in the US and Australia are successfully treated by early surgery. However, 10 percent of melanomas have been highly reactivated to treatment. In the quest for better understanding, multiple investigators are evaluating the role of genetic factors in survival. Williams and colleagues suggested that melanomas occurring in association with high ambient sun exposure might be biologically “more benign.” Reinforcing this notion, solar elastosis changes in the skin due to sun exposure has also been linked to greater melanoma survival.

Given the role of skin exposure in the synthesis of vitamin D and the anti-proliferative and anti-carcinogenic actions of vitamin D, genetic alterations in the gene that controls the vitamin D receptor or related genes might reasonably be associated with poorer survival of melanoma. It may be that individuals who have aggressive melanomas have a different set of genetic mutations from those common in more indolent melanomas.

The genetic factors associated with melanoma progression and survival are still being explored. While genetics in other cancers can be assessed by gene expression analyses from fresh tumor tissue, this is extremely difficult in melanoma, as primary melanomas are so small, and pathologists need all of the lesion in diagnosis to disease correctly. Another alternative is to measure single nucleotide polymorphisms (SNPs) — either in germline DNA (that is inherited) or in tumor DNA, using the DNA from paraffin-embedded tumors. However, these studies are still few in number and have usually been performed on small numbers of patients that are not usually representative of the general population of melanoma patients. Therefore, they are difficult to interpret so far.

CONCLUSION

At this point, the role of genetics in melanoma is still unclear. While intense, intermittent sun exposure is clearly important in the etiology of melanoma, its importance for survival is not known. Therefore, one cannot reliably say whether nature or nurture (i.e., behavior) is more important in either the etiology or the progression of melanoma. Hopefully, this uncertainty will continue to spur research to answer these questions.

DR. BERNICK is professor and chief of the Division of Epidemiology and Biostatistics at the University of New Mexico’s Department of Internal Medicine and associate director of the Population Science Program, UNM Cancer Center, Albuquerque. She has co-authored over 60 peer-reviewed publications and is a member of the Society for Melanoma Research’s Steering Committee and the National Cancer Institute’s Subcommitte-A.

References available on p.112.

Merkel Cell Carcinoma: An Uncommon But Often Lethal Skin Cancer

JAYASRI IYER, MD, AND PAUL NGHEM, MD, PHD

The number of reported cases of Merkel cell carcinoma (MCC), a relatively rare but dangerous skin cancer, has tripled in the last 20 years to approximately 1500 new cases annually in the US. There are several reasons for the increase. MCC was not routinely recognized by pathologists until the 1990s, when a highly effective microscopic stain (“CK20”), differentiating it from other cancers, was developed. In addition to better recognition of MCC, the reported incidence has grown due to true increases in its known risk factors, which include solar ultraviolet (UV) exposure, immune suppression and age over 50 years. MCC arises most often on sun-exposed areas in fair-skinned individuals over age 50. It derives its name from the similarity of these cancer cells to normal Merkel cells in the skin that are thought to be associated with touch sensation (Figure 1). Normal Merkel cells therefore were discovered over 100 years ago by Friedrich Sigmund Merkel. Merkel cell carcinoma usually appears as a firm, painless lesion on sun-exposed areas (Figure 2a, 2b). These tumors are typically red, blue or skin-colored and vary greatly in size. The average size at presentation is about the diameter of a dime (1.7 cm).

MELANOMA AND NONMELANOMA SKIN CANCER VS. MCC

Melanoma and nonmelanoma (basal and squamous cell carcinoma) skin cancers are the most common cancers in the US, with over a million cases of nonmelanoma skin cancer and approximately 62,480 cases of melanoma reported each year. While MCC is 30 times rarer than melanoma, it is twice as lethal. MCC kills approximately one in three patients compared to a one in six mortality for melanoma.

THE NEWLY DISCOVERED VIRUS

Scientists at the University of Pittsburgh recently discovered a “Merkel cell polyomavirus” — a human virus that is present in approximately 80 percent of MCC tumors but in fewer than 10 percent of melanomas and other skin cancers. People are generally exposed to polyomaviruses (members of a family of double-stranded DNA viruses) prior to age 20. When the Merkel polyomavirus infects a cell, it produces proteins that may cause cells to grow (divide) inappropriately, promoting cancer. The fact that about 20 percent of MCC tumors do not have this virus clearly indicates that the virus (or its continued presence) is not required in all cases of MCC.

KEY RISK FACTORS

Age over 50, light skin color, sun/ultraviolet exposure, and immune suppression are all significant risk factors for MCC. We have created an acronym, “AKDD,” to help recognize factors associated with MCC diagnosis.

AEIDU Features of MCC

A. Asymptomatic/lack of tenderness
B. Expanding rapidly
C. Immune suppression
D. Older than 50 years
E. Ultraviolet-exposed/fair skin

Figure 1: Normal Merkel cells in the skin. In this illustration of a cross section of skin, normal Merkel cells are shown in red and connective tissue shown in yellow. The structures shown include the epidermis, dermis, hair follicles, blood vessels, subcutaneous fat tissue, and the skin (Right)

Figure 2a, 2b: Merkel cell carcinoma on the arm of a 60-year-old man (left), and on the scalp of an 80-year-old woman (right)

For more information, visit Cancersource.com

References available on p.112.

Variant Gene Is Linked To Melanoma In Young Women

A new study from New York University Medical Center shows that women with a certain gene variant have a four times greater risk of developing melanoma when they are under age 50 than women in whom the gene is normal. Lead author David Polsky, MD, PhD, says the higher risk may be related to estrogen activity. Estrogen binds more strongly to the abnormal version of the MDM2 gene, switching on greater production of the MDM2 protein, which can lead to uncontrolled (cancerous) growth. Women with the genetic variation who also have high estrogen levels might be at especially high risk.

Melanoma, the deadliest form of skin cancer, is more common among women than men under the age of 40, and the new findings suggest that abnormal versions of the MDM2 gene may be a reason. The gene variation was found in 40 percent of the female melanoma patients under age 50 who were studied. Median age at diagnosis was 13 years earlier for women with this gene variation.

The hope, says Dr. Polsky, would be to develop a genetic test to help identify women at risk of developing melanoma young, so that they would be committed to sun protection and regular skin checkups.

MCC and a Newly Discovered Polyomavirus

- Discovered in early 2008
- Present in ~80 percent of MCC tumors but very rare in other skin cancers
- Viral DNA is integrated into cancer cells early in MCC development
- People are likely exposed to this virus early in life
- Fewer than 1 in 100,000 virus-infected people will develop MCC
Of all of these factors, the two most important are extensive UV exposure and profound immune suppression. Extensive UV exposure not only damages the skin, increasing skin cancer risk, but also helps to deplete the immune system, reducing its ability to fight off skin cancers and other diseases. The immune system helps the body recognize and eliminate cancers of the skin and other organs. People with profoundly weakened immune systems are 10–20 times more likely to develop MCC. Relevant forms of immune deficiency include immune suppression by viruses (people with HIV), transplant medications (solid organ transplant recipients); or malignancies (those with chronic lymphocytic leukemia or lymphomas). Patients with these types of immune suppression are twice as likely to die of MCC as immune-competent individuals. This suggests that the immune system is involved in blocking the spread of MCC cancer cells as well as preventing their development. Despite the increased risk posed by immune suppression, 99 percent of MCC cases occur in patients who do not have known immune system defects.

CHALLENGES IN DIAGNOSIS AND TREATMENT

There are several challenges in the diagnosis and management of this lethal cancer. At the time of presentation, MCC tumors are often considered benign by patients and physicians alike. In fact, 58 percent of MCCs are thought to be benign by physicians at the time of biopsy. The single most common presumed diagnosis is a cyst/folliculitis lesion.

Unlike other skin cancers, it is common for MCC to have spread to lymph nodes at the time of diagnosis even though the nodes are not enlarged or detectable on physical examination. Even a small MCC has a 30 percent chance of having spread to lymph nodes by the time of diagnosis. In comparison, the chance of an average melanoma having spread to the lymph nodes at time of diagnosis is only one percent.

A sentinel lymph node biopsy (SLNB) is a technique by which one to three relevant (“draining”) lymph nodes from the lymph node basin closest to the tumor are identified, removed and examined microscopically for the presence of cancer cells. (See SLNB Box.) This technique is routinely recommended to determine whether the MCC has spread to the lymph nodes and is a very important determinant in a patient’s prognosis.

TREATMENT GUIDELINES

Treatment is generally based on the stage of the disease. As with other cancers, the three major treatments for MCC are: 1) surgical treatment of the primary lesion and any lymph nodes also indicated, 2) radiation therapy, and 3) chemotherapy.

At all stages of MCC, complete excision of the primary lesion, verified by pathologic examination, is recommended. When the lymph nodes are involved, surgical excision or radiation treatment to the involved nodes should be carried out; it diminishes the risk of recurrence in the affected region. In most cases it is important for patients with no obvious lymph node disease to undergo sentinel lymph node biopsy to determine their prognosis and the necessity of further treatment. Radiation therapy is typically recommended for the site of the primary lesion when the risk of recurrence is high (large primary tumor; incomplete excision, immune-suppressed patient, etc.). Chemotherapy is usually reserved for patients with distant metastatic spread (liver, lung, etc.).

SUMMARY

MCC is a skin cancer that typically arises on sun-exposed areas of fair-skinned individuals over the age of 50. Significant progress has been made in recent years in improving diagnosis and therapeutic management as well as in our understanding of this cancer’s causes—in particular the new Merkel cell polyomavirus. Because survival after diagnosis is highly dependent on stage at presentation, it is critical to identify and treat this cancer early. An annual total-body skin examination is advisable.

To help educate patients and physicians about MCC, we have created an extensive website (http://www.merkelcell.org) focused on this often lethal disease. Our website highlights the key findings from the literature as well as treatment guidelines.

SENTINEL LYMPH NODE BIOPSY TECHNIQUE

- A radioactive tracer and/or blue dye is injected at the tumor site
- They travel along the same path that the cancer cells would, spreading through the lymphatic vessels and collecting in the sentinel lymph node(s), which are the first nodes in the local lymphatic basin
- An instrument that detects the tracer maps the path from the skin to the sentinel lymph node(s) (SLN)
- The SLN is removed and examined microscopically for the presence of cancer cells; if cancer cells are found, all the other nearby nodes are removed or radiated
- The technique is minimally invasive, has low risk of side effects and is also used to detect melanoma and breast cancer

SENTINEL LYMPH NODE BIOPSY AND MCC

- Good prognostic marker: If SLN negative, ~90% five-year survival, if positive, ~50% five-year survival
- Identifies the region containing the SLN
- Helps to determine if lymph nodes should have further treatment

DR. NGHIEM cares for skin cancer patients at the Seattle Cancer Care Alliance and is an associate professor of dermatology at the University of Washington in Seattle. He leads a research laboratory focused on MCC as well as other UV-induced cancers. His team gratefully acknowledges research support from The Skin Cancer Foundation, National Institutes of Health, the Jerry Wachter Fund for MCC; the UW Fund for MCC research and the American Cancer Society. Dr. Nghiem is also founder of the Merkel Cell Carcinoma Multicenter Interest Group (MMIG) composed of 60 physicians interested in MCC, across 30 institutions in 6 countries.

DR. IVYR is a clinical research fellow working in Dr. Nghiem’s group. Her research interests are the characterization of the immune response to the Merkel polyomavirus, examination of new prognostic markers for MCC and the development of clinical trials for MCC.

References available on p.112.
THE EYELIDS: HIGHLY SUSCEPTIBLE TO SKIN CANCER (p.53)


Merkel Cell Carcinoma (p.59)


Nature or Nurture — Which Is Responsible for Melanoma? (p.56)


