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Gene Expressing Profiling of Iris Melanomas

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Melanomas can arise in any component of the uveal tract of the eye, including the iris, ciliary body, and choroid.[1] Iris melanomas have a better prognosis and are often considered separately from posterior uveal melanomas of the ciliary body and choroid. A possible explanation for the less aggressive behavior of iris melanomas could be that they have acquired fewer genetic alterations than posterior uveal melanomas. To test this hypothesis, we performed gene expression profiling on 20 iris melanomas using a prospectively validated 15-gene assay that is now used in routine clinical practice to stratify posterior uveal melanomas into class 1 tumors (low metastatic risk) and class 2 (high metastatic risk) based on biopsy samples.[2]

The study was conducted at 3 centers associated with the Collaborative Ocular Oncology Group[3] and represents the second report from that group. Institutional review board approval was obtained from each institution, and informed consent was obtained from each patient. Inclusion criteria included (1) a clinical diagnosis of melanoma arising from the iris as judged by slit lamp examination, gonioscopy and anterior segment ultrasonography, and (2) lack of prior treatment. Cases were not included in which iris involvement was judged to represent secondary invasion from a posterior uveal melanoma. Tumor dimensions were determined using 20-, 35- or 50-MHz anterior segment ultrasonography.

The study included 11 (52%) women and 10 (48%) men (Table 1, Fig 1, available at http://aaojournal.org). The mean age was 55 years (median, 61; range, 8 – 85). Mean largest tumor diameter was 7.1 mm (median, 7.0; range, 3.3–11.0). Mean tumor thickness was 2.8 mm (median, 2.9; range, 1.1–5.0). The tumor involved the anterior chamber angle in 19 of 21 (90%) cases. Extrascleral tumor extension was absent in all cases. Tumor samples were

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obtained by fine-needle biopsy in 16 cases (76%), vitrector-assisted biopsy in 3 (14%), and enucleation in 2 (10%). No biopsy-related complications were reported. Tumor cell type was predominantly spindle in 4 cases (19%), mixed in 3 (14%), epithelioid in 4 (19%), and indeterminate owing to insufficient cellular material in 10 (48%), yet the sample was sufficient for gene expression profiling in 100% of cases. The gene expression profiling was class 1 in 14 cases (67%) and class 2 in 7 cases (33%). Treatment after tumor sampling included I-125 plaque radiotherapy in 16 cases (76%), surgical excision in 3 (14%), and enucleation in 2 (10%). One class 2 tumor developed local recurrence after plaque radiotherapy, which presented as vitreous seeding 71 months after initial treatment (Fig 1E, F). The class 2 gene expression profile was associated with increased patient age ($P = 0.003$) and the presence of epithelioid cells ($P = 0.004$; Table 2, Fig 2, available at http://aaojournal.org). After a median follow-up of 24 months (mean, 34; range, 3–96), no patients had developed detectable metastatic disease. By comparison, at this median follow-up, >30% of patients with a class 2 posterior uveal melanoma will have developed detectable metastasis.[3]

To our knowledge, this is the first study of gene expression profiling in iris melanoma. The most surprising finding was that one third of iris melanomas exhibited the class 2 gene expression profile, indicating that the less aggressive behavior of iris melanomas cannot be explained simply on the basis of their having less advanced genetic alterations. Limitations of this study include small sample size and short follow-up. This patient cohort continues to be monitored to determine whether the class 2 patients begin developing metastasis after a longer follow-up, which would suggest a lag-time bias as a result of iris melanomas being diagnosed earlier, on average, than posterior uveal melanomas. Finally, it is important to emphasize that the iris melanomas in this study required operative intervention owing to their aggressive features and, hence, do not represent the typical spectrum of iris melanocytic neoplasms, most of which have a negligible risk of malignant behavior.[4]

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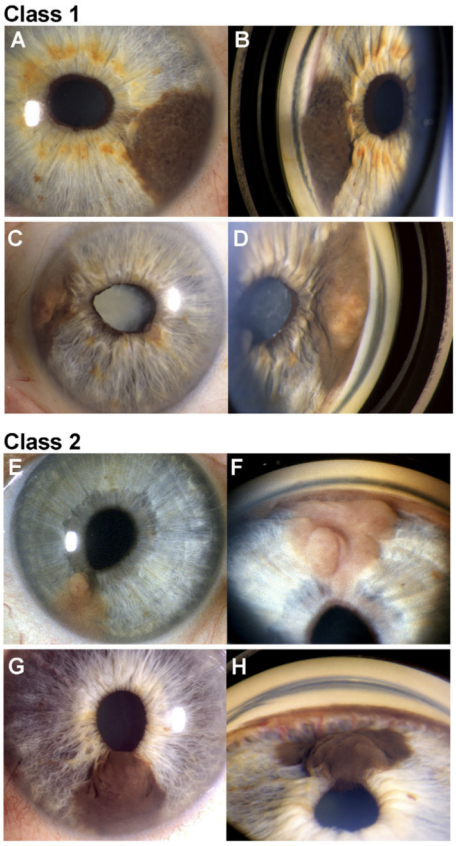

Figure 1.

Examples of class 1 and class 2 iris melanomas. Paired slit-lamp photographs (left panels) and goniophotographs (right panels) of 2 class 1 iris melanomas (**A**–**D**) and 2 class 2 iris melanomas (**E**–**H**). Patient NB018 (**A**–**B**) presented with a dark brown tumor arising from the iris stroma and extending into the angle and causing slight peaking of the pupil (not a diagnostic criterion for iris melanoma). Patient NB006 (**C**, **D**) presented with a variably pigmented iris melanoma with angle involvement, peaking of the pupil, and secondary cataract. Patient NB206 (**E**, **F**) presented with a minimally pigmented, multilobular iris melanoma with angle involvement and peaking of the pupil. This tumor recurred with vitreous seeding 71 months after I-125 plaque radiotherapy. Patient NB138 (**G**, **H**) presented with a dark brown iris stromal tumor with no angle involvement. Prominent feeder vessels emanating from the angle could be seen on gonioscopy (**H**). Despite the lack of angle involvement, the tumor grew substantially on observation, so I-125 plaque radiotherapy was performed.

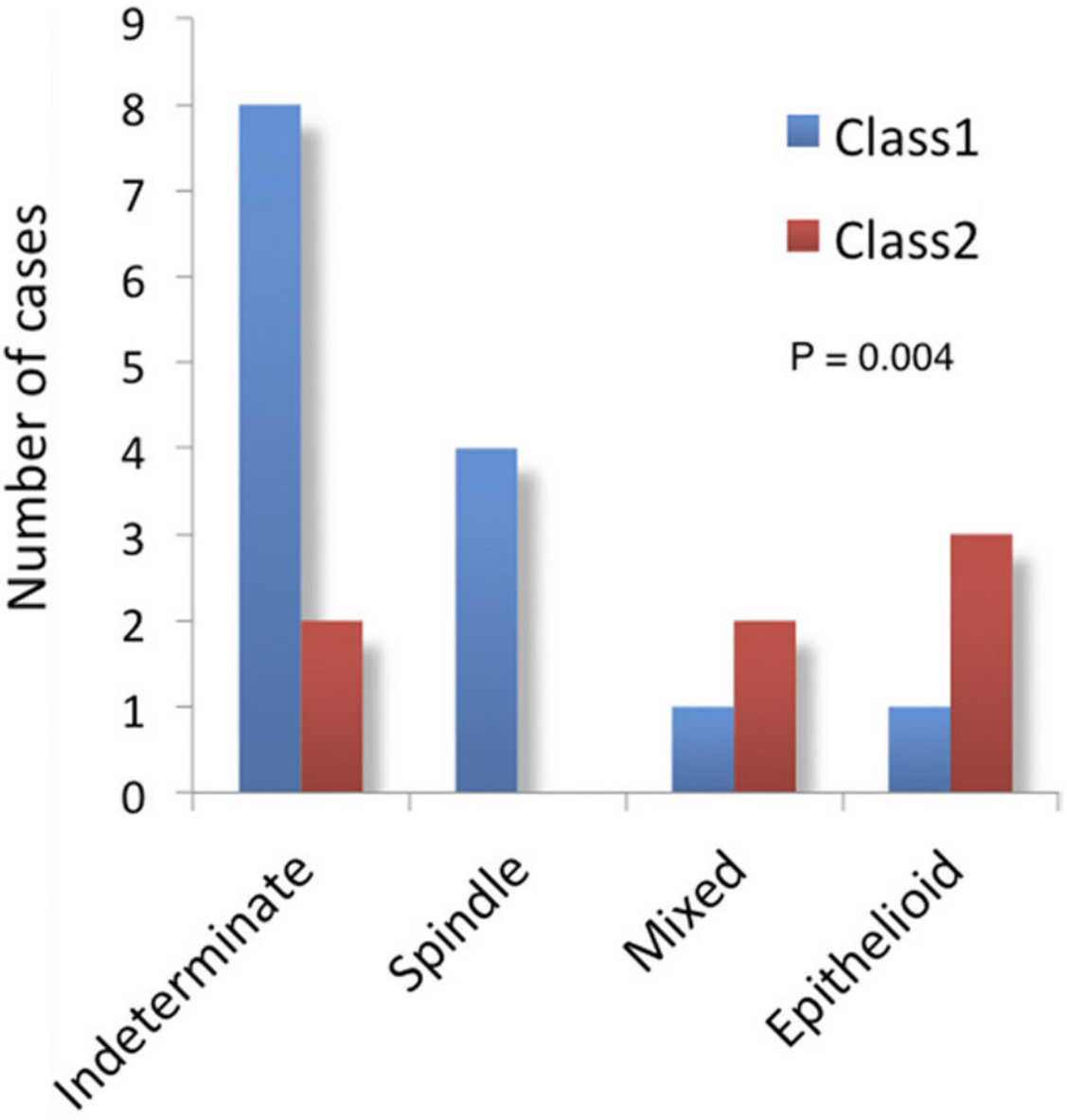

Figure 2.

Association between gene expression profile, patient age, and tumor cell type. (**A**) Box and whiskers plot illustrating the relationship between patient age and gene expression class. The box represents the 25th–75th quartiles, and the line within the box represents the mean. T-bars indicate the range of values. (**B**) Bar graph illustrating the relationship between tumor cell type and gene expression class. “Indeterminate” indicates that insufficient sample was obtained for cytopathologic diagnosis.

Table 1

Summary of Patients

Tumor Number	Gene Expression Profile	Age	Gender	Largest Tumor Diameter	Tumor Thickness	Angle Involvement	Extrascleral Tumor Extension	Type of Sample	Cytopathologic Cell Type	Treatment	Follow-up (mos)	Metastasis
2062942	Class 1	44	Female	6	2.0	Yes	No	Vitrector	Indeterminate	Excision	37	No
2109680	Class 1	69	Female	6	1.5	Yes	No	Vitrector	Spindle	Excision	21.7	No
CEI-005	Class 1	18	Female	NA	NA	Yes	No	FNAB	Spindle	Plaque	22.1	No
NB 002	Class 1	42	Male	5	3.0	Yes	No	FNAB	Indeterminate	Plaque	95.8	No
NB 006	Class 1	55	Female	6	3.0	Yes	No	FNAB	Indeterminate	Plaque	78.7	No
NB 044	Class 1	42	Male	6	3.3	Yes	No	FNAB	Indeterminate	Plaque	60.9	No
NB 051	Class 1	61	Male	3	1.1	Yes	No	FNAB	Mixed	Plaque	65.6	No
NB 099	Class 1	76	Male	17	5.3	Yes	No	Vitrector	Spindle	Enucleation	2.5	No
NB 118	Class 1	46	Male	10	3.0	Yes	No	FNAB	Indeterminate	Plaque	21.5	No
NB 160	Class 1	64	Male	7	2.8	No	No	FNAB	Indeterminate	Plaque	26.2	No
NB 163	Class 1	49	Male	9	4.5	Yes	No	FNAB	Indeterminate	Plaque	24.3	No
NB 168	Class 1	8	Male	7	3.1	Yes	No	FNAB	Indeterminate	Plaque	14.8	No
NB 198	Class 1	46	Female	6	2.4	Yes	No	FNAB	Spindle	Plaque	23	No
NB 295	Class 1	25	Female	11	2.7	Yes	No	FNAB	Epithelioid	Plaque	6.2	No
MM 127	Class 2	79	Male	NA	NA	Yes	No	Enucleation	Epithelioid	Enucleation	20	No
NB 049	Class 2	63	Male	9	5.0	Yes	No	FNAB	Epithelioid	Plaque	63.9	No
NB 065	Class 2	63	Female	7	3.3	Yes	No	FNAB	Indeterminate	Plaque	35.6	No
NB 134	Class 2	76	Female	5	2.3	Yes	No	FNAB	Indeterminate	Plaque	20.4	No
NB 138	Class 2	63	Female	9	2.7	No	No	FNAB	Mixed	Plaque	32.3	No
NB 193	Class 2	82	Male	6	2.9	Yes	No	FNAB	Mixed	Plaque	27.7	No
NB 206	Class 2	85	Female	8	3.4	Yes	No	FNAB	Epithelioid	Plaque	20.9	No

FNAB = fine-needle aspiration biopsy; NA = not available.

Table 2

Association Between Gene Expression Class and Clinical Variables

Variable	Class 1	Class 2	*P* Value
Ages (yrs)			0.003
Mean	46.1	73.0	
Median	46.0	76.0	
Minimum–maximum	8–76	63–85	
Largest tumor diameter			0.6
Mean	6.9	7.4	
Median	6.3	7.5	
Minimum–maximum	3.3–11.0	5.1–9.4	
Tumor thickness			0.2
Mean	2.6	3.3	
Median	2.8	3.1	
Minimum–maximum	1.1–4.5	2.3–5.0	
Cell type			0.004
Epithelioid	1	3	
Mixed	1	2	
Spindle	4	0	
Indeterminate	8	2	