

New Insights into Merkel Cell Carcinoma

Bruce R. Smoller, MD

Professor and Chair, Department of
Pathology

Professor, Department of Dermatology

University of Arkansas for Medical
Sciences

Merkel cell carcinoma

- Clinical features:
 - Sun-exposed head, neck and upper extremities
 - Elderly patients (mean age 75), male predominance
 - Rarely in children
 - Red color often resembles angiosarcoma, but usually indistinguishable from other cutaneous neoplasms
 - Usually about 2 cm in diameter at time of presentation

Merkel cell carcinoma



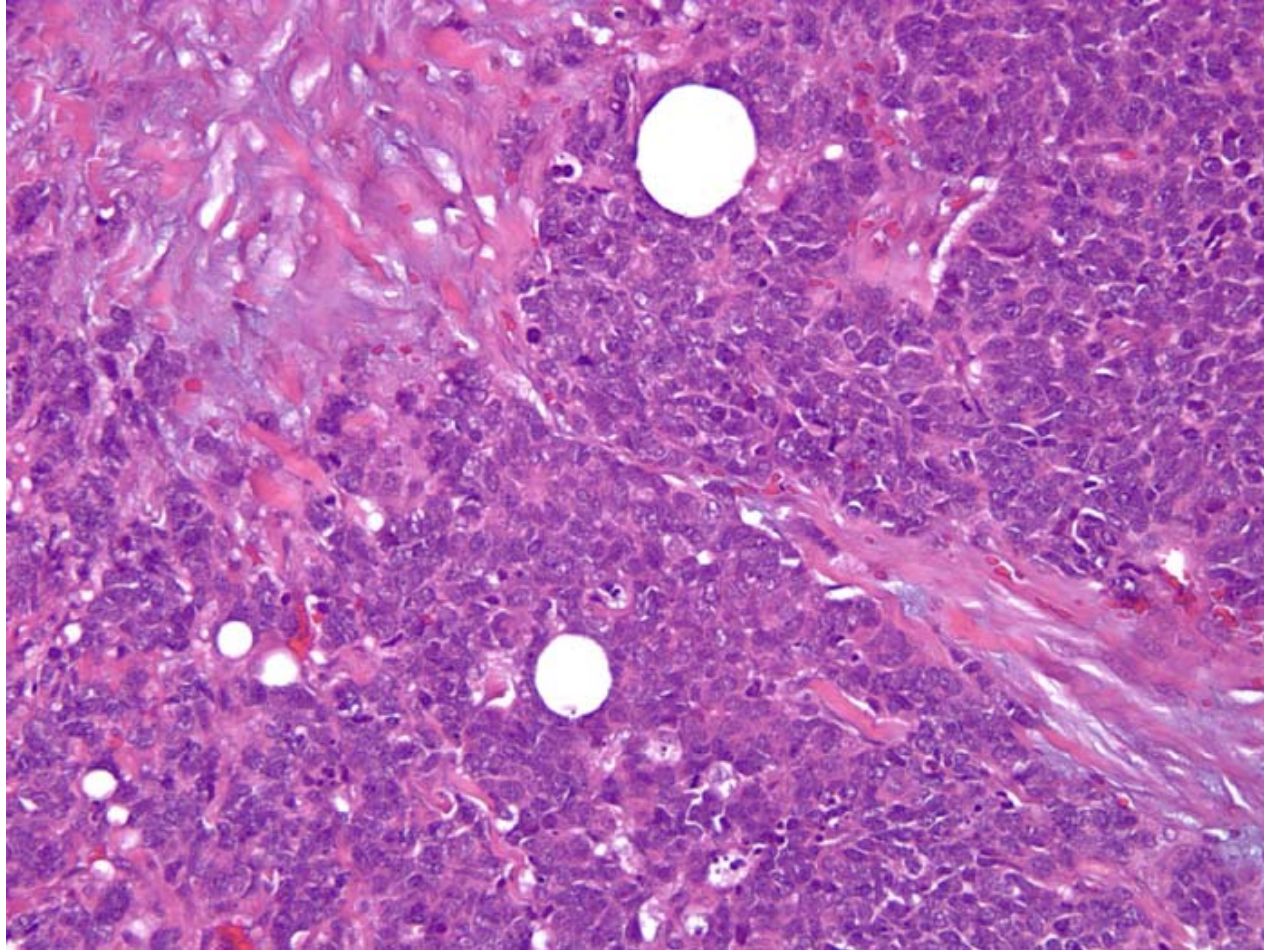
Merkel cell carcinoma

- Highly aggressive neoplasm
- Incidence of 0.23/100,00 in Caucasian Americans, very rare in African Americans
- 1500 new cases/ year in USA – incidence rising rapidly
- Local recurrence 25%
- Metastasis to regional nodes 50%
- Distant metastases 34%
- Death 34%

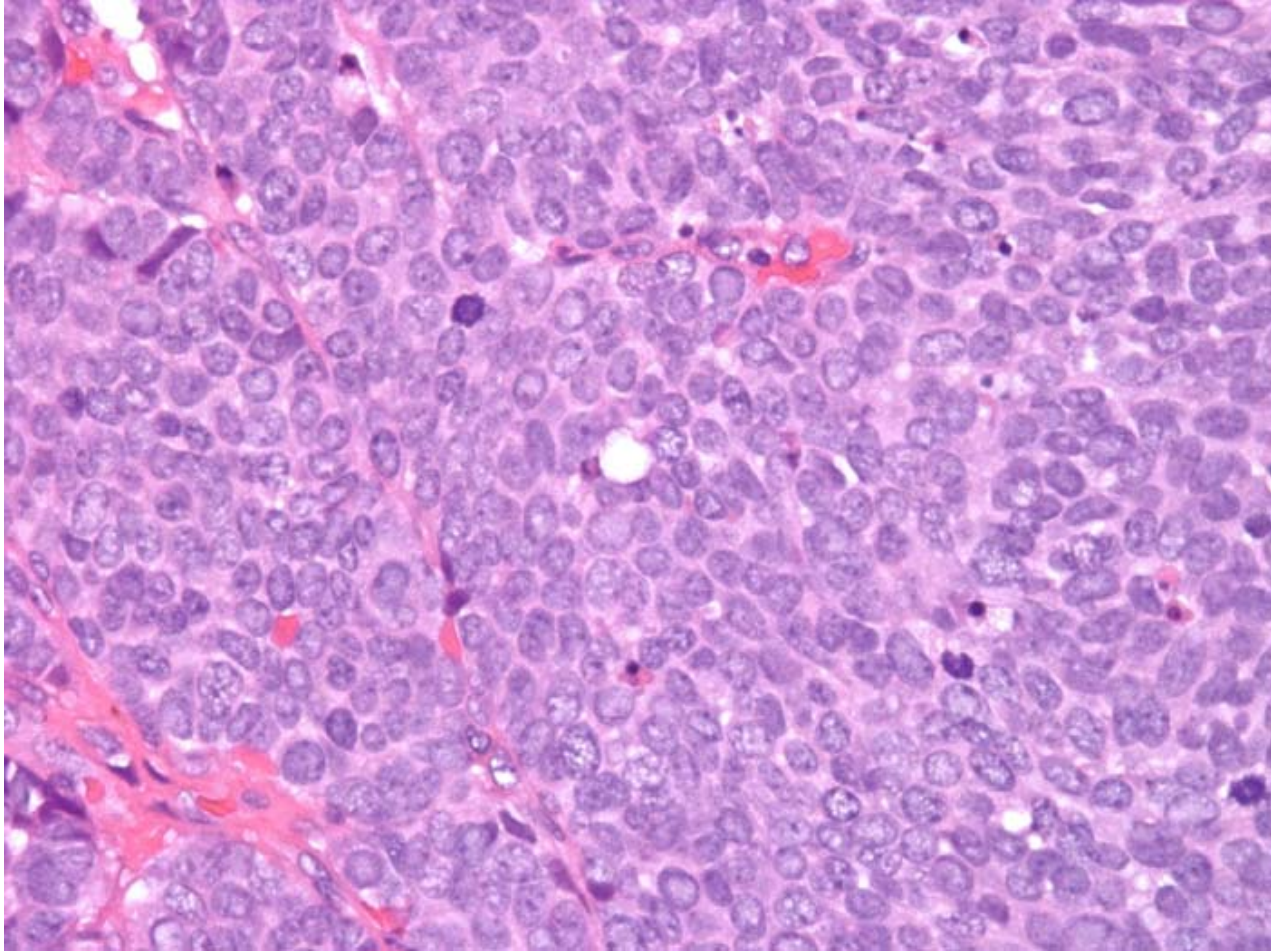
Merkel cell carcinoma

- Histologic features:
 - Small round, uniform cells distributed in sheets and trabeculae
 - Vesicular nucleus, inconspicuous nucleoli
 - “salt-and-pepper” chromatin
 - Minimal cytoplasm
 - Multiple mitoses and apoptotic cells
 - Epidermotropism in about 10% of cases
 - Often areas with divergent differentiation (SCC, BCC, rarely melanocytic)

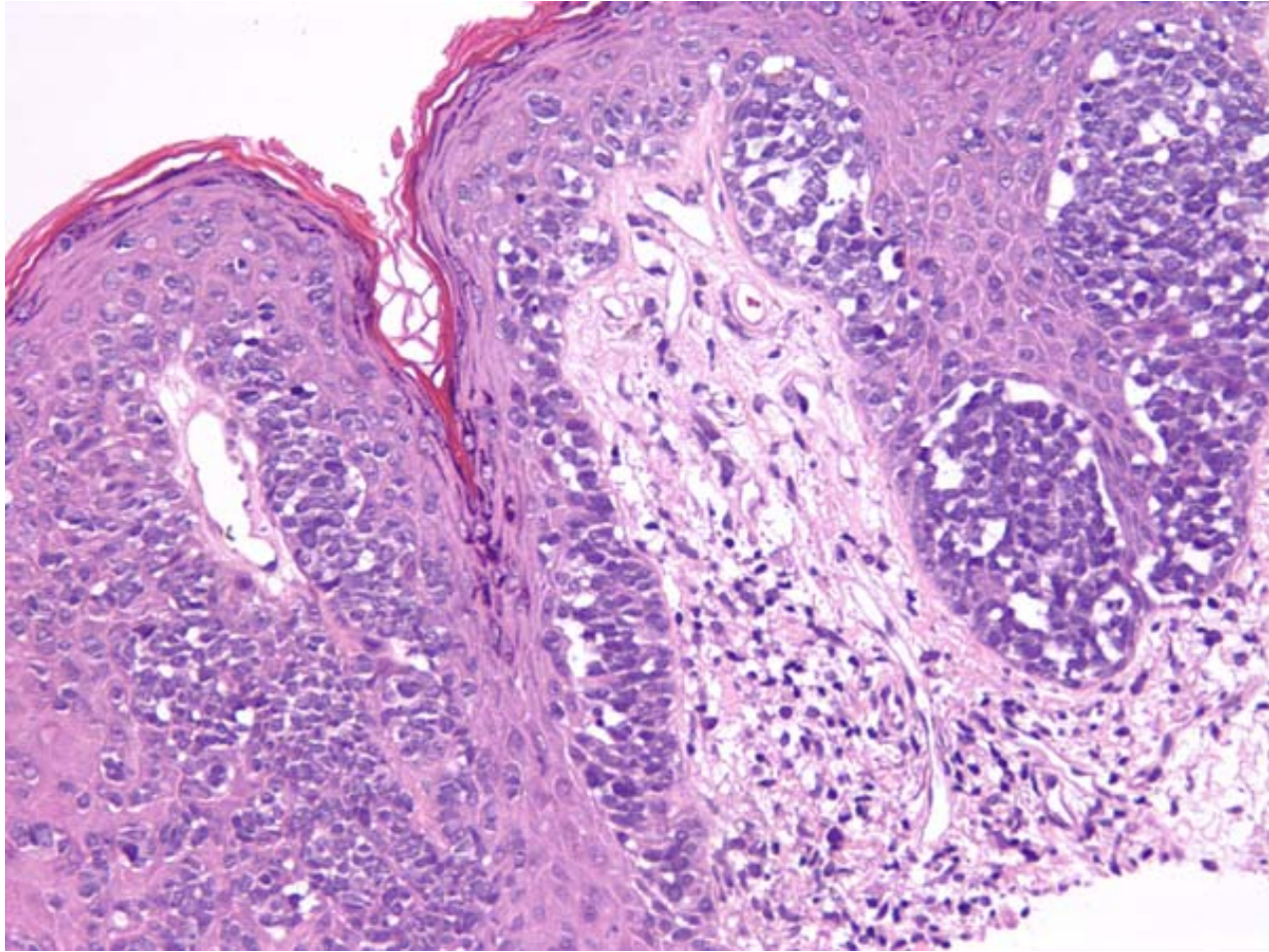
Merkel cell carcinoma



Merkel cell carcinoma



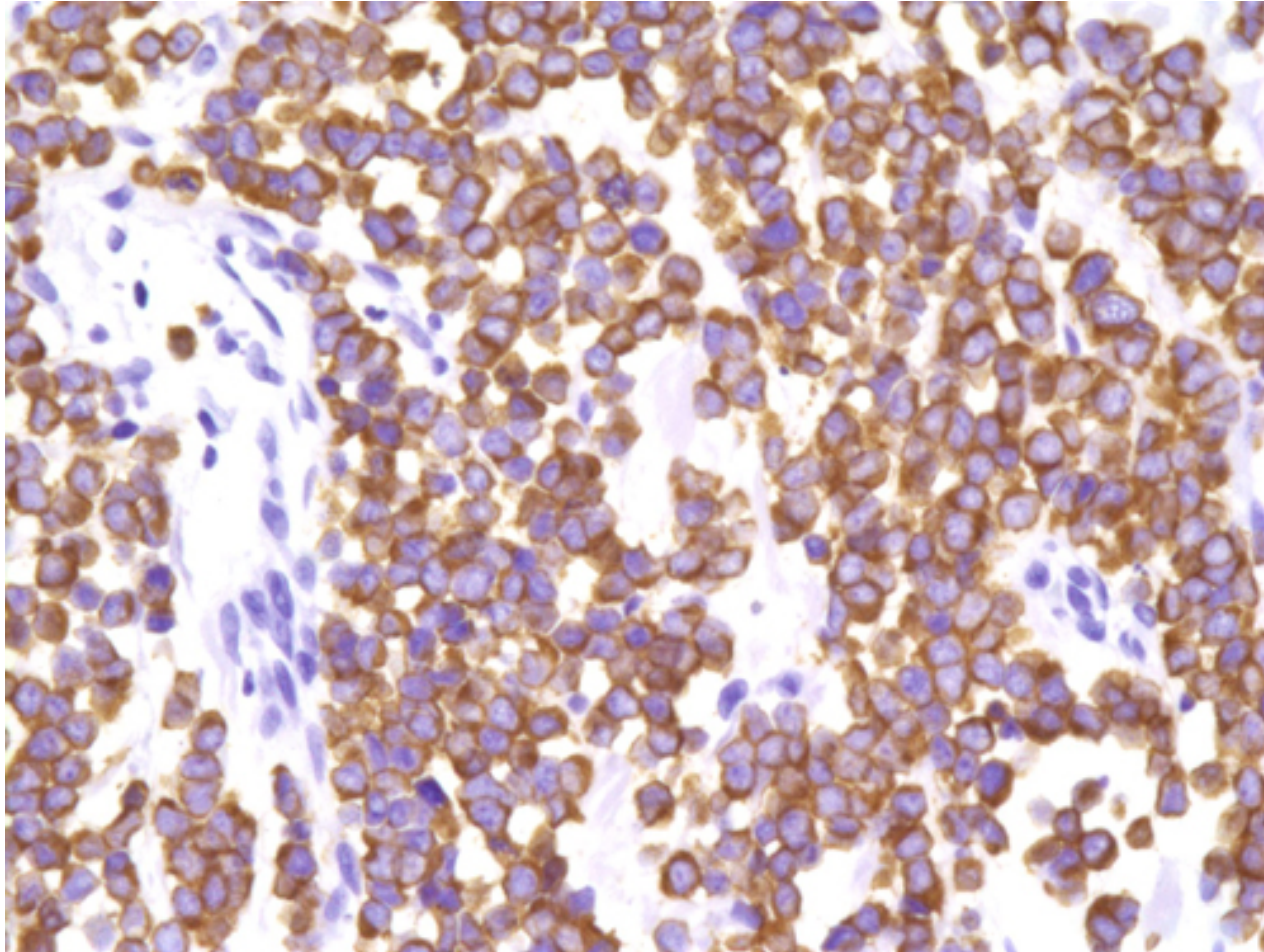
Merkel cell carcinoma



Merkel cell carcinoma

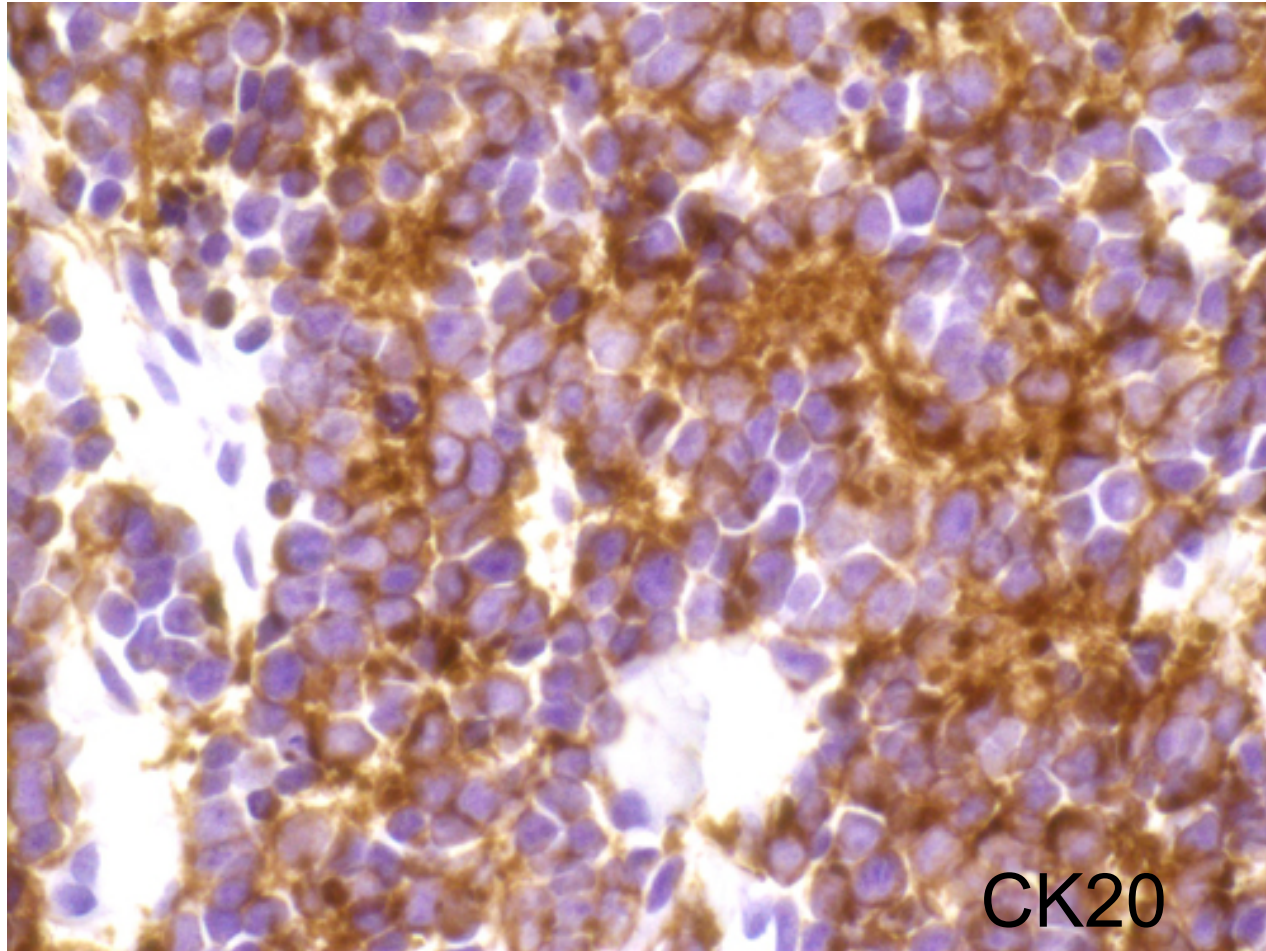
- Immunohistochemical features:
 - Cytokeratin positive (dot-like pattern – paranuclear)
 - CK20 sensitive marker (not totally specific)
 - TTF-1 positive in small cell carcinomas of lung, but also rarely positive in MCC
 - Somatostatin and chromogranin frequently positive
 - NSE and EMA also positive but very non-specific
 - S100 negative

Merkel cell carcinoma

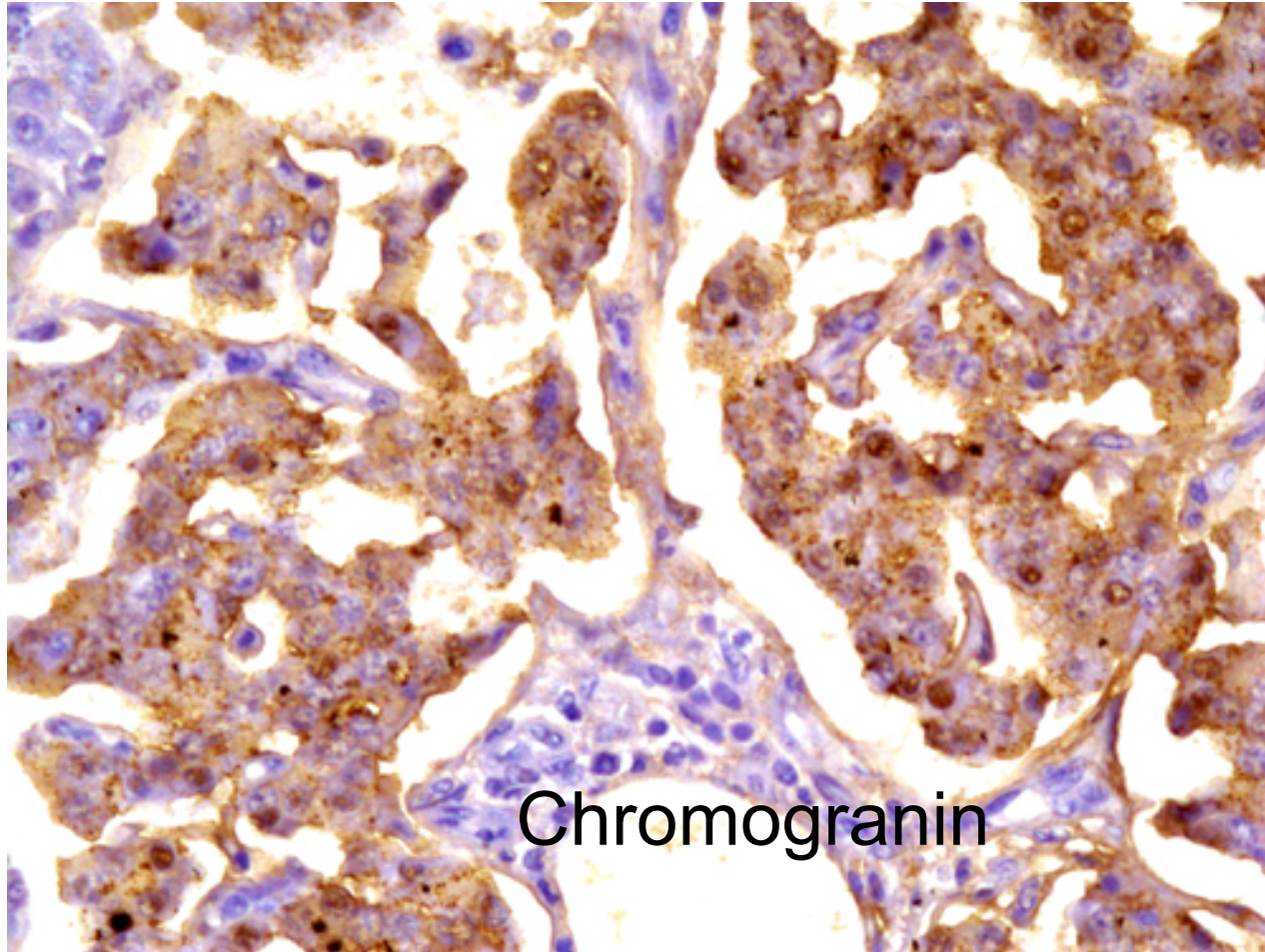


CK20

Merkel cell carcinoma



Merkel cell carcinoma



Merkel cell carcinoma

- Indicators of poor prognosis:
 - Male
 - Age > 55 years
 - Location on head and neck
 - Advanced stage at time of diagnosis
 - Tumor > 2 cm
 - Immunosuppression
 - Diffuse growth pattern
 - Heavy lymphocytic infiltrate
 - High mitotic rate
 - P63 expression

Merkel cell carcinoma: staging and prognosis

- 5 year survival rates:
 - Stage I: (T1 N0 M0 - primary tumor < 2 cm) – 81%
 - Stage II: (T2 N0 M0) – primary tumor \geq 2 cm) – 67%
 - Stage III: (any T, N1 M1) – 52%
 - Stage IV: (any T, any N M1) – 11%

Bichakjian CK et al. Cancer 2007; 1101.

Insights into Merkel cell carcinoma

- Etiology and Pathogenesis
- Prognosis
 - Histologic
 - Immunohistochemical
 - Cytogenetic
- Therapy and treatment

Merkel cell carcinoma

- Insights into etiology
 - Probably NOT derived from cutaneous “Merkel” cells of the skin, but rather, likely originates from pluripotential stem cells that undergo neuroendocrine differentiation
 - Many articles citing:
 - Merkel cell carcinoma + SCC (J Cutan Pathol 2008; 35: 955-959)
 - Merkel cell carcinoma + melanocytic tumor
 - Merkel cell carcinoma + fibrosarcomatous differentiation (Pathology 2008; 40:314)

Merkel cell carcinoma

- Insights into pathogenesis
 - Strong association with presence of MC-polyomavirus
 - Virus found in integrated and clonal form in 70% of MCC (only 10 cases)
 - Polyomavirus has proven transforming abilities in mammalian cells – related to SV40 virus
 - Some cases were clearly negative, so not “necessary” for the development of MCC

Feng et al. Science 2008; 319: 1096.

Merkel cell carcinoma

- Immunohistochemical advances in diagnosis:
 - Achaete-scute complex-like I (MASH1, ASCL1) involved in development of brain and neuroendocrine system
 - 30 MCC compared with 59 small cell carcinoma of lung with anti-MASH1 antibodies
 - 83% of small cell carcinoma expressed MASH1 and 73% expressed TTF-1
 - 0% of MCC expressed MASH1 while 1/30 (3%) expressed TTF-1
 - MASH1 may be superior to TTF-1 in making this distinction

Ralston et al. Mod Pathol 2008; 21: 1357.

Histologic contributions to prognosis

- High mitotic rate
- Depth of invasion*
- Small cell size*
- Angiolymphoid invasion*
- Diffuse growth pattern*
- Heavy lymphocytic infiltrate”

*Not all studies agree

Histologic contributions to prognosis

- Depth of invasion:
 - no relationship between tumor thickness and disease free survival or overall survival

Goldberg SR et al. J Surg Oncol 2007; 95:

618

- MCC >10 mm thick associated with higher rate of distant metastases

Llombart B et al. Histopathology 2005; 10.111:

1

Histologic contributions to prognosis

- Depth of invasion:
 - Extension of tumor into the subcutaneous fat was strongly predictive of shortened survival in study of 25 patients

Mott RT et al. J Cutan Pathol 2004; 31:
217

Histologic contributions to prognosis

- 36 MCC evaluated for numbers of mast cells as identified by mast cell tryptase
- Significant relationship between tumor mast cell count and survival
- 1.75 increase in risk of death for each additional mast cell per 250X field

Beer et al. Am J Dermatopathol 2008;30:27.

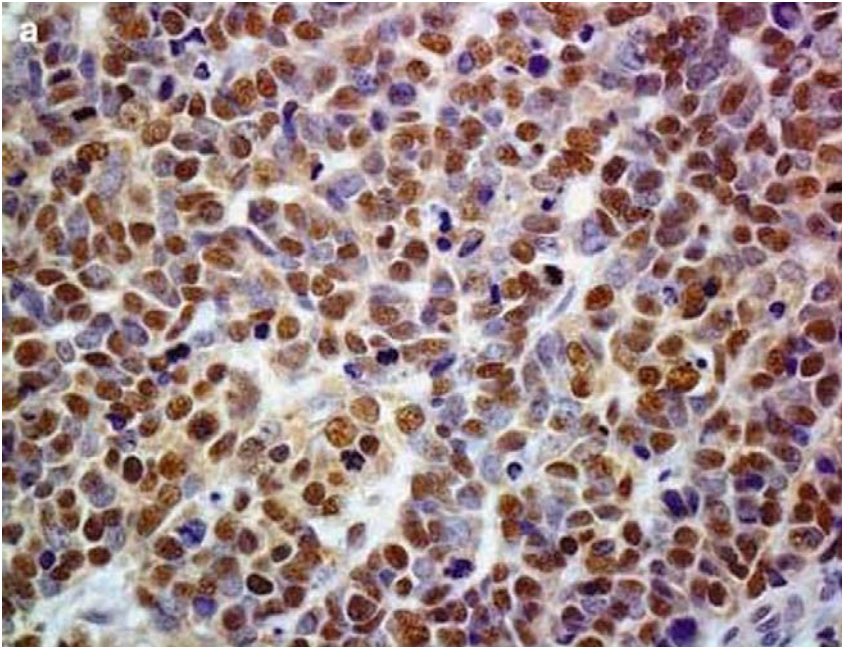
Immunohistochemical contributions to prognosis

- Survivin expression
 - 16.5 kDa intracellular protein – functions as inhibitor of apoptosis – prevents activation of caspases
 - Expressed in 19/19 cases (Yale Univ.)
 - Nuclear staining pattern associated with high rate of metastasis (50%) and mortality (38%) within 3 year f/u period
 - Cytoplasmic staining associated with increased disease free survival

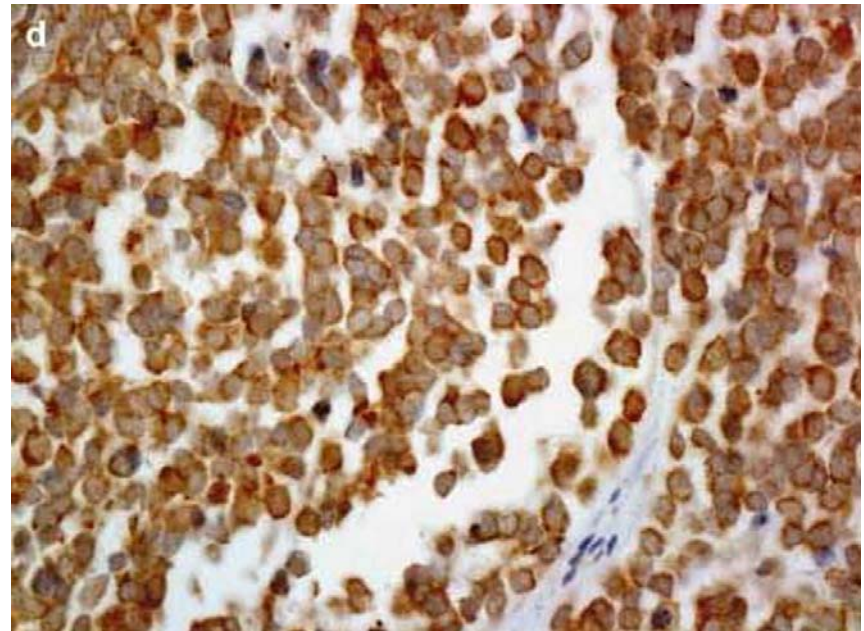
Kim and McNiff. Mod Pathol 2008; 21: 764.

Survivin expression in Merkel cell carcinoma

Nuclear staining



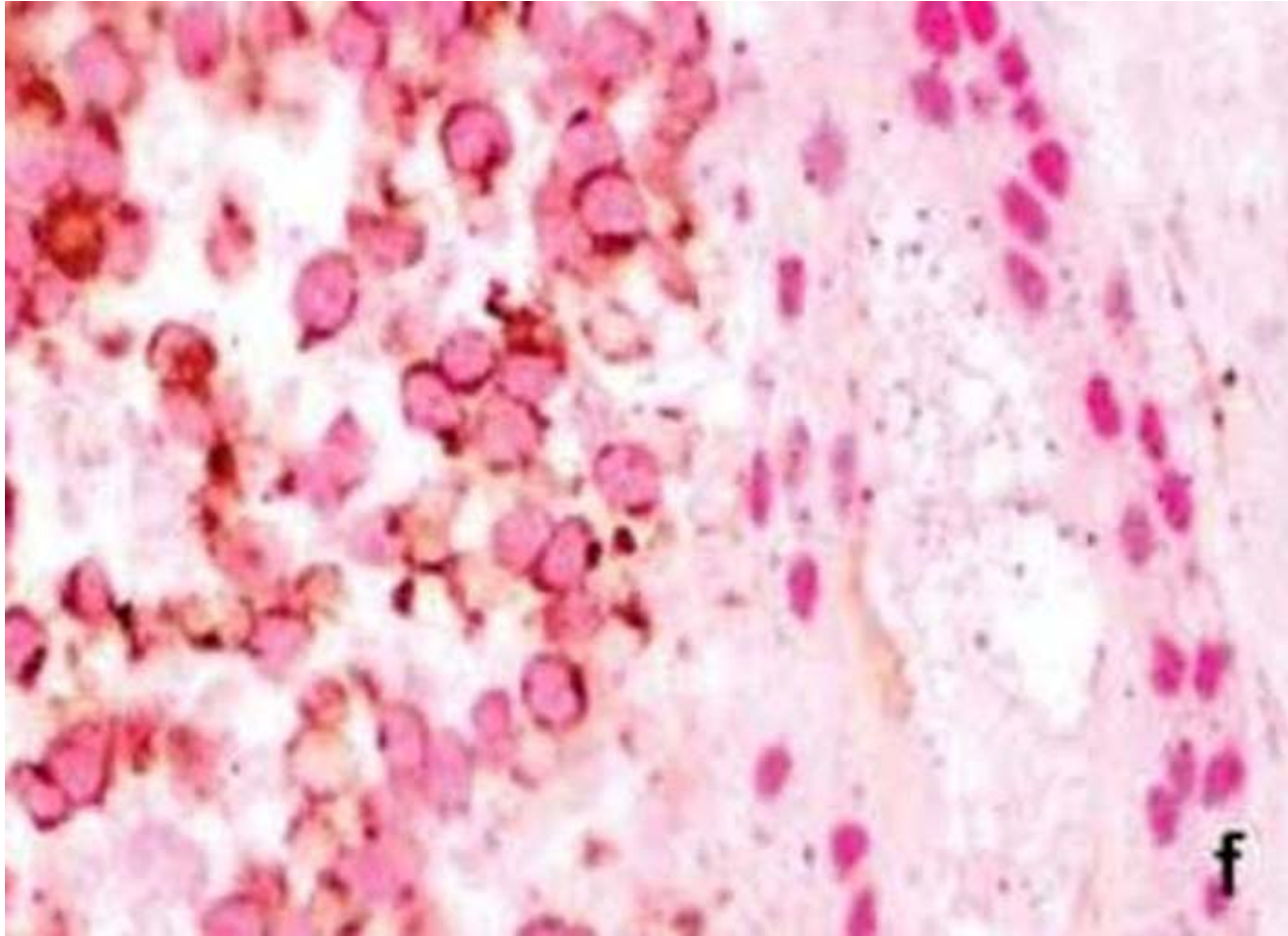
Cytoplasmic staining



Immunohistochemical contribution to prognosis

- P63 expression
 - 47 cases of MCC stained with p63 antibodies
 - 25/47 demonstrated staining with p63
 - More aggressive course (lower overall survival) in tumors with p63 expression (P= .0003)
 - Caveat – p63 expression correlated with Ki-67 staining, so may not be an independent predictor

P63 Expression in Merkel cell carcinoma



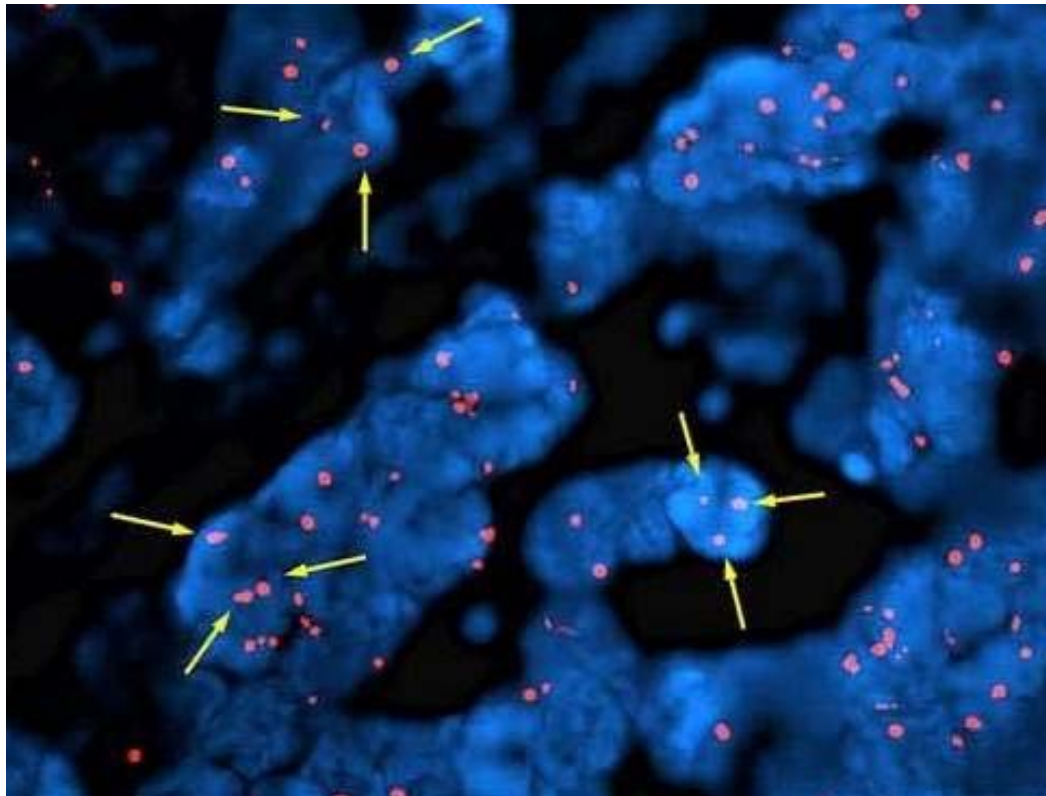
Immunohistochemical contributions to prognosis

- Tissue microarray of 31 MCC (15 free of disease, 16 metastasized)
- 43 markers examined
- Over expression of following associated with metastasis:
 - Matrix metalloproteinase (MMP) 7
 - MMP 10/2
 - Tissue inhibitor of metalloproteinase 3
 - Vascular endothelial growth factor (VEGF)
 - P38
 - Stromal NF-kappa B
 - Synaptophysin

Fernandez-Figueras et al. Mod Pathol 2007; 20: 90

Cytogenetics and Merkel cell carcinoma

- Trisomy 6 present in $> 60\%$ of cases of MCC, but not all



Current treatments for Merkel cell carcinoma

- Wide local excision – standard therapy
 - < 1 cm margins NOT associated with higher risk of recurrence
 - 2 cm margins best reserved for lesions > 2 cm

Warner RE et al. Ann Surg Oncol
2008

Current treatment options for Merkel cell carcinoma

- Sentinel node (SN) biopsy – controversial
 - 241 patients from about 20 studies in literature suggest that about 30% of patients have positive SNs at time of presentation
 - 18.7% recurrence rate for patients with positive SN vs. 7.5% recurrence for those with negative SN

Warner RE et al. Ann Surg Oncol 2008

Current treatment options for Merkel cell carcinoma

- Adjuvant post-operative radiation therapy – also controversial
 - SEER registry:
 - Improved median survival for RT + surgery over surgery alone for primary tumors of all sizes
 - MSKCC – adjuvant RT added nothing to surgery alone for survival (only a small percentage of patients received RT in this series)
 - No difference in 3 year survival between patients who received adjuvant RT or chemotherapy and those who didn't (Gupta et al. Arch Dermatol 2008; 142: 685.)

Current treatment options for Merkel cell carcinoma

- Adjuvant chemotherapy:
 - Of little use at this time – most Merkel cell carcinomas do not respond to standard chemotherapeutic regimens
 - Current work addresses targeting therapies directed against antigens expressed by neoplastic Merkel cells

Histologic contributions to treatment options

- 32 MCC analyzed using tissue microarray for expression of following antigens:
 - C-kit (CD117)
 - Vascular endothelial growth factors A, C, VEGF receptor-2
 - Platelet-derived growth factors α and β
 - Epidermal growth factor receptor
 - Her-2/Neu
 - Mcl-1, Bmi-1
- All except c-kit, Her-2/Neu and EGFR uniformly expressed by vast majority of MCC by immunohistochemistry

Contributions to treatment options in MCC

- Her-2/Neu – involved in protein kinase signaling network – ligand binding domain – absence in MCC suggests this is not an effective potential therapeutic option
- Receptor tyrosine kinases (VEGF, PDGF) – expressed in low levels in this study (perhaps more expression in larger cell type)
- C-kit – no mutations found so not very promising treatment option
- Anti-sense Mcl-1 and Bmi-1 oligonucleotides suggest possible promise

Brunner M et al. Mod Pathol 2008; 21: 876.

Mcl1 and Bmi-1

- Genes are involved in cell proliferation and cell death
 - Mcl-1 is a member of the bcl-2 family – anti-apoptotic – promotes cell survival
 - Bmi-1 is a transcriptional repressor – over expression may be related to immortality in cancer cells
- Introduction of antisense oligonucleotides targeting these genes may reverse their roles
- Anti-sense Bmi-1 oligonucleotide inhibits proliferation in some leukemias
- Neither yet tried in Merkel cell carcinomas

Contributions to treatment options for MCC

- Platelet growth factor receptor α mutation found in exon 10 in 3/9 MCC – immunohistochemistry results and PCR results were identical
- PDGF- α is a transmembrane receptor tyrosine kinase
- Transmits extracellular signals into cells that activate and control proliferation, differentiation, survival and apoptosis
- If truly mutational, imatib mesylate may be useful as a treatment option

Swick BL et al. J Cutan Pathol 2008; 35: 197

Merkel cell carcinoma – theories of oncogenesis

Table 1. Cancer-associated pathways and genes studied in MCC oncogenesis

Cancer-associated pathway/gene	Likely relevant	Summary of findings	Reference
p53	–	No mutations found in 12 of 15 samples	Van Gele <i>et al.</i> , 2000
Ras	–	No activating mutations in <i>H-ras</i> , <i>K-ras</i> , or <i>N-ras</i> found in six MCC cell lines	Popp <i>et al.</i> , 2002
B-Raf ^{V600E}	–	No mutations in 46 MCCs	Houben <i>et al.</i> , 2006
MAP kinase activity	–	MAP kinase silenced in 42/44 MCCs	Houben <i>et al.</i> , 2006
Wnt	–	No mutations in β -catenin, APC, AXIN1, or AXIN2 in 12 MCC tumors	Liu <i>et al.</i> , 2007
c-Kit	–	No activating mutations in nine MCC tumors	Swick <i>et al.</i> , 2007
PTEN	?	No mutations in 20 of 21 samples but loss of heterozygosity for region in 43%	Van Gele <i>et al.</i> , 2001
bcl-2	+	High expression in 15 of 20 MCC tumors; bcl-2 antisense decreases tumor size in xenograft model	Kennedy <i>et al.</i> , 1996; Plettenberg <i>et al.</i> , 1996; Schlagbauer-Wadl <i>et al.</i> , 2000

**Companion Society Meeting
Sunday, March 8, 1:30 pm
American Society of Dermatopathology
“An update of cutaneous carcinomas”**

BASOMELANOCYTIC TUMORS: ANOTHER NAIL IN THE NEURAL CREST COFFIN?

**Juan Rosai, M.D.
Centro Diagnostico Italiano, Milan, Italy
Genzyme Corp., New York, NY**

The evolution of our concepts on the neural crest-derived cells and their tumors constitutes one of the most fascinating sagas in pathology. The story started in a rather modest fashion, with Kultschitsky¹³ detecting a chromaffin cell at the base of the normal crypts of Lieberkühn of the intestine, and Lubarsch and Oberndorfer¹⁸ describing a peculiar little tumor of the small bowel and appendix with the almost apologetic terms of *small carcinoma* and *carcinoid tumor*, respectively. It took the brilliant intuition of Masson¹¹ to make the link between the two observations through his proposal that carcinoids of the appendix are “endocrine tumors,” and the vision of Feyrter⁹ to advance the notion that the isolated cells described by Kultschitsky¹³ are part of a vast system of endocrine cells scattered throughout practically all organs endowed with an epithelial lining (his diffuse endocrine or paracrine system).

The saga took a spectacular turn with the observation by A. G. E. Pearse²⁰ that these cells share important biochemical pathways (symbolized acronimically as APUD) and his daring suggestion that this commonality of biological attributes derives from their common origin from the neural crest, a transient embryonal neural structure already known to be the progenitor of autonomic ganglia and plexuses, paraganglia, and melanocytes. The attractiveness of the theory was weakened by the questionable accuracy of the experimental methods offered in its support¹⁹ and undermined by more rigorous experiments done by other investigators, particularly the ingenious quail-chick chimeric model devised by the French embryologist Nicolle LeDouarin¹⁴.

These new data led to the abandonment of the neural crest theory and its replacement by the present dogma, according to which neural crest derivatives include ganglia, paraganglia, melanocytes, and thyroid C cells, but none of the other neuroendocrine cells (NE) cells, now thought to derive from the same local epithelial stem cells that give rise to all other epithelial cell types of the particular mucosa in which those cells are located. The widely reproduced scheme by Cheng and Leblond⁶ provides the best pictorial demonstration of this interpretation as far as the small bowel mucosa is concerned. Predictably, this paradigm switch has led to a substantial change in terminology. Not only terms such as *APUD*, *APUDoma* and the awkward *neurolophoma* have been expunged from the literature, but the very notions of NE cell and NE tumor have been called into question. While some authors still retain the use of these terms to signify the presence of neural-like phenotypical and biological *features* regardless of embryologic *derivation*, others believe that the attribute *neuro* should not apply to cells of endodermal or other non neural derivation, and they refer to these cells as *endocrine tumors*. The pancreas is the best example of this approach, in that no tumor of this organ carries any longer the qualifier *neuro* in the WHO classification of neoplasms of this organ. I think it is fair to conclude that in current scientific language the prefix *neuro* has become objectionable when used in this context.⁵ Actually, one could carry this reasoning further by pointing out that legitimate questions are beginning to arise even about the thyroid C cells, the neural crest origin of which had thought to have been validated by the chick-quail model.¹⁰ If the C cell is of neural origin, the question has been asked, how does one explain the immunohistochemical demonstration of thyroid transcription factor-1 (TTF-1),¹² the presence of the thyrotropin receptor gene transcript, and the existence of mixed follicular-C cell and papillary-C cell

carcinomas?¹⁴ I trust the reader will recognize in these arguments a reasoning analogous to that which was employed years ago to help debunking the neural origin of endocrine cells and endocrine tumors of the gastrointestinal tract and pancreas.⁵

If we then put a question mark on the neural crest origin of thyroid C cells, the only remaining epithelium-related cell of putative neural crest origin is the melanocyte. This seemed to be firmly established by the already mentioned chimeric experiments of Le Douarin,¹⁴ the outstanding morphologic studies done by Pierre Masson, and numerous clinico-pathologic observations. One of the latter was the fact that, in contrast to the GI tract, lung and even thyroid, no combined tumors of epithelial cells and melanocytes seemed to exist. If we think specifically of skin and breast, we find that all tumor types combining keratinocytes and melanocytes have been thought to be neoplasms of one or another of these cell types, with a secondary “colonization” by the other cell type.^{2,4,21} This applies to lesions such as Pinkus’ melanoacanthoma, pigmented basal cell carcinomas, pigmented sweat gland tumors, and pigmented breast carcinomas. However, exceptions to this scenario were eventually found. Several authors have reported cases of pigmented breast carcinomas and provided convincing evidence that the tumor contained both neoplastic mammary epithelial cells and melanocytes.^{16,17,23} The same has happened in the skin, in which a few cases of mixed keratinocytic/melanocytic tumors of both basal cell and squamous cell type have been recently described.^{3,8,22}

If these cutaneous tumors have indeed a dual keratinocytic-melanocytic component (and not everybody is convinced that this is the case), the neural crest origin of cutaneous melanocytes may also come under attack, as heretical the thought may appear. For one thing, this questioning would vindicate the position of Arthur Allen,¹ who maintained to the bitter end the belief that melanocytes are, like keratinocytes, ectodermal derivatives.

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SARCOMATOID CARCINOMA

Earl J. Glusac, M.D.
Professor of Pathology and Dermatology
Yale University School of Medicine

“UNKNOWN” CASES WILL BE PRESENTED DURING THIS LECTURE. IT IS RECOMMENDED THAT YOU NOT READ THIS HANDOUT UNTIL AFTER THE LECTURE (OR YOU WILL SPOIL THE FUN).

Spindled cell squamous cell carcinoma (SCSCC) is a lesion that is usually seen in a setting of severe sun damage or other irradiation. It shows a behavior similar to ordinary squamous cell carcinoma, but SCSCC may be difficult to diagnose. It typically shows spindled cells with vesicular nuclei that may exhibit prominent eosinophilic cytoplasm. Contiguity with the epidermis or a hair follicle may be seen. Single cell keratinization serves as a good clue to the diagnosis. Some cells may exhibit perinuclear halos and corp-rond-like rings of tonofilaments. SCSCC is usually positive for cytokeratins AE1, AE3 or Cam 5.2. Some lesions, however, fail to stain with these markers. In these cases, positive cells may be seen with cytokeratin 903 or cytokeratin MNF116. Vimentin may also be positive in these lesions. This may be the result of reduced cell-to-cell contact. Keratin/vimentin co-positivity is not a unique phenomenon and may also be seen epithelioid sarcoma, adenoid cystic carcinoma, renal cell carcinoma, and thyroid carcinoma.

p63 can be a useful adjunct marker for spindle cell SCC. P63 is a member of the p53 gene family. In the skin, it is expressed in the nuclei of basal and spinous cells of the epidermis, peripheral cells of the eccrine dermal ducts, germinative cells of sebaceous glands, myoepithelial cells of the terminal portion of the eccrine glands and apocrine glands. In the differential diagnosis of cutaneous spindle cell malignancies, p63 labeling is supportive of spindle cell SCC and adds a useful nuclear marker to the repertoire used in this differential.

Dotto JE, Glusac EJ. p63 is a useful marker for cutaneous spindle cell squamous cell carcinoma. *Journal of Cutaneous Pathology* 2006; 33: 413-417.

In 1965, Rosai described two unusual pancreatic tumors containing osteoclast-like giant cell, with ultrastructural evidence of pancreatic acinar cell origin. Similar malignancies have been described in various organ systems, and these tumors have frequently been lethal. These malignancies typically contain sarcomatoid spindled cells as well as osteoclast-like giant cells. Several studies have suggested that at least the spindled cells are of epithelial origin. Some have suggested that the giant cell of are of histiocytic origin.

Two individual case reports have described SCC with osteoclast-like giant cells in the skin. Algerian et al reported the first, a lesion of the cheek in a 42 yo. Immunosuppressed

man. This case also exhibited a rhabdoid component. The spindled and rhabdoid components were keratin positive, but the giant cell component was not. No recurrence was noted at 10 months follow up. Emanuel et al reported a poorly differentiated SCC of the lip of an 86-year-old male that also contained a component resembling giant cell tumor of bone/soft tissue. This later component was AE1/3 negative, and it was postulated that this was a reactive response. At Yale, we have seen two examples of aggressive SCCs of the scalp, each treated by Mohs surgery, with large defects necessary for complete removal, that later presented the nodules near the scar site composed of sarcomatoid spindle cells and osteoclast-like giant cells. In our laboratory, these cases were positive for keratins, when several keratin stains were performed, especially CAM 5.2. These cases appear to represent sarcomatoid de-differentiation of SCC.

Algerian et al. SCC with rhabdoid phenotype and osteoclast-like giant cells. *J Clin Pathol* 2006; 59: 1309.

Emanuel et al. Poorly Differentiated SCC with osteoclastic giant cell-like proliferation. *J Cutan Pathol* 2007; 34: 930.

Metastatic carcinoma may be confused with a wide variety of sclerosing cutaneous neoplasms. The significant majority of cases are metastatic breast carcinoma. Some examples of metastatic carcinoma may show few tumor cells in association with abundant fibrosis. The tumor cells may appear fibroblast-like or even resemble a dermatofibroma. The nuclei are often elongated, large, angular and basophilic. The tumor cells may exhibit a single cell or “Indian file” pattern. As in the case with S100 and melanocytic lesions, it is often helpful to order a keratin stain in the differential diagnosis of sclerosing neoplasms, so as not to miss a metastatic carcinoma.

CASE PRESENTATION:

93 yo male, Right posterior thigh. “? T-Cell; B-Cell infiltrate vs. other”

Histopathology, Immunohistochemistry:

- Monomorphous infiltrate of cells with very high N/C ratio
- Diffuse, nearly patternless arrangement
- CD56 positive, negative for T and B cell markers
- Focal, subtle nuclear molding
- Chromatin slightly salt and pepper-like

The history above is exactly as I received it, suggesting lymphoma. This is actually a case of a “lymphomatoid” (or “lymphosarcomatoid”) carcinoma. An initial battery of stains included negative B cell markers, negative T cell markers and positivity for CD56, suggesting natural killer (NK) cell lymphoma. Additional study revealed subtle nuclear molding and salt and pepper chromatin. Additional staining revealed positivity for Cam 5.2 and CK20.

It is important to note that CD56 labels natural killer (NK) cell lymphomas *and* neuroendocrine tumors such as Merkel cell carcinoma (MCC). In MCC altered by crush artifact or obscured by lymphocytes, histologic features and CD56 positivity can lead to an erroneous impression of NK-cell lymphoma.

In classic examples, the histologic diagnosis of MCC is straightforward. The combination of a small blue cell tumor with nuclear molding, salt and pepper chromatin and paranuclear dot-like positivity for immunohistochemical markers, including CK20 and CAM5.2, enable definitive diagnosis. Recently, CD56 staining was reported to be more sensitive than CK20 staining in 25 cases of MCC (100% cases labeled with CD56 compared to 89% with CK20). As such, CD56 can also be employed to label MCC, although positive staining does not exclude neuroendocrine carcinoma metastatic to the skin.

Crush artifact and loss of cellular cohesion can lead to a histologic impression of malignant lymphoma. In these cases, CD56 positivity may be noted in conjunction with absence of staining for CD3 and/or CD20, suggesting a diagnosis of NK-cell lymphoma. Because CD56 tends to label cell membranes in MCC, in contrast to the dot-like paranuclear pattern seen with cytokeratin staining, the diagnosis of MCC may not be immediately obvious.

It is important to remember that CD56 will stain both MCC and NK-cell lymphomas diffusely. Cytokeratin stains are not always added to a panel of presumed lymphoma, and pankeratin alone is unreliable in excluding MCC, since antibodies directed against high molecular weight keratins (such as DAKO pankeratin) typically do not label MCC. Therefore, consideration of the diagnosis of MCC in this setting is crucial. Cytokeratin markers CAM5.2 and MNF116 show excellent sensitivity for detecting MCC, while CK20 adds specificity with good sensitivity.

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Immunohistochemistry in cutaneous adnexal carcinomas vs metastatic adenocarcinomas

Victor Prieto, M.D., Ph.D.
University of Texas MD Anderson Medical Center
Houston, TX

The wide spectrum of cutaneous neoplasms includes lesions that share many histologic features with malignancies from internal organs. This is especially true for intradermal tumors with minimal or no epidermal connection. Such situations are not unusual in common pathology practice. The two main goals of this lecture are to emphasize the importance of distinguishing cutaneous primary tumors from metastatic lesions and to provide an algorithm designed to help in these differential diagnoses.

Cutaneous metastases occur in 0.7% to 10% of patients with visceral tumors. Their recognition is important since they portend a poor prognosis and, in rare cases, they can be the first sign of an internal malignancy. The most common sites of metastases are the abdominal wall and chest, scalp and neck regions. Furthermore cutaneous metastases are most commonly seen in the skin in the region of the primary carcinoma, such as the chest for lung and breast carcinomas and the abdominal wall for gastrointestinal carcinomas. Most cutaneous metastases present as painless nodules, but also as bullae, cellulitis, zosteriform rashes, sclerotic plaques, and vasculitic processes. Most common primary tumors are breast (60-70%), GI, lung, and ovary in women while lung, GI, head and neck, and GU are most common in men. Less common are thyroid, adrenal, endometrium, prostate, and mesothelioma.

In the skin sweat glands, the cells in the excretory coil express low molecular weight keratin (LMWK), EMA, CEA, and GCDFP15, with scattered S100-positive basal cells. Myoepithelial cells express S100, SMA, p63, and calponin. The intraepidermal component express high molecular weight keratin (HMWK) and CK14. Eccrine cells usually express ER/PR while apocrine cells more commonly express androgen receptors.

Histologically, connection with the epidermis or growth within skin adnexa (~ *in situ* component) or the presence of a benign counterpart component usually indicates a primary lesion. In contrast, nodular, multifocal lesions, central necrosis and vascular invasion suggest metastases.

The most common metastatic tumors that resemble primary skin lesions are those with ductal differentiation (particularly microcystic adnexal carcinomas, hidradenocarcinomas, and eccrine/apocrine adenocarcinomas), tumors with a predominance of clear cells (xanthomas, trichilemmal carcinomas, hidradenocarcinomas, sebaceous carcinomas), and mucinous tumors. Those lesions may resemble carcinomas from the breast, gastrointestinal tract, lung, kidney, or ovary.

GCDFP-15, ER, and PR have been historically used as markers for breast differentiation. However, those markers have been shown in benign cutaneous glands and in cutaneous adnexal neoplasms, an expected finding since the breast is a modified apocrine gland. CK7 is expressed in both primary adnexal tumors and most metastatic carcinomas to skin. Both CEA and EMA label ductal cells but since renal cell carcinomas express EMA but not CEA, the latter is favored in order to highlight ductal structures. Therefore, CEA is recommended over EMA to highlight the ductal structures.

Gastrointestinal metastases (intestinal adenocarcinomas) usually show dirty necrosis. Strong CK20 expression and lack of CK7 expression favors a metastasis from an intestinal primary over a primary cutaneous (usually CK7 positive and CK20 negative). Although CDX-2 is fairly specific for gastrointestinal origin, it has been reported in ovarian mucinous tumors, and rare tumors of the lung, bladder, and head and neck.

Both adnexal tumors and lung adenocarcinomas usually are CK7+ / CK20-. A number of primary pulmonary adenocarcinomas and thyroid neoplasms express TTF-1, but the expression of this marker has not been extensively studied in their cutaneous metastases.

Cytokeratin 5/6 is expressed in most primary cutaneous adnexal neoplasms, and only in a minority of metastatic adenocarcinomas. CK7 is relatively equally expressed in primary cutaneous adnexal neoplasms and cutaneous metastases (lung and breast), but it is mostly focal in the primary neoplasms versus a strong and diffuse expression in the metastases.

Podoplanin (D2-40) appears to be mostly positive in adnexal tumors but not in metastatic adenocarcinomas.

In our opinion, p63 is one of the most helpful markers. It is routinely expressed by cutaneous epidermal and glandular basal cells, and in myoepithelial cells and in transitional, prostate, and respiratory epithelia. p63 is expressed in trichilemmal, eccrine, and apocrine cutaneous adnexal tumors in more than 25% of the cells (not in mucinous ones, which are negative) but it is not expressed in most metastatic adenocarcinomas to skin (breast, lung or GI). The only exception of breast carcinoma that routinely expresses p63 is high grade, myoepithelial carcinoma, but those lesions do not resemble the common, well to moderately differentiated cutaneous adnexal carcinoma. Also supporting the usefulness of p63, metastasis of cutaneous adenocarcinomas maintain their p63 expression

Primary mucinous adenocarcinoma of the skin is morphologically indistinguishable from metastasis (GI, breast and ovary). Immunohistochemically, all these lesions express CK7; only GI adenocarcinomas express CK20, which may be helpful as a distinction from primary skin mucinous adenocarcinomas. Furthermore, p63 may be helpful to distinguish primary from metastatic lesions, since it may highlight the presence of myoepithelial cells in sweat glands partially occupied by adenocarcinoma cells, thus consistent with an *in situ* component and a primary lesion.

Regarding tumors with clear cell histology, sebaceous carcinomas usually present at least focal scalloping of the nuclei. These cells are positive for EMA and adipophilin; however it is important to notice that adipophilin can be positive also in macrophages so, in order to be considered positive, it has to label the vacuoles of the tumor cells. CD10 is only relatively helpful since it is expressed by both renal cell carcinomas and skin lesions (sebaceous, balloon cell nevi, and xanthomas). The renal cell carcinoma antigen (RCC-Ma) is fairly specific for clear cell renal cell carcinoma (80-85% of primary clear cell renal carcinomas). In general, positive RCC-Ma is highly suggestive of metastatic renal cell carcinoma while negative CD10 should be considered inconsistent with a renal cell carcinoma.

Immunohistochemical summary

Adenocarcinomas (ductal differentiation):

- Primary cutaneous:
- In situ component (p63 in normal cells)
 - Diffuse (>25%) p63 expression by tumor cells
 - Podoplanin+
 - CK7+/CK20-

- Metastasis:
- GI: CK7/20 +, cdx2+
 - CK5/6- (adenocarcinomas)
 - p63/podoplanin-
 - Breast may be mammoglobin +

Clear cell neoplasms:

- Primary:
- RCC-Ma-/CD10-(+)
 - Sebaceous lesions are EMA and adipophilin+ (vacuoles)
- Metastasis:
- Renal: RCC-Ma+(-)/CD10+

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**AMERICAN SOCIETY OF DERMATOPATHOLOGY
COMPANION MEETING HANDOUT**

1:30 pm Sunday 8 March 2009
Boston, Massachusetts

SEBACEOUS NEOPLASIA AND THE MUIR-TORRE SYNDROME

Alexander Lazar MD/PhD

Sections of Dermatopathology and Soft Tissue/Sarcoma Pathology
Departments of Pathology and Dermatology
Sarcoma Research Center
The University of Texas M. D. Anderson Cancer Center

The classification of sebaceous tumors has become more complex with time. Sebaceous adenoma, sebaceoma¹, sebaceous epithelioma^{2, 3}, sebaceous carcinoma, superficial epithelioma with sebaceous differentiation^{4, 5}, sebomatricoma⁶ (a term proposed to unify the spectrum of benign sebaceous neoplasia) and an interesting spectrum of lesions associated with Muir-Torre syndrome have been described⁷. Sebaceous neoplasia can also arise secondarily in the context of nevus sebaceus⁸⁻¹². Other cutaneous epithelial and appendageal neoplasms with a significant sebaceous component have been noted including basal cell carcinoma^{13, 14}, trichofolliculoma¹⁵, and microcystic adnexal carcinoma¹⁶. Given the intimate association of pilar and sebaceous units, the association of sebaceous differentiation with tumors showing follicular differentiation is not surprising¹⁷. In the following paragraphs, a simple classification scheme for sebaceous neoplasms will be presented. In addition, the biology of these intriguing neoplasms and their relationship to Muir-Torre syndrome will be briefly discussed.

The most significant clinical differentiation to make in sebaceous neoplasia is between benign and malignant (i.e. sebaceous carcinoma). There are two types of sebaceous carcinoma – periocular and extraocular. Periocular sebaceous carcinoma accounts for approximately three-quarters of cases and is associated with local morbidity and significant mortality upon metastasis^{14, 18}. In

contrast, extraocular sebaceous carcinomas may be considerably less aggressive, but this finding has not been universal and more studies are needed^{14, 18-20}. Occasionally, the diagnosis of periocular sebaceous carcinoma will be required on frozen section and oil red O can be helpful in challenging cases. Alternatively, other recently employed immunohistochemical stains such as adipophilin can be useful in formalin-fixed, paraffin-embedded cases^{21, 22}. It should be noted that benign sebaceous neoplasms are relatively rare in the periocular region (relative to carcinomas) and thus diagnosis of a benign sebaceous tumor at this site should be carefully considered.

Benign sebaceous neoplasms have been more subclassified than their malignant counterparts. However, all benign sebaceous neoplasms share a similar clinical appearance/setting and are typically characterized by a flesh-colored to slightly yellowed papule involving the head and neck region of older individuals. Histologically, benign sebaceous neoplasms form a spectrum of lesions ranging from an organoid appearance with prominent mature sebocytes (classic sebaceous adenoma) to cases with more prominent germinative cells (sebaceoma). All of the other described benign sebaceous lesions appear to fall along this continuum. In recognition of this, the unifying term sebomatricoma was proposed for this family of benign sebaceous neoplasms, but this terminology has not been widely adopted⁶. Although, different names are helpful for recognizing individual cases as sebaceous neoplasia, there is currently limited evidence of significant biological or clinical relevance. However, more studies and comparisons are needed.

Muir-Torre syndrome (MTS) was described virtually simultaneously in the late 1960's^{23, 24} and is now known to be a subset of the hereditary non-polyposis colorectal carcinoma syndrome (HNPCC)²⁵⁻²⁷. MTS is the combination of sebaceous neoplasia and internal malignancy with colonic carcinoma being the most common²⁸. The molecular hallmark of this syndrome is microsatellite instability, resulting primarily from loss of the DNA mismatch repair (MMR) genes

MSH2 and *MLH1*, with the former being much more common in MTS. Microsatellite instability (MSI) can be demonstrated by PCR-based methods and loss of mismatch repair genes can be revealed by immunohistochemistry with excellent sensitivity and specificity²⁹⁻³². Demonstration of MMR defects by either method suggests the need for a clinical evaluation for MTS and can guide germline testing performed with the guidance of genetic counseling³³⁻³⁶. The accompanying internal carcinomas show a similar molecular signature³⁷.

The described array of sebaceous neoplasms seen in the context of MTS includes virtually all of those described above³⁸. However, superficial epithelioma with sebaceous differentiation has been only rarely described and its association with MTS is uncertain. Interestingly, non-ocular sebaceous carcinomas encountered outside of the head and neck region are much more commonly associated with loss of MMR proteins and MTS than peri-ocular sebaceous carcinomas³⁹. Head and neck non-ocular (and peri-ocular) sebaceous carcinomas very rarely show MMR protein loss and are not commonly associated with MTS³⁹⁻⁴¹. The same trend is true for benign sebaceous lesions, though more than a third of head and neck forms also show MMR loss and are linked to MTS³⁹. Importantly, the diagnosis of any cutaneous sebaceous tumor outside of the head and neck region is rare, but when encountered is strongly associated with MMR loss and MTS.

The array of sebaceous neoplasia associated with MTS can show unusual features and resist precise classification^{38, 42}. Both cystic features^{43, 44} and “keratoacanthoma-like” architecture⁴² have been described. Distinguishing benign from malignant forms of MTS-associated sebaceous neoplasia can be challenging given the unusual features sometimes encountered in these tumors^{38, 42}. Thus, many recommend conservative complete excision of virtually all sebaceous neoplasms encountered in this setting. This can be somewhat challenging in those forms of MTS that show many sebaceous neoplasms (sometimes more than 100 over a lifetime).

Recent work on skin adnexal developmental pathways has shed insight into the molecular pathogenesis of sebaceous neoplasia. It seems that the balance of the Wnt, hedgehog and c-Myc pathways influences primitive cutaneous stem/precursor cell fate between cutaneous squamous epithelium, follicular and sebaceous fates⁴⁵⁻⁴⁷. Since stem cells are long-lived, they represent a potential compartment for the accumulation of the often multiple genetic mutations required to produce neoplasia and malignant degeneration^{48, 49}. Cells with immunohistochemical markers characteristic of stem cells can be identified in sebaceous neoplasia^{50, 51} and stem-like cells have been isolated from a sebaceous carcinoma cell line (Stephen Lyle, unpublished data). Inactivating mutations in the *LEF1* gene, a downstream effector in the Wnt pathway, have been described in benign sebaceous neoplasia⁵². These mutations appear to both foster a sebaceous fate and promote tumor development possibly by blocking the induction of p53⁵³. Based on this and other observations, it is now possible to manipulate *in vitro* cutaneous epithelial precursor or stem cells to show sebaceous differentiation^{46, 54}. These findings may shed light on the cancer stem (or progenitor) cell hypothesis and the pathogenesis of sebaceous neoplasia.

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EXTRAMAMMARY PAGET'S DISEASE

Hideko Kamino, M.D.

New York University School of Medicine

Extramammary Paget's disease (EMPD) was first described in 1889 by Crocker in a paper entitled "Paget's disease affecting the scrotum and penis". Since then lesions of EMPD have also been reported on the vulva, perianal skin, perineum, groin, buttocks, pubis and other distant sites such as axilla, scalp, ear canal and eyelid. It usually affects areas with numerous apocrine glands.

Clinical presentation:

EMPD usually presents as a slowly growing erythematous patch or plaque with a scaly or eroded surface. The lesions measure from a few to several centimeters in diameter. However, they can evolve to very large lesions that involve the entire vulva or perianal area. The lesions are commonly pruritic. In addition to EMPD, the clinical diagnoses include: squamous cell carcinoma in situ, leukoplakia, eczema, psoriasis and tinea. Because some lesions can be pigmented, the clinical differential diagnosis includes melanoma. EMPD is classified as primary if only the skin is involved and secondary when associated with an underlying adenocarcinoma from the rectum, vagina, cervix, urethra, bladder or prostate (approximately 25% of cases). In rare cases, there is an associated apocrine gland carcinoma.

Histopathologic findings:

The typical Paget cells are large and round with pleomorphic vesicular nuclei, prominent nucleoli and abundant pale staining, sometimes vacuolated cytoplasm. Some cells may have hyperchromatic nuclei. Typical and atypical mitotic figures are present. The nucleus can be displaced to the periphery of the cell, which acquires a signet-ring appearance. The pattern of distribution is usually as single cells or small clusters of cells between epidermal keratinocytes at all levels of the epidermis, and they may reach the cornified layer. In some cases the cells form glandular structures. Very often the Paget cells are above the basal layer and compress the basal keratinocytes. The PAS-diastase and mucicarmine stains often show that the Paget cells contain cytoplasmic mucin. Even when the Paget cells extend down the epithelium of the adnexa, the disease is still considered *in situ*. In approximately 21% of vulvar EMPD the Paget cells infiltrate from the epidermis into the dermis. In cases of secondary EMPD with an underlying cervical or rectal adenocarcinoma, the skin is involved by irregularly shaped glands lined with atypical columnar cells.

Immunohistochemistry:

Immunohistochemistry is important for establishing a definitive diagnosis and for evaluating the possibility of an associated underlying adenocarcinoma in some cases. The Paget cells stain positively for CK7, carcinoembryonic antigen and epithelial membrane antigen. Cutaneous cases are positive for gross cystic disease fluid protein (GCDFP). Approximately 50% of cases are androgen receptor positive. EMPD lacks progesterone and estrogen receptors. Secondary EMPD is CK7+, CK20+ and GCDFP15-. Positive reaction for uroplakin III distinguishes EMPD secondary to urothelial carcinoma from primary EMPD. Ki-67 and cyclin D1 expression have been reported at significant higher levels in invasive lesions than in situ cases. Contrary to Paget's disease of the breast, which demonstrates HER-2 gene amplification in almost all cases, various studies report that EMPD shows HER-2 gene amplification from 0% to 43% of cases. HER2 oncogene amplification appears to be more common in recurrent EMPD.

Pathogenesis:

Approximately 25% of EMPD are secondary to an underlying adenocarcinoma. The pathogenesis of the primary EMPD which comprise the majority of the cases is unclear. Probably most of the primary EMPD originate in the epidermis from a pluripotential stem cell, pre-existing Toker cells or the epithelial cells of the intraepidermal apocrine duct.

Differential Diagnosis:

Pagetoid squamous cell carcinoma
Malignant melanoma pigmented and amelanotic
Mycosis fungoides (Pagetoid reticulosis or Woringer-Kolopp disease)
Langerhan's cell histiocytosis

Prognosis:

EMPD *in situ* has a good prognosis. However, because EMPD can be multifocal, local recurrences are commonly seen. Invasive EMPD and EMPD secondary to an underlying adenocarcinoma have a poor prognosis with 50% mortality.

Treatment:

Wide local excision.
Mohs' micrographic surgery.
Recurrent primary EMPD: radiotherapy, CO2 laser ablation and photodynamic therapy.

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