MIMICKERS OF CARCINOMA

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I. Introduction

Each year in the United States approximately 1,000,000 cases of non-melanoma skin cancer are diagnosed. Of these cases roughly 80% are basal cell carcinomas and 20% are squamous cell carcinomas.1 A small percentage of these carcinomas are rare malignancies of adnexal origin and cutaneous metastases. In the typical practice of dermatopathology carcinomas are commonly seen and expected. However, there are also numerous benign conditions of the skin that can mimic cutaneous carcinomas and lead to an erroneous diagnosis of malignancy. In this presentation we will review some of the benign mimics of cutaneous carcinomas. These mimics may take the form of reactive, primary inflammatory, infectious, and benign neoplastic processes. The clinical presentation and histopathology of these mimics will be examined and ancillary studies that aid in confirming the correct (benign) diagnosis will be presented.

II. Pseudoepitheliomatous hyperplasia

Pseudoepitheliomatous hyperplasia (PEH), which may also be called pseudocarcinomatous hyperplasia is defined as reactive epithelial hyperplasia that mimics the epithelial hyperplasia of squamous cell carcinoma. In this entity the epidermis shows irregular acanthosis with jagged extension into the dermis. Follicular and eccrine gland hyperplasia may also be observed. The constituent keratinocytes show slightly enlarged nuclei, small nucleoli, and ample eosinophilic cytoplasm. Unlike carcinoma, this type of hyperplasia fails to demonstrate high grade nuclear atypia or a significant number of mitotic figures.

This reactive phenomenon is seen in a wide variety of clinical settings, including wound healing reactions, infectious and inflammatory processes, and in degenerative processes. The most common of these settings is in a wound healing reaction. In general practice we frequently observe this hyperplasia in re-excision specimens of skin, in which a prior biopsy was performed. In these cases recognition that a prior procedure has been done, and review of prior biopsy material is usually sufficient to arrive at the correct diagnosis.

Chronic ulcers also almost invariably show some degree of pseudoepitheliomatous hyperplasia, and are frequently biopsied to rule out carcinoma. Exclusion of carcinoma can be very difficult if the biopsy is small and if there is marked PEH. Multiple level sections to search for keratinocytic atypia and mitoses are necessary. One study demonstrated p53 staining in squamous cell carcinoma arising in chronic ulcers. No p53

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1 National Cancer Institute, United States National Institutes of Health
staining was noted in reactive epithelial hyperplasia, therefore allowing a separation of a benign from a malignant process.²

Another very common setting in which pseudoepitheliomatous hyperplasia occurs is in chondrodermatitis nodularis helicis (CNH). This is a degenerative phenomenon which occurs on the helix of older individuals and is though to be primarily the effect of chronic pressure, vascular insufficiency and actinic damage. This condition has also been reported as a sequela of cellular telephone use.³

CNH typically presents as a crusted papule and may clinically simulate a squamous or basal cell carcinoma. Histologic examination reveals a zone of ulceration with an underlying proliferation of blood vessels and variable dermal fibrosis. There may be a central plug comprised of keratin, fibrin, and cellular debris. The adjacent epidermis shows marked epidermal hyperplasia with irregular acanthosis. Hypergranulosis may be present. If the biopsy is deep enough, portions of degenerated cartilage are also observed. Recognition of ulceration, a blood vascular proliferation, and degenerated cartilage (if present) in association with reactive rather than malignant nuclear epidermal characteristics allows a definitive diagnosis to be made. Similar changes may be seen as the result of poorly fitting eyeglasses and this condition is called “acanthoma fissuratum.” Indeed any type of chronic pressure may result in pseudoepitheliomatous hyperplasia.

Marked pseudoepitheliomatous hyperplasia is also classically seen in association with a wide variety of infectious agents including fungal, mycobacterial, and parasitic. Typically these deep infectious processes present as exophytic crusted lesions that often mimic squamous cell carcinoma clinically. Some of the infectious agents may exhibit lymphangitic or “sporotrichoid” spread in which a nidus of infection is formed at the site of initial inoculation of the organisms, with subsequent development of subcutaneous nodules along the draining lymphatics. This clinical information may aid in making the correct diagnosis.

Histologic examination typically reveals pronounced epidermal hyperplasia with irregular jagged epidermal downgrowth into the underlying dermis. Intraepidermal neutrophilic abscesses may be present. The epidermal hyperplasia mimics a keratoacanthoma/well differentiated squamous cell carcinoma. Deeper in the dermis a dense inflammatory infiltrate of mono and multinucleated histiocytes and neutrophils is noted. Special stains for infectious agents (including Periodic acid-Schiff (PAS), Grocott methenamine silver (GMS), Fite, and Ziehl-Nielsen) may reveal variable numbers of infectious organisms. A high index of suspicion is essential and numerous special stains or multiple level sections stained with a single special stain may be required to reveal sparse organisms. Microbiology culture studies can also reveal infectious agents that cannot be


demonstrated by routine histopathology. Superficial biopsies of only the overlying hyperplastic epidermis may be very difficult to interpret as reactive. In these cases a deeper biopsy with culture study should be recommended to the clinician.

Patients infected with human immunodeficiency virus may also suffer from chronic herpes zoster infection that results in marked epidermal hyperplasia that can simulate a squamous cell carcinoma. Again clinical suspicion and recognition of viral cytopathic changes is necessary.⁴

A variety of benign and malignant dermal based non-epithelial neoplasms have been noted to produce pseudoepitheliomatous hyperplasia of the overlying epidermis. Classic examples include granular cell tumors of the tongue and other sites as well as CD30+ lymphoproliferative disorders.⁵ Usually recognition of the underlying neoplasm precludes an erroneous diagnosis of a carcinoma.

Another rare cause of pseudoepitheliomatous hyperplasia is a reaction to ingested halides. This condition is known as “halogenoderma” and its histopathology is similar to that seen in a deep fungal infection. Clinical information is essential in arriving at the correct diagnosis.

III. Primary inflammatory lesions

**Hypertrophic lichen planus** can mimic squamous cell carcinoma. This variant of lichen planus is typically seen on the lower shins, a site which is also commonly affected by squamous cell carcinomas of the keratoacanthoma type. It is characterized by marked epidermal hyperplasia that can have a jagged contour at its base and therefore mimics an invasive squamous cell carcinoma. Like ordinary lichen planus, hypertrophic lichen planus is characterized by a “lichenoid” or band like inflammatory infiltrate of lymphocytes. Necrotic keratinocytes are noted at the dermoepidermal junction and the rete assume a pointed or “saw-tooth” appearance. One clue to the diagnosis is the presence of necrotic keratinocytes at tips of the epidermal rete. The keratinocytes have ample cytoplasm with an eosinophilic glassy appearance. There is wedge shaped hypergranulosis. Associated changes of rubbing (lichenification) such as hyperplasia of non-involved epidermis and vertically oriented collagen bundles in the dermal papillae may also be noted. Recognition of the benign cytology, necrotic keratinocytes, lack of


significant mitotic activity, and presence of a band like inflammatory change is necessary to arrive at the correct diagnosis. However, this diagnosis can be very difficult in small superficial biopsies. To complicate matters, squamous cell carcinomas and keratoacanthomas have also been reported to occur in long-standing lesions of hypertrophic lichen planus.  

IV. Benign squamous neoplastic lesions

Benign squamous lesions (verrucae, keratoses) are extremely commonly seen in routine dermatopathology practice. While often recognized by clinicians as benign lesions, they frequently simulate malignancy clinically and may be biopsied to rule out a carcinoma. Additionally variants of these lesions may present a benign clinical appearance, but have worrisome histopathologic features. From time to time true squamous cell carcinomas may evolve in association with or exist in proximity to these benign lesions. Small and superficial biopsies taken from cosmetically sensitive areas also can increase diagnostic uncertainty.

Two lesions that are not-infrequently encountered and that may pose diagnostic confusion are the desmoplastic trichilemmoma and the inverted follicular keratosis.

Desmoplastic trichilemmoma was first described in 1990 by Hunt et al. This lesion typically presents as a dome shaped papule on the face of a middle aged male. Clinically they suggest verrucae, squamous, or basal cell carcinomas. Histologically thin strands of clear to basaloid cells are noted embedded in a desmoplastic, sclerotic stroma which results in an infiltrative appearance and therefore can mimic an infiltrating carcinoma of either squamous or basal cell type. These cellular aggregates typically occur in the center of the lesion, but may occur near its base. The authors that originally described this entity believed that this desmoplastic change was a secondary phenomenon arising in a pre-existing trichilemmoma. Usually diagnostic findings of a trichilemmoma can be observed elsewhere in the specimen (namely a palisaded external layer of clear cells resembling the outer root sheath of the hair follicle, and a thick PAS positive basement membrane). The cells of desmoplastic trichilemmomas have been shown to react positively with CD34, while the cells of common cutaneous carcinomas do not. This staining pattern may be helpful in partial or small biopsies.

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Inverted follicular keratosis is a designation given to a benign tumor of follicular origin. This term is also widely used to describe a variety of benign keratoses and verrucae that show a predominantly endophytic growth pattern with the presence of numerous squamous eddies within the lesion. These squamous eddies may show an infiltrative growth pattern through a fibrotic dermis, and therefore simulate a carcinoma. These eddies are formed by concentric layers of squamous cells that have a whorled growth pattern. At the center of these eddies keratohyaline granules and small collections of ortho- and para-keratin may be observed. Despite these worrisome features, the cytology of the keratinocytes is benign. Recognition of the rounded circumscribed contour of the margin of the lesion as well as the bland cytology of the constituent keratinocytes is necessary to arrive at the correct benign diagnosis.

V. Mimickers of Metastasis

Cutaneous metastasis of underlying visceral carcinomas is an uncommon complication of visceral malignancy. Almost any type of malignancy can involve the skin secondarily. In women the most common metastatic tumor is breast carcinoma. Metastases most frequently involve the scalp, anterior chest, and abdomen. They clinically simulate a wide variety of clinical entities, including cysts, inflammatory conditions, infection, and primary tumors. Conversely some benign cutaneous neoplasms may simulate metastatic disease. Here we will consider the clear cell hidradenoma as a mimic of metastatic renal cell carcinoma of clear cell type.

Clear cell hidradenoma (CCH) presents clinically as a nodular lesion or cyst. It may present at any age and at any site on the body. Histopathologic examination reveals a circumscribed multilobular proliferation that is variably solid and cystic. This lesion is comprised of two cell types, eosinophilic and clear. The amount of each type varies and goblet cell metaplasia may also be noted. The cells may from small whorls. The nuclear characteristics are bland and there are often dense islands of hyalinized eosinophilic stroma scattered throughout. Blood vessels may be noted in the dense stroma. Small ductal structures can also be observed. Mitoses are usually few.

Metastatic renal cell carcinoma of clear cell type (MRCC) typically presents as a rapidly growing mass. It may be ulcerated. Histopathologic examination demonstrates a nodular tumor that is comprised of variable number of clear cells arranged as irregular cords and acinar structures associated with delicate fibrovascular cores. Nuclear atypia, prominent nucleoli, mitoses, and necrosis may be observed. Hyalinized stroma is absent.

Immunohistochemistry can be employed when the diagnosis is not obvious based on routine histologic examination. CCH shows positivity for low molecular weight keratins (CAM 5.2), cytokeratin 7 and carcinoembryonic antigen (CEA). MRCC shows positivity for vimentin, CD10, epithelial membrane antigen, and RCC antibody. These findings are summarized in the table below.

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>CLEAR CELL HIDRADENOMA</th>
<th>METASTATIC RENAL CELL CARCINOMA</th>
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VI. Mimickers of Basal cell carcinomas

As previously mentioned basal cell carcinomas are exceedingly common and account for approximately 80% of the non-melanoma skin cancers diagnosed in the United States each year. In this section we will examine some common mimics of basal cell carcinomas and strategies to distinguish them.

The most obvious mimics of basal cell carcinoma are benign adnexal neoplasms with differentiation toward hair germ, namely trichoepitheliomas and trichoblastomas. Clinically these lesions may be solitary or multiple and may present as a carcinoma. Much has been written about histopathologic characteristic distinguishing benign from malignant basaloid neoplasms. The benign lesions show evidence of pilar differentiation, papillary mesenchymal bodies, small keratinizing cystic spaces and calcifications. Trichoblastomas are comprised predominantly of geminative cells but still show some evidence of pilar differentiation. Clefting within the fibrotic tumor stroma may be observed in both. Basal cell carcinomas in contrast show a more disorderly growth pattern with nuclear pleomorphism, numerous necrotic tumor cells, and tumor clefting from the surrounding stroma. Desmoplastic trichoepitheliomas, in which in thin cords of basaloid cells are embedded in a fibrotic stroma, may cause considerable diagnostic difficulty as they mimic an infiltrative or morpheaform basal cell carcinoma. Careful examination of these lesions with regard to hair follicle differentiation is necessary.

In addition basaloid proliferations may be occasionally seen above dermatofibromas. These proliferations tend to be small and associated with papillary mesenchyme. They lack significant cytologic atypia. Bone fide basal cell carcinoma may also develop in this setting as well.

Immunohistochemistry may be of help to differentiate benign basaloid neoplasms from basal cell carcinomas. Benign basaloid neoplasms typically retain Merkel cells, and therefore cytokeratin 20 staining to demonstrate the presence of Merkel cells within the lesion is helpful. Basal cell carcinomas show loss of Merkel cells, and therefore absence of staining for CK20. Androgen receptor positivity is seen in basal cell carcinomas but usually not in benign basaloid proliferations. Bcl-2 also diffusely stains basal cell

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Basaloid Neoplasms</th>
<th>Basal Cell Carcinomas</th>
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<tbody>
<tr>
<td>CK7</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>CEA</td>
<td>+</td>
<td>-</td>
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<tr>
<td>EMA</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>VIMENTIN</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>RCC Antibody</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

carcinomas, and is typically only seen in the basal layer of trichoepitheliomas.\textsuperscript{11} The immunophenotype of the stroma of these lesions is also different. CD34 positivity is typically seen in the stroma of trichoepitheliomas and is absent in the stroma of basal cell carcinomas. CD10 stains the stroma of trichoepitheliomas (especially papillary mesenchymal bodies) and the tumor cells of basal cell carcinoma.\textsuperscript{12} These staining patterns are summarized in the table below.

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>T-EP TUMOR CELLS</th>
<th>T-EP STROMA</th>
<th>BCC TUMOR CELLS</th>
<th>BCC STROMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>+ in Merkel cells in the tumor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ANDROGEN RECEPTOR</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>CD34</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCL-2</td>
<td>+ only in basal layer</td>
<td>-</td>
<td>+ diffusely</td>
<td>-</td>
</tr>
</tbody>
</table>
