

Vigilance Key to Avoid Missing Melanomas

BY KERRI WACHTER

Misdiagnosis of melanoma is a major cause of litigation against both physicians and dermatopathologists.

Of all claims between 1985 and 2001, 14% involved the misdiagnosis of melanoma, Dr. Ashfaq A. Marghoob reported at the annual Hawaii Dermatology Seminar sponsored by Skin Disease Education Foundation.

Furthermore, the majority of claims involving the misdiagnosis of melanoma were because of a false negative diagnosis, which may translate to a reduced chance of survival for some patients, said Dr. Marghoob, who is a dermatologist at Memorial Sloan-Kettering Cancer Center in New York.

Two important strategies can help minimize missing melanoma, he said.

First, remain vigilant and remember that many melanomas lack the classic ABCD features. "Questioning yourself and your pathologist regarding the diagnosis will help towards identifying many of these melanomas. In other words, remain skeptical of lesions lacking clinical-dermoscopy correlation or lesions lacking dermoscopy-histopathology correlation.

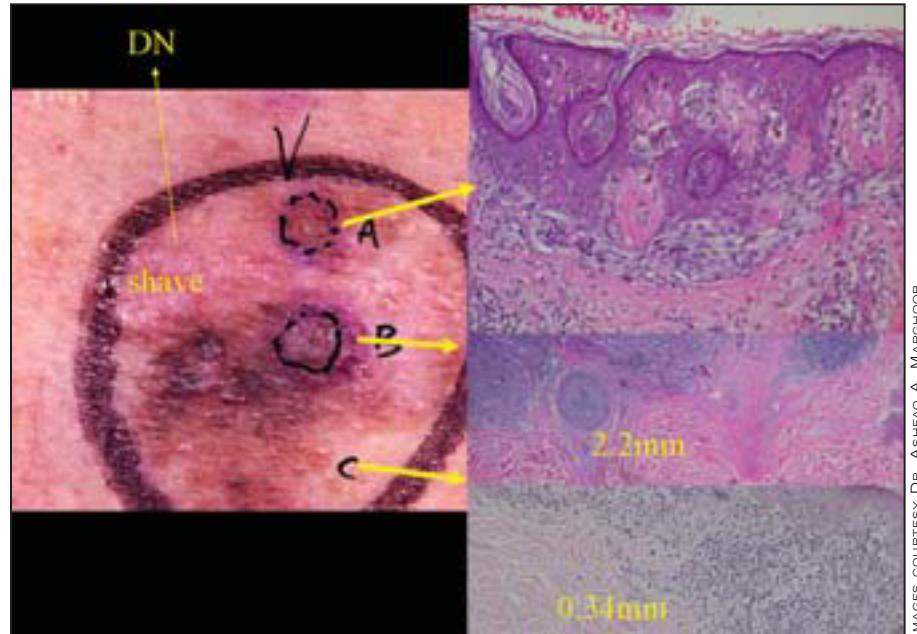
"Second, engage patients in their own

care by having them share the responsibility of detecting early melanoma by encouraging them to examine their own skin on a regular basis," he said.

Some melanomas may not manifest concerning features, and can mimic benign lesions. As a way to ensure that a malignant melanoma will eventually be found, periodic total body examinations by a physician, and regular patient self-examinations, are key. He stressed that physician examinations and self-skin exams are complementary.

Although it is widely accepted that early detection means better prognosis, modest delays of up to 6 months have not been shown to affect ultimate outcomes. However, there is one exception. Nodular melanoma can grow rapidly, and even small delays in diagnosis can have serious consequences.

The most common scenarios in melanoma litigation cases include nodular melanoma being misdiagnosed by a clinician or pathologist; a partial biopsy not capturing the most diagnostically relevant part of the lesion; malignant melanoma being misdiagnosed as a dysplastic or spitz nevus; unrecognized desmoplastic malignant melanoma; and metastatic malignant melanoma with an unknown primary



IMAGES COURTESY DR. ASHFAQ A. MARGHOOB

As can be seen from the histology, this lesion was a melanoma, but depending on the location of a partial biopsy the results can range from a Clark's nevus to melanoma in situ to microinvasive to deeply invasive melanoma.

or recurrence of melanoma (Am. J. Surg. Pathol. 2003;27:1278-83).

Dr. Marghoob discussed each of the following cases in detail:

► **Misdiagnosis of nodular melanoma as nevus by a clinician or pathologist.** Many nodular melanomas lack helpful diagnostic features, such as those in the ABCD criteria for malignant melanoma, which can lead to a misdiagnosis. However, the ABCDE criteria that take lesion evolution into account may be of some help, noted Dr. Marghoob.

In order to track lesion evolution, ask patients about the history of changes and symptoms. Total body photography may help on rare occasions to detect new lesions, some of which may be subtle. In addition, dermoscopy results may persuade the clinician to obtain a biopsy of a clinically banal-appearing lesion that is in fact a nodular melanoma.

► **Partial biopsy issues.** If a biopsy is performed of a lesion that clinically looks like melanoma and the pathology diagnosis is nevus, it is imperative that the clinician and pathologist reconcile the difference. In cases where there is discordance, consider asking for step-sectioning, special stains, or—in very rare instances—fluorescence in situ hybridization to look for signature chromosomal aberrations. In addition, a partial biopsy may not be representative of the rest of the lesion. If a partial biopsy was performed, re-excise the lesion.

Excisional biopsy is the preferred method for melanocytic lesions, when possible, because partial biopsy may sample nondiagnostic areas or miss the prognostically worse portion of the lesion.

"Partial biopsy assumes that a clinician can consistently predict the portion of a suspicious pigmented lesion that will have the worst representative histology," said Dr. Marghoob. In one study, 40% of excised melanomas had worse pathology, compared with initial punch biopsy, and 20% of melanomas revealed invasion, which was not seen in initial punch biopsy (Arch. Dermatol. 1996;132:1297-302).

The ideal biopsy is excisional with a 2-

to 3-mm margin, is oriented along the lines of lymphatic drainage, and is step sectioned. This limits sampling error, removes dysplastic nevus completely (preventing recurrence), and better predicts the Breslow depth if the lesion proves to be a melanoma, said Dr. Marghoob.

► **Misdiagnosis of a melanoma as dysplastic or spitz nevus.** When a partial biopsy reveals dysplastic or spitz nevus, it is important to completely excise the lesion. Malignant melanoma can sometimes masquerade as a spitz nevus, and focus of malignant melanoma may have been missed on the biopsy. Many dermatologists are of the opinion that spitz nevi should be completely excised—at least in adults, he said.

► **Unrecognized desmoplastic malignant melanoma.** Desmoplastic melanoma can be banal in appearance, with 70% appearing amelanotic, he said. These lesions may only present as firmness in the subcutaneous tissue. For "banal"-appearing firm lesions on chronically sun-damaged skin, suspicion should be raised if the lesions are symptomatic, growing, are associated with a lentigo maligna, or reveal irregular vessels with dermoscopy, said Dr. Marghoob.

► **Metastatic melanoma with unknown primary or recurrence of melanoma.** Whenever possible, do not remove seemingly benign lesions and discard them, he said. Also, be careful and selective about the use of liquid nitrogen or a laser on lesions that have not been confirmed to be benign through biopsy.

He noted that cases of assumed benign lesions that recur after ablation (via liquid nitrogen, curettage, or laser) may ultimately prove to be melanoma on histopathology. Furthermore, in the unlikely event that a patient develops metastatic melanoma with an unknown primary, it may be presumed that one of the ablated lesions was the primary.

Dr. Marghoob disclosed having no conflicts of interest. SDEF and this news organization are owned by Elsevier ■

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CONTRAINDICATIONS

Hypersensitivity to any components of this product.

WARNINGS

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PRECAUTIONS

Information for Patients

As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red.

PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

Pregnancy: Teratogenic effects: Pregnancy Category C

Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers:

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use:

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

ADVERSE REACTIONS

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

The following adverse experiences have been reported in 5% or less of patients:

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion. Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye once a day.

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NDC 0065-0272-25

2.5 mL fill in 4 mL oval bottle

Storage:

Store at 2°C to 25°C (36°F to 77°F)
U.S. Patents Nos. 4,871,865; 4,923,892; 5,116,863; 5,641,805; 6,995,186

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