Original Article

Cytogenetic results of choroidal nevus growth into melanoma in 55 consecutive cases

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Abstract

Purpose: To investigate the cytogenetic results of choroidal nevus with photographically-documented transformation into choroidal melanoma.

Methods: Retrospective analysis of 55 consecutive patients who underwent fine needle aspiration biopsy (FNAB) for DNA isolation and whole genome array based assay for chromosomes 3, 6, and 8 analysis prior to plaque radiotherapy. Tumors with abnormalities in chromosomes 3 and 8 were considered high-risk for metastasis.

Results: At diagnosis of choroidal nevus the mean patient age was 57 years (median 57, range 10–83 years). All patients were Caucasian and 36 (65%) were female. At the time of nevus diagnosis, the mean tumor basal diameter was 7.4 mm (median 6.5, range 1.5–18.0 mm) and tumor thickness was 2.2 mm (median 2.2, range 0.5–3.9 mm). The mean interval between diagnosis of choroidal nevus and transformation into choroidal melanoma was 58 months (median 42, range 3–238 months). At the time of melanoma diagnosis, the mean tumor basal diameter was 9.7 mm (median 9.0, range 5.0–19.0) and tumor thickness was 3.5 mm (median 3.4, range 1.3–8.1). Cytogenetic analysis of FNAB-isolated melanoma revealed 25 patients (45%) with high-risk and 30 (55%) with low-risk cytogenetic findings. The rate of tumor growth into melanoma was inversely related to high-risk cytogenetic profile (p = 0.03) as those with fast transformation ≤ 1 year showed high-risk in 80% compared to those with slow transformation > 1 year who showed high-risk in only 38%. Fast transformation into melanoma conferred a relative risk (RR) of 2.116 for high-risk cytogenetic profile, compared to slow transformation.

Conclusions: Choroidal nevus with rapid transformation into melanoma within 1 year is significantly more likely to demonstrate high-risk cytogenetic profile, at risk for metastatic disease, compared to those with slow transformation.

Keywords: Choroidal nevus, Melanoma, Cytogenetic profile

Introduction

Genetic testing is often used for prognostication of uveal melanoma risk for metastasis.1-16 Most centers gather genetic information using fine needle aspiration biopsy of the intraocular tumor immediately preceding conservative treatment with radiotherapy or at the time of enucleation. Genetic analysis employs either a DNA-based or RNA-based technique. In a comprehensive analysis of DNA-based cytogenetic evaluation of 1059 patients with uveal melanoma, it was found that increasing patient age, increasing melanoma size and more peripheral location, particularly in the ciliary body, conferred greater high-risk cytogenetic alterations.1,2 This suggested that management of small
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melanoma at the earliest point in tumorigenesis could potentially reduce chromosomal abnormalities and improve overall patient survival.1,2

Choroidal nevus is fairly common in the United States adult population, found in approximately 5% of Caucasian adults.17,18 For patients with choroidal nevus, especially those near the foveola, documentation of risk factors predictive of tumor growth or frank photographic documentation of growth are employed to more confidently establish the diagnosis of melanoma before therapeutic intervention.19–22 The most common therapies for uveal melanoma include radiation therapy or enucleation, both of which can impart risk for permanent visual acuity loss.23

In this analysis, we focused on patients with choroidal nevus referred for our evaluation and management, who eventually demonstrated tumor growth into melanoma. We investigated the cytogenetic profile of this cohort based on rate of transformation.

Methods

A retrospective analysis was performed on the clinical and cytogenetic records of 55 consecutive patients, managed on the Ocular Oncology Service of Wills Eye Hospital, Philadelphia USA, with initially diagnosed choroidal nevus that demonstrated photographic documentation of growth into choroidal melanomaduring follow up. At the time of melanoma therapy, all eyes underwent fine-needle aspiration biopsy (FNAB) for cytogenetic testing of melanoma. Institutional review board approval was obtained for this study.

The patient data at initial examination included age, race, gender, affected eye, visual acuity and symptoms. The tumor data for both the choroidal nevus and the choroidal melanomaincluded tumor quadrant, anteroposterior location, distance to the optic nerve (in millimeters [mm]), distance to the foveola (mm), diameter (mm), tumor thickness (mm by ultrasonography) and acoustic features, and clinical features of presence of tumor-related halo, subretinal fluid, overlying orange lipofuscin pigment and drusen.

Fine needle aspiration biopsy (FNAB) procedure

Our technique of single-pass FNAB was performed in the operating room under sterile conditions immediately prior to plaque radiotherapy. A 10 cc syringe was attached to a 10-inch tube connected to a 27 gauge needle and tumor was sampled using one of two techniques including the trans pars planatransvitreal approach with indirect ophthalmoscopy visualization of needle pass into the tumor apex or by the transcleral approach with needle pass through the sclera into the tumor base.1,2,13 The cells were stored in refrigerated Hank’s solution (Gibco, Life Technologies, Grand Island, NY) at 48 degrees Celsius and subsequently submitted for genetic evaluation. Immediately following genetic sampling, plaque radiotherapy was applied for melanoma therapy.

DNA analysis

Genomic DNA was isolated from the FNAB specimen using DNA Microkit (Qiagen, Valencia, CA). DNA samples were processed for amplification, fluorescent labeling and hybridization to a high-throughput SNP array (AffymetrixCytoscan HD). Mean fluorescence for each SNP locus was compared to a normal reference (HapMap) and copy number was inferred by genomic segmentation (ChAS v2.0 Affymetrix). Copy number and heterozygosity were reported for chromosomes 3,6 and 8. The techniques used for cytogenetic analysis of the tumors have been described previously.1,2,10–12

All tumor samples underwent analysis for chromosome 3 (disomy/partial loss/loss) and 39 tumors underwent analysis for additional chromosomes 6 (6p disomy/loss/gain, 6q disomy/loss/gain) and 8 (8p disomy/loss/gain, 8q disomy/loss/gain). Alterations in chromosome 3 and 8 were considered high-risk cytogenetic features predictive of increased risk for systemic metastasis, based on previous publications.1,2,10–12

Statistical analysis

The patients were divided into two groups based rate of tumor growth into choroidal melanoma including slow growth (>1 year interval) or fast growth (≤1 year interval). A correlation of cytogenetic features with rate of growth was performed. For the continuous variables, a student’s t-test was applied to the differences in the means, relative to the rates of growth. For the categorical variables, Fisher’s exact test was used to determine the significance of the differences between the two rates of growth. A p-value of 0.05 was considered statistically significant.

Results

The patient demographic features are shown in Table 1. The mean patient age was 57 years and all were Caucasian (100%). The nevus location at initial consultation is listed in Table 1. Most were located between the macula and equator (87%).

| Features                        | At initial presentation number (%) |
|---------------------------------|-----------------------------------|
| Patient age (years)             | 57 (57, 10–83)                    |
| Mean (median, range)            |                                    |
| Patient race                    |                                    |
| Caucasian                       | 55 (100%)                         |
| African American                | 0 (0%)                            |
| Asian                           | 0 (0%)                            |
| Hispanic                        | 0 (0%)                            |
| Patient gender                  |                                    |
| Male                            | 19 (35%)                          |
| Female                          | 36 (65%)                          |
| Nevus quadrant location         |                                    |
| Superior                        | 11 (20%)                          |
| Nasal                           | 10 (18%)                          |
| Inferior                        | 8 (15%)                           |
| Temporal                        | 22 (40%)                          |
| Macula                          | 4 (7%)                            |
| Nevus anteroposterior location  |                                    |
| Macula (≤3mm to foveola)        | 4 (7%)                            |
| Macula to equator               | 48 (87%)                          |
| Equator to oraserrata           | 3 (6%)                            |
A comparison of the choroidal nevus and subsequent melanoma features is listed in Table 2. At the time of choroidal nevus diagnosis, the mean tumor diameter was 7.4 mm and mean thickness was 2.2 mm. After documentation of growth with transformation into melanoma, mean diameter was 9.7 mm and thickness was 3.5 mm. This growth represented 31.6% increased diameter (p < 0.001) and 59.0% increase in thickness (p < 0.001). There was no difference (nevus vs melanoma) regarding distance to optic disc or foveola, tumor color, shape, presence of drusen, halo, Bruch membrane rupture, retinal invasion, or extraocular extension. There was a significant difference in presence of melanoma-related subretinal fluid (p < 0.001), orange pigment (p < 0.001), and hollowness on ultrasonography (p < 0.001).

A comparison of rate of transformation of choroidal nevus to melanoma, relative to cytogenetic results is presented in Table 3. There were 10 tumors that showed fast growth (≤1 year) and 45 tumors with slow growth (>1 year). (Figs. 1 and 2).

Comparison (fast vs slow growth) showed no differences in individual chromosome 3, 6, or 8 abnormalities, but there was significant difference in the combination high-risk of 3 and 8 abnormalities, demonstrated in 80% of fast growth and only 38% of slow growth (p = 0.03). Those with fast growth had a 2.116 relative risk for high-risk cytogenetic profile compared to those with slow rate.

**Discussion**

Cytogenetic analysis for uveal melanoma is a complex science, useful for prognostication and based on abnormalities in one or a combination of three chromosomes (chromosome 3, 6, and 8).\(^1\)\(^-\)\(^14\) In 2017, Shields et al. published a comprehensive analysis on clinical features of uveal melanoma relative to cytogenetic (DNA) features in 1059 patients.\(^2\) In that large cohort, the clinical features significantly (p < 0.05) related to any cytogenetic abnormality in chromosomes 3, 6, or 8 (versus [vs.] no abnormality) included older mean age (55 vs. 58 years old), presence of ocular melanocytosis (1% vs. 5%), reduced visual acuity (VA) (20/30 vs. 20/50), ciliary body location (5% vs. 11%), extramacular tumor location (73% vs. 87%), increased mean distance to optic disc (3.3 vs. 5.0 mm) and foveola (3.1 vs. 4.7 mm), and increased mean basal diameter (9.8 vs. 12.6 mm) and thickness (3.8 vs. 5.9 mm). Further comparison of small vs large melanoma revealed abnormalities in chromosome 3 (35% vs. 65%), chromosome 6 (15% vs. 51%), and chromosome 8 (19% vs. 69%).\(^2\) Subsequent study of this large cohort for personalized prognosis based on cytogenetic abnormalities revealed significant increased metastatic risk was increased (compared to normal disomy) for chromosome 3 partial monosomy (hazard ratio [HR] 2.8), chromosome 3 complete monosomy (HR 6.7), chromosome 6q loss (HR 3.1), chromosome 8p loss (21.5), and 8q gain (HR 9.8).\(^1\)

**Table 2.** Cytogenetic results of choroidal nevus with growth into melanoma in 55 patients. Change in tumor features over time.

| Tumor features | Choroidal nevus features at initial presentation number (%) n = 55 tumors | Choroidal melanoma features after transformation number (%) n = 55 tumors | Percentage change (%) | P-value* |
|----------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------|---------|
| Diameter (mm)  | Mean (median, range) 7.4 (6.5, 1.5–18.0)                                  | 9.7 (9.0, 5.0–19.0)                                                    | +31.6%                | <0.001  |
| Thickness (mm) | Mean (median, range) 2.2 (2.2, 0.5–3.9)                                  | 3.5 (3.4, 1.3–8.1)                                                    | +59.0%                | <0.001  |
| Distance to optic disc (mm) | Mean (median, range) 4.9 (4.5, 0.0–15)                                   | 4.2 (4.0, 0.0–15.0)                                                   | −14.2%                | 0.357   |
| Distance to foveola (mm) | Mean (median, range) 4.5 (4.0, 0.0–15.0)                               | 4.2 (3.0, 0.0–12.0)                                                   | −9.5%                 | 0.495   |
| Color           | Pigmented completely 44 (80%)                                           | 44 (80%)                                                              | 0%                    | N/A     |
|                | Pigmented partially 10 (18%)                                           | 10 (18%)                                                             | 0%                    | N/A     |
|                | Non-pigmented 1 (2%)                                                   | 1 (2%)                                                               | 0%                    | N/A     |
| Shape           | Dome/plateau 55 (100%)                                                 | 53 (96%)                                                             | −3.6%                 | 0.495   |
|                | Mushroom 0 (0%)                                                        | 2 (4%)                                                               | +3.6%                 |         |
| Subretinal fluid| None 44 (80%)                                                          | 15 (27%)                                                             | −52.2%                | <0.001  |
|                | Over tumor only 11 (20%)                                               | 29 (53%)                                                             | 32.7%                 |         |
|                | Up to 1 quadrant 0 (0%)                                                | 10 (18%)                                                             | 18.2%                 |         |
|                | >1 quadrant 0 (0%)                                                     | 1 (2%)                                                               | 1.8%                  |         |
| Other features  | Drusen 32 (58%)                                                        | 32 (58%)                                                             | 0%                    | N/A     |
|                | Orange pigment 4 (7%)                                                  | 25 (46%)                                                             | 38.2%                 | <0.001  |
|                | Halo 2 (4%)                                                            | 2 (4%)                                                               | 0%                    | N/A     |
|                | Bruch membrane rupture 0 (0%)                                          | 2 (4%)                                                               | 3.6%                  | 0.495   |
|                | Retinal invasion 0 (0%)                                                | 2 (4%)                                                               | 3.6%                  | 0.495   |
|                | Extraocular extension 0 (0%)                                           | 0 (0%)                                                               | −                     | N/A     |
|                | B-scan ultrasonography hollow 19 (36%)                                  | 51 (93%)                                                             | 58.2%                 | <0.001  |

Fisher’s exact test was used for categorical data. Student’s t-test was used for continuous data. Bold values are significant.
Choroidal nevus has been estimated to carry a low risk for transformation into melanoma, mathematically estimated at 1 in 8845. Clinical features have been identified to predict the nevus at-risk for transformation and these include thickness over 2 mm, subretinal fluid, symptoms, orange pigment, tumor margin within 3 mm of the optic disc, ultrasound hollowness, surrounding halo absence, and overlying Table 3.

| Cytogenetic results | Total number number (%) | Fast growth ≤ 1 year number (%) | Slow growth > 1 year number (%) | P-value | Relative risk (RR) for fast growth to show high-risk cytogenetic features |
|---------------------|--------------------------|----------------------------------|----------------------------------|---------|-------------------------------------------------|
| Chromosome 3 (n = 55 tumors) | n = 55 tumors | n = 10 tumors | n = 45 tumors | 0.111 | 0.563 |
| disomy 3 | 36 (65%) | 4 (40%) | 32 (71%) | 2.703 |
| monosomy 3, complete | 8 (15%) | 3 (30%) | 5 (11%) | 0.901 |
| monosomy/disomy 3, mixed | 6 (11%) | 1 (10%) | 5 (11%) | 2.985 |
| monosomy 3, partial | 5 (9%) | 2 (20%) | 3 (7%) |
| Chromosome 6 (n = 39 tumors) | n = 39 tumors | n = 8 tumors | n = 31 tumors | 0.494 | 1.259 |
| disomy 6 | 32 (82%) | 7 (88%) | 25 (81%) | 0.000 | 6.52 |
| 6p gain | 7 (18%) | 1 (13%) | 6 (19%) | 0.000 | 6.52 |
| 6q loss | 2 (5%) | 0 (0%) | 2 (6%) | 0.000 | 6.52 |
| 6q gain | 2 (5%) | 0 (0%) | 2 (6%) | 0.000 | 6.52 |
| 6q with no abn | 35 (90%) | 8 (100%) | 27 (87%) | 0.000 | 6.52 |
| 6p gain and 6q gain | 2 (5%) | 0 (0%) | 2 (6%) | 0.000 | 6.52 |
| 6p gain and 6q loss | 2 (5%) | 0 (0%) | 2 (6%) | 0.000 | 6.52 |
| 6p gain and 6q with no abn | 3 (8%) | 1 (13%) | 2 (6%) | 0.000 | 6.52 |
| Chromosome 8 (n = 39 tumors) | n = 39 tumors | n = 8 tumors | n = 31 tumors | 0.494 | 1.259 |
| disomy 8 | 29 (74%) | 5 (63%) | 24 (77%) | 1.000 | 9.904 |
| 8p loss | 2 (5%) | 0 (0%) | 2 (6%) | 0.555 | 0.000 |
| 8p gain | 5 (13%) | 2 (25%) | 3 (10%) | 2.985 | 0.000 |
| 8p with no abn | 32 (82%) | 6 (75%) | 26 (84%) | 1.038 | 0.000 |
| 8q gain | 10 (26%) | 3 (38%) | 7 (23%) | 0.399 | 1.923 |
| 8q with no abn | 29 (74%) | 5 (63%) | 24 (77%) | 0.904 | 0.000 |
| 8p loss and 8q gain | 2 (5%) | 0 (0%) | 2 (6%) | 0.000 | 6.52 |
| 8p gain and 8q gain | 5 (13%) | 2 (25%) | 3 (10%) | 2.577 | 0.000 |
| 8q gain and 8p with no abn | 3 (8%) | 1 (13%) | 2 (6%) | 1.923 | 0.000 |
| Cytogenetic high risk findings (chromosome 3 and 8 mutations) [increased risk for metastasis] (n = 55 tumors) | n = 55 tumors | n = 10 tumors | n = 45 tumors | 0.032 | 2.116 |

Abn – abnormality.
Analysis for chromosome 6 and 8 were performed on 39 tumors.
Fischer’s exact test was used for categorical data. Student’s t-test was used for continuous data.
Bold values are significant.

**Fig. 1.** Slow growth of (A) choroidal nevus into (B) melanoma over 69 months, more likely to demonstrate normal cytogenetic results of chromosomes 3, 6, and 8.

**Fig. 2.** Fast growth of (A) choroidal nevus into (B) melanoma over 3 months, more likely to demonstrate abnormal cytogenetic results of chromosomes 3, 6, and 8.

Choroidal nevus has been estimated to carry a low risk for transformation into melanoma, mathematically estimated at 1 in 8845. Clinical features have been identified to predict the nevus at-risk for transformation and these include thickness over 2 mm, subretinal fluid, symptoms, orange pigment, tumor margin within 3 mm of the optic disc, ultrasound hollowness, surrounding halo absence, and overlying...
The presence of 3 or more of these risk factors impart 50% chance or greater for nevus growth into melanoma. These factors were studied in this analysis and were present in some cases of choroidal nevus. (Table 2) However, comparative analysis of the tumors at the nevus vs. melanoma point revealed significant differences in that melanoma showed greater thickness, presence of subretinal fluid, overlying orange pigment and hollowness on ultrasound. (Table 2)

A previously-mentioned comprehensive study on cytogenetics of choroidal melanoma in 1059 cases was the first to recognize that choroidal melanoma that arose from previously documented nevus showed reduced risk for any chromosomal abnormality, particularly chromosome 3 (p < 0.001). This published finding was the stimulus for this current investigation comparing slow versus fast rate of nevus transformation into melanoma. Our results are the first to correlate higher rate of cytogenetically high-risk melanoma in those patients with fast-growing nevus to melanoma (<1 year transformation rate).

There are limitations in this analysis that primarily includes the relatively small cohort of 55 patients with documented nevus transformation into melanoma. However, if it is realized that this is a rare event, mathematically estimated at 1 in 8845 cases, this small group is highly valuable. Additional limitations include the fact that we collected only clinical and cytogenetic information and we do not know if these results correlate with prognosis, but we suspect there is a correlation based on previous reports.

In summary, choroidal nevus is common in the general population and carries low risk for transformation into melanoma. Those tumors with slow growth (>1 year interval) demonstrate 38% with high-risk cytogenetic profile compared to those with fast growth (<1 year interval) with 80% high-risk profile.

Conflict of interest

The authors declared that there is no conflict of interest.

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