Saudi Journal of Ophthalmology (2018) xxx, xxx–xxx

Original Article

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

Carol L. Shields [a,*]; Maria Pefkianaki [a]; Arman Mashayekhi [a]; Jerry A. Shields [a]; Arupa Ganguly [b]

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 whoshowed high-risk profile 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

https://doi.org/10.1016/j.sjopt.2018.02.004

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 an 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

Received 4 December 2017; accepted 1 February 2018; available online xxxx.

[a] Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA
[b] Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

* Corresponding author at: Ocular Oncology Service, 840 Walnut Street, Suite 1440, Philadelphia, PA 19107, USA. Fax: +1 (215) 928 1140.
e-mail address: carolshields@gmail.com (C.L. Shields).

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online: www.saudiophthaljournal.com www.sciencedirect.com

melanomaat 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 establishthe diagnosis of melanoma before therapeutic intervention.[19–22] The most common therapies for uveal melanoma includes radiotherapy 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 recordsof 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 intochoroidal 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 lipofuscinpigment 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%).

Table 1. Cytogenetic results of choroidal nevus with growth into melanoma in 55 patients. Patient demographics and tumor location.

Features	At initial presentation number (%) n = 55 eyes
Patient age (years)	
Mean (median, range)	57 (57, 10–83)
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%)

Please cite this article in press as: Shields C.L., et al. Cytogenetic results of choroidal nevus growth into melanoma in 55 consecutive cases. *Saudi J Ophthalmol* (2018), https://doi.org/10.1016/j.sjopt.2018.02.004