American College of Mohs Surgery
Diagnostic Quality Control Self-Examination 2016
Review of Answers

Question 1

A 66–year-old Caucasian male was sent for treatment of a tumor on the upper back. A representative frozen section of the tumor is shown.

What is most likely diagnosis?

A. Atypical fibroxanthoma
B. Spindled squamous cell carcinoma
C. Leiomyosarcoma
D. Desmoplastic melanoma
Main Histologic and Immunohistochemical Features of Leiomyosarcoma

- May be 1) superficial or dermal leiomyosarcomas (at least 90% of the tumor confined to the dermis) \(\rightarrow\) arising from arrector pili or genital smooth muscle, or 2) subcutaneous leiomyosarcomas \(\rightarrow\) arising from vascular smooth muscle.
- Histopathologic features span a morphologic continuum.
- Well-differentiated leiomyosarcoma features overlap with leiomyomas, while poorly differentiated lesions closely resemble atypical fibroxanthoma, and moderately differentiated leiomyosarcomas cytologically resemble normal smooth muscle cells.
- Dermal leiomyosarcoma are composed of poorly circumscribed fascicles of spindled cells with blunt-ended nuclei and eosinophilic cytoplasm that infiltrate between the collagen. Leiomyosarcomas have a high nucleocytoplasmic ratio, and contain mitotic figures.
- Subcutaneous leiomyosarcomas may be better circumscribed and surrounded by a pseudocapsule of compressed tissue. They have a higher degree of pleomorphism and nuclear atypia, higher mitotic rate and can demonstrate focal necrosis.
- Immunohistochemical studies are important in supporting the cell lineage. Leiomyosarcoma will usually be actin-positive and desmin-positive, but negative for keratin, S100 protein and CD68.

Histologic Differential Diagnosis:

- Atypical fibroxanthoma – Well-circumscribed dermal tumor, contiguous with epidermis or separated by thin zone of collagen, usually contain 3 cell types: 1) plump, spindle-shaped cell in poorly arranged fascicles with prominent vesicular nucleus, 2) large polyhedral cells, some have a vacuolated cytoplasm, 3) giant cells, can be mono or multinucleated, with hyperchromatic nuclei and with bizarre mitoses. The spindle-shaped cells are positive for muscle-specific actin, while the large histiocyte-like cells stain positively with \(\alpha\)-antichymotrypsin, CD68 and CD10.
- Spindled squamous cell carcinoma – A squamous cell carcinoma showing fibroblastic and myofibroblastic differentiation. Histologically, it commonly presents as a pleomorphic spindled cell population with no evidence of epidermal derivation or squamous differentiation. However, spindle cell squamous carcinoma can present as spindled cell areas in an otherwise recognizable squamous tumor. Location in sun-damaged skin and the presence of actinic keratosis in the adjacent non-ulcerated epidermis can be clue to the diagnosis. Immunohistochemically, spindle squamous cell carcinoma stain positively for keratin and often EMA is at least focally present.
- Desmoplastic melanoma – Diffusely infiltrative, sometimes paucicellular, malignant spindle cell tumor with marked interstitial fibrosis and collagenization. The infiltrate often spares the subpidermal papillary dermis, but frequently is found to extend into the subcutaneous fat or beyond (skeletal muscle or bone involvement is not uncommon). Cells are usually elongated and commonly have basophilic cytoplasm. Nuclei may be tapered and hyperchromatic or cigar-shaped and vesicular with prominent eosinophilic nucleoli. Most commonly, the tumor has a fascicular arrangement. Lymphocytic infiltrates, which form nodular aggregates, are a characteristic feature. The overlying epidermis may show features of atypical melanocytic hyperplasia, most often of the lentigo maligna pattern.
Immunohistochemically, desmoplastic melanoma expresses S-100 protein (94–100%), neuron-specific enolase and vimentin.

Clinical Concerns:

- Cutaneous and subcutaneous leiomyosarcomas typically present as a solitary, firm, skin-colored to red–brown nodule or plaque.
- Dermal tumors range from 0.5 to 4 cm in diameter, while subcutaneous lesions are typically larger. The tumors maybe painful and ulcerated.
- Dermal tumors favor the extremities (most commonly the lower leg) of older adults (fifth to seventh decades of life). There is a male preponderance (3:1).
- Metastasis of dermal leiomyosarcomas has been reported in up to 14% of cases.
- Subcutaneous tumors occur most frequently in patients aged 50 to 80 years and in contrast to dermal tumors have an equal gender occurrence.
- Subcutaneous leiomyosarcomas have locally recurred in up to 61% of cases and metastasized in up to 62% cases.
- Patients with multiple tumors should be evaluated to exclude the possibility of metastases due to a primary retroperitoneal or visceral leiomyosarcoma.
- Wide local excision with minimum 1-cm margins has demonstrated statistically lower rates of recurrences and metastasis compared with excision with narrow surgical margins. Treatment with Mohs micrographic surgery also has demonstrated very low recurrence rates.

References:

Question 2

A 62–year-old Caucasian male was sent for treatment of a tumor on the scalp. A representative frozen section of the first stage of Mohs surgery is shown.

What is most likely diagnosis?

A. Basal cell carcinoma and dermatofibrosarcoma protuberans
B. Basal cell carcinoma and spindle cell lipoma
C. Basal cell carcinoma and rudimentary meningocele
D. Basal cell carcinoma and neurofibroma
Question 2 Discussion

Correct Answer:

D. Basal cell carcinoma and neurofibroma

Main Histologic and Immunohistochemical Features of Neurofibroma

- Loosely arranged spindled cells with scanty pale cytoplasm and elongated wavy nuclei in the setting of a fibrillar, collagenous and sometimes myxoid stroma.
- Multinucleated floret-like giant cells may be present.
- Mast cells are a prominent feature.
- The ratio of stromal collagen and mucin vary both within and between lesions; hyalinization of collagen may sometimes occur.
- Positive staining for S-100 protein is seen in only 30–50% of cells. Variable staining with CD34 and EMA.

Histologic Differential Diagnosis:

- Dermatofibrosarcoma protuberans – Proliferation of dermal spindle cells that infiltrate into the subcutaneous fat. Bland appearing cells with low degree of pleomorphism and mitotic rate. Dermal spindle cells are arranged in storiform or cartwheel pattern. Infiltration of tumor into the subcutaneous fat results in a honeycomb appearance. CD34 positive.
- Spindle cell lipoma – Subcutaneous lesions are well circumscribed, whereas dermal tumors are ill defined. Mature univacuolated adipocytes, irregular collections of slender spindled cell with pale eosinophilic cytoplasm and uniform nuclei associated with bundles of hyalinized collagen are seen. Mitoses are rare. Numerous mast cells are present. The ratio of adipose tissue to spindled cells can vary. Some cases contain few and rarely, no adipocytes. Extensive myxoid change can result in degenerative features with a pseudovascular pattern in which papillary structures project into empty spaces. The spindled cells are CD34 positive and S-100 negative. Mature adipocytes are positive for S-100.
- Rudimentary meningocele – Congenital, but may be recognized during childhood and adolescence. Nonspecific cutaneous or subcutaneous nodule or plaque on the scalp. There is no underlying bone abnormality. Located in the deep dermis and subcutis and show irregular, elongated, anastomosing and dilated spaces resembling vascular channels dissecting between collagen bundles. The spaces are filled or lined by small, round eosinophilic epithelioid meningotheelial cells with minimal or no atypia and showing no mitotic activity. Psammoma bodies are seen. Consistently EMA positive.

References:

An otherwise healthy 36-year-old female was referred for Mohs surgery for a small fleshy papule on the glabella. A panel of immunohistochemical studies was performed on the biopsy specimen. The tumor cells stained strongly positive for CD10, MiTF, NKI/C3, weakly positive for CD68, PGP9.5, and negative for pankeratin, S-100, melanoma cocktail, P63, Caldesmon, CD34, EMA, muscle specific antigen, and SOX10. The frozen section slides from the residual tumor and the first Mohs layer are submitted for your review.

The most likely diagnosis is:

A. Atypical Spitz nevus or spitzoid melanoma
B. Pilar leiomyoma
C. Dermal nerve sheath myxoma
D. Cellular neurothekeoma
E. Plexiform fibrohistiocytic tumor
Question 3 Discussion

Correct answer: D. Cellular neurothekeoma

Main Histopathologic Features:

- The term “neurothekeoma” (Gr. theke, sheath) was first coined by Gallager and Helwig in 1980 to describe benign cutaneous tumors of possible nerve sheath derivation. Subsequently, depending on the amount of myxoid matrix, neurothekeoma was divided into cellular, mixed, or myxoid subtypes.
- Histologically, cellular neurothekeoma is composed of variably epithelioid to spindled cells with pale eosinophilic cytoplasm. These cells have a tendency to form a lobulated or micronodular architecture separated by dense hyaline collagen, with whorled and sometimes focal fascicular growth. Up to 60% tumors show appreciable nuclear atypia and up to 25% contain pleomorphic cells. Osteoclastic giant cells and Touton giant cells are occasionally seen. Most tumors are superficial lesions infiltrating dermal collagen and superficial subcutis.
- Immunoreactivity is typically present for vimentin, NKI/C3, CD10, microphthalmia transcription factor, and PGP9.5, and focal reactivity is sometimes noted for smooth muscle actin and CD68. These tumors are negative for S100 protein, glial fibrillary acidic protein, and Melan A.
- The gene expression array data confirm that dermal nerve sheath myxoma is of peripheral nerve sheath origin, and suggest that neurothekeoma may be a variant of fibrous histiocytomas.

Differential Diagnosis:

- Atypical Spitz nevus or spitzoid melanoma
- Pilar leiomyoma
- Dermal nerve sheath myxoma
- Plexiform fibrohistiocytic tumor

Clinical Concerns:

- Cellular neurothekeoma typically presents as an asymptomatic nodule on the upper extremities and head and neck skin of young patients with a female predominance. The mean tumor size is 1 cm and 90% are less than 2 cm. Deep involvement of the subcutis is uncommon, and skeletal muscle involvement is rare and largely restricted to the facial region.
- Cellular neurothekeoma behaves in a benign fashion and only occasionally recurs with prior incomplete excision. Large tumor size (>2 cm) and atypical histologic features (including high mitotic rate, pleomorphism, and infiltration of fat) seem to have no clinical significance.
- It is speculated that cellular neurothekeoma may be a superficial form of plexiform fibrohistiocytic tumor. In contrast to cellular neurothekeoma, which has excellent clinical outcome, plexiform fibrohistiocytic tumor can recur and occasionally even have regional and distant metastasis.
- Complete excision is recommended. Mohs micrographic surgery has been successfully used in four published cases.
References:
Question 4

A 63-year-old man with history of malignant fibrohistiocytoma of the sciatic nerve treated by resection, flap repair and radiation 30 years ago developed a large and deep “decubitus” ulcer within the flap closure scar on the lower back/buttock for a decade. Subtotal biopsy from the ulcer revealed basal cell carcinoma and he was referred for Mohs micrographic surgery. Of note he has no family or personal history of polymyositis or dermatomyositis. The slide from the first Mohs layer that was taken around the entire ulcer is submitted for your review.

The most likely diagnosis is:

- A. Alveolar rhabdomyosarcoma
- B. Rhabdomyoma
- C. Autoimmune inflammatory myopathy such as polymyositis
- D. Focal myositis, a benign inflammatory pseudotumor of skeletal muscle
- E. Inflammatory myofibroblastic tumor
Question 4 Discussion

Correct answer:
D. Focal myositis, a benign inflammatory pseudotumor of skeletal muscle

Main Histopathologic Features:
- Focal myositis, a benign inflammatory pseudotumor of skeletal muscle, was first described as a distinct clinicopathologic entity within the group of inflammatory pseudotumors of soft tissue by Heffner et al. in 1977.
- Histologically, there are myopathic and focal neurogenic features along with fibrosis, and inflammation. The most consistent alterations of muscle fibers are necrosis and regeneration. Necrotic atrophic muscle fibers are infiltrated with macrophages and lymphocytes. Hypertrophic muscle fibers are composed of regenerating cells containing multiple large nuclei. Regenerating muscle cells need to be differentiated from rhabdomyosarcoma. Chronic lesions may contain more fibrosis and less inflammation.
- Denervation changes are conspicuous histological features in some cases of focal myositis. Severe myopathic changes without inflammation may develop in chronic denervating condition as seen in our case.

Differential Diagnosis:
- Rhabdomyoma
- Alveolar rhabdomyosarcoma
- Autoimmune inflammatory myopathy such as polymyositis
- Inflammatory myofibroblastic tumor
- Lymphoma

Clinical Concerns:
- Benign inflammatory pseudotumor of skeletal muscle typically presents with a localized painful soft tissue swelling or intramuscular mass of an extremity over a period of several weeks in both children and adults, clinically simulating a sarcoma.
- Infection, trauma, family history of muscle disease, and relationship with polymyositis have all been speculated but the etiology remains unclear. Some cases suggest that denervation may play a role. The current case presents differently than reported cases in that there is known history of trauma and denervation, and chronic denervation has likely triggered myositic and myopathic changes.
- The prognosis for focal myositis is excellent. Most lesions regress spontaneously over time. Recurrence is documented in approximately 18% of cases in the literature, and no malignant transformation or systemic disease is seen at follow-up. Nevertheless, these lesions pose significant diagnostic challenges both clinically and histologically, and often receive exploratory surgical excision to rule out sarcoma.

References:
Question 5

An 80-year-old gentleman presents for treatment of a 1.2 cm sclerotic plaque of the mid upper forehead. This slide is from the first Mohs stage.

Based on the findings on this slide, the most appropriate diagnosis would be:

A. Infiltrative squamous cell carcinoma
B. Eccrine squamous syringometaplasia
C. Squamoid eccrine ductal carcinoma
D. Microcystic adnexal carcinoma (MAC)
Question 5 Discussion

Correct Answer:

C. Squamoid eccrine ductal carcinoma

Main Histologic Features:

- Numerous tubular structures lined by one or more layers of atypical basaloid cells, lacking a desmoplastic stroma.
- Prominent cellular pleomorphism and numerous, atypical mitotic figures are present.

Differential Diagnosis:

- Eccrine squamous syringometaplasia
- Infiltrative squamous cell carcinoma
- Microcystic adnexal carcinoma

Clinical Concerns:

- Primary eccrine carcinoma is a rare tumor that most commonly presents as a slow growing plaque on the scalp, extremities, or trunk.
- While metastases are rare, local recurrence is common.
- Recommended treatment is wide surgical excision. However, due to relatively few cases, no large studies have been performed to date and MMS with complete margin examination may lead to a lower rate of recurrence.

References:

Question 6

An 81-year-old gentleman presents for treatment of a biopsy positive well-differentiated squamous cell carcinoma of the left hand. This slide is from the first Mohs stage.

Based on the findings on this slide what would you do?

A. Stop the margin is clear.
B. The peripheral margin is positive, take an additional layer.
C. The peripheral and deep margins are positive, take an additional layer.
D. Check the original biopsy for eccrine carcinoma.
Question 6 Discussion

Correct Answer:

A. Stop the margin is clear.

Main Histologic Features:

- Non-inflammatory squamous metaplasia of the eccrine sweat ducts
- Squamous metaplasia of the cuboidal eccrine epithelium
- Keratinization, hyperplasia, and apoptosis is seen
- Occasional typical mitoses may be present but significant cellular atypia is absent

Differential Diagnosis:

- Infiltrative squamous cell carcinoma
- Primary eccrine carcinoma
- Neutrophilic eccrine hidradenitis

Clinical Concerns:

- Eccrine squamous syringometaplasia is a tissue reaction pattern often found incidentally to a number of known cutaneous pathologies including skin trauma, adjacent to cutaneous tumors, in areas of prior radiation, and due to direct toxic injury from numerous chemotherapeutic agents.
- It is important to recognize this benign reactive tissue process to avoid unnecessary additional surgery.

References:

Question 7

A 70-year-old white male underwent Mohs surgery for a 25 x 15mm infiltrated plaque on the left cheek. The first Mohs stage demonstrated the following.

The correct diagnosis is:

A. Microcystic adnexal carcinoma
B. Squamoid eccrine ductal carcinoma
C. Squamous cell carcinoma, poorly differentiated
D. Basosquamous cell carcinoma
Question 7 Discussion

Correct Answer:

B. Squamoid eccrine ductal carcinoma (SEDC)

Main Histologic Features:

- Poorly circumscribed, infiltrative neoplasm with frequent epidermal connection and extension into the deep dermis and subcutaneous fat with frequent perineural invasion
- The superficial portion of the neoplasm shows squamoid differentiation, whereas the central and deeper regions display eccrine differentiation, including tubular structures reminiscent of syringoma and ductal lumina with eosinophilic cuticles, in a desmoplastic stroma
- Cystic structures resembling those seen in microcystic adnexal carcinoma (MAC) have not been described in SEDC.
- The tumor aggregates in SEDC stain positively for keratin markers including CK5/6, CK903, Cam 5.2, and CK116
- EMA and CEA show reliably positive staining in all cases of SEDC, with a preference for tumor cells and ductal epithelium.

Differential Diagnosis:

- Squamous cell carcinoma, poorly differentiated
- Microcystic adnexal carcinoma

Clinical Concerns:

- SEDC is a rare eccrine neoplasm, which presents predominantly on the head and neck in elderly men
- Tends to be broadly infiltrative
- Case series of 30 SEDC reports local recurrence risk of 25% and 3 cases of lymph node metastasis, and one case of death from metastatic disease

References:

Question 8

An 84-year-old white male presents with a 20mm exophytic nodule on his left ala. Punch biopsy demonstrated carcinoma seen on this slide. One month following successful radiation therapy to the left ala, the patient developed numbness and aching pain in the distribution of his left infraorbital nerve. MRI and CT demonstrated abnormal enlargement of the left infraorbital nerve, with extension to the foramen.

A treatment consideration for this patient with ‘inoperable’ carcinoma is:

A. Vismodegib
B. Pembrolizumab
C. Trametinib
D. Vemurafenib
Question 8 Discussion

Correct Answer:

B. Pembrolizumab

Clinical Concerns:

- The programmed cell death protein 1 (PD-1) and PD-1 ligand (PD-L1) pathway in cancer is implicated in tumors escaping immune destruction by inhibiting anti-tumor T cell mediated cytotoxicity
- PD-L1 may be highly expressed in squamous cell carcinoma, often leading to aggressive clinical behavior by local down-regulation of the anti-tumor immune response
- Immune checkpoint blockade PD-1 antibodies, such as pembrolizumab, represent a novel strategy to treat unresectable squamous cell carcinoma and have recently been documented in case reports

References:

Question 9

A 14-year-old male with an “atypical fibrohistiocytic proliferation” (Factor XIIIa and CD34 positive; CK and S100 negative) located on the mid-back is referred for Mohs micrographic surgery (MMS).

On the day of surgery, the Mohs debulking specimen is examined.

Select the most likely diagnosis and best course of action:

A. Dermatofibrosarcoma protuberans (DFSP); Continue MMS but send “safety” layer for permanent sections after tumor is cleared
B. Cellular dermatofibroma; Continue MMS and send debulk for molecular testing
C. Aneurysmal benign fibrous histiocytoma; Continue MMS
D. Epithelioid sarcoma; Stop MMS and involve surgical oncology
Question 9 Discussion

Correct Answer:

B. Cellular dermatofibroma; Continue MMS and send debulk for molecular testing

Main Histologic Features:

- Relatively well-circumscribed dermal tumor
- Spindle-shaped, stellate, and epithelioid fibrohistiocytic cells without significant cytologic atypia
- Variable widening of epidermal rete ridges; some epidermal induction visible
- Some collagen trapping note peripherally

Differential Diagnosis:

- Dermatofibrosarcoma protuberans (DFSP)
- Other subtypes of benign fibrous histiocytoma (aneurysmal, epithelioid, atypical, etc.)
- Other spindle cell tumors: atypical fibroxanthoma, pleomorphic dermal sarcoma, spindle cell squamous cell carcinoma, spindle cell melanoma, leiomyosarcoma, epithelioid sarcoma

Clinical/Histologic Concerns:

- Cellular DFs are often hypercellular, storiform, and may involve the subcutis. They may sometimes be difficult to distinguish from DFSP on routine staining.
- Aneurysmal DF would be expected to exhibit cleft-like hemorrhagic spaces lacking an endothelial lining.
- Epithelioid sarcoma arises chiefly in young adult males with almost all lesions arising on the extremities as slow-growing ulcerated nodules involving tendons and fascial structures. These tumors would be expected to be cytokeratin positive.
- Immunohistochemistry is typically helpful in distinguishing cellular DF from DFSP. Factor XIIIa and CD34 are the most commonly utilized markers. Cellular DF is most commonly factor XIIIa positive and CD34 negative, and DFSP exhibits the opposite profile. Unfortunately, the reliability of these staining patterns is not absolute.
- Other immunostains have been proposed (including stromelysin 3, tenascin, CD99, nestin, HMGA1/2, among others), but none exhibits ideal characteristics for delineating DFSP from cellular DF.
- In settings where histology is inconclusive, molecular testing may be helpful since the vast majority of DFSP exhibit the characteristic fusion gene (COL1A1-PDGFB).
- Both reverse-transcription PCR (RT-PCR) and fluorescence in situ hybridization analysis (FISH) techniques may be utilized. FISH may be slightly more sensitive (~90%) and easier to perform in practice than RT-PCR.

References:

Question 10

A 74-year-old male with a 2-centimeter nodule on the frontal scalp is referred for biopsy.

Which of the following represents the most appropriate next step:

A. Send biopsy specimen for cytogenetic testing  
B. Schedule patient for MMS  
C. Refer for sentinel lymph node biopsy  
D. Perform systemic workup for internal malignancy
Question 10 Discussion

Correct Answer:

D. Perform systemic workup for internal malignancy

Main Histologic Features:

- Primary cutaneous mucinous carcinoma (PCMC) is a rare subtype of sweat gland carcinoma (approximately 150 cases reported).
- PCMC are composed of large pools of basophilic mucin separated by thin fibrous septa, creating a honeycomb pattern. Islands of neoplastic epithelial cells reside centrally within lakes of mucin.
- Histopathological features (including IHC) are helpful, but alone cannot exclude metastases from a mucin-producing internal malignancy with 100% certainty.
- PCMC are negative for cytokeratin 20, in contrast to most mucin-producing tumors of the GI tract. Expression of cytokeratin 7 and p63 by PCMC is helpful since these markers are rarely found in metastatic mucinous adenocarcinomas (including mucinous breast carcinoma).

Differential Diagnosis:

- Metastasis of mucinous carcinoma

Clinical Concerns:

- Diagnosis of PCMC should not be made without a systemic workup (typically whole-body CT or PET/CT plus colonoscopy) performed to help rule out internal malignancy.
- Metastases from mucinous adenocarcinoma most commonly derive from the breast or GI tract, although ovary, lung, salivary gland, and prostate origin have been reported.
- PCMC most commonly arise on the scalp and face—with a predilection for the eyelid—in elderly patients.
- Tumors are typically slow-growing, but have a high rate of local recurrence after conventional excision (29-34%) and may uncommonly metastasize (3-11%).
- MMS has been demonstrated to be effective in treating PCMC and should be strongly considered, especially when tissue conservation is necessary.

References:

Question 11

A 57-year-old woman was treated for a lesion on the right 4th toe. A representative section from the first stage of Mohs surgery is shown.

What is the most likely diagnosis?

A. In situ subungual melanoma  
B. Squamous cell carcinoma  
C. Onycholemmal carcinoma  
D. Onychomatricoma  
E. Subungal epidermoid inclusions
Question 11 Discussion

Correct Answer:

C. Onycholemmal Carcinoma

Main Histologic Features of Onycholemmal Carcinoma:

- Solid, lobular collections of atypical keratinocytes with eosinophilic cytoplasm
- Small, keratin-filled cysts.
- Absence of keratin horn pearls and compact parakeratosis

Histologic Differential Diagnosis:

- Subungual squamous cell carcinoma- increased mitotic figures above the basal layer, dyskeratosis, acanthosis, and parakeratosis. Parakeratotic horn pearls may be present. Viropathic changes may be encountered in HPV-driven disease
- Subungual epidermoid inclusions (aka: Follicular microcysts of the nail bed, Onycholemmal cysts) - small rounded or elongate aggregates of eosinophilic keratinocytes without atypia that are typically contiguous with nail epithelium or located superficially within the dermis of the nail bed
- Onychomatricoma-multiple fingerlike projections of matrical-type epithelium, fibrocellular stroma, thick nail plate with serum filled cavities

Clinical Concerns:

- Rare malignant tumor that originates from nail bed epithelium and can extend to the nail matrix
- Warty, discolored, crusted, or ulcerative lesions that may present with pain, swelling, or onycholysis
- Rare bony involvement.
- No HPV association identified.

References: