

Merkel Cell: It's Rare, Lethal, And Often Gets Misdiagnosed

BY MIRIAM E. TUCKER
Senior Writer

OUR LUCAYA, BAHAMAS — Merkel cell carcinoma is more deadly than melanoma, and it is almost always misdiagnosed clinically, Dr. Henry W. Randle said at a meeting of the American Society for Mohs Surgery.

In a recent survey of 135 biopsy-confirmed Merkel cell carcinomas, 44% had been judged clinically to be cysts or acneiform lesions, 19% to be other non-melanoma skin cancers, 9% to be dermatofibrosarcoma protuberans, and 28% received various other misdiagnoses. Just 2 of the 135 were accurately identified as Merkel cell carcinoma prior to biopsy. "Clinically, it's a problem. Almost no one identifies these up front. Keep it in mind in your differential," said Dr. Randle of the Mayo Clinic in Jacksonville, Fla.

Indeed, Merkel cell carcinoma's clinical presentation is very nonspecific, consisting of firm, red to purple, nontender papules or nodules usually appearing on sun-damaged skin. Patients are typically over 65 years of age, with incidence about equal in men and women. Those who are severely immunosuppressed or who have undergone psoralen-ultraviolet-light (PUVA) treatment are at increased risk.

Although Merkel cell carcinoma is uncommon, its incidence tripled between 1986 and 2001, going from 0.15 per 100,000 age-adjusted population to 0.44/100,000 (J. Surg. Oncol. 2005;89:1-4). Absolute numbers are hard to obtain, but estimates range from 400 to 800 cases per year in the United States, he said.

Mortality is 25% within the first 3 years. However, patients who survive past 3 years are not likely to die of the disease. Survival is highly dependent on stage at diagnosis: Those with localized disease and lesions of less than 2 cm in diameter (stage 1) have a 90% survival rate at 3 years, whereas larger localized lesions (stage 2) reduce 3-year survival to 70%. Nodal disease (stage 3) reduces survival to just 30%, and metastatic disease (stage 4) kills 90%.

Sentinel lymph node biopsy (SLNB) should be performed routinely in these patients, because clin-



COURTESY DR. HENRY W. RANDLE

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ical examination is insufficient: In one study, 10 of 31 patients without palpable lymph nodes had a positive SLNB. Adjuvant treatment should be considered in all Merkel cell carcinoma patients with positive lymph nodes, Dr. Randle advised.

Treatment of the primary lesion involves either Mohs or wide (1-3 cm) excision. Dr. Randle tends not to use Mohs, however, because surgeons prefer to do both procedures at once rather than taking the node after the dermatologist has already operated on the cancer. "I usually send for wide excision and [SLNB], but you can use Mohs," he noted.

Currently, radiation is the adjuvant treatment of choice for patients with positive sentinel nodes, while data on chemotherapy are less definitive. In one study, the addition of radiation to surgery, compared with surgery alone, resulted in lower rates of local recurrence (3% vs. 25%), nodal recurrence (22% vs. 42%), and distant spread (11% vs. 21%). "It's been questioned in the literature, but I think radiation clearly does help," Dr. Randle remarked.

The risk for Merkel cell carcinoma is elevated 100-fold among individuals who have had PUVA treatment (N. Engl. J. Med. 1998;339:1247-8). For more information, visit www.merkelcell.org.

Merkel Cell Raises the Risk of Other Tumors

BY NANCY WALSH
New York Bureau

MANCHESTER, ENGLAND — Patients with Merkel cell carcinoma are at high risk for multiple malignancies and should be closely examined at the time of diagnosis for other possible tumors, Dr. Julia K. Gass said at the annual meeting of the British Association of Dermatologists.

A review of the data of all 27 cases of Merkel cell carcinoma treated at Addenbrooke's Hospital National Health Service Trust, Cambridge, England, between 1995 and 2004 found additional tumors in 70% of cases, she said. The patients were elderly, with a mean age of 78 years. A total of 44% of these patients had one other tumor, 22% had three, and 4% had four additional malignancies.

Using information from the Eastern Region Cancer Registry, the rate of multiple malignancies was compared with that in the background population. When adjusted for advanced age, an incidence ratio of 3.47 was found, said Dr. Gass of Addenbrooke's dermatology department. Additional malignancies were cutaneous in 18 patients. Two of these were melanomas, seven were squamous cell carcinomas, and nine were basal cell.

An association of squamous cell carcinoma with Merkel cell carcinoma has been noted previously. Mixed tumors have also been seen, leading to the hypothesis that both types of tumor arise from a pluripotential epidermal stem cell damaged by ultraviolet light. Supporting the role of UV light in the pathogenesis of Merkel and squamous cell carcinomas is the finding that some of these tumors share UVB-type specific mutations of the p53 tumor suppressor gene and the Harvey-ras oncogene, she said.

The noncutaneous tumors in these patients included colorectal cancer in five, hematologic malignancies in three, and a breast tumor in one. The rare phenomenon of synchronous metastases from a Merkel cell carcinoma and from a second tumor to the same lymph node was seen in two patients, one with chronic lymphocytic leukemia and one with breast cancer. The synchronous metastasis of Merkel cell carcinomas and B-cell tumors, such as chronic lymphocytic leukemia, has previously been reported and may relate to genetic susceptibility, advanced age, immunosuppression by one tumor, or a common inducing agent.

New Link Is Found Between Psoriasis and Heart Disease

BY NANCY WALSH
New York Bureau

MANCHESTER, ENGLAND — The latest piece of evidence linking psoriasis with cardiovascular disease suggests that patients with the skin disease are at high risk of having elevated serum levels of homocysteine, Dr. Anne-Marie Tobin said at the annual meeting of the British Association of Dermatologists.

In the general population, hyperhomocysteinemia has been shown to be an independent risk factor for the development of cardiovascular disease, with a magnitude of risk similar to that of smoking and hyperlipidemia. Elevated levels of homocysteine have been linked to atherosclerosis, endothelial damage, and thrombogenesis.

Cardiovascular disease is the leading cause of mortality among patients with psoriasis. The precise reasons why patients with psoriasis are at risk for cardiovascular disease remain unclear, although several possible contributory factors exist. Some of the excess cardiovascular risk may relate to

increased rates of smoking and hypertension, risk factors that have been documented in this patient population.

"Moreover, there has been a suggestion from the rheumatology literature that chronic inflammation elevates cardiovascular risk, although this has yet to be confirmed in psoriasis," said Dr. Tobin of the department of dermatology, Adelaide and Meath Hospital, Incorporating the National Children's Hospital, Dublin.

Patients with psoriasis also have raised levels of lipoprotein A, which further increases risk for coronary heart disease and ischemic stroke. Moreover, small uncontrolled studies have suggested patients with psoriasis may have low levels of folate, which helps break down homocysteine. The accelerated rate of keratinocyte turnover seen in psoriasis is thought to lower levels of folate, she said.

"Based on these observations, we undertook a study to assess homocysteine levels in outpatients with moderate to severe psoriasis who were not on systemic treatment, and to assess the homocysteine lev-

els in the context of major conventional cardiovascular risk factors," Dr. Tobin said.

Twenty patients, of whom 11 were women, were recruited. Mean age was 42 years, and mean Psoriasis Area and Severity Index (PASI) was 12.8. Twenty age- and sex-matched controls were also enrolled. The patients were evaluated for body mass index (BMI), blood pressure, and levels of glucose, lipids, homocysteine, and folate.

One patient with psoriasis had extremely low levels of folate and also had atrophic gastritis and pernicious anemia and was excluded from further analysis.

Five patients with psoriasis had homocysteine levels of 12 $\mu\text{mol/L}$ or higher, compared with only one control subject. Population-based studies suggest that slightly more than 5% of the general population has elevated homocysteine, which was similar to the figure for the controls in this study. "But with more than 27% of our patients with psoriasis having raised levels of homocysteine, the odds ratio of their having hyperhomocysteinemia was greater than 7," com-

pared with controls, Dr. Tobin reported.

There was no correlation between levels of homocysteine and PASI. Patients with psoriasis also had a trend for low levels of red-cell folate, but this was not statistically significant. "Hyperhomocysteinemia was not related to either folate status or disease severity in psoriasis patients, as had been supposed," she said.

Likelihood of high BMI also was increased among psoriasis patients: A total of 17 patients with psoriasis had a BMI greater than 25, compared with only 4 controls. Three of the 17 were clinically obese and 2 were morbidly obese, she noted.

Patients with psoriasis also had significantly raised systolic blood pressure. "However, because diastolic blood pressure was normal and the fact that blood pressure readings were not repeated, we were unsure of the significance of this result," Dr. Tobin said. She said the significance of the results warrants a large population-based study to identify the risk factors that should be routinely measured in patients with psoriasis.