Aggressive Skin Cancers: On Rise and Easily Missed

BY BETSY BATES
Los Angeles Bureau

SCOTTSDALE, ARIZ. — There are four aggressive skin cancers that are increasing in incidence and can be easily overlooked, warned Dr. Marc D. Brown during the Harold O. Perry lecture at the annual meeting of the Noah Worcester Dermatological Society.

Lentigo Maligna

Once cavalierly called a "Hutchinson's freckle" because it can resemble a dab of shoe polish, patients may not even notice the subtle appearance and growth of a lentigo maligna. Even dermatologists may overlook the amelanotic variety of this in situ tumor, said Dr. Brown, director of the division of dermatologic surgery, oncology, and Mohs surgery at the University of Rochester (N.Y.).

"It's very, very difficult to make the diagnosis," Dr. Brown said. "I've missed it several times."

Lentigo maligna lesions are slow to develop and evolve almost imperceptibly. They may lie camouflaged in contiguous solar lentigos or pigmented actinic keratoses, as was the case in nearly half of 147 lesions described in a recent study (J. Am. Acad. Dermatol. 2005;52:859-62).

However, it is not a disease to be trivialized, according to Dr. Brown.

"It's my feeling that if you give it a long enough period of time, it will become an invasive tumor," he said.

Two decades ago, when he began performing Mohs surgery, Dr. Brown almost exclusively encountered lentigo malignas on elderly patients. Now he's making it a practice to hunt for them on much younger patients. "It's not at all unusual for me to see patients …in their 40s or 50s with their first lentigo maligna," he said.

Finding a surefire treatment approach to lentigo malignas remains challenging.

Increasing evidence suggests that the lesions often extend far beyond the 5-mm clinical margins that once were considered adequate for melanoma in situ lesions. Frozen section proponents have reported low recurrence rates, but, Dr. Brown advised, "you really have to have an excellent lab and be very good at this."

He said he prefers a "modified Mohs," or "slow Mohs" approach that involves sending sequential sections to a histopathologic laboratory over several days after a "very meticulous" collection of tissue around the peripheral margin. In 210 cases performed in such a manner, he reported a recurrence rate of less than 2%.

For elderly patients and difficult anatomic sites, radiation therapy or daily use of imiquimod has been proposed. Dr. Brown cautioned that the use of the immune response modifier should be considered experimental, because only 67 cases in which it has been used are described in the literature, and 8 of those involved treatment failures.

Atypical Fibroxanthoma

Also increasing in incidence is this tumor, which is believed to be secondary to UV exposure, said Dr. Brown.

Unlike lentigo maligna, atypical fibroxanthoma (AFX) seems to be confined to an older population.

"It usually appears relatively nonspecifically," he said. "Most of the time when I submit a specimen to the pathologist, I don't say, 'Rule out AFX.' It's usually squamous cell versus basal cell cancer [in my mind]."

In general, these tumors are small, superficial, and well managed by excision with a 1-cm margin or Mohs surgery, said Dr. Brown. He was a coinvestigator in a study that found a 100% cure rate in 20 such tumors (J. Dermatol. Surg. Oncol. 1989;15:1287-92).

"If it sounds too good to be true, it's too good to be true," he said, noting that he has now had 6 cases of metastatic AFX in his practice, and 25 have been reported in the literature.

In his experience with metastatic cases, the original lesion was small (average, 1.5 cm) and metastasis occurred early (on average, 9 months after diagnosis). The most common metastatic site was the regional lymph nodes.

Fortunately, there is a clue to potential aggressive behavior in such tumors, he said. The immunostain LN-2 (CD74) often "lights up" in more aggressive AFX tumors, including five of the six of his cases. When he sees a worrisome clinical AFX tumor and LN-2 is strongly positive, he refers patients for adjunctive radiation therapy.

Merkel Cell Carcinoma

Unknown until 1972 and then considered exceedingly rare, Merkel cell carcinoma appears to be on the rise. More than 1,000 cases have been reported in patients aged 7-75 years (although most patients are older than 65 years).

Up to 15% of cases are seen in immunocompromised patients, a number that is driven by long-term survivors of HIV, chronic lymphocytic leukemia, and organ transplantation. "I'm seeing a lot of these," said Dr. Brown. Sometimes dome shaped and distinctly red or violaceous, they may present more subtly.

Long-term survivors of organ transplantation have a 65-fold increased risk of squamous cell carcinoma.

DR. BROWN

In one case, the small scalp lesion was barely pink, ill defined, and bound down to the adjacent skin. "No way I thought this was a Merkel cell," he admitted.

When the diagnosis is confirmed by its blue cell clusters in sheets or a trabecular pattern in the dermis, with frequent mitosis and cell necrosis, dermatologists should take heed. "This is probably one of the worst cutaneous tumors that we, as dermatologists, can see. It's right up there with a bad angiosarcoma," he said.

Local recurrences are seen in 25%-33% of cases, regional spread in 25%, and distant metastasis in 33% of cases—50% by some reports—with a 3-year overall survival of 31%.

Treatment is controversial, noted Dr. Brown. Wide local excision down to the fascia or Mohs surgery with sentinel lymph node biopsy is recommended, guiding the need for total lymph node dissection, postoperative radiation therapy, and perhaps adjuvant chemotherapy. A negative sentinel lymph node carries a fairly reassuring prognosis.

He added that an immunostain for anti-CK20 antibody may detect micrometastases in patients who appear to be tumor free on routine histology, according to a small study (J. Am. Acad. Dermatol. 2002;46:661-6).

SCC in Organ Transplant Patients

The growing population of long-term survivors of organ transplantation has a 65-fold increased risk of squamous cell carcinoma.

Their cancers may be multiple, fast growing, and atypical in appearance, Dr. Brown said.

In one such case, a liver transplant patient he had seen 3 weeks previously presented with a 3-cm SCC at the base of his thumb. He had a positive lymph node in his axilla and developed metastatic disease in his lung within 3 months.

"We're all going to be seeing more and more of these patients," Dr. Brown predicted.

The keys to management of these challenging patients are education first, then vigilance. Many transplant centers fail to warn patients that they may be at elevated risk for skin cancers and that they should be examined frequently.

When a lesion appears, have a low threshold for suspicion, he said. "It is very difficult sometimes to determine which is the bad [lesion] and which is not."

High-risk SCCs are those that are large, multiple, deeply invasive, painful or tender, rapidly growing, recurrent, and on high-risk sites: the scalp, ear, lip, neck, and face. Warning signs histologically include poor cell differentiation and perineural invasion.

"How do you manage these? Aggressively," he emphasized.

Employ whichever tools work: surgery, cryotherapy, 5-fluorouracil, photodynamic therapy, or topical imiquimod. Systemic retinoids, perhaps in conjunction with a reduction in immunosuppressive therapy, may be appropriate for patients with recurrent, aggressive, or metastatic SCCs, he added.

Dr. Brown disclosed that he is a consultant to Graceway Pharmaceuticals LLC and Novartis. His presentation, however, was not sponsored by any company. ■

Immunostaining May Help Predict Nodal Metastasis Risk

BY MARY ANN MOON
Contributing Writer

Positive immunostaining with monoclonal antibody D2-40, together with younger patient age and lesion ulceration, might identify which melanoma patients are likely to have nodal metastasis and should undergo sentinel node biopsy, according to Dr. Firouzeh Niakosari of Sunnybrook Health Sciences Centre, Toronto, and associates.

"The recently developed monoclonal antibody [Mab] D2-40 reacts with endothelial cells of lymphatics but not with endothelial cells of blood vessels in normal tissues," the investigators wrote (Arch. Dermatol. 2008;144:462-7).

Mab D2-40 immunostaining more readily identifies lymphatic invasion in primary melanomas than does conventional staining with hematoxylin-eosin. Dr. Niakosari and associates assessed the technique's predictive value using blocks of primary tumor taken from 96 patients who were treated in 1998-2004 and had no clinical evidence of metastasis.

On biopsy, sentinel lymph nodes had been found to be positive in 23 of the cases.

Mab D2-40 immunostaining was positive for invasion of the lymphatic vessels within the tumor samples in 32 of the 96 cases (33%). The result was correct in ruling out lymphatic invasion in 56 (77%) of the cases that proved to have no invasion on sentinel node biopsy, and it was correct in identifying lymphatic invasion in 15 (65%) of the cases that did have lymphatic invasion on sentinel node biopsy.

On its own, then, the technique had a negative predictive value of 88% and a positive predictive value of 47%, the investigators found.

Mab D2-40 immunostaining was even more predictive when the results were combined with two clinical factors: younger patient age and the presence of ulceration in the lesion. "The probability of sentinel lymph node positivity was 13% when lymphatic invasion identified by immunostaining with Mab D2-40 was negative, no ulceration was present, and the patient was 50 years or older," they noted.

In cases in which the immunostaining indicated that there was lymphatic invasion, ulceration was present, and the patient was younger than 50 years, the probability of sentinel lymph node positivity increased to 61%, Dr. Niakosari and associates reported.

Lymphatic invasion on Mab D2-40 immunostaining correlated with deeper Clark Level of Invasion and increased Breslow tumor thickness, "indicating that lymphatic invasion occurs more frequently in later stages of melanoma," they wrote. ■