Halo Nevus of the Choroid in 150 Patients

The 2010 Henry van Dyke Lecture

Carol L. Shields, MD; Azza My Maktabi, MD; Erica Jahnle, BS; Arman Mashayekhi, MD; Sara E. Lally, MD; Jerry A. Shields, MD

Objective: To evaluate choroidal halo nevus.

Methods: We performed a retrospective medical record review on all patients with a clinical diagnosis of choroidal halo nevus treated at the Ocular Oncology Service at Wills Eye Institute from April 1, 1974, through June 30, 2008. Their clinical characteristics and natural history were studied.

Results: The choroidal halo nevus showed 2 components, including a distinct central pigmented region surrounded by a yellow halo. Of the 150 patients, 107 (71.3%) were women and 43 (28.7%) were men; and 149 (99.3%) were white, with a median age at presentation of 54 years. Autoimmune disorders were found in 4 patients (2.7%), a rate similar to the prevalence in the US population (2.7% vs 3.1%, P = .74). Preexistent cutaneous melanoma was found in 5 patients (3.3%), which was significantly more prevalent than the rate for the US population (3.3% vs 0.3%, P < .001). The halo was peripheral in 139 patients (92.7%) and slightly internal in 11 (7.3%). Two patients (1.3%) had multifocal halo nevi. The nevus location was superior in 31 patients (20.7%), temporal in 43 (28.7%), inferior in 29 (19.3%), nasal in 27 (18.0%), and macular in 20 (13.3%). Related features included drusen in 85 patients (56.7%), subretinal fluid in 21 (14.0%), orange pigment in 13 (8.7%), and retinal pigment epithelial atrophy in 15 (10.0%). There were no intraocular inflammatory findings. Of the 110 patients with nevi with follow-up, growth into melanoma occurred in 4 patients (3.6%) at a median interval of 41 months.

Conclusions: Halo nevus is a variant of choroidal nevus that has a brown center and yellow halo. No relationship was found with autoimmune disorders, but a relationship with previous cutaneous melanoma is possible.

A retrospective medical record review was performed on all patients with the clinical diagnosis of choroidal halo nevus treated at the Ocular Oncology Service at Wills Eye Institute from April 1, 1974, through June 30, 2008. Halo choroidal nevus was defined as a melanocytic choroidal lesion with a central portion of hyperpigmentation (brown) and surrounding nonpigmented halo (yellow). Institutional review board approval was obtained for this retrospective study. All patients were examined by one of the senior authors (C.L.S. or J.A.S.) using modern techniques of indirect ophthalmoscopy, optical coherence tomography, intravenous fluorescein angiography, and autofluorescence. The nevus was followed up for change in the central portion, halo, and overall growth into melanoma.

Stata statistical software, version 9 (StataCorp LP, College Station, Texas), was used to compare the prevalence rates of autoimmune diseases and cutaneous melanoma with published rates for the United States. A 1-sample test of proportion was used to compare prevalence rates. The prevalence rate of autoimmune diseases in the United States in 1996 was 3.1%. The prevalence rate of cutaneous melanoma in the United States in 2005 was 0.26%. This rate was calculated by dividing the number of cutaneous melanoma cases on January 1, 2006 (758 688), by the total population on July 1, 2005 (296 507 061).10

The patient characteristics are listed in Table 1. Nearly all patients were white (99.3%), and 71.3% were women. Autoimmune disorders were found in 4 patients (2.7%), and no difference was found in the prevalence of autoimmune disorders between our series and the US population (2.7% vs 3.1%; 95% confidence interval, 0.09%-6.2%; P=.74). Preexistent cutaneous melanoma was found in 5 patients; this rate was significantly more prevalent than that for the US population (3.1% vs 0.3%; 95% confidence interval, 0.46%-6.2%; P < .001).

The eye characteristics are listed in Table 2. The iris color was blue or green in 101 eyes (76.5%) and brown in 100 eyes (75.3%). There were 6 eyes (4.0%) with red irides.
in 31 (23.5%). Of the 150 patients, 148 showed 1 halo nevus and 2 showed 2 halo nevi. In 1 patient the multifocal halo nevi were in 1 eye, and in the other patient the nevi were in both eyes. These 2 patients were women, and neither showed autoimmune disease nor cutaneous melanoma. In 15 eyes, there was an additional nonhalo nevus. Overall, the mean halo nevus basal dimension (including the central part and the halo) was 6 mm (median, 5 mm; range, 1-12 mm), and the mean halo width was 1 mm (median, 1 mm; range, 0.3-4 mm). The encircling halo width was uniform in 42 (28.0%) and nonuniform in 108 (72.0%) patients. The halo encircled the nevus completely in 120 patients (80.0%), and the mean circumferential extent was 11.3 clock hours (median, 12 clock hours; range, 4-12 clock hours).

The halo nevus characteristics are listed in Table 3. The nevi were located relatively equivalently throughout the 4 quadrants of the fundus. The mean base was 6 mm and the thickness was 2 mm, as measured by ultrasonography. In 145 patients (96.7%), the pigmented central region was surrounded by a yellow halo, whereas in 5 patients (3.3%), the reverse was found. In 139 patients (92.7%) the halo was located at the periphery of the pigmented portion of the nevus, whereas in 11 patients (7.3%) the halo was noted slightly internal to the periphery. The halo nevus characteristics are listed in Table 3.

Figure 1. Clinical spectrum of the halo nevus of the choroid. A, Small halo nevus in the macular area with central brown pigment and a surrounding yellow halo. B, Juxtapapillary halo nevus. C, Halo nevus in the temporal macular area with a slightly wider-than-average halo. D, Classic halo nevus of median basal and thickness dimensions. E, Halo nevus with overlying drusen, found in 56.7% of patients. F, Atypical halo nevus with a wider-than-average halo. G, Halo nevus with a slightly internal halo found in 7.3% of patients. H, Reverse halo nevus with a central yellow region and surrounding brown pigmentation.
cent in 17 (65.4%) and slightly hyperfluorescent in 9 (34.6%). The halo portion was hypofluorescent in 4 (15.4%), isofluorescent in 3 (11.5%), and slightly hyperfluorescent in 19 (73.1%). Optical coherence tomography was performed in 43 patients and disclosed overlying subretinal fluid in 6 (14.0%), retinal edema in 5 (11.6%), cystoid edema in 1 (2.3%), and pigment epithelial detachment in 2 (4.7%) (Figure 2). Autofluorescence photography was performed in 71 patients and showed slight hypofluorescence of the pigmented portion and slight hyperautofluorescence of the nonpigmented portion in all patients.

Of the 110 patients who were followed up (mean, 76 months; median, 54 months; range, 6-316 months), the halo showed an increased width in 4 (3.6%) (mean, 1.7 mm; median, 0.5 mm; range, 0.3-1.5 mm), a decreased width in 1 (0.9%) (0.25 mm), and stable findings in 105 (95.4%). The mean interval to change was 162 months (median, 220 months; range, 67-234 months).

Growth into melanoma was detected in 4 patients (3.6%) at a mean interval of 44 months (median, 41 months; range, 13-79 months) (Table 4 and Figure 3). Of those patients with melanoma that showed growth, the mean age at presentation was 52 years (median, 53.5 years; range, 41-60 years), and no patient displayed autoimmune dysfunction, cutaneous melanoma, or ocular melanocytosis. One halo nevus was present in each patient, and quadrant location was inferior (n=2), temporal (n=1), or superior (n=1). At presentation, the mean basal dimension was 6.8 mm (median, 6.75 mm; range, 5.5-8.0 mm) and the mean thickness was 2.2 mm (median, 2.2 mm; range, 2.0-2.5 mm), with proximity to the optic disc at a mean of 1.9 mm (median, 1.5 mm; range, 0-4.0 mm) and to the fovea at a mean of 2.6 mm (median, 1 mm; range, 1.0-7.5 mm). Associated features included subretinal fluid (n=1), orange pigment (n=1), and hollowness on ultrasonography (n=3). Chronic features of drusen and retinal pigment epithelial changes were not present in any patient. In each patient, the halo encircled the nevus for all 12 clock hours, the width was 2 mm, and there was no change in halo over time. Two to 4 risk factors present were predictive of growth,11-13 with a median number of 3.5 factors. In comparison, of the 106 halo nevi that showed no growth, the features included a mean basal dimension of 5.6 mm (median, 5.0 mm; range, 1.5-12.0 mm), a thickness of 1.5 mm (median, 1.6 mm; range, 1.5-3.3 mm), a proximity to the optic disc of 5.7 mm (median, 5.3 mm; range, 0-17.0 mm), a proximity to the fovea of 4.9 mm (median, 4.0 mm; range, 0-19.0 mm), subretinal fluid in 6 (5.7%), orange pigment in 8 (7.5%), hollowness on ultrasonography in 31 (29.2%), and related symptoms in 16 (15.1%).

**Table 4. Change in Appearance of Halo Nevus of the Choroid**

<table>
<thead>
<tr>
<th>Change in Halo Appearance</th>
<th>No. (%) of Nevi (n=110)</th>
</tr>
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<tbody>
<tr>
<td>Increased width</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Decreased width</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>No change</td>
<td>105 (95.4)</td>
</tr>
<tr>
<td>Growth of nevus into melanoma</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Interval to growth, mean (median), [range], mo</td>
<td>44 (41) [13-79]</td>
</tr>
</tbody>
</table>

*a Data are presented as number (percentage) of nevi unless otherwise indicated. Mean follow-up was 76 months, median follow-up was 54 months, and range was 6 to 316 months.

Cutaneous halo nevi frequently undergo spontaneous slow involution during many months or years.13 The exact mechanism is unclear, and several theories have been proposed. Evidence supports humoral and cell-mediated immunity for the halo formation and nevus disappearance.14-15 By immunophenotyping, T lymphocytes with
a high proportion of CD8⁺ cells predominate in the inflammatory type of halo nevus.¹⁷,¹⁸

There is an occasional association between cutaneous halo nevi and malignant melanoma, and it has been speculated that cytotoxic lymphocytes acting against melanoma cells also affect similar antigens on the nevus cells, leading to halo formation.¹⁹-²¹ Epstein and coworkers²² described 5 patients with recently diagnosed cutaneous melanoma who displayed simultaneous prominent development of multiple cutaneous halo nevi. Serum autoantibodies against melanocytes have been found in patients with halo nevi and vitiligo.¹⁴,²⁰ Albert and coworkers²³ described the development of cutaneous vitiligo in 1 patient and cutaneous halo nevi in another patient after a diagnosis of choroidal melanoma. On the basis of these findings, immune mechanisms could be responsible for melanocytic destruction in halo nevi.¹⁹,²⁰

In a clinic-based population from an ocular oncology practice, halo nevus represented 5% of all choroidal nevi.⁶ The significance of the choroidal halo nevus remains unknown, but in a previous study, the presence of halo around a choroidal nevus was a factor predictive of stability of the choroidal nevus with statistically less risk for growth to melanoma. In this report, we evaluated 150 consecutive patients with halo nevi and found no increased prevalence of autoimmune dysfunction or vitiligo but observed a higher prevalence of previously treated cutaneous melanoma compared with the US population. There was no increased prevalence of uveal melanoma in this group. Even though these findings suggest a relationship with cutaneous melanoma, there could be inherent bias because identified patients with melanoma might be more prone to ocular examination for potential metastatic disease.

Compared with cutaneous halo nevi, which is most often found in children,³ choroidal halo nevus is most often found in middle-aged adults at a mean age of 55 years; the youngest patient in our series was 18 years old. This age discrepancy might be influenced by a delayed date of initial complete fundus examination in asymptomatic patients. Multifocal halo nevi were detected in 2 patients, neither with a history of cutaneous melanoma or vitiligo. All patients displayed a single halo, 92.7% showed a peripheral halo, and 7.3% showed a slightly internal halo (Figure 1). None of the slightly internal halo nevi showed growth to melanoma.

Tumors from 4 patients with documented growth into melanoma displayed a more suspicious appearance: those tumors appeared thicker (median of 2.2 mm vs 1.6 mm for stable nevi), closer to the optic disc (median of 1.5 mm vs 5.3 mm for stable nevi), and acoustically hollow on ultrasonography (75% vs 31% of stable nevi) and had related symptoms (100% compared with 15% of stable nevi). Subretinal fluid (25% vs 6%) and orange pigment (25% vs 8%) were also more common in the halo nevi that showed growth compared with the stable halo nevi. On the basis of this information, it is uncommon for halo nevi to transform into melanoma; however, all affected patients should undergo an initial 3-month to 4-month examination to confirm stability and, thereafter, annual dilated fundus examination. If risk factors for growth¹¹-¹³ are detected, then closer follow-up on a 4-month to 6-month basis is advised.

The histopathologic features of choroidal halo nevi are not well described because these features rarely come to the enucleation stage. However, histopathologic examination of choroidal melanoma with halo formation has revealed that the halo is composed of large cells with foamy cytoplasm and minimal pigment, hypothesized to be owing to an arrest in synthesis of melanin,²⁴ altered melanocytic activity with passive or active imbibition of lipid,²⁵ or autoimmune response with cellular destruction.²⁶ There is conflicting evidence regarding the presence²⁷,²⁸ or absence²⁹ of lipid in the balloon cells of choroidal melanoma.

In summary, we report a clinical series of 150 consecutive patients with halo nevus of the choroid. The prevalence of autoimmune disease was no higher than that in the general population, but previous cutaneous melanoma was more common than in the US population, implying a relationship. Transformation into melanoma occurred in 3.6% and was found in slightly thicker halo nevi that exhibited established risk factors¹¹-¹³ of subretinal fluid, symptoms, orange pigment, close proximity to the optic disc, lack of drusen, and hollowness on ultrasonography. All patients with halo nevus of the cho-
roid should be inspected for cutaneous melanoma, and the nevus should be followed up long term.

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Correspondence: Carol L. Shields, MD, Ocular Oncology Service, Wills Eye Institute, 840 Walnut St, Ste 1440, Philadelphia, PA 19107 (carol.shields@shieldsoncology.com).

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