

American College of Mohs Micrographic  
Surgery & Cutaneous Oncology

Diagnostic Quality Control Program 2009

(Review of Answers)

**Question 1**

This 71-year-old woman presents with an erythematous 0.6 centimeter papule on her face.

**The correct diagnosis is:**

- a. Infiltrative squamous cell carcinoma
- b. Desmoplastic trichoepithelioma
- c. Infiltrative basal cell carcinoma
- d. Inflammation with early scar formation, no evidence of tumor

## Discussion

### Question 1

#### Correct Answer

- a. Infiltrative squamous cell carcinoma

#### Main Histologic Features

- The tumor consists of small aggregates arranged in linear strands and some cords.
- The strands are small and infiltrating throughout the mid and deep dermis
- The malignant cells are hyperchromatic but do not show significant pleomorphism.
- Most of the tumor strands consist of the malignant cells that demonstrate single-cell Indian filing which may be confused with metastatic breast cancer in an elderly woman
- The tumor lacks key features of squamous cell carcinoma: lack of connection to the epidermis, lack of areas demonstrating keratinization, squamous eddies/keratin pearls, significant solar damage, mitotic and apoptic cells
- A cytokeratin stain can help delineate the small tumor aggregates and the malignant single cells infiltrating throughout the dermis that can be easily missed and mistaken for some inflammation

#### Differential Diagnosis:

- Infiltrative basal cell carcinoma
- Metastatic breast cancer
- Scar tissue

#### Clinical concerns:

- Infiltrating squamous cell carcinoma with single cells/small tumor strands can lack significant inflammation and features of epithelial keratinization and be easily misread or overlooked.

#### References:

- Kane CL, Keehan CA, Smithberger E, and Glass LF. Histopathology of cutaneous squamous cell carcinoma and its variants. *Seminars in Cutaneous Medicine and Surgery*. 23(1):54-61, 2003.
- Maguire B, Smith NP. Histopathology of cutaneous squamous cell carcinoma. *Clinics in Dermatology*. 13(6):559-68, 1995.
- Lever's Histopathology of the Skin. Edited by David Elder. Lippincott, Williams and Wilkin: Philadelphia, 2005.

## Question 2

These slides are from a lesion on the forehead/glabella of an elderly man. This tumor shows positive staining with cytokeratin 15.

**The correct diagnosis is:**

- a. Morpheaform basal cell carcinoma with perineural invasion
- b. Microcystic adnexal carcinoma with perineural invasion
- c. Infiltrative basal cell carcinoma with squamatization and perineural invasion
- d. Desmoplastic trichoepithelioma

## Discussion

### Question 2

#### Correct Answer

- b. Microcystic adnexal carcinoma with perineural invasion

#### Main Histologic Features

- Poorly circumscribed, infiltrative dermal tumor that often extends into the subcutis and skeletal muscle as demonstrated in this case
- Basaloid keratinocytes arranged in strands and cords in a desmoplastic stroma
- Focal areas with horn cysts and abortive hair follicles often present.
- Ducts and gland-like structures are also common.
- The tumor aggregates become smaller as they progress deeper in the dermis/subcutis.
- Cells are bland without significant atypia, and rare (if any) mitoses.
- Perineural invasion is common and may explain the high recurrence rate
- Cytokeratin 15 stain can help delineate microcystic adnexal carcinoma from infiltrative basal cell carcinoma and squamous cell carcinoma with ductal differentiation.
- The infiltrative, poorly circumscribed nature of this tumor distinguishes it from desmoplastic trichoepithelioma

#### Differential Diagnosis:

- Infiltrative basal cell carcinoma
- Desmoplastic trichoepithelioma

#### Clinical concerns:

- The neoplastic aggregates in this tumor are small, bland, and highly infiltrative. They can be easily missed on frozen sections.
- Perineural invasion is common and tumor extirpation with meticulous sections that follow the perineural invasion are critical.

#### References:

- Hoang MP, Dresser KA, Kapur P et al. Microcystic adnexal carcinoma: an immunohistochemical reappraisal. *Mod Pathol.* 21(2):178-85, 2008.
- Lever's Histopathology of the Skin. Edited by David Elder. Lippincott, Williams and Wilkin: Philadelphia, 2005.

### Question 3

These slides are the first stage from an incompletely excised tumor on the cheek of a 50-year-old woman with severe actinic damage.

**The correct diagnosis is:**

- a. New scar tissue with inflammation
- b. Scar with focal spindle cell squamous cell carcinoma
- c. Scar with focal atypical fibroxanthoma
- d. Malignant fibrous histiocytoma

## Discussion

### Question 3

#### Correct Answer

- a. New scar tissue with inflammation

#### Main Histologic Features

- Atypical fibroxanthoma is a pleomorphic spindle cell neoplasm and is regarded as a low-grade malignancy
- Other histological features: unencapsulated, often exophytic, densely cellular
- AFX is rarely connected to the overlying epidermis (whereas SCC often is).
- AFX contains cells with abundant foamy cytoplasm
- Multinucleated, atypical giant cells as well as large atypical round or histiocyte-like cells are present
- Numerous (and often atypical) mitotic figures can be seen in AFX.
- AFX expresses vimentin, and in many cases actin, and CD68. It is nonreactive for cytokeratin, CEA, S-100, Melan-A, and usually desmin.
- Scar tissue contains spindle-shaped fibroblasts arranged in a horizontal fashion, along with collagen fibers.
- Scar tissue lacks large atypical cells with foamy cytoplasm. In addition, mitotic figures are not present.
- Granulomatous inflammation consists of multinucleated giant cells but, again, they are contrasted with the bizarre giant cells present in AFX.
- Malignant fibrous histiocytoma (MFH) can be histologically indistinguishable from an AFX. However, MFH demonstrates deep invasion (often into muscle), necrosis, and vascular invasion.

#### Differential Diagnosis:

- Atypical fibroxanthoma
- Malignant fibrous histiocytoma
- Spindle cell squamous cell carcinoma

#### Clinical concerns:

- Recognize the features of uncommon tumors with features of scar tissue and be able to differentiate them from inflammation/scar tissue on frozen sections. In difficult cases, immunoperoxidase stains are useful.

#### References:

- Lever's Histopathology of the Skin. Edited by David Elder. Lippincott, Williams and Wilkin: Philadelphia, 2005.
- Differential Diagnosis in Dermatopathology II. Edited by A. Bernard Ackerman et al. Lea and Febiger: Philadelphia, 1988.

#### Question 4

An 89-year-old female presents with a squamous cell carcinoma in situ on her left temple. The slide from her first layer of Mohs surgery is provided.

**Which of the following is the most appropriate next course of action:**

- a. Alert the nursing staff that the patient is now tumor-free and prepare to close the wound.
- b. Alert the nursing staff that there is residual squamous cell carcinoma in situ at the epidermal margins and a collision basal cell carcinoma is present in the deep margin and prepare to take another layer.
- c. Prepare to take another layer and instruct the histotechnician to thaw the block for consultation and request CK-20 and TTF-1 immunohistochemical stains.
- d. Prepare to take another layer and instruct the histotechnician to thaw the block for consultation and request CD 34 and factor XIIIa immunohistochemistry stains.

## Discussion

### Question 4

#### Correct Answer:

- c. Prepare to take another layer and instruct the histotechnician to thaw the block for consultation and request CK-20 and TTF-1 immunohistochemical stains.

#### Main Histologic Features:

- At low power, there is no peripheral palisading, retraction artifact, or nests. At high power, the cells are not basaloid in nature. Thus, diagnosis other than collision basal cell carcinoma needs to be considered (small cell lung cancer or Merkel cell cancer). This eliminates choice B.
- CD 34 and Factor XIIIa are useful for discriminating dermatofibromas from dermatofibrosarcoma protuberans. There is no evidence of a spindle tumor. Thus, answer D is incorrect.
- Thyroid transcription factor-1 (TTF-1) is usually negative in Merkel cell and positive with small cell lung and done to discriminate the two. Answer C is the best answer. Some advocate chest x-rays in addition to histologic stains to be certain one is not overlooking the possibility of small cell lung cancer.
- Neuroendocrine granules are usually seen in Merkel cell carcinoma. Nuclei are uniform, with finely dispersed chromatin. Mitotic figures are frequent. Intercellular junctions are usually prominent.
- Paranuclear intermediate filaments are seen when stained with cytokeratin (CK) stain 8, 18, 19, and 20 (paranuclear dot pattern). CK 20 is the most specific for Merkel cell carcinoma.
- Three potential patterns are possible in Merkel cell carcinoma: trabecular, small cell, and intermediate.
  - Trabecular. Least common. Typically admixed with adnexal structure. Always stains with neuron-specific enolase. Lymphatic invasion common. Tends to be more indolent than other subtypes. Trabecular pattern is rarely dominant and many feel this name is inappropriate.
  - Small type. Resembles small cell cancer of lung. Mostly dermal tumor. Formed of clusters of smaller cells with abundant stroma (unlike small cell lung cancer). Large areas of necrosis are common. Nuclei are hyperchromatic and nucleoli are difficult to see. Cytoplasm is scant. Prognosis is similar to intermediate type.
  - Intermediate. Named because cell size is "intermediate" between other two types. Represents over 50% of cases. Most are dermal tumors. Diffuse growth pattern with characteristic dissociation between cells. Fewer neurosecretory granules than trabecular type. More aggressive subtype than trabecular. Death is common. The illustrated case is most likely this subtype.

Question 4 - continued

**Differential Diagnosis for Merkel cell carcinoma (small blue cells):**

- Lymphoma
- Small cell melanoma
- Metastatic small cell carcinoma and squamous cell carcinoma

**References:**

- Pathology in Focus Merkel cell carcinoma of the pinna. B. Skia, M.SC, A.Bibas, FRCSI, S.A. Hickey, M.A., FRCS, N.G. Ryley, M.R.C. PATH. The Journal of Laryngology and Otology, December 1997, Vol. III, pinpointed. 1195-1198.
- Gurdip S. Sidhua a; Pranil Chandra b; Nicholas D. Cassai c. Merkel Cells, Normal and Neoplastic: An Update. Ultrastructural Pathology, 29:287-294, 2005.

### Question 5

The following slide was received for review after performing the first stage of Mohs surgery on the right lower eyelid for a biopsy-proven basal cell carcinoma. Pigment-laden cells were identified in the deep dermis. A Perl's Prussian blue stain was performed.

**Your diagnosis is:**

- a. Desmoplastic malignant melanoma
- b. Monsel's solution reaction
- c. Tattoo pigment
- d. Postinflammatory hyperpigmentation resulting from previous biopsy

## Discussion

### Question 5

#### Correct Answer:

- b. Monsel's solution reaction

#### Main Histologic Features:

- Melanoma can be simulated by Monsel's reagent. This possibility can be eliminated by the use of Perl's iron stain, which stains the iron in Monsel's solution. The specimen stains quite well here. Thus, choice A is eliminated.
- All tattoo pigment appears black, regardless of tattoo color. The pigment in this specimen is reddish brown. Thus, choice C is eliminated.
- Postinflammatory hyperpigmentation typically shows melanin-laden melanophages, often with basilar hyperpigmentation. Melanin does not stain with Perl's iron stain. Thus, choice D is eliminated.
- Ferric subsulfate (Monsel's solution) is detectable via Perl's iron stain. The presence of a scar indicating prior biopsy is helpful in recognition of this diagnosis. An orange-reddish pigment resembling hemosiderin is usually seen. The pigmentation often extends horizontally along a biopsy site.
- Pigment is granular but may also be "smudgy" or diffuse. Pigment is most abundant in macrophages, fibroblasts, and collagen bundles but may also be found in epithelium and adnexal structures, nerves, venules, and smooth muscle. Shrinkage and discoloration of collagen bundles is usually present.
- A fibrohistiocytic proliferation consisting of large fusiform fibroblasts tending to lie parallel to each other and in the direction of the collagen bundles is characteristic. Atypical macrophages with large irregular-shaped hyperchromatic nuclei and prominent nucleoli are typical.

#### Differential Diagnosis:

- Melanocytic proliferation

#### References:

- Monsel's solution: A histologic nuisance. Olmstead PM, Lund HZ, Leonard DD. J Am Acad Dermatol. 1980 Nov; 3(5):492-8. PMID: 7217377.
- Monsel's solution and histologic lesions. Hanau D, Grosshans E. Am J Dermatopathol. 1981 Winter;3(4):418-9. No abstract available. PMID: 6461273.

### Question 6

A patient with a 0.6 mm depth malignant melanoma on the cheek is treated with slow Mohs surgery utilizing sections stained with Melan-A.

Which of the following is true:

- a. Melanocytes are present at densities of more than 1 melanocyte per 10 basal keratinocytes, but this is normal for sun-exposed skin. Another layer is not necessary.
- b. Large atypical melanocytes are present in the epidermis at higher than normal numbers indicating that melanoma in situ is present at the margin and another layer should be taken.
- c. Pagetoid spread is present within some of the rete ridges, a worrisome finding that requires another layer to be certain no more neoplastic cells remain.
- d. No abnormal melanocytes are seen but, since they are present at higher densities than usual, it is assumed they are a part of the original tumor and another layer should be taken.

## Discussion

### Question 6

#### Correct Answer:

- a. Melanocytes are present at densities of more than 1 melanocyte per 10 basal keratinocytes, but this is normal for sun-exposed skin. Another layer is not necessary.

#### Main Histologic Features:

- This permanent section demonstrates an increase in density of melanocytes on sun-damaged skin; a normal finding.
- The melanocytes that appear to be above the basal layer are the result of tangential cutting. Thus, choice C is incorrect.
- There are no significant numbers of atypical melanocytes present. Thus, choice B is incorrect.
- An excellent study exists on this topic by Hendi, et al. (see below)

#### Differential Diagnosis:

- Sun-damaged skin
- Residual malignant melanoma

#### References

- Melanocytes in long-standing sun-exposed skin: quantitative analysis using the MART-1 immunostain. Hendi A, Brodland DG, Zitelli JA. Arch Dermatol. 2006 Jul; 142(7):871-6.

**Question 7**

A 72-year-old white man presented with an ill-defined fleshy plaque on the forehead. Biopsy was done.

**The most likely diagnosis is:**

- a. Basal cell carcinoma with monster cells
- b. Sebaceous epithelioma (sebaceoma)
- c. Sebaceous carcinoma
- d. Basal cell carcinoma with sebaceous differentiation

## Discussion

### Question 7

#### Correct Answer:

- c. Sebaceous carcinoma

#### Main Histologic Features:

- Irregular, asymmetric, lobular or diffuse proliferation of basaloid cells with focal sebaceous differentiation (foamy/vacuolated, lightly eosinophilic bubbly cytoplasm)
- Pagetoid extension/in situ component can be seen and is more common in ocular sebaceous carcinoma
- Most common cases are seen in the infiltrating phase and should be classified into low-grade (more sebaceous duct formation, less atypia and pleomorphism) and high-grade (less sebaceous duct differentiation, more atypia and pleomorphism, bizarre mitoses)

#### Differential Diagnosis:

- Basal cell carcinoma with sebaceous differentiation
- Sebaceoma
- Clear cell hidradenocarcinoma
- Metastatic colon adenocarcinoma

#### Clinical Concerns:

- Can be confused with other basaloid cell neoplasms with real or artifactual cytoplasmic clearing
- Mohs surgery has proven to be the best treatment modality
- Mohs surgeons should be aware of the presence or absence of an accompanying in situ/pagetoid component (can be easily missed in frozen sections)

#### References:

- Hassanein A: Sebaceous carcinoma and the T-antigen. (Review article). *Semin Cutan Med Surg* 2004;23(1):62-72.
- Hassanein AM, Al-Quran SZ, Kantor GR, Pauporte M, Telang GH, Spielvogel RL. Thomsen-Friedenreich (T) antigen: A possible tool for differentiating sebaceous carcinoma from its stimulators. *Appl Immunohistochem Mol Morphol* 2001;9(3):250-254.

### Question 8

This frozen section represents the first stage of Mohs surgery for nodular basal cell carcinoma of the cheek.

**The most likely next step the Mohs surgeon will perform is:**

- a. Reconstruction, since a tumor-free plane was reached
- b. Take a second stage, tumor is present with peritumoral fibrosis
- c. Refer patient for radiation due to perineural invasion
- d. None of the above

## Discussion

### Question 8

#### Correct Answer:

- b. Take a second stage - tumor is present with peritumoral fibrosis

#### Main Histologic Features:

- Carcinomas usually stimulate stromal fibroplasia known as desmoplastic reaction. In basal cell and squamous cell carcinomas, tumor formations can be seen surrounding or surrounded by compressed fibrous tissue mimicking perineural invasion. This phenomenon is called peritumoral fibrosis.
- Immunohistochemistry can help in difficult cases to differentiate peritumoral fibrosis (S-100 negative) from perineural invasion (S-100 positive)

#### Differential Diagnosis:

- Perineural invasion

#### References:

- Hassanein AM, Proper SA, Depcik-Smith ND, Flowers FP. Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: A potential pitfall in Mohs micrographic surgery. *Dermatol Surg*. 2005;31:1101-1106.

### Question 9

A 3.2 cm erythematous, firm plaque was present on the left lower back of an otherwise healthy 31-year old female. What is the most common immunohistochemical profile for this tumor?

**The correct answer is:**

- a. CD34 -, Factor XIIIa +
- b. S-100 +, HMB-45 -
- c. CD 43 +, CK1 +
- d. CD 34 +, Factor XIIIa -

## Discussion

### Question 9

#### Correct Answer:

- d. CD 34 +, Factor XIIIa -

#### Main Histologic Features: Dermatofibrosarcoma Protuberans

- Epidermis normal, atrophic, or ulcerated (rarely hyperplastic)
- Very cellular proliferation of thin spindled fibroblasts and collagen in the dermis, extending into the subcutaneous fat
- Cartwheel pattern (fibroblast whorl around like spokes of a wheel) or storiform (whirligig or mat-like) pattern
- Infiltration of fat in a fascicular pattern or honeycomb-like pattern
- Cytologic atypia mild to moderate, very few mitoses
- CD34 positive in 85% of cases, factor XIIIa negative (opposite of dermatofibroma)

#### Differential Diagnosis:

- Dermatofibroma
- Fibrosarcoma
- Atypical fibroxanthoma
- Other spindle cell tumors

#### Clinical Concerns:

- Indolent growth pattern with propensity to recur after surgical excision
- Metastases are rare, 5% or less, and are usually preceded by multiple local recurrences
- Recurrence rates after WLE range from 10-20%, Mohs surgery (either traditional or modified) recurrence rates range from 0-7%

#### Reference:

- Hancox JG, Kelley B, Greenway HT. Treatment of dermatofibroma sarcoma protuberans using modified Mohs micrographic surgery: No recurrences and smaller defects. Dermatol Surg. 2008;34:780-784.
- Gloster HM. Dermatofibrosarcoma protuberans. J Am Acad Dermatol. 1996;35:355-374.

**Question 10**

The following Mohs section was taken from the lip of a 54-year-old female with a history of a morpheaform basal cell carcinoma

**The correct answer is:**

- a. Screen the patient for diabetes to rule out possible scleredema
- b. Obtain a CT scan to rule out regional spread of a primary cutaneous adenoid cystic carcinoma
- c. Take another layer to completely remove the mucous cyst
- d. Ask the patient about a history of any soft tissue filler substance injections

## Discussion

### Question 10

#### Correct Answer:

- d. Ask the patient about a history of any soft tissue filler substance injections

#### Main Histologic Features:

- Blue, amorphous mass in deep dermis,
- The material was not associated with BCC cells or follicular structures
- Spaces with amorphous mass are not lined by epithelium, granulation tissue or inflammatory cells

#### Differential Diagnosis:

- Cystic basal cell carcinoma with artifact of tumor “falling out” of frozen sections
- Mucous cyst of the mouth

#### Clinical Concerns:

- It is important to ask patients who will be undergoing Mohs surgery about any past history of soft tissue filler injections. This patient had soft tissue filler injection in her lip 3 years prior, this was in Europe and she was unsure of the type of filler, presumably a hyaluronic acid filler
- When staining, Mohs sections with toluidine blue hyaluronic acid fillers may mimic hyaluronic acid that normally surrounds basal cell carcinoma nests

#### Reference:

- Bennett R, Taher M. Restylane persistent for 23 months found during Mohs micrographic surgery: A source of confusion with hyaluronic acid surrounding basal cell carcinoma. Dermatol Surg. 2005;31:1366-1369.

