

Halo Nevus of the Choroid: An Innocent Bystander

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The choroidal nevus classically appears as a brown or slate gray pigmented mass located in the choroid and is without retinal component.¹ This lesion is generally less than 2 mm in thickness.¹ Previous clinical studies have found that the presence of choroidal nevi vary from an estimated 0.2% to 30% of patients.² In an analysis of the clinical features of 3422 eyes with choroidal nevi, it was found that, when separately evaluating the young patients (<20 years), mid-adult patients (21-50 years), and older adult patients (>50 years), race was predominantly white in 95%, 98%, and 99%, and sex was female in 63%, 65%, and 63% of patients, respectively.² The tumor was located in the extrafoveal location in 86%, 93%, and 94% of patients and more often in the nasal or temporal quadrant than inferior or superior quadrant.² The nevus was pigmented in 89%, 74%, and 77% of patients. From this oncology clinic-based survey, many patients were referred with highly suspicious lesions, and growth into melanoma occurred in 14%, 9%, and 6% of patients, respectively.²

There is an interesting variant of choroidal nevus that manifests a central brown color with a yellow surrounding halo, termed “halo nevus”.³ Halo nevi can occur in the skin and in the eye.⁴ From a dermatology perspective, a review of 35 patients with cutaneous halo nevi revealed mean age at presentation of 18 years, sex 54% female, and race nearly all white. From an ophthalmology perspective, halo nevus represents 5% of all choroidal nevi.² Herein, we report a case and further explore this nevus variant.

CASE

A 53-year old white woman noted decreased vision in the right eye (OD) for 3 years and a suspicious pigmented choroidal lesion was found. The patient reported no

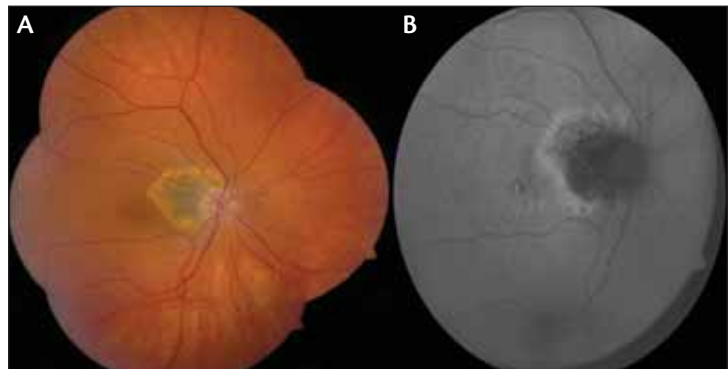


Figure 1. A halo choroidal nevus touching the optic disc showing central brown color and surrounding yellow halo (A). Autofluorescence of halo nevus shows mild hypoautofluorescence of the pigmented portion and slight hyperautofluorescence of the nonpigmented portion (B).

cutaneous or ocular melanoma or autoimmune disease.

On examination, visual acuity was 20/60 OD and 20/20 OS. Intraocular pressures were normal. Bilateral iris freckles were detected. Fundus examination OS was unremarkable. Fundus examination OD disclosed a central brown choroidal mass with a circumferential yellow ring surrounding it. The lesion displayed slightly irregular margins and measured 3.5 x 3.5 x 1.4 mm. There was no overlying subretinal fluid or orange pigment (Figure 1A). Autofluorescence showed mild hypoautofluorescence of the pigmented portion and moderate hyperautofluorescence of the non-pigmented portion. (Figure 1B) Ultrasound revealed a plateau-shaped lesion with thickness of 1.4 mm. These features were consistent with halo choroidal nevus. At 2-year follow-up, the nevus remained stable, with no change in size or color.

COMMENT

Cutaneous halo nevus can appear on the face, scalp, thigh, arm, neck, forearm, and leg, in decreasing frequen-

cy.⁵ Most cutaneous halo nevi appear as a solitary finding, but in one analysis 15% of patients had 2 halo nevi and 6% had 3 halo nevi.⁵ It has been reported that benign cutaneous halo nevus can evolve to malignant melanoma, and therefore monitoring is warranted.⁵

There have been few publications on choroidal halo nevus. In a large analysis of 3422 cases of choroidal nevi, halo nevus represented 5%.³ Choroidal halo nevus was found in 2% of young patients (0-20 years), 8% of mid-adults (20-50 years), and 4% of older adults (>50 years).² In an analysis of risk factors predictive of growth of choroidal nevus into melanoma, one study found that the presence of a halo around a choroidal nevus was a protective factor that statistically lessened the risk for transformation.⁶ In that analysis, the absence of a halo around a nevus promoted a 7 times greater risk for transformation into melanoma compared to a nevus with a halo.⁶

In an analysis of 150 cases of choroidal halo nevi, symptoms such as decreased vision and flashes/floaters were present in 17%.³ This nevus variant was recognized at median age of 55 years with median size of 6 mm base and 1.6 mm thickness.³ In this analysis, only 2 patients (1%) showed multifocal halo nevi. Over a mean of 6 years follow up, transformation into melanoma was found in 4% of cases, at a mean interval of 44 months, and often with predictable risk factors.^{3,5}

Some investigators speculate that halo nevi of the skin and eye might be related to autoimmune disease or vitiligo.⁷ Some publications conjecture a relationship with cutaneous melanoma and favor the halo to be an immune ring of cytotoxic lymphocytes directed to melanocytic cells.⁷ There may be a relationship of choroidal halo nevus with pre-existent cutaneous melanoma.²

Although the risk for transformation into melanoma is small, it is advised that patients with choroidal halo nevi be monitored biannually and then annually. It is also recommended that all patients be checked by a dermatologist for coincident or undiscovered cutaneous melanoma. Perhaps the halo nevus is an innocent bystander or marker of underlying cutaneous melanoma. ■

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MEMBRANEBLUE™

0.15% (trypan blue ophthalmic) injection, solution for intraocular use

Initial U.S. Approval: 2004

Indications and Usage

MembraneBlue™ 0.15% is indicated for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

Dosage and Administration

Before injection of MembraneBlue™ 0.15% perform a 'fluid-air exchange', i.e. filling the entire vitreous cavity with air, to prevent aqueous dilution of MembraneBlue™ 0.15%. MembraneBlue™ 0.15% is carefully applied to the retinal membrane using a blunt cannula attached to the MembraneBlue™ 0.15% syringe, without allowing the cannula to contact or damage the retina. Sufficient staining is expected on contact with the membrane. All excess dye should be removed from the vitreous cavity before performing an air-fluid exchange, to prevent unnecessary spreading of the dye.

MembraneBlue™ 0.15% can also be injected directly in a BSS filled vitreous cavity (instead of injecting under air). Clinical use demonstrated that, after complete vitreous and posterior hyaloid removal, sufficient staining is achieved after 30 seconds of application under BSS.

MembraneBlue™ 0.15% is intended to be applied directly on the areas where membranes could be present, staining any portion of the membrane which comes in contact with the dye. The dye does not penetrate the membrane.

Dosage Forms and Strength

MembraneBlue™ 0.15% (trypan blue ophthalmic solution) is supplied in 2.25 mL syringes filled to a volume of 0.5 mL.

Contraindications

MembraneBlue™ 0.15% is contraindicated when a non-hydrated (dry state), hydrophilic acrylic intraocular lens (IOL) is planned to be inserted into the eye. The dye may be absorbed by the IOL and stain it.

Warnings and Precautions

Excessive staining. It is recommended that after injection all excess MembraneBlue™ 0.15% be immediately removed from the eye.

Adverse Reactions

Adverse reactions reported following use of MembraneBlue™ 0.15% include discoloration of high water content hydrogen intraocular lenses (see Contraindications) and inadvertent staining of the posterior lens capsule and vitreous face. Staining of the posterior lens capsule or staining of the vitreous face is generally self limited, lasting up to one week.

To report SUSPECTED ADVERSE REACTIONS contact Dutch Ophthalmic, USA at 1-800-75-DUTCH or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Use in Specific Populations

Pregnancy

Teratogenic Effects: Pregnancy Category C. Trypan blue is teratogenic in rats, mice, rabbits, hamsters, dogs, guinea pigs, pigs, and chickens. The majority of teratogenicity studies performed involve intravenous, intraperitoneal, or subcutaneous administration in the rat. The teratogenic dose is 50 mg/kg as a single dose or 25 mg/kg/day during embryogenesis in the rat. These doses are approximately 4,000- and 2,000-fold the maximum recommended human dose of 0.75 mg per injection based in a 60 kg person, assuming that the whole dose is completely absorbed. Characteristic anomalies included neural tube, cardiovascular, vertebral, tail, and eye defects. Trypan blue also caused an increase in post-implantation mortality, and decreased fetal weight. In the monkey, trypan blue caused abortions with single or two daily doses of 50 mg/kg between 20th to 25th days of pregnancy, but no apparent increase in birth defects (approximately 4,000-fold maximum recommended human dose of 0.75 mg per injection, assuming total absorption). There are no adequate and well-controlled studies in pregnant women. Trypan blue should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trypan blue is administered to a nursing woman.

Pediatric use

The safety and effectiveness of trypan blue have been established in pediatric patients. Use of trypan blue is supported by evidence from an adequate and well-controlled study in pediatric patients.

Geriatric use

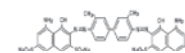
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Description

MembraneBlue™ 0.15% (trypan blue ophthalmic solution) is a sterile solution of trypan blue (an acid di-azo group dye). MembraneBlue™ 0.15% selectively stains epiretinal membranes during ophthalmic surgical vitrectomy procedures.

Each mL of MembraneBlue™ 0.15% contains: 1.5 mg trypan blue; 1.9 mg sodium mono-hydrogen orthophosphate (Na2HPO4.2H2O); 0.3 mg sodium di-hydrogen orthophosphate (NaH2PO4.2H2O); 8.2 mg sodium chloride (NaCl); and water for injection. The pH is 7.3 - 7.6. The osmolality is 257-314 mOsm/kg.

The drug substance trypan blue has the chemical name 3,3'-(3,3'-dimethyl-4,4'-biphenylene) bis (azo) bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetra sodium salt, a molecular weight of 960.8, a molecular formula of C34H24N6Na4O14S4, and has the following chemical structure:



Clinical Pharmacology

Mechanism of Action

MembraneBlue™ 0.15% selectively stains membranes in the human eye during posterior surgery, such as epiretinal membranes (ERM) and Internal Limiting Membranes (ILM).

Nonclinical Toxicology

Carcinogenesis, mutagenesis, impairment of fertility

Trypan blue is carcinogenic in rats. Wistar/Kyoto rats developed lymphomas after receiving subcutaneous injections of 1% trypan blue dosed at 50 mg/kg every other week for 52 weeks (total dose approximately 100,000-fold the maximum recommended human dose of 0.75 mg per injection in a 60 kg person, assuming total absorption).

Trypan blue was mutagenic in the Ames test and caused DNA strand breaks in vitro.

How Supplied/Storage and Handling

MembraneBlue™ 0.15% is supplied as follows:

0.5 mL of MembraneBlue™ 0.15% in a sterile single-use Luer Lok, 2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod in a peel pouch. Five pouched products are packed in one distribution box.

MembraneBlue™ 0.15% is stored at 15-25°C (59-77°F). Protect from direct sunlight.

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