Merkel Cell Carcinoma: Not Just Another Skin Cancer

Merkel cell carcinoma (MCC) is a rare, aggressive, and often fatal neuroendocrine skin cancer. The incidence of MCC has been increasing in recent decades.[1] Although it shares some risk factors with other skin cancers, early and recurrent MCC is managed very differently from those cancers. To clarify misunderstandings about MCC and learn how it is unique among skin cancers, Medscape spoke with Paul Nghiem, MD, PhD, professor and division head, Department of Dermatology, University of Washington, Seattle.

Medscape: With skin cancers, the emphasis is typically on risk factors and early identification. What are the risk factors for MCC?

Figure 1. Paul T. Nghiem, MD, PhD

Dr Nghiem: The starting populations that are truly at elevated risk are people with multiple prior skin cancers and those who are immune suppressed, such as organ transplant patients. Hopefully, most of those people are already being watched very carefully because they are at risk for a variety of skin cancers. MCC is about 30 times less common than melanoma and far less common than basal or squamous cell carcinoma, and the clinical features of MCC are not extremely specific. Putting those two facts together, if we started a big public health effort to identify MCC early, we would just worry people, and most of the bumps that look like cysts will, of course, turn out to be cysts.

Most cases of MCC don't appear in an obvious high-risk population. That being said, the "AEIOU" characteristics can be helpful in identifying a suspicious lesion[2]:

- "A" is for asymptomatic. An MCC is typically not tender compared with a similar-appearing inflamed cyst, which is often tender.
- "E" is for expanding rapidly; a bump that has grown significantly in the last month or two.
- "I" is for immune compromised. This is a tricky one because 92% of MCC patients are not immune compromised, but those with long-term T-cell dysfunction (organ transplant recipients, autoimmune disease patients receiving immune suppression, HIV patients, chronic lymphocytic leukemia patients) are at much higher risk of developing MCC, but they represent less than 10% of all cases.
- "O" is older than 50 years. Every decade of increasing age raises the risk for this cancer by several fold, and that's not really true of other cancers, which increase with age but eventually tail off and then decline with age after 70, 80, or 90 years. With MCC, the incidence skyrockets with every decade, and we believe that's because of immunosenescence. The immune system becomes less able to detect this very immunogenic cancer as we age. As the baby boomers enter their 60s and 70s, we are seeing a population bump that significantly increases the incidence of this age-sensitive cancer.
- "U" is for ultraviolet (UV)-exposed fair skin.

When you consider the AEIOU characteristics together, almost 90% of Merkel patients have three or more of those five features. It is thus a sensitive test but not a very specific one. Most bumps that fit two, three, or four of

these criteria are still going to be a lipoma, an inflamed cyst, or another nonmelanoma skin cancer.

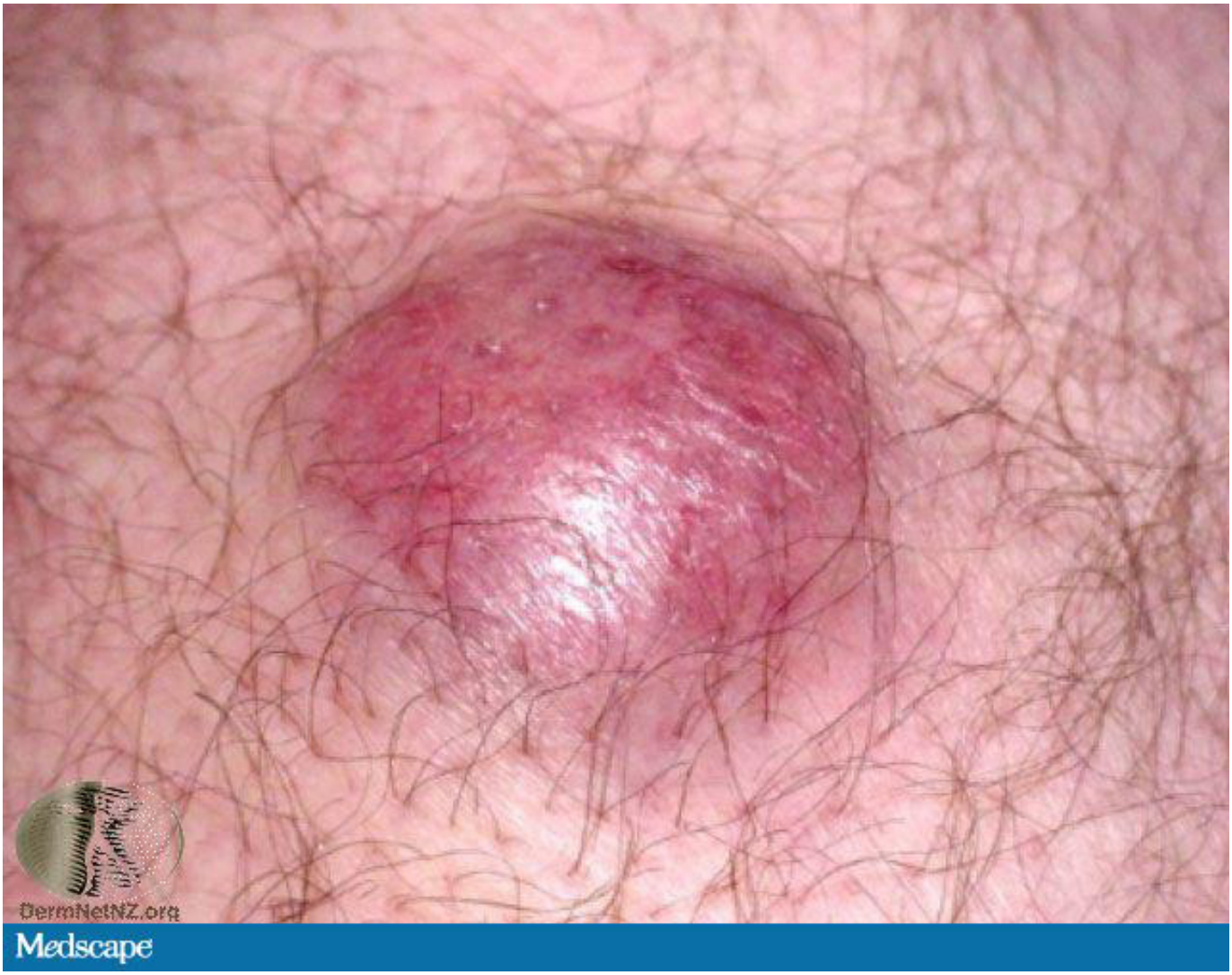

Figure 2. Merkel cell carcinoma on a patient's sun-exposed forearm. Courtesy of Dermnetnz.org.

Medscape: To clarify, are you saying that dermatologists and other clinicians shouldn't focus on recognizing MCC, per se, but on appropriately biopsying a lesion that has the AEIOU features?

Dr Nghiem: Yes. In aggregate, those AEIOU characteristics are not just useful for identifying MCC. They should raise alarm bells in general and

suggest that a biopsy is indicated. Most of the time, it's not going to be an MCC, but if you've got somebody with fair skin, a rapidly growing nontender bump on UV-exposed skin, and especially if the patient is immune suppressed, that bump probably deserves a biopsy. Indeed, it may well turn out that it was good to have biopsied the lesion, whether it's an MCC or something else.

In summary, there are features associated with MCC, but our focus shouldn't be on trying to train people to recognize this cancer early. In one study,[2] on the day the provider did a biopsy of what turned out to be MCC, nearly 60% of the providers thought it was a benign lesion—a cyst, folliculitis, or lipoma, for example—and most were simply doing the biopsy at the request of the patient. Only about one fourth of doctors thought that it might be some kind of skin cancer. We decided more than a decade ago (and I still believe this) that the way to make a big difference in MCC patient care is to focus on what happens after that suspicious bump is biopsied, and the diagnosis is clearly MCC. With immunohistochemistry for cytokeratin 20 and other markers, we aren't missing MCC if we have a biopsy. The focus needs to be on how patients are managed after the diagnosis is made. Until recently, the number of patients who are not managed according to basic guidelines[3] has been frustratingly high.

Medscape: In what way do you believe that patients have been mismanaged in the past?

Dr Nghiem: Management has been carried out by physicians who think, "Let's just treat this like a melanoma," or, "Let's treat this like a small cell carcinoma." Dermatologist and surgeons who aren't familiar with MCC tend to think that it is the same as melanoma, and medical oncologists think that it's like small cell lung cancer. Those are both inaccurate. MCC is its own beast. Either the physicians managing these patients need to become very

familiar with and review the guidelines for managing MCC,[3] or they should refer the patient to a center, of which there are many in this country and around the world, that offers multidisciplinary expert care in managing MCC. That's where the important educational message is.

Medscape: Let's turn to management of MCC. How does it differ from other skin cancers?

Dr Nghiem: We not only have management on the early side with surgery and radiation (unique compared with the management of melanoma, squamous cell carcinoma, basal cell carcinoma, or small cell lung cancer), but for patients who have developed distant metastatic disease, we also have unique approaches that involve immune therapy, including programmed death 1 (PD1) pathway blockade therapy.

We have been fine-tuning our approaches for managing early disease over the last 1-2 decades. There are going to be controversies; for example, which patients require adjuvant radiation is a very controversial area. Nearly everyone would agree that there are extreme cases that would benefit from adjuvant radiation, and other cases do not need this. But there is a very large gray zone where it's not clear that adjuvant radiation is indicated. I don't see that controversy being resolved soon.

After a simple excision, MCC is much more likely than other skin cancers (melanoma, squamous cell, or basal cell) to recur in adjacent areas, 1-4 cm away. Most physicians agree that MCC does not just grow as a contiguous ball of tumor cells but that it jumps through local as well as distant lymphatic channels. There is a significant role for adding radiation to surgery in a subset of cases, but exactly which cases require radiation is extremely controversial. With a different type of skin cancer, you wouldn't consider giving radiation in early disease with clear pathologic margins; but with MCC, recurrence rates

approach 50%.

It's a murky area that won't be resolved overnight. There are always trade-offs. Radiation has side effects and is costly, but it can markedly lower the risk for local and lymph node recurrence.

Medscape: Can you tell us about the recent advances in immune therapy for MCC?

Dr Nghiem: The big news in the past year is a stunning shift from cytotoxic chemotherapy as the standard of care for metastatic disease to a clear preference for immune therapy with the PD1 pathway agents. We now have public data on the striking efficacy of three drugs for MCC: avelumab (approved for MCC in the advanced setting), pembrolizumab (currently listed in the National Comprehensive Cancer Network guidelines), and nivolumab, which is approved for other indications and will likely be moving forward for MCC. These drugs are night and day better than chemotherapy in offering patients the possibility of long-term disease control.

The tricky thing is that the response rates of immune therapy are not better in the first line than the response rates of chemotherapy. Chemotherapy achieved about a 55%-60% shrinkage in most cases, or 55%-60% of patients would experience a response with chemotherapy. That's almost exactly the same response rate that is achieved by the immune therapy drugs in first-line treatment. So, the immune therapy drugs really don't change the chance of response. But the benefit is that most of those responders to immune therapy will stay in response for many months or years. After starting chemotherapy, disease will progress within 1 year in more than 90% of patients. So, there's a huge difference in the ability of these drugs to control the disease in the long term.

Medscape: **How long do patients have to continue on immune**

therapy?

Dr Nghiem: The therapeutic courses are typically between 1 and 2 years. It depends on how rapid and deep the response is. No one knows the precise answer to how long people should be treated. We typically say that if a patient is not experiencing significant autoimmune or other side effects from these agents, we treat them for about a year after they accomplish a very deep partial response or a complete response to the drug. But obviously, many factors can affect that decision, including insurance, availability, and side effects. These are expensive drugs, and they can have major side effects. If a patient develops autoimmune side effects, we are often pressed to stop the drug, even as early as the first dose. But it's been remarkable that some patients who receive only a handful of doses have had very long responses.

Medscape: Can you tell in advance who is most likely to respond to immune therapy?

Dr Nghiem: The simple answer is no, we don't have black-and-white criteria to suggest who is eligible and who isn't, or who has a good chance of responding and who doesn't. We think that quite a few factors are relevant, but we have nothing that tells us more than about 60% versus 40% chance of response—not much better than flipping a coin. At the moment, we are not using biomarkers to decide whether a patient should be treated with immune therapy drugs. Of course, there are contraindications to these drugs, such as a cardiac transplant recipient. We can't risk rejecting the heart. A renal allograft recipient is different. If the patient is willing to give up their graft, then perhaps we would try immune therapy, but those people are much less likely to respond than someone with a normal immune system.

The enormous burning question is: What do we do about people who don't respond to PD1 checkpoint blockade? First, can we identify them, and then

how can we rescue them by using other types of immune stimulation? We have done that in a handful of cases. We know it's possible in at least some cases that failed to respond to initial immune therapy, and we need to increase our ability to do that. Of course, predicting who is going to respond in the first place, who may need more than one modality of therapy, and how those agents should be combined are huge areas of investigation.

Medscape: What is the role of the Merkel cell polyomavirus (MCPyV) in response to immune therapy and recurrence of disease?

Dr Nghiem: MCC is caused either by heavy UV exposure or the MCPyV. Approximately 80% of MCC tumors contain the virus. The remaining 20% do not and were very clearly caused only by sunlight and UV damage, which leaves behind UV-induced neoantigens. The virus-positive cancers are immunogenic, but so are the tumors caused by UV damage because those UV mutations are visible to the immune system. Indeed, we see essentially equivalent rates of response to immune therapy in both types of patients.

About half of patients with MCPyV make antibodies to the virus. This can serve a useful purpose in managing these patients because the patients who don't make any antibodies to the virus at the time of diagnosis are at higher risk for recurrence and need to be followed more closely with imaging studies and other follow up. For the patients who do make the antibodies, an increase in the amount of those antibodies is a very good way to detect recurrent disease. So, it's possible to find disease earlier and to rely less on imaging routinely by using the antibody test, which is clinically available.

I would call MCC a 'poster child cancer' for needing multidisciplinary evaluation.

Medscape: What else would you like to say about MCC?

Dr Nghiem: The most important thing is that there has been a lot of progress, with increasing consensus that this cancer is not the same as the other skin cancers or small cell lung cancer. It's very important to use updated information, and whether you refer the patient or not, use multidisciplinary consultation. You should be talking to specialists in radiation oncology, medical oncology, surgical oncology, dermatology, and diagnostic radiology because a careful radiologic workup is also indicated. I would call MCC a poster child cancer for needing multidisciplinary evaluation. MCC needs multidisciplinary evaluation, ideally with people who are either very motivated to learn about what's new or who manage this cancer regularly.

Interested readers can find many resources, guidelines, publications, and clinical images at www.merkelcell.org.