Introduction

This talk will focus on the understanding of Merkel Cell Carcinoma, a rare but lethal form of skin cancer. Due to its predilection for the head and neck, this cancer is often encountered in the Otolaryngologist practice. Also, its rapid progression makes it a disease that requires a high level of suspicion. When identified early, there is a much greater 5 year prognosis which due to the disease’s spread makes a significant difference.

History

This disease is a relatively new diagnosis. In 1875, the Merkel cell was first described by Friedrich Merkel when isolated in the skin of ducks and geese. In 1972, Cyril Toker described the first case of Merkel Cell Carcinoma. It has been described under various aliases, trabecular carcinoma of the skin, neuroendocrine cancer of the skin, and small cell carcinoma of the skin. Due to its recently relative description, much remains to be known regarding Merkel cell carcinoma. Further, its rarity prevents large case studies or reports.

Incidence

In the United States, the age-adjusted incidence has been increasing. In 1986, the incidence was 0.15 in 100,000 which has now risen to 0.44 per 100,000 as of 2001. As with skin cancers, there is an increased incidence amongst lighter skinned individuals. The incidence amongst Caucasians in the US is 0.23 per 100,000 when compared to 0.01 per 100,000 amongst African-Americans. When compared to other skin cancers, Merkel cell carcinoma is the most lethal. Fatality rates for Merkel cell carcinoma reach nearly 1 in every 3 patients while melanoma is only 1 in every 6. These diagnoses carry an
obviously significantly worse prognosis than squamous cell carcinoma (1 in 50) and basal cell carcinoma (less than 1 per 10,000).

For an Otolaryngologist, Merkel cell carcinoma is an important diagnosis to note due to its frequency in the head and neck region. Nearly 47% of all primary Merkel cell carcinoma is found in the head and neck region. In the head and neck, the most common sites are perioral and periocular. While mucosal presentations are rare, only 4.5%, this number should be taken with a grain of salt as the low incidence of this disease makes any percentage somewhat uncertain.

Merkel cell carcinoma most often presents in a patient greater than 65 years of age. While there are a few studies stating a 1 to 1 ratio between genders, most studies demonstrate a significant male predilection, nearly 1.5-2.5 to 1. Risk factors for Merkel cell are much like those for other skin cancers. These include fair skin, prolonged sun exposure, UVA therapy, and immunosuppressed individuals. Immunosuppressed individuals have a significantly increased risk, especially noted with HIV, Organ Transplant patients, and patients with chronic diseases like leukemia. The risk for individuals with HIV to develop Merkel Cell carcinoma is nearly 13.4 times increased. Similarly, patients with a history of an organ transplant are at a 10-fold increased risk.

**Basics of Merkel Cells**

Merkel cells are Type I mechanoreceptors. They provide the sense of fine touch as well as sensation of hair movement. Thus, they may operate independently or in conjunction with a tactile hair disc. They are typically located in the basal layer of the epidermis – located at the dermal-epidermal junction. They arise from neural crest cells and as such arise in the same lineage of cells which are capable of amine precursor uptake and decarboxylation. As a reminder, neural crest cells constitute a vast group of specialized cells. Some examples include odontoblasts, enterochromaffin cells, parafollicular thyroid cells, carotid body/glomus cells, adrenal medulla cells, Merkel cells, satellite glial cells, Schwann cells, Melanocytes, and Iris pigment cells. It is important and interesting to note that both Merkel cells and Melanocytes arise from the same lineage as melanoma is an important differential diagnosis for Merkel cell carcinoma.

**Typical Presentation**

An example of a typical patient would be a 70-year-old male patient who presents to the clinic with a rapidly enlarging mass near the upper lip. He is likely a fair-skinned individual who lives on a farm or in a sun-exposed profession. When asked about sun-protection, he would likely deny the use of sunscreen or wearing sun-protective clothing. When describing the mass, he notes that it has been steadily increasing in size since it was first noted nearly 2 months prior. He denies any pain from the mass or noting any bleeding from the mass. A variety of past medical history may be noted from none or include a chronic disease placing the patient in an immunocompromised state. Social history may include a long history of smoking tobacco or alcohol use. However, the patient’s profession and any cause of sun exposure is the most important history needed.
The physical exam typically reveals a firm, red, non-tender papule in the upper lip. On initial presentation, Merkel cell carcinomas are usually from 1-1.5 cm with no ulceration, no cervical lymphadenopathy, and no synchronous lesions. As stated earlier, these lesions are typically peri-oral or peri-ocular but also present on the cheek, nose, forehead, and other frequent sun-exposed areas – neck, upper back, and shoulders. While nearly ½ the presentations of this disease are in the head and neck region, the extremities are another common site for presentation.

**Cytopathology**

One of the most perplexing aspects of this disease is the cytopathology. Despite being visible on the skin and often initially detected in early stages, the outcome for a patient is poor. One of the key reasons why this discontinuity exists is the difficulty in obtaining a diagnosis from initial biopsies. When viewing the pathology with a typical hematoxylin and eosin stain, it is extremely challenging to identify the Merkel cells which typically arise as individual cells and at times clusters. Therefore, it is important to have Merkel cell carcinoma as a differential diagnosis to alert the pathologist to stain for this disease. Remembering this fact is further important when observing the pathology from a lymph node where it is further challenging to identify the Merkel cells which also appear as small blue cells among the lymphocytes.

Cytopathology typically reveals predominantly single cells with round, vesicular nuclei and scant neoplasm. They show scan to absent molding and have numerous mitoses. Within each cells, there are small vesicles which appear attached to the nucleus and are termed “perinuclear button-like inclusions.” Finally, of utmost importance, these cells stain specifically for cytokeratin 20, neurofilament, and neuron-specific enolase. On high power microscopy, the nuclei are round and surrounded by a thin rim of cytoplasm. The chromatin is fine to dark with one or more inconspicuous nucleoli. Little or no molding is present, and numerous mitoses are seen. Some authors have described “paranuclear button-like inclusions” consisting of 2- to 3-μm crescentic shaped or discoid globules located in the cytoplasm adjacent to the nucleus. These are best seen in hematoxylin and eosin preparations.

The importance of learning these cytopathologic features is to maintain a high index of suspicion. In a series by Dr. Paul Nghiem of a 100 patients, the initial biopsy results only correctly diagnosed a non-melanoma skin cancer is 14% of patients. His table of results is shown below.
There are three main histologic patterns noted which include the intermediate type, small cell type, and trabecular type. The Intermediate type is the most common type and must be distinguished from small blue cell tumors, melanoma, and lymphoma. The small cell type must be distinguished from a metastasis of small cell lung cancer. The trabecular type should be distinguished from metastatic carcinoid in its differential diagnosis. However, regardless of the type, the prognosis remains roughly the same and is poor.

**Neuroendocrine Role**

While this tumor has the potential to secrete hormones, it is rarely the case that it does. Most information on this topic exists as case reports or small case series. Case reports often show an association with adrenocorticotropic hormone or anti-diuretic hormone.

Adrenocorticotropic hormone is normally secreted by the anterior pituitary gland but is a fairly common hormone to be secreted in paraneoplastic syndromes especially with lung cancer. Its principal effects are increased production and release of cortisol. It acts on the adrenal cortex and is seen in small cell lung cancer which is a key differential diagnosis. Excess adrenocorticotropic hormone causes Cushing’s disease which typically presents with increased weight gain, central obesity, moon facies, hirsutism, purple striae due to thinning of skin, polyuria, hypertension, and hyperpigmentation.

Anti-diuretic hormone is made in the posterior pituitary gland and acts on the distal renal tubule and collecting duct in the nephron. It results in water retention without retaining the solute — thus lowering the serum concentration of the electrolytes. Similar to ACTH, it is also secreted in paraneoplastic syndromes and most often seen with small cell lung cancer. Excess anti-diuretic hormone results in symptoms which are predominantly reflective of hyponatremia. Early findings include headache, nausea, and vomiting. If the hyponatremia worsens, the patient may have irritability, confusion, seizures, or even a coma. Severe symptoms start to present once the sodium level drops below 120.
Staging

Staging was originally started in 2002 with the initial AJCC system. The system was based on size with 2 cm being the differentiation and nodal/metastatic involvement deciding the remainder of the stages.

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Primary tumor ≤2 cm, no nodal involvement, no metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>Primary tumor &gt;2 cm, no nodal involvement, no metastases</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any tumor size with nodal involvement, but no metastases</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any tumor size with nodal involvement and metastases</td>
</tr>
</tbody>
</table>

The updated 2009 staging criteria involve the individual TNM staging as seen with other cancers. The T score is based on the size of the tumor with 2 cm and 5 cm being the cutoffs. The N score is based on differentiation micrometastasis and macrometastasis as well as placing importance on differentiating between a clinically and pathologically negative neck for lymph nodes.
Staging therefore proceeds as follows with a pathologically negative neck getting a better stage when compared to a clinically negative neck. This importance will be touched on shortly.

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor (e.g., nodal/metastatic presentation without associated primary)</td>
</tr>
<tr>
<td>Tis</td>
<td>In situ primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Less than or equal to 2 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Greater than 2 cm but not more than 5 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Over 5 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Primary tumor invades bone, muscle, fascia, or cartilage</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>cN0</td>
<td>Nodes negative by clinical exam* (no pathologic node exam performed)</td>
</tr>
<tr>
<td>pN0</td>
<td>Nodes negative by pathologic exam</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>N1a</td>
<td>Micrometastasis**</td>
</tr>
<tr>
<td>N1b</td>
<td>Macrometastasis***</td>
</tr>
<tr>
<td>N2</td>
<td>In transit metastasis****</td>
</tr>
</tbody>
</table>
The differences between each stage in this disease are drastic. Stage I disease carries an 81% rate of survival while stage II only carries 67%. Stage III carries 52% while stage IV has a drastic decrease to 11%. Studies that help understand survival for patients with Merkel cell carcinoma state that disease stage is the only independent predictor of survival. Graphs reflecting percent relative survival to years from diagnosis show a nearly 20% difference between Stage IA and Stage IB. This is a remarkable difference in survival when realizing that both Stage IA and Stage IB have T1 disease but are only differentiated by a clinically negative neck versus a pathologically negative neck. This large gap only places more emphasis on the importance of lymph node evaluation in patients with Merkel cell carcinoma despite clinical exam.

Returning back to our thoughts on the initial presentation, the average size of a Merkel cell carcinoma presenting in the head and neck region is 1.59 cm along with a clinically negative neck. This places patients at a T1 and cN0 which is a Stage IB. Despite this early presentation, survival rates and prognosis remains poor for this disease. One of these reasons was the delay in diagnosis secondary to difficulty in identification with biopsies. When treating the neck for other head and neck cancers, CT scans typically help in predicting nodal disease. However, this is not the case for Merkel cell carcinoma as the sensitivity for a CT Neck is only 20% while the specificity is better but still not great at 87%. For distant spread, CT still shows benefit with good sensitivity.
In order to better treat these patients, the pathologic diagnosis must be made as soon as possible. As stated above, it is integral to ask for the specific stains including neuron-specific enolase, cytokeratin 20, and neurofilament. After obtaining an accurate diagnosis, the uncertainty that currently exists regarding treatment of the neck leads to worse outcomes. In one study, nearly 50% of patients had microscopic evidence of disease in a clinically negative neck. Such a finding mandates the need for evaluation of nodal disease in all patients. Finally, the disease carries a poor prognosis as the disease spreads fast and a significant percentage of patients present late. Nearly 6% of patients present after distal metastasis. Further, studies estimate anywhere from 10-30% of patients present with nodal involvement at initial presentation. These three factors provide much of the reason for the poor prognosis for patients with this disease.

**Treatment**

Treatment for Merkel Cell carcinoma consists of wide local excision of the mass followed by a selective lymph node biopsy or regional lymph node. Following surgical treatment, radiation therapy, chemotherapy, or a combined therapy are also options. For primary resection, wide local excision is mandated. The uncertainty is the amount of margins needed. While some authors suggest upto 3 cm, this amount may be and often is unfeasible in the head and neck region where a 1 cm lesion would require 7 cm of excision. Several studies report a range of negative margins from 1 cm – 3 cm. The only note to gather here is that the wider the margin that may be safely performed and closed should be done.

Next, unlike Squamous cell carcinoma and basal cell carcinoma, Merkel cell carcinoma has a high propensity for early spread to lymph nodes. It tends to have nearly 30% lymph node involvement which is the greatest among all skin cancers. For perspective, melanoma is the second most common at 5%. Approximately 75% of patients with Merkel cell carcinoma present with evidence of nodal metastasis. A study by Dr. Schmalbach where a selective lymph node biopsy was performed in patients with Stage I Merkel Cell carcinoma showed nodal metastasis in 2 patients. Further, a literature review showed a 12% false-negative rate when a selective lymph node biopsy was negative. Due to the importance of lymph node involvement, current practice guidelines by the National Comprehensive Cancer Network recommend a selective lymph node biopsy for untreated, localized, stage I disease. When performing selective lymph node biopsies, it is important to remind once more that the pathologist should be made aware of the diagnosis of Merkel cell carcinoma. Among the lymphocytes, identifying the individual Merkel cells is difficult but can be made easy with staining – typically cytokeratin 20.

Radiation therapy and its role remain uncertain at this time with more data needed. Several case series and retrospective reviews have shown a role for radiation, but this is an area that requires further evaluation. Currently, the National Comprehensive Cancer Network recommends radiation therapy for the primary tumor site post-operatively, in-transit lymphatics, and for the draining nodal basin in patients who only undergo a wide local excision. The argument against post-operative XRT is highlighted by a study by Allen et al. They showed that the combination of a wide local excision with negative margins and a selective neck dissection results in only an 8% local recurrence rate. On the other hand, there are also those that argue in favor of post-surgical XRT. A study by Medina-Franco et al.
reviewed 11 case series and determined that the local recurrence rate was decreased from 52.6% to 10.5% in those patients who underwent post-operative radiation therapy. Other similar studies tend to also demonstrate a nearly 4 fold decrease in local recurrence and nearly 20% greater 1-year and 5-year event-free survival when post-operative radiation therapy is used. Post-operative radiation therapy also lower regional recurrence nearly 3 fold and improves event-free survival by 20% and 30% at 1-year and 5-year intervals, respectively.

Some authors have also suggested the use of radiation therapy as a primary treatment. Pape et al. compared the treatment of Stage I Merkel cell carcinoma patients with primary radiation therapy versus those treated with wide local excision and radiation therapy and found comparable rates of recurrence. Further, Mortier et al. treated a small patient group with primary radiation therapy and found no recurrence in 3 years. While these findings suggest that a role does exist for primary radiation therapy, further studies are needed to better clarify if radiation therapy as a primary option may be seriously considered or only used in those individuals who cannot tolerate surgical intervention. Currently, it is endorsed as a possible treatment option in the elderly who cannot tolerate surgery or if the disease presents a location that does not allow for wide local excision with margins.

Chemotherapy is currently not employed in the treatment of Merkel Cell carcinoma. Chemotherapy is not typically used as it suppresses immune function – something often already seen in patients with Merkel cell carcinoma. Chemotherapy also causes a decreased quality of life, especially in the elderly, as it causes fatigue, hair loss, nausea, and vomiting. Neutropenic fever and sepsis are also complications of treatment. Due to the myriad of side effects and the fact that the typical patient with Merkel cell carcinoma is an elderly patient, chemotherapy has not been endorsed in treatment of this disease.

A suggested treatment protocol is shown below from the dermatology journals.
Conclusion/Highlights

The disease is a devastating one which requires a high index of suspicion and early, aggressive management. Its clinical presentation is best characterized by the acronym, “AEIOU.” The letters stand for Asymptomatic or non-tender, Expanding rapidly, Immunosuppressed patients, Older than 65 years of age, and UV exposure in fair skinned individuals. It is important to look for per-nuclear inclusions on H&E staining. Cytokeratin 20 is necessary to differentiate the disease from small cell lung cancer, melanoma, and lymphoma. Early treatment in stage I, which is less than 2 cm, has a fairly good prognosis of nearly 80%. Finally, regardless of treatment, it is imperative to rule out lymph node metastasis, ideally through a selective lymph node biopsy.

DISCUSSION: Remarks by Vicente Resto, MD, PhD

First of all there is going to be a bias between specialties from an open surgical specialty such as ours and Dermatology in which they do a lot more minimally invasive approaches and I think that really from a very high level perspective that already begins to explain some of the biases in each of the literature bodies. They have merits and weaknesses no matter which approach you choose. The first thing to recognize that only a sentinel node bias is only as good as the technical prowess of the surgeon performing it as the pathologic assessment. In its best applied form it should be highly effective in identifying the relevant
draining lymph node and a benefit is that the pathology assessment of those few earlier lymph nodes can be a lot more precise and in depth than it would be for a larger specimen. That's when you really slice specimens every five millimeters and every so number of sections with immuno-histochemical stains. As you saw, this tends to be single cell presence in a lymph node so would expect that kind of analysis likely would be a lot more sensitive at identifying those single cells.

Now again, the weakness is that if you're given the wrong lymph node no matter how well prepared, you're not going to find them.

The other approach, is where you do the selective either single or multilevel dissection which takes away some of the operator variability from a surgical perspective. Chances are that you're going to get the relevant lymph node in there for pathologic assessment but no pathologist is going to do five millimeter sectioning and immunochemistry on the entirety of a mega-section specimen. So if you happen to have experience doing signal sentinel lymph node mapping and you have great comfort, not a little comfort, with that technique then probably sentinel lymph node mapping is the preferred approach to go after this issue. Now, even in a sentinel lymph node negative setting I think you have to be highly committed to surveillance in these patients. In PET CT, where your mortality numbers are so impacted by such a low volume of single cell lymph nodes and the like, PET CT is never going to be as sensitive-it's not a microscopic technique.

My second comment is that the idea of using radiation therapy as the primary modality for "elderly and infirm patients" whom you cannot operate on, all I will do is remind you what all surgeons do, so who is really sufficiently infirm not to cut out a skin tumor in fact short of something that is truly massive in size in which case it really doesn't matter how you treat that patient for that patient is probably not going to have a good outcome.

The question is what to do with a large primary in an advanced stage and what to do with the neck even if it's a negative neck. You can argue that given the results in terms of outcome and at that point you're looking at relatively poor outcomes so that the question is, is there a value in really cleaning out the disease in its primary site and likely first echelon metastasis site even though there's a high rate of recurrence, and I would argue that yes, there is value, and yes it should be done mostly because it obeys very difficult ways to die with this disfiguring growth, this lesion in your face and neck. And you're always going to be more effective in clearing all this early on.

Again, back to the question of sentinel lymph node biopsy in a T3, you really have to sit down and think about lymph node mapping and how it's done. More often than not what you do is you basically inject dye in quadrants around your tumor. While if your tumor is very large the likelihood of getting a truly circumferential drainage of your radio tracer is low, and the larger it is the less representative and the less accurate it is in particular for large lesions.
Bibliography:


6. Miller et al., Cancer Epidemiol Biomarkers Prev, 1999, using SEER.


21. AJCC 2009 Cancer Staging Guidelines