Merkel Cell Carcinoma:
An Uncommon But Often Lethal Skin Cancer

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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 tumors, 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 were first described over 100 years ago by Friedrich Sigmund Merkel.

Merkel cell carcinoma usually appears as a firm, painless lesion on a sun-exposed area **(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.

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 1000 virus-infected people will develop 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, "AEIOU", to help recognize factors associated with MCC diagnosis.

AEIOU Features of MCC

A Asymptomatic/lack of tenderness
E Expanding rapidly
I Immune suppression
O Older than 50 years
U Ultraviolet-exposed/fair skin

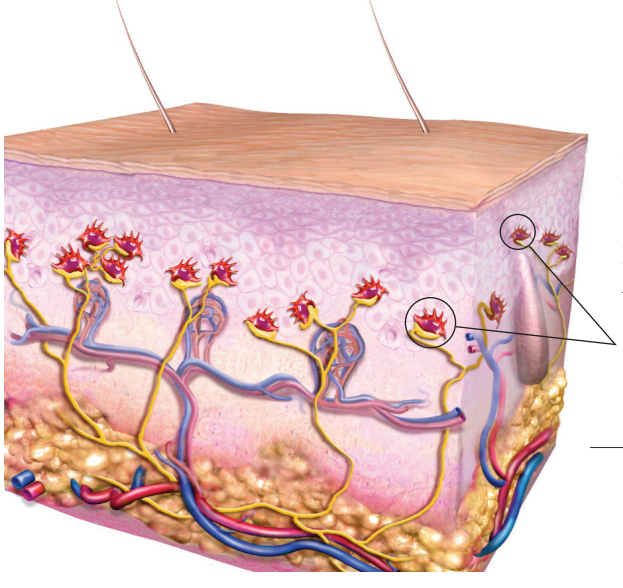

Figure 1: *Normal Merkel cells in the skin: In this illustration of a cross-section of skin, normal Merkel cells are shown in red and connect to nerves shown in yellow. The structures drawn include the epidermis (upper third), dermis (middle), and deeper adipose layer containing the fatty tissue. Arteries are depicted as red and veins are blue. Figure Copyright © by Paul Nghiem & Quade Medical Group.*

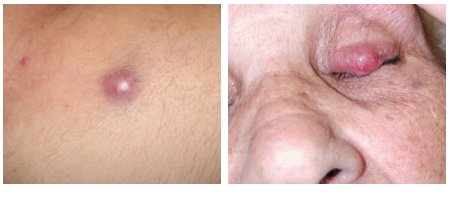

Figure 2a, 2b: *Merkel cell carcinoma on the arm of a 68-year-old man (left), and on the eyelid of an 85-year-old woman (right).*

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, 90 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.[1]

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 (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, ~80% 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

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DR. IYER *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.*

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