance of each lesion was documented by color fundus photography. Fluorescein angiography or indocyanine green angiography was performed in some cases but was not obtained routinely in all cases.

INFORMED CONSENT

All patients in this series were advised completely about my clinical findings and differential diagnosis, the implications of the tumor for sight in the affected eye and survival, and the recognized potential benefits versus potential risks of available treatment options ranging from observation as management[1] to enucleation of the affected eye. Patients who underwent fine-needle aspiration biopsy during the first few years of the study were required to sign an investigational informed consent document that had been reviewed and approved by the institutional review board (IRB) of Wills Eye Hospital, Baltimore, Maryland. The same IRB reviewed the results obtained over the first 3 years and approved the procedure as a standard diagnostic method by the senior author in 1985. Since that time, patients have only had to review and sign a standard informed consent document for diagnostic or therapeutic procedure.

BIOPSY TECHNIQUE

The biopsy in every case was performed in the operating room as an outpatient surgical procedure with the patient under local anesthesia (retrobulbar injection of carbocaine or xylocaine). In every patient, the biopsy was performed by means of an eye-wall puncture in the pars plana region using a 25-gauge sharp hollow-lumen biopsy needle. The meridional location of the eye-wall puncture site was selected on the basis of the intraocular tumor location. The site was prepared by making a partial-thick-

TABLE I: BASELINE PREBIOPSY FEATURES OF 34 PATIENTS AND THEIR TUMORS

CASE NO.	AGE (YR)	SEX	AFFECTED EYE	BEST CORRECTED DISTANCE VISUAL ACUITY IN AFFECTED EYE (SNELLEN)	SIZE OF TUMOR			LOCATION OF POSTERIOR TUMOR MARGIN	
					MAXIMAL BASAL DIAMETER (MM)	MINIMAL BASAL DIAMETER (MM)	THICKNESS (MM)	LOCATION RELATIVE TO FOVEA	LOCATION RELATIVE TO OPTIC DISC
1	33	F	R	20/30	7.5	7.0	1.9	subfoveal	≤3 mm from disc
2	57	F	L	20/15	8.5	7.5	2.5	>3 mm from fovea	>3 mm from disc
3	37	F	R	20/20	6.0	5.5	1.9	subfoveal	to disc margin
4	64	M	L	HM	8.0	6.0	2.0	≤3 mm from fovea	>3 mm from disc
5	27	F	R	CF	5.5	5.5	3.0	subfoveal	to disc margin
6	39	F	R	CF	7.0	5.5	2.2	subfoveal	to disc margin
7	26	F	L	20/40	8.5	7.0	2.9	≤3 mm from fovea	to disc margin
8	33	F	R	20/20	8.0	6.5	2.2	>3 mm from fovea	≤3 mm from disc
9	41	F	R	20/50	9.5	7.0	1.7	>3 mm from fovea	>3 mm from disc
10	30	M	L	20/40	5.5	5.0	2.9	≤3 mm from fovea	≤3 mm from disc
11	73	M	L	20/15	10.0	10.0	2.9	≤3 mm from fovea	>3 mm from disc
12	68	F	L	20/30	9.0	5.5	2.8	>3 mm from fovea	>3 mm from disc
13	60	M	L	20/25	8.5	4.5	2.0	>3 mm from fovea	>3 mm from disc
14	62	F	R	20/20	6.5	6.5	2.9	≤3 mm from fovea	to disc margin
15	40	M	L	20/15	7.0	5.5	2.4	>3 mm from fovea	>3 mm from disc
16	67	M	R	20/20	8.5	6.5	2.4	>3 mm from fovea	>3 mm from disc
17	44	M	R	20/15	9.5	8.5	2.7	>3 mm from fovea	>3 mm from disc
18	62	F	L	20/25	9.0	9.0	2.2	≤3 mm from fovea	>3 mm from disc
19	54	F	L	20/15	7.0	5.0	2.0	≤3 mm from fovea	>3 mm from disc
20	45	F	R	20/20	7.5	6.5	2.7	≤3 mm from fovea	>3 mm from disc
21	55	F	L	CF	8.5	8.5	2.2	subfoveal	to disc margin
22	38	F	R	20/20	8.5	7.5	2.9	>3 mm from fovea	>3 mm from disc
23	64	M	R	20/20	9.0	9.0	2.4	subfoveal	≤3 mm from disc
24	73	M	L	20/40	7.0	5.0	2.4	≤3 mm from fovea	>3 mm from disc
25	54	F	R	20/20	8.0	8.0	2.2	≤3 mm from fovea	≤3 mm from disc
26	29	F	L	CF	9.0	7.5	2.7	subfoveal	≤3 mm from disc
27	42	M	R	20/20	8.5	5.5	1.7	>3 mm from fovea	>3 mm from disc
28	64	M	L	20/100	7.0	6.0	2.2	≤3 mm from fovea	≤3 mm from disc
29	60	F	R	20/40	10.0	5.0	2.2	subfoveal	≤3 mm from disc
30	53	F	R	20/15	8.5	8.0	2.7	>3 mm from fovea	>3 mm from disc
31	46	M	L	20/20	9.0	8.0	3.0	≤3 mm from fovea	>3 mm from disc
32	57	F	L	20/50	7.5	4.5	1.7	subfoveal	≤3 mm from disc
33	59	M	L	20/60	8.0	5.0	1.7	subfoveal	to disc margin
34	60	F	R	20/15	8.5	8.0	2.4	≤3 mm from fovea	to disc margin

ness scleral incision parallel to the limbus in the selected meridian at a measured 3.5 mm from the limbus. This partial-thickness scleral incision was generally 0.5 to 1.0 mm in length. In every case, the needle was bent with a hemostat just above the end of the bevel. The angle of the bend was determined by the intraocular location of the tumor. The hub of the needle was attached via a 12- to 18-inch-long segment of sterile plastic tubing to a 10-mL aspirating syringe. Before the eye wall was punctured with the biopsy needle, the globe was fixed in appropriate position using two or more traction sutures of 4-0 black silk passed behind the insertions of selected rectus muscles. After the eye wall was punctured with the tip of the needle, the position of the needle was monitored during its passage through the vitreous and retina into the substance of the choroidal tumor using indirect ophthalmoscopy. Once the tip of the needle was in the tumor, aspiration was performed by the surgical assistant. The tip of the needle was moved slightly in and out along its path, and aspiration was repeated after each slight repositioning. In most cases, at least 10 aspirations were performed. All suction was released, and the needle was quickly withdrawn from the eye. Light digital pressure was maintained for about 60 seconds on the puncture site to provide hemostasis.

The aspirate within the needle was submitted to our cytopathologists for analysis. In most cases, a second needle was used to sample a different portion of the tumor. In some cases, a third needle was used to sample yet another site within the tumor. The determining factors regarding

a second or third needle pass were the amount of bleeding encountered and the ability to safely visualize the tumor.

PATHOLOGIC PROCESSING OF ASPIRATES

Several different processing methods have been used by the various cytopathologists involved in this series over the years. From 1981 through 1999, all aspirates were suspended in approximately 1 to 2 mL of balanced salt solution and delivered in suspension to the cytopathologist. Until 1991, the fluid specimen was divided into two unequal portions (about 67% and 33%). The larger portion was processed by membrane filtration and stained by a modified Papanicolaou method for cytomorphologic evaluation. The smaller aliquot was processed by the cytospin method and used for histochemical (Fontana-Masson) and immunocytochemical stains when indicated.[8] From 1991 through 1999, the fluid specimen was processed entirely by the cytospin method. From 1999 through the present, a cytopathologist has attended the surgery, prepared at least two direct smears from each aspirate (one air-dried, the other alcohol-fixed) in the operating room, and processed the remainder of the specimens by membrane filter technique or cytospin after return to the cytopathology laboratory. The air-dried direct smears were processed by the Dif-Quik method, while the alcohol-fixed smears were stained with the Papanicolaou stain. The reserve portion of the specimen used immunocytochemical stains, including HMB-45, Melan-A, and S-100.

CYTOPATHOLOGIC DIAGNOSIS

Stained slides were interpreted with use of conventional cytomorphological criteria for distinguishing benign from malignant cells. Histochemically or immunocytochemically stained slides were reviewed to refine the diagnosis in difficult cases.

REVISED DIAGNOSIS AFTER BIOPSY

Following fine-needle aspiration biopsy, the working diagnosis was revised to reflect the cytopathologic findings in the cases with a sufficient specimen for cytodiagnosis but remained nevus versus melanoma in the cases with an insufficient aspirate for cytodiagnosis.

POSTBIOPSY TUMOR MANAGEMENT

Management of the tumor following biopsy was directed by the cytopathologic findings. In cases with a revised diagnosis of choroidal melanoma, prompt treatment of the tumor was routinely recommended. In cases with a cytopathologic diagnosis of benign choroidal nevus, observation as management was recommended after the biopsy. In cases with an insufficient specimen for cytodiagnosis or intermediate melanocytic cells (ie, borderline between nevus and melanoma), the patient was advised of the nondiagnostic result and then managed as if the biopsy had not been performed. In some of these cases, the tumor was managed by observation, and in others the tumor was treated by a locally destructive therapy (usually plaque radiotherapy).

FOLLOW-UP AND FINAL DIAGNOSIS

The final diagnosis in each case was regarded as the diagnosis assigned the tumor on the basis of all information accumulated during available follow-up. In cases managed by enucleation following the biopsy, the final diagnosis was the histopathologic diagnosis assigned to the tumor on the official pathology report. In all other cases, the final diagnosis was determined by the clinical course. Tumors treated by a locally destructive treatment were considered to be genuine malignant melanomas. Tumors managed by observation were given a final diagnosis of choroidal melanoma if the tumor eventually exhibited invasive clinical features or substantial enlargement. In contrast, tumors managed by observation were given a final diagnosis of choroidal nevus if the tumor exhibited minimal or no subsequent enlargement and no invasive features during available follow-up.

RESULTS

PATIENTS

The 34 study patients ranged in age from 26.5 to 73.1 years (mean, 50.9 years) (Table I). Thirteen patients were male (38.2%) and 21 were female (61.8%). The right eye was affected in 18 patients (52.9%) and the left eye in 16 (47.1%). Twenty of the 34 patients (58.8%) had visual symptoms attributable to the tumor, and 14 (41.2%) were visually asymptomatic. Visual acuity in the affected eye at the prebiopsy examination was ≥20/25 in 19 (55.9%), <20/25 but ≥20/40 in 6 (17.6%), <20/40 but ≥20/200 in 4 (11.8%), and <20/200 in 5 (14.7%).

TUMORS

The anterior margin of the tumor was at or posterior to the ocular equator in 32 of the 34 cases (94.1%) (Table I). The posterior margin of the tumor extended to the optic disc margin in 8 cases (23.5%), was within 2 disc diameters of the optic disc in 9 (26.5%), and was over 2 disc diameters from the optic disc in 17 (50.0%). It extended to or beneath the fovea in 10 eyes (29.4%), was within 2 disc diameters from the fovea in 13 (38.2%), and was over 2 disc diameters from the fovea in 11 (32.4%). The maximal basal diameter of the tumor ranged from 5.5 mm to 10.0 mm (mean, 8.0 mm), and the maximal tumor thickness ranged from 1.7 mm to 3.0 mm (mean, 2.4 mm).

ASSOCIATED FEATURES

A limited shallow serous retinal detachment was present overlying and surrounding the tumor in 13 (38.2%) of the 34 eyes, but the retina was fully attached in 21 eyes (61.8%). Prominent clumps of orange pigment were present on the surface of the tumor in 9 cases (26.5%) but were absent in 25 cases (73.5%). Eighteen of the 34 tumors (52.9%) had been documented to enlarge at least slightly following initial detection but prior to transvitreal biopsy.

ADEQUECY OF ASPIRATES

Transvitreal fine-needle aspiration biopsy yielded a sufficient aspirate for cytodiagnosis (Table II) in 22 of the 34 cases (64.7%). In the other 12 cases (35.3%), the aspirate was graded as insufficient for cytodiagnosis. Rebiopsy of the tumor was performed in two cases that yielded an insufficient specimen for cytodiagnosis initially (cases 14 and 21). In case 14, rebiopsy of the slightly enlarged tumor 42 months after the initial biopsy again produced an insufficient specimen for cytodiagnosis. We continue to regard this tumor as a benign choroidal nevus. In case 21, rebiopsy of the slightly enlarged tumor 10 months after the initial nondiagnostic biopsy yielded cells consistent with malignant melanoma of spindle-cell type. This tumor was treated by an eye-preserving therapy immediately following the second biopsy.

CYTODIAGNOSIS

Among the 22 cases with a sufficient aspirate (Table II), the cytologic diagnosis was malignant cells consistent with melanoma in 16 cases (72.7%), benign cells consistent with choroidal nevus in 2 (9.1%), and intermediate cells consistent with either atypical nevus or low-grade melanoma in 4 (18.2%). The mean thickness of the tumor in the 12 cases with an insufficient specimen for cytodiagnosis was 2.27 mm, while that for the 22 cases with an adequate specimen was 2.43 mm. This difference was not statistically significant (independent groups *t* test, $P = .33$).

POSTBIOPSY TUMOR DIAGNOSIS

Our working diagnosis following fine-needle aspiration biopsy (Table II) changed from nevus versus melanoma to choroidal melanoma in 17 of the 34 cases (50%) and to benign choroidal nevus in 2 (5.9%). Our working diagnosis remained nevus versus melanoma in 15 cases (44.1%). Among these 15 cases, the reason that the biopsy did not result in a changed working diagnosis was insufficient aspirate for cytodiagnosis in 12 cases (35.3% of the total) and identification of intermediate cells (ie, borderline between nevus and melanoma by cytologic criteria) in 3 (8.8% of the total).

CYTOLOGIC-HISTOLOGIC CORRELATION

The affected eye was enucleated in only 4 of the 34 cases in this series (cases 1, 3, 5, and 7). In case 2, enucleation was performed after a period of observation following an inconclusive biopsy. During observation, the tumor enlarged and also showed new invasive features. In the other three cases, enucleation was performed primarily following the fine-needle aspiration biopsy. In all four cases, the tumor proved to be a malignant melanoma by histopathologic criteria. It was classified as a spindle-cell melanoma in cases 1, 3, and 7 and as an epithelioid melanoma in case 5. Histopathologic study identified the same melanoma cell type as did cytopathologic study of the needle aspirates in cases 1, 3, and 5. No melanoma cell type was specified by the cytopathologist who evaluated case 7, so accuracy of cell type identification in this case cannot be determined.

FOLLOW-UP AND FINAL DIAGNOSIS

Follow-up after fine-needle aspiration biopsy in the 34 cases (Table III) ranged from just over 1 month (case 5) to 13.7 years (case 1). The mean follow-up interval was 4.2 years, and the median follow-up interval was 2.6 years. Our final diagnosis at last available follow-up examination (Table III) was choroidal melanoma in 24 cases (70.6%) and choroidal nevus in 10 cases (29.4%). The final diagnosis in the 16 cases categorized as choroidal melanoma following the biopsy remained melanoma in all 16. Similarly, the final diagnosis in the two cases categorized as benign nevus following the biopsy remained choroidal nevus in both. The final diagnosis in the four cases categorized as intermediate lesion following the biopsy was choroidal melanoma in all four. Our final diagnosis in the 12 cases that yielded an insufficient aspirate for cytodiagnosis was benign nevus in eight and malignant melanoma in four.

None of the patients in this series developed metastatic disease or died during available follow-up. No patient in the series developed any evidence of implantation tumor seeding along the needle tract in the pars plana.

DISCUSSION

If the results of this study are representative, between one fourth and one third of small melanocytic choroidal tumors in the nevus versus melanoma category (as defined in the "Methods" section) are really benign nevi and not malignant melanomas. This information is important, because tumors of this type are currently regarded by many ophthalmic tumor specialists as unequivocal small choroidal melanomas and treated accordingly. Most clinically diagnosed small choroidal melanomas are currently treated by eye-preserving, locally destructive therapies

TABLE II: RESULTS OF BIOPSY AND INITIAL POSTBIOPSY MANAGEMENT OF 34 SMALL MELANOCYTIC CHOROIDAL TUMORS CLASSIFIED AS "NEVUS VERSUS MELANOMA"

CASE	AQEQUACY OF ASPIRATE	CYTOPATHOLOGIC DIAGNOSIS	MELANOMA CELL TYPE	REVISED CLINICAL DIAGNOSIS	INITIAL MANAGEMENT
1	insufficient			nevus vs melanoma	observation
2	insufficient			nevus vs melanoma	observation
3	sufficient	malignant melanoma	spindle	choroidal melanoma	enucleation
4	sufficient	intermediate	spindle	nevus vs melanoma	observation
5	sufficient	malignant melanoma	epithelioid	choroidal melanoma	enucleation
6	insufficient			nevus vs melanoma	observation
7	sufficient	malignant melanoma	unspecified	choroidal melanoma	enucleation
8	sufficient	malignant melanoma	unspecified	choroidal melanoma	plaque radiotherapy
9	insufficient			nevus vs melanoma	plaque radiotherapy + laser
10	sufficient	malignant melanoma	unspecified	choroidal melanoma	plaque radiotherapy + laser
11	sufficient	benign nevus		choroidal nevus	observation
12	sufficient	malignant melanoma	unspecified	choroidal melanoma	plaque radiotherapy + laser
13	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy + laser
14	insufficient			nevus vs melanoma	observation (rebiopsied)
15	sufficient	malignant melanoma	spindle	choroidal melanoma	proton beam irradiation
16	sufficient	malignant melanoma	mixed	choroidal melanoma	plaque radiotherapy + laser
17	insufficient			nevus vs melanoma	observation
18	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy + laser
19	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy + laser
20	sufficient	benign nevus		choroidal nevus	observation
21	insufficient			nevus vs melanoma	observation
22	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy + laser
23	sufficient	intermediate	spindle	nevus vs melanoma	observation (rebiopsied)
24	insufficient			nevus vs melanoma	observation
25	insufficient			nevus vs melanoma	observation
26	insufficient			nevus vs melanoma	observation
27	insufficient			nevus vs melanoma	observation
28	insufficient			nevus vs melanoma	observation
29	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy
30	sufficient	malignant melanoma	epithelioid	choroidal melanoma	plaque radiotherapy
31	sufficient	intermediate	spindle	choroidal melanoma	plaque radiotherapy
32	sufficient	malignant melanoma	spindle	choroidal melanoma	plaque radiotherapy + laser
33	sufficient	intermediate	spindle	nevus vs melanoma	plaque radiotherapy
34	sufficient	malignant melanoma	mixed	horoidal melanoma	plaque radiotherapy

such as long-duration large spot size infrared laser therapy (transpupillary thermotherapy),[9-14] plaque radiotherapy, or proton beam irradiation. Inclusion of benign nevi in a series of clinically diagnosed small choroidal melanomas will falsely overestimate the reported success of that treatment and underestimate the frequency of failure in true small choroidal melanomas.

The accuracy of clinical diagnosis of medium-sized and larger choroidal melanomas that exhibit classic clinical features is extremely high.[15] However, the accuracy of clinical diagnosis of presumed small choroidal melanomas has never been established by any clinicopathologic correlation study. Melanocytic choroidal nevi larger than the usually accepted upper limit of size of classic benign choroidal nevi (5 mm in diameter, 1 mm in thickness) but smaller than the conventional boundary dimensions for medium-sized choroidal melanomas (10 mm in diameter, 3 mm in thickness) are documented pathologically from time to time,[16-18] and such tumors can simulate small malignant melanomas quite closely.[19] Our study suggests that such large benign choroidal nevi are substantially more common than is generally appreciated. Because most small melanocytic choroidal tumors in the nevus versus melanoma category are currently managed by eye-preserving methods, determining which lesions in this category are benign nevi or borderline lesions and which are malignant melanomas requires a method other than histopathologic study of the enucleated eye. In our opinion, fine-needle aspiration biopsy is a useful technique for obtaining this information.

The most important limitation of fine-needle aspiration biopsy of small melanocytic choroidal tumors revealed by this study is its frequent inability to obtain sufficient cells for cytodiagnosis (35.3% in this series). Early in our experience, an insufficient aspirate for cytodiagnosis caused us great concern. However, we now believe that an insufficient specimen is a meaningful nondiagnostic result. Tumors that yield a limited specimen tend to be

TABLE III: FINAL DIAGNOSIS AND FOLLOW-UP INFORMATION ON 34 PATIENTS WITH "CHOROIDAL NEVUS VERSUS MELANOMA" EVALUATED BY DIAGNOSTIC FINE-NEEDLE ASPIRATION BIOPSY

CASE	FINAL DIAGNOSIS	LIFE STATUS AT MOST RECENT ENCOUNTER	DURATION OF FOLLOW-UP (YR)
1	choroidal melanoma	alive	13.7
2	choroidal nevus	alive	2.9
3	choroidal melanoma	alive	12.6
4	choroidal melanoma	alive	10.8
5	choroidal melanoma	alive	0.1
6	choroidal nevus	alive	7.9
7	choroidal melanoma	alive	7.8
8	choroidal melanoma	alive	8.8
9	choroidal melanoma	alive	6.8
10	choroidal melanoma	alive	8.0
11	choroidal nevus	alive	5.1
12	choroidal melanoma	alive	5.6
13	choroidal melanoma	alive	7.9
14	choroidal nevus	alive	5.2
15	choroidal melanoma	alive	4.1
16	choroidal melanoma	alive	4.8
17	choroidal melanoma	alive	3.4
18	choroidal melanoma	alive	0.9
19	choroidal melanoma	alive	0.9
20	choroidal nevus	alive	0.4
21	choroidal melanoma	alive	2.0
22	choroidal melanoma	alive	1.2
23	choroidal melanoma	alive	3.1
24	choroidal nevus	alive	2.4
25	choroidal nevus	alive	2.3
26	choroidal nevus	alive	2.4
27	choroidal nevus	alive	2.2
28	choroidal nevus	alive	2.0
29	choroidal melanoma	alive	1.9
30	choroidal melanoma	alive	1.6
31	choroidal melanoma	alive	1.8
32	choroidal melanoma	alive	1.4
33	choroidal melanoma	alive	1.2
34	choroidal melanoma	alive	1.0

composed of strongly cohesive cells. Cohesiveness of tumor cells is a relative indicator of benignity. On the basis of our experience to date, small melanocytic choroidal tumors in the nevus versus melanoma category that yield an insufficient specimen for cytodiagnosis should probably be managed, at least initially, by observation rather than by prompt treatment.

I do not expect the results of this study to convince skeptics of the utility, diagnostic accuracy, or safety of diagnostic transvitreal fine-needle aspiration biopsy of small melanocytic choroidal tumors in the nevus versus melanoma category or to alter current management of such lesions at most centers. However, I do expect these results to stimulate discussion of and reflection about the nature of small melanocytic choroidal tumors and the possible role of fine-needle aspiration biopsy in their future evaluation.

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DISCUSSION

DR HANS E. GROSSNIKLAUS. Uveal melanoma is the most common cause of death from an eye disease in the United States. During the past several decades, numerous treatments for primary uveal melanoma have been devised. The theory of cancer is that the earlier a cancer is detected and treated, the more likely it is cured. Uveal melanoma is unusual because it is generally diagnosed and treated with clinical evaluation and without examination of a biopsy. In recent years, small uveal melanomas have been treated by transpupillary thermotherapy. A problem with this treatment is that we don't know how many of these small melanomas are really nevi, if the morbidity and mortality associated with treatment outweigh the morbidity and mortality of observing these lesions, and if the morbidity of doing an FNAB outweighs the risks of clinical diagnosis and management without doing a fine-needle aspiration biopsy. We do know that uveal melanomas treated by transpupillary thermotherapy that fail to respond or recur tend to be located near the optic nerve and may exhibit extraocular spread along emissary canals.

In this study, Dr Augsburger and coworkers attempt to answer some of these questions. Thirty-four patients with small melanocytic choroidal tumors were evaluated over an 8-year interval. The tumors had a mean maximal basal diameter of 8.0 mm and a mean maximal thickness of 2.4 mm. All patients underwent a transvitreal fine-needle aspiration biopsy of the tumor. Results showed 22 of 34 with sufficient specimen (group I) and 12 of 34 with insufficient specimen (group II). Sixteen from group I were diagnosed as having melanoma and treated. Two from group I were diagnosed as having nevus and not treated. Four tumors from group I were diagnosed as indeterminate and eventually treated as small choroidal melanomas. Of the group II patients, 8 were observed and 4 were eventually treated because of tumor enlargement. What we can learn from this study is that there is approximately a 65% diagnostic yield from fine-needle aspiration biopsy of uveal melanocytic proliferation. If we assume that all patients in the study might have had transpupillary thermotherapy for the clinical presumption of melanoma, 24% of these patients likely had nevi and didn't need the transpupillary thermotherapy.

This was a retrospective descriptive series rather than a case-control study. The fine-needle aspiration biopsy technique varied, with patients having one, two, or three needle passages. The cytological processing technique varied, with filter, cytospin, and direct smear employed. The follow-up time ranged from less than 1 month to 13.7 years. These are all weaknesses. However, as long as one doesn't try to make this a statistically sound case-control study and accepts this work as an observational case series, it provides useful information. What this study does show is that in the hands of an experienced ocular oncologist, a sizable number of small uveal melanocytic proliferations suspected to be melanoma and eligible for treatment are really nevi. We do not know if treatment of any small uveal melanocytic proliferation, nevus or melanoma, prolongs survival. According to the theory of cancer, much of the improvement in survival rates associated with early detection is due to treatment of a higher proportion of benign tumors, not curing malignancies. McLean has indicated that if this theory is correct, modifications of local treatment will not result in any significant improvement in survival. Recent evidence supports this concept, as Eskelin and coworkers have shown that it is likely that uveal melanoma forms micrometastases in

susceptible patients within 5 years prior to diagnosis of the ocular tumor. All of this information, including Augsburger and coworkers' study, needs to be considered when one develops a clinical plan for a patient with a small uveal melanocytic proliferation.

I would like to thank Dr Jackson Coleman for his comments regarding this work.

DR STEPHEN S. FEMAN. It looked like you were doing a fine-needle biopsy through the vitreous without a vitrectomy. Do you have any concerns concerning tumor growth or vitreous fibrotic reaction from doing this procedure?

DR FRONCIE A. GUTMAN. How do you select the biopsy site? You can have false negatives simply by missing that portion of the lesion that contains the melanoma. Have you modified your attitude about the associated findings? I was surprised that you don't regard the finding of an associated serous detachment significant. Have you modified the standard significant risk factors that we have used in the past to distinguish melanoma from a nevus?

DR RICHARD K. FORSTER. Have the intraoperative complications changed in association with your modifications of the technique over this 20-year period?

DR VINOD LAKHANPAL. You stated that if you document growth in these melanocytic tumors or lesions, you have done a disservice to the patient. In recent literature, it has been suggested that small melanomas should be watched. So you are suggesting a change in the management of these lesions. How do you manage those 35% of patients that remain indeterminate after the aspiration?

DR J. BROOKS CRAWFORD. The technique depends not only on the technical ability to obtain the biopsy, but also on the expertise of the cytopathologist.

DR JAMES J. AUGSBURGER. Let me respond first to Dr Feman's question about the technique. I do this technique without a vitrectomy. When I started the technique in the early 1980s, Jay Federman advised me to perform a core vitrectomy. I told him that I would try it without the vitrectomy and modify the technique if necessary. I have never had major vitreoretinal problems from the technique. In over 400 biopsies, there have been two instances of localized peripheral retinal detachment after the procedure, both of which I have walled off with laser and they have not progressed.

Now for the question of local tumor recurrence in the field. Many of you are familiar with the work of Karcioglu and coworkers, who looked at the high frequency of tumor cell seeding along the needle track when you biopsy directly into the tumor through the sclera. I found the same results when doing practice eyes and enucleated eyes and in postenucleation biopsies, so I do not go through the sclera. When you use the transvitreal route, or what I call the indirect technique, we have not seen a single instance of implantation tumors along the needle track at the puncture site in the pars plana nor to my knowledge has there ever been one reported. I should add a caveat on that—that although melanocytic tumors can be handled like this, I would never handle a retinoblastoma with this technique.

With regard to Dr Gutman's question on selection of the biopsy site, it depends on where the lesion is located. I tend not to go over the macula. If it is in the inferotemporal midzone of the fundus posterior to the equator, I will select a pars plana position inferotemporally and come at it from that position. As you can imagine, doing this with an indirect ophthalmoscope means I'm standing on the other side of the table from the patient's eye and viewing it on a screen with a video indirect ophthalmoscope (so my assistants can watch it) and I pass the needle directly into it under ophthalmoscopic visualization. Are there sampling errors? I'm sure that there may be sampling errors in these cases. How do I try to avoid that? It's based on our prior work with postenucleation specimens where I tried to sample at least three different sites within the tumor. I will use either a single needle or multiple needles but I will not sample only one site. Will we still miss some occasionally? I don't think we miss very many of them.

The orange pigment and the subretinal fluid are undoubtedly factors associated with the likelihood that the lesion will grow; however, there has never been a study to my knowledge that has shown that in the small melanocytic choroidal tumors, growth, especially, very slight growth without other invasive features occurring, is a clear indication of malignancy in these tumors. Nevi are almost never congenital lesions. What does that imply? They occur as adult lesions; they are acquired lesions; to be acquired, they have to grow. So growth and activity, in my opinion, are relative predictors of malignancy, but they are not the same as clear invasive features within the tumor.

With regard to Dr Forster's questions, are there intraocular complications? The major complication we see is some bleeding. As you pull the needle out, you will get a little bit of bleeding in most of those cases. I very lightly press on the eye for about a minute after the needle has been withdrawn, and at that time we will look at the bleeding site. In most of the cases the bleeding will have stopped. You will get a clot right there; that clot is actually very helpful in terms of preventing development of a retinal hole that would lead to a retinal detachment, in my opinion. In some cases, we have had enough intravitreal

bleeding that we've actually obscured the view of the fundus for up to several months. We have followed these tumors with ultrasound and we have generally not had to treat them.

What do we do now with the cases given the diagnosis "quantity not sufficient"? You might look at these numbers that I have and say, "Why did you treat some of them if you received a biopsy that indicated an insufficient aspirate?" When we started these biopsies, back in the early 1980s, I would tell the patients that we would get one of three answers. If it's malignant, I'm going to recommend that you be treated. If it's benign, I'm going to simply recommend that it be observed periodically. If we don't get enough tissue to confirm a diagnosis or if it is indeterminate, we will have to proceed as we would have routinely done in the past, without that biopsy. And in some of those cases, after discussing the options, some patients elected treatment and some did not.

We find that the frequency of a "quantity not sufficient" result varies greatly by the type of tumor. For example, take the case of a medium-sized to large melanoma, where the patient says, "Doctor, you might be a very nice guy, and I'll probably go along with your treatment recommendation, but I would rather have you confirm it with a biopsy before you do the procedure, especially if it's going to be an enucleation." We have almost 100% recovery of cells in those kinds of tumors. We've found over the years that those patients that we observe after a "quantity not sufficient" diagnosis have tumors that are very dormant, on the average. Some of them will grow; a few of them will show invasive features eventually. We may treat them, but they seem to have very low metastatic risk. A lot of them turn out to be benign. Now I tell patients something different: "If we get insufficient cells, that tells me that this is a very cohesive tumor. I equate cohesiveness with a favorable prognosis for that tumor." I recommend that those tumors be observed rather than treated.

Finally, regarding my comment that if you watch a patient who has a small choroidal melanoma and his or her tumor grows during observation, you've done a disservice. Consider the survival prognosis of patients who have small, medium, and large tumors. Survival of patients having larger choroidal melanomas is clearly substantially worse than that of patients with smaller choroidal melanomas. But, prognosis is not equal for all patients having a tumor of a certain size category. If you subdivide patients into smaller categories—very small, small, a little bit bigger than small, etc, the survival prognosis decreases as tumor size increases. So if you decide to observe a choroidal melanoma, and the tumor grows during follow-up, you have not done your patient any favor.