Question 1

50-year-old healthy male with a family history of colorectal carcinoma presents with a rapidly growing nodule on the left nasal sidewall. A biopsy was performed, and he was referred for MMS.

Review the 1st stage (H&E stain) section, and select the true statement:

A. This is a basal cell carcinoma and will stain with BerEP4.

B. This is a merkel cell carcinoma and will stain with CK20.

C. This is a sebaceous carcinoma and may show loss of staining with MSH2, MSH6 or MLH1.

D. This is a squamous cell carcinoma and will stain with cytokeratin stains.

Discussion

Question 1

Correct Answer:

C. This is a sebaceous carcinoma and may show loss of staining with MSH2, MSH6 or MLH1.

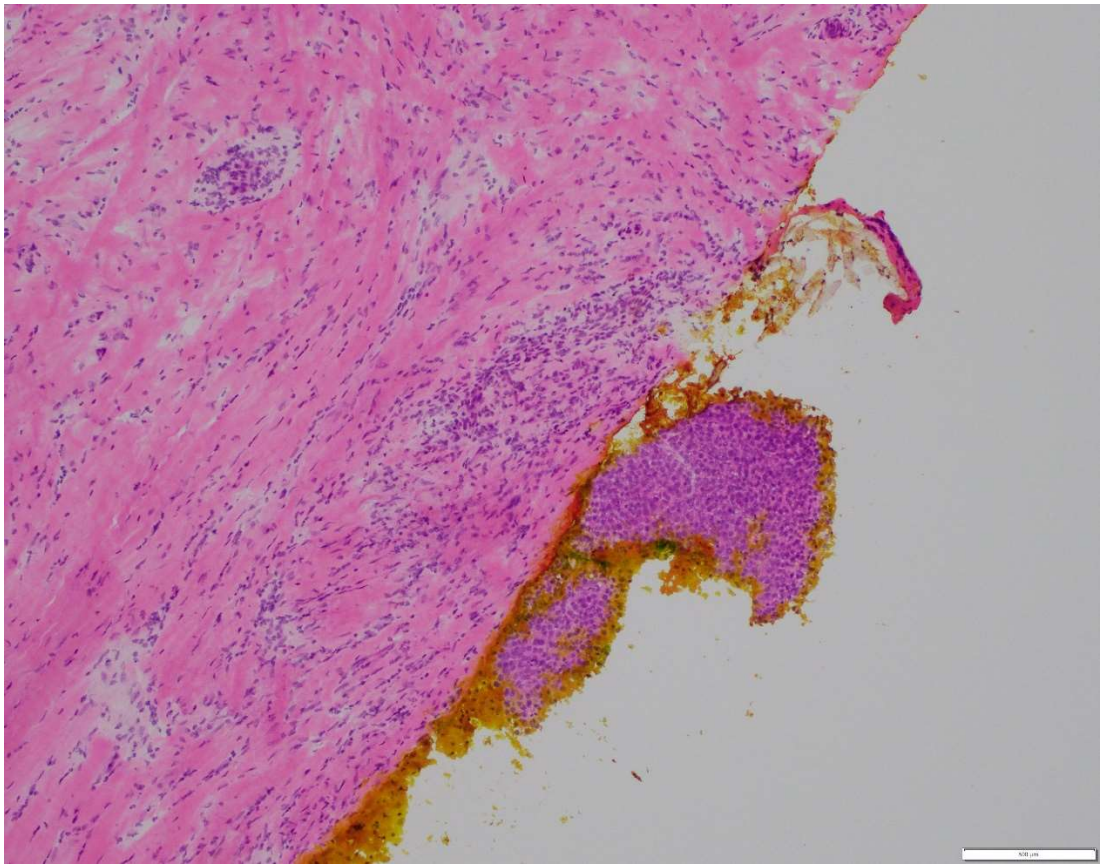

Fig. 1 – Collection of atypical basaloid cells with prominent nucleoli that exhibit vacuolization within the cytoplasm indicating sebocytic differentiation.

Main Histologic Features:

- Dermally based basaloid tumor that forms a uniformly nested or lobular pattern and does not demonstrate peripheral palisading or clefting
- On high power, cells demonstrate multivacuolated foamy cytoplasm and scalloped nuclei designating sebocytic differentiation
- May demonstrate infiltrative features including invasion into the subcutis and native structures such as nerves, vessels, and lymphatics
- Atypia, mitosis, and necrosis may be seen
- Pagetoid spread is more commonly observed in periocular tumors
- Over 60% of tumors are moderately or poorly differentiated, necessitating immunohistochemistry for definitive diagnosis
- IHC markers that may aid in diagnosis include androgen receptor (AR), adipophilin (ADP), cytokeratin-7, BerEP4, EMA
- IHC with EMA, CEA or cytokeratin-7 immunopositivity can help to distinguish SC from BCC or SCC.
- IHC profile for SC: EMA+, AR+, Ber-EP4-, and ADP+
- IHC profile for SCC: CEA-, EMA+, AR-, Ber-EP4-, and ADP-
- IHC profile for BCC: CEA-, EMA-, Ber-EP4+, and ADP-.
- The detection of AR and ADP is useful for differentiating SC from SCC, whereas the Ber-EP4 is helpful in differentiating SC from BCC.

Differential Diagnosis:

- Basal cell carcinoma
- Squamous cell carcinoma with clear cell features
- Sebaceoma

Clinical Concerns:

- The majority of sebaceous carcinoma occurs on the head and neck (periocular 26% and extraocular head and neck site 55-69%)
- Risk factors include underlying Muir-Torre Syndrome, UV damage, radiation therapy, solid organ transplantation, and AIDS
- Extraocular sebaceous carcinoma is staged by the UICC TNM staging system for skin carcinomas
- Periocular sebaceous carcinoma is staged according to the AJCC 8th edition
- There are no established imaging protocols for direct tumor extension, regional lymph nodes, or distant metastasis; clinical exam should guide imaging
- Subclinical nodal extension is rare for extraocular sebaceous carcinoma
- Ultrasound or CT can be used for clinically palpable nodes and subsequent FNA or core needle biopsy should be performed to assess for lymph node metastasis
- Consider imaging of nodal basin for periocular tumors that are stage T2c or higher, poorly differentiated, or those that exhibit pagetoid spread or PNI
- CT or PET-CT for distant metastasis should only be considered if there are confirmed nodal metastasis
- Screening for Muir-Torre Syndrome should be performed for patients with extraocular sebaceous carcinoma with Mayo MTS risk score greater than or equal to 2 or age less than 50 years old with loss of mismatch repair proteins (MSH2, MSH6, MLH1) on IHC
- Perform complete skin and nodal exam every 6 months for 3 years following diagnosis and then annually

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1. Eisen DB, Michael DJ. Sebaceous lesions and their associated syndromes: Part I. Journal of the American Academy of Dermatology. 2009;61(4):549-560.
2. Kibbi N, Worley B, Owen JL, et al. Sebaceous carcinoma: controversies and their evidence for clinical practice. *Arch Dermatol Res*. 2020;312(1):25-31.
3. McKee Pathology of the Skin 4th Ed, J. Eduardo Calonje, Thomas Brenn, Alexander Lazar, and Phillip McKee, Elsevier 2011
4. Owen JL, Kibbi N, Worley B, et al. Sebaceous carcinoma: evidence-based clinical practice guidelines. The Lancet Oncology. 2019;20(12):e699-e714.
5. Roberts ME, Riegert-Johnson DL, Thomas BC, et al. A clinical scoring system to identify patients with sebaceous neoplasms at risk for the Muir–Torre variant of Lynch syndrome. *Genet Med*. 2014;16(9):711-716
6. Schon K, Rytina E, Drummond J, et al. Evaluation of universal immunohistochemical screening of sebaceous neoplasms in a service setting. *Clin Exp Dermatol*. 2018;43(4):410-415
7. TNM Classification of Malignant Tumours 8th edition
8. Wu A, Rajak SN, Huilgol SC, James C, Selva D. Cutaneous sebaceous carcinoma. *Australas J Dermatol*. 2020;61(3)
9. Ansai S, Takeichi H, Arase S, Kawana S, Kimura T. Sebaceous carcinoma: an immunohistochemical reappraisal. Am J Dermatopathol. 2011 Aug;33(6):579-87

Question 2

A 74-year-old patient comes for Mohs surgery for a skin cancer on his right upper lip. A vertical frozen section of the debulk is shown below.

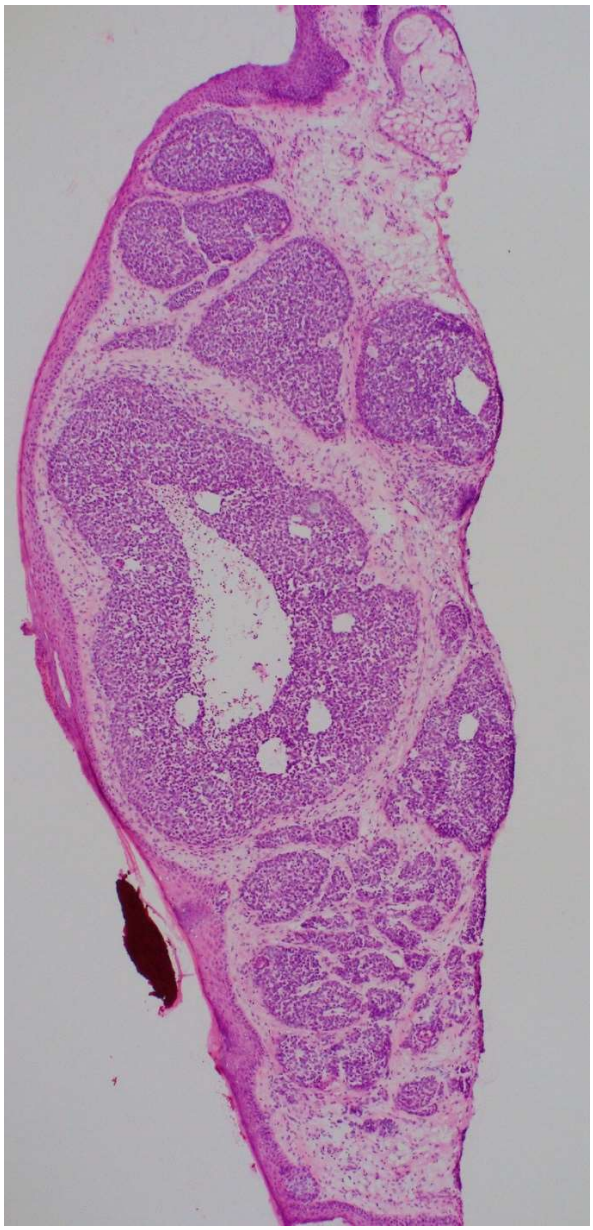
Which of the following statements below is mostly likely true?

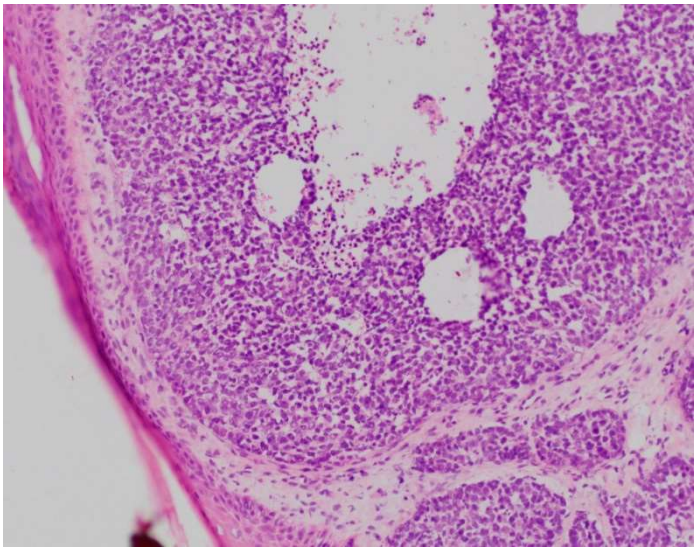
A. This is a nodular BCC; the most sensitive stain is AE1/AE3.

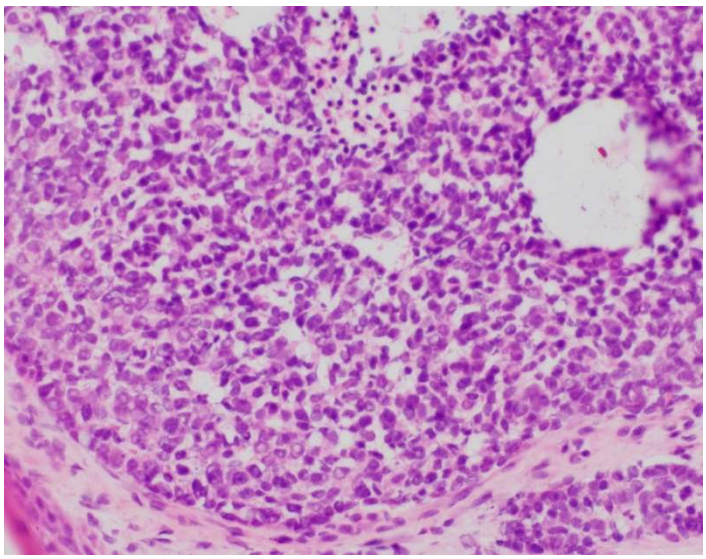
B. This is a nodular BCC; the most sensitive is BerEp4.

C. This is an MCC and will stain mostly positive for CK20.

D. This is a melanoma; this tumor will most likely stain positive for HMB-45.







Discussion

Question 2

Correct answer:

C. This is an MCC; this tumor will mostly stain positive for CK20.

Main histologic features:

- Similar histologic features of Merkel cell carcinomas (MCC) and basal cell carcinomas (BCC) that can occur: nodular growth pattern (20-40% of MCCs), basaloid appearance, mucinous stroma, stromal retraction, and focal peripheral palisading.
- Absence of widespread peripheral palisading and the unique cytologic features are the most reliable differentiators of MCCs and BCCs on hematoxylin and eosin (H&E) staining.
- Unique cytologic features of MCCs: high nuclear-to-cytoplasmic ratio, nuclear molding, a characteristic chromatin pattern (open chromatin with peripheral heterochromatin aka "salt-and-pepper" nuclear pattern)
- The immunostains neurofilament (NF) and cytokeratin 20 (CK20) display a dot-like staining pattern for MCC and are very sensitive for the tumor; most MCCs stain with Ber EP4 as well.
- The most sensitive immunostain for BCC is Ber EP4. BCCs rarely stain for CK20.
- HMB-45 is positive in melanoma and negative in MCC.

Differential diagnosis:

- Basal cell carcinoma
- Adnexal tumor
- Small cell melanoma

Clinical concerns:

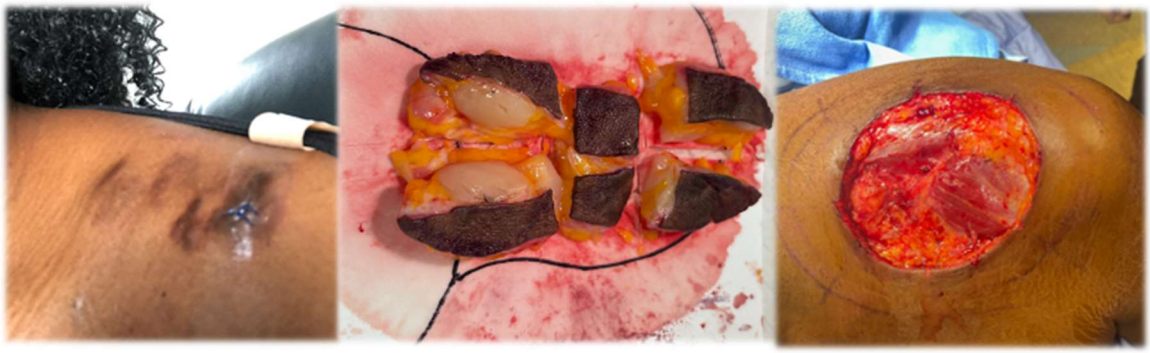
- Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine carcinoma with a high overall 5 year mortality rate of ~30%. It most commonly occurs on the head & neck and extremities (sun-exposed sites) in older patients (mean age ~70 years old) with a slight predilection for men.
- Increased mortality is associated with infiltrative histologic growth pattern and greater depth of invasion.
- Merkel cell polyoma virus is thought to play a causative role in up to 80% of MCCs.
- MCCs and BCCs can look similar clinically and histologically. Thus, MCCs are at risk of misdiagnosis as a BCC even though they have can have dramatically different treatment algorithms and prognoses.
- Large percentage of MCC can have subclinical lymph node involvement. Therefore, sentinel lymph node biopsies should be discussed and considered.
- MCC are radiosensitive tumors and adjuvant radiation therapy can be considered.
- PDL1 inhibitors are now approved for the treatment of advanced MCC.

References

1. Ball NJ, Tanhuanco-Kho G. Merkel cell carcinoma frequently shows histologic features of basal cell carcinoma: a study of 30 cases. *J Cutan Pathol.* 2007;34(8):612-619.
2. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer.* 2008;113(9):2549-2558.
3. Duncavage EJ, Zehnbauer BA, Pfeifer JD. Prevalence of Merkel cell polyomavirus in Merkel cell carcinoma. *Mod Pathol.* 2009;22(4):516-521.
4. Song HS, Kim YC. Small cell melanoma. *Ann Dermatol.* 2014;26(3):419-421.

Question 3

A 50-year-old African American woman, otherwise healthy, was referred for Mohs surgery for a multinodular cutaneous tumor on her left shoulder, which was cleared with two stages (photos show clinical presentation, gross tumor (1st layer), and final defect). Please review the section from the 1st stage (H&E stain).



The molecular pathogenesis of this tumor is mostly characterized by the following fusion gene product → resulting in:

A. COL1A1-PDGFα → generation of activated PDGFα tyrosine kinase receptor

B. COL1A1-PDGFβ → generation of activated PDGFβ tyrosine kinase receptor

C. COL1A1-PDGFα → overexpression of mature PDGFα

D. COL1A1-PDGFβ → overexpression of mature PDGFβ

Discussion

Question 3

Correct Answer:

D. COL1A1-PDGFβ → overexpression of mature PDGFβ

Main Histologic Features:

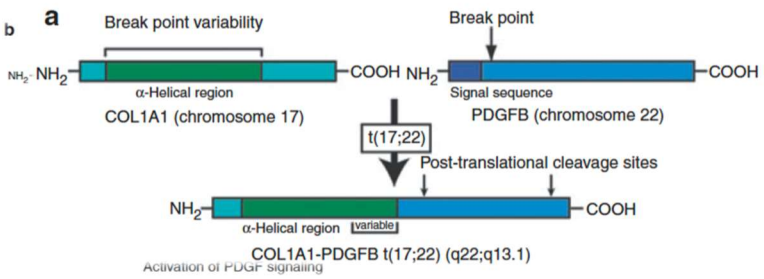
- Dermatofibrosarcoma Protuberans (DFSP) tumors are generally centered within the dermis or subcutis and characterized by spindle cells with a storiform to a whorled pattern.
- The lesion is composed almost entirely of relatively uniform spindled cells with elongated nuclei showing little or no pleomorphism and scanty pale cytoplasm.
- Tumors infiltrate and expand fibrous septa; interdigitation amongst lobules of fat yields a so-called "honeycomb" or “lace-like” pattern.
- Adnexal structures typically spared.
- Little mitotic activity, rarely abnormal in appearance (< five mitoses/10HP fields)
- The stroma may be collagenous, myxoid, or microcystic, chronic inflammatory cells occasionally present at the periphery, but necrosis is rarely a feature.
- Multiple variants exist, including those with:
    - Giant cells
    - Melanin pigmentation (Bednar tumor)
    - Myoid differentiation
    - Myxoid stroma
    - Pseudocysts change
    - So-called "sarcomatous" transformation (mimics undifferentiated pleomorphic sarcoma)
- Fibrosarcomatous transformation denotes those with cellular spindle cell fascicles or a "herringbone" pattern; there is generally greater atypia and mitotic activity; CD34 expression may be diminished/absent.
- Immunohistochemically, tumor cells are usually diffusely positive for CD34; they are negative for factor XIIIa, desmin, smooth muscle actin, S100 and keratin (AE1/AE3), and CD117 (c-kit).

Differential Diagnosis:

- Desmoplastic Melanoma (positive for S-100 protein)
- Leiomyosarcoma (positive for actin and desmin)
- Fibrous histiocytoma, especially its cellular variant (positive for CD34 and factor XIIIa)
- Dermatomyofibroma
- Plaque-like CD34-positive dermal fibroma (medallion-like dermal dendrocyte hamartoma)

Clinical Concerns:

- Locally aggressive sarcoma of intermediate malignancy with predilection for young to middle-aged adults.
- DFSP occurs on the trunk in 50–60% of patients, the proximal extremities in 20–30%, and the head and neck in 10–15%.
- Complete surgical excision (WLE or Mohs) is the standard of care.
- Virtually all cases contain fusion genes; COL1A1-PDGFB is the most common fusion product due to chromosomal translocation t(17;22)(q22;q13), although others have been reported.



(note: Figures from reference #4)

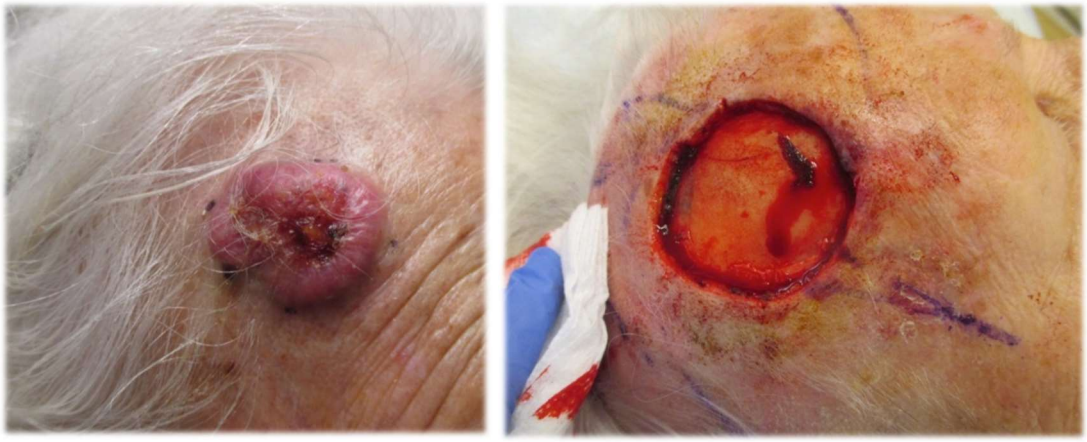
- The translocation places the platelet-derived growth factor (PDGF) β- chain gene under the control of the collagen 1A1 promoter, which drives COL1A1 and PDGFB fusion protein production. The fusion protein is then processed into functional PDGF-B and subsequently interacts with the PDGF receptor on the cell surface of DFSP tumor cells. The activation of the PDGF receptor tyrosine kinase triggers the proliferation of DFSP tumor cells.
- The PDGF receptor tyrosine kinase antagonist imatinib mesylate is FDA-approved for adults with unresectable, recurrent and/or metastatic DFSP.
- For recurrence consider re-resection with MMS or Radiation therapy or imatinib
- Metastasis is exceedingly rare, less than 0.3%
    - Metastasis usually occurs after repeated recurrences, often with fibrosarcomatous transformation (FS-DFSP).
    - Aggressive behavior appears to be related to mitotic activity, pleomorphism and necrosis.
- Tumors lacking the t(17;22) translocation may not respond to imatinib. Molecular analysis of a tumor using cytogenetics may be useful prior to the institution of imatinib therapy.
- Final Mohs layer or additional excised tissue can be sent for IHC to confirm clearance

References:

1. McKee's Pathology of the Skin. 5th Ed. Connective tissue tumors, Chapter 35. Calonje E, et al. 2020 Elsevier Limited
2. NCCN Guidelines Version 1.2020 – Dermatofibrosarcoma Protuberans. http://www.nccn.org
3. Loghdey MS, et al. Mohs micrographic surgery for dermatofibrosarcoma protuberans (DFSP): a single-centre series of 76 patients treated by frozen-section Mohs micrographic surgery with a review of the literature. *J Plast Reconstr Aesthet Surg*. 2014 Oct;67(10):1315-21
4. Anderson JL, et al. Pediatric sarcomas: translating molecular pathogenesis of disease to novel therapeutic possibilities. *Pediatr Res*. 2012 Aug;72(2):112-21. doi: 10.1038/pr.2012.54.

Question 4

A 93-year-old Caucasian woman otherwise healthy, was referred for Mohs surgery to treat an exophytic, non-mobile violaceous Well-Mod diff SCC on the R Upper Forehead (photos show clinical presentation, and final defect down to bone).



Review the section from the 1st and 2nd stage (H&E stain) which demonstrates:

A. Stage 1: linear cords of deeply invasive tumor (SCC) with PNI
   Stage 2: positive for tumor with deep invasion

B. Stage 1: linear cords of deeply invasive tumor (SCC) without PNI
   Stage 2: positive for tumor with deep invasion

C. Stage 1: linear cords of deeply invasive tumor (SCC) with PNI
   Stage 2: negative for tumor but with dystrophic calcification

D. Stage 1: linear cords of deeply invasive tumor (SCC) with PNI
   Stage 2: positive for tumor with dystrophic calcification

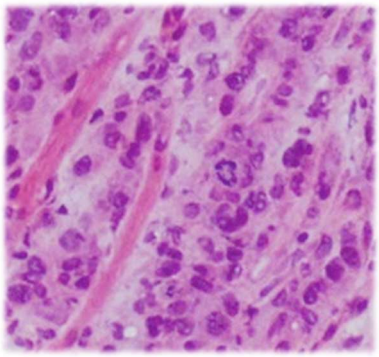
Discussion

Question 4

Correct Answer:

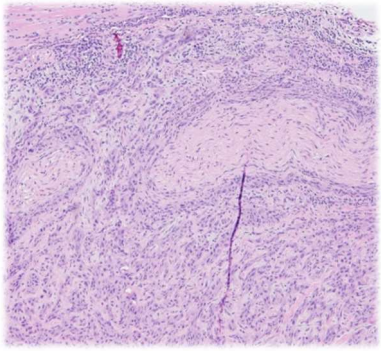
C. Stage 1: linear cords of deeply invasive tumor (SCC) with PNI
Stage 2: negative for tumor but with dystrophic calcification

Fig 1



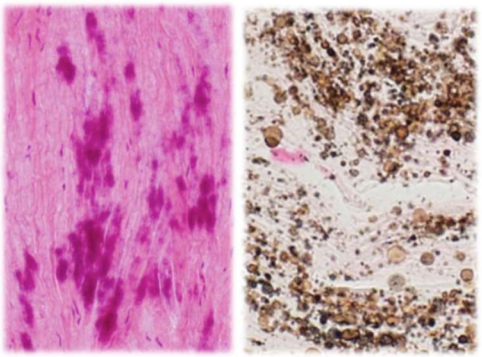
Stage 1: Linear cords of deeply invasive tumor (SCC)

Fig 2



Stage 1: Positive for perineural invasion (PNI)

Fig 3

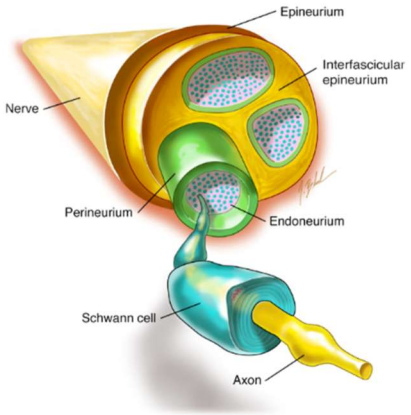


Stage 2: Dystrophic calcification on Mohs frozen sections mimicking invasive SCC confirmed with Von Kossa

Main Histologic Features:

- Perineural invasion (PNI):
  - Invasion of the nerve fiber or the presence of neoplastic cells within the perineural space, located between the perineurium and the nerve fiber
  - Perineural lymphocytes are an important clue to the likely presence of perineural invasion in deeper sections
  - Important to measure diameter of involved nerves for staging (AJCC and BWH)
- Dystrophic Calcification
  - Defined as deposition of Ca^{2+} within abnormal tissue in the absence of serum Ca^{2+} or PO_4^{3-} abnormalities
  - Typically seen within tissue injured by ischemia, trauma, or inflammation
  - Dystrophic Ca^{2+} has been reported in association with SCCs and BCCs
  - Cause unknown

Differential Diagnosis:



- Perineural invasion (PNI):
  - With PNI of SCC, malignant keratinocytes invade the any of the three nerve sheaths (perineurium, endoneurium, ad epineurium) and track along the nerve
  - Perineural fibrosis when accompanied by tumor cells can mimic microscopic PNI
  - Reparative perineural proliferation can be seen in healing surgical wounds and is characterized by concentric rings of spindle shaped cells enveloping a nerve adjacent to surgical scar
- Dystrophic Calcification
  - Ca^{2+} stains blue with hematoxylin and eosin
  - Deposits appear as homogeneous deep blue material either as small superficial deposits or as deeper globular ones

- Ca^{2+} deposits can be confirmed with Von Kossa (stains black)

Clinical Concerns:

- Perineural invasion is estimated to be seen in 6% of cutaneous SCC.
- Presence of large caliber PNI (>0.1mm) is considered an adverse risk factor in both AJCC and BWH staging systems for cutaneous SCC, and when present may warrant a discussion of adjuvant treatment options (RT) to reduce the risk of recurrence of the primary tumor.
- In this case, tumor was upstaged intraoperatively according to both the AJCC (T3) and BWH (T2b) staging systems due to size, invasion beyond fat, and the presence of perineural invasion. BWH T2b tumors carry a significant risk of nodal metastasis, and nodal staging should be considered.
- The recent 40 GEP test (DecisionDx SCC) can also help further stratify the tumor based on biological behavior
- In our case:
    - After the first 2 stages, the peripheral margins were clear, but the deep margin remained positive for tumor. The deepest galeal layer was adherent to the periosteum and revealed hematoxylin-rich cellular-appearing structures mimicking invasion and concerning for malignant cells (Fig 3).
    - This suggested possible tumor extension into the periosteal layer of the frontal bone. Mohs surgery was stopped to obtain intraop dermpath consult & recommendations.
    - Non-marginal Mohs tissue was sent for permanent sections and an ENT consult was arranged for possible outer table removal and post-operative RT given the presence of extensive PNI (Fig 2).
    - Permanent sections revealed the deep hematoxylin-rich material to be focal dystrophic calcification supported by a positive Von Kossa stain (Fig 3). IHC with AE1/AE3 and P63 were negative confirming tumor clearance.
- This case represents an example of unusual calcification mimicking tumor invasion and highlights the importance of permanent sections in helping resolve the diagnosis.

References:

1. Dunn M, Morgan M, et al. Histologic mimics of perineural invasion. *J Cutan Pathol*. 2009: 36: 937-942.
2. McKee's Pathology of the Skin. 5th Ed. Connective tissue tumors, Chapter 35. Calonje E, et al. 2020 Elsevier Limited
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4. França K, et al. Histopathologic pitfalls of Mohs micrographic surgery and a review of tumor histology. *Wien Med Wochenschr* 2018;168:18–227.
5. Wysong *et al* JAAD 2021

Question 5

A 68-year-old male returns to clinic for Mohs surgery 1 year after excision with positive margins for an infiltrative BCC on the right neck.

Review the section from the 1st stage (H&E stain). The best next step is:

A. Take a 2nd stage at the deep margin

B. Take a 2nd stage at the peripheral margin

C. Request a consult with radiation oncology for perineural invasion

D. A and C

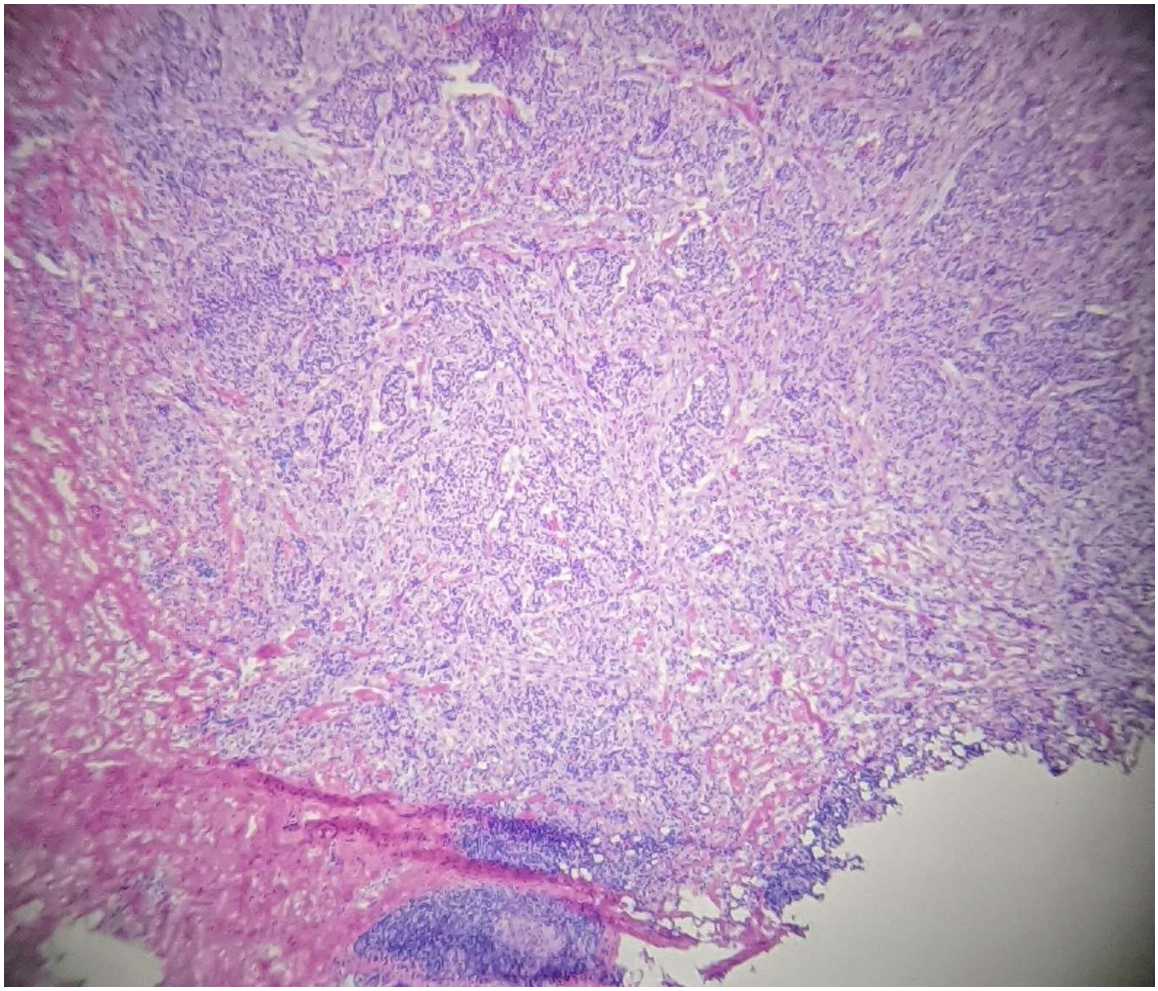
E. B and C

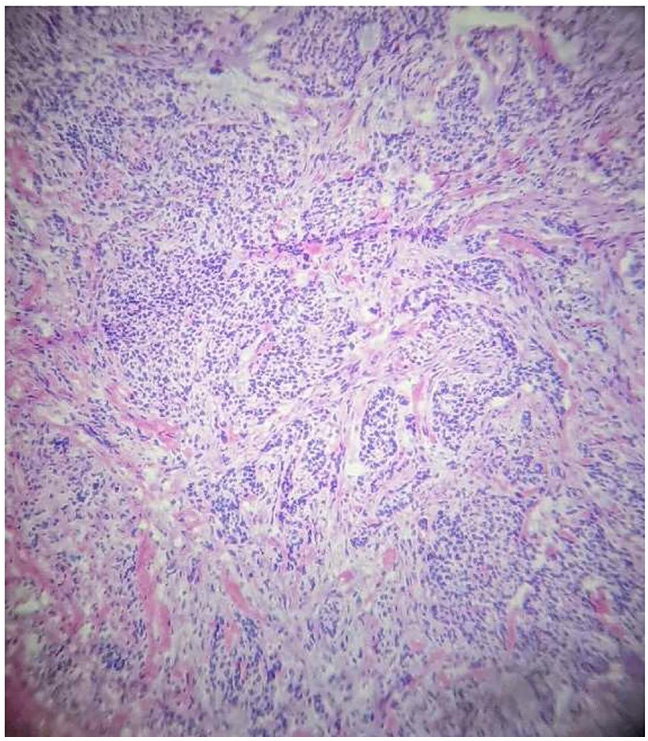
Discussion

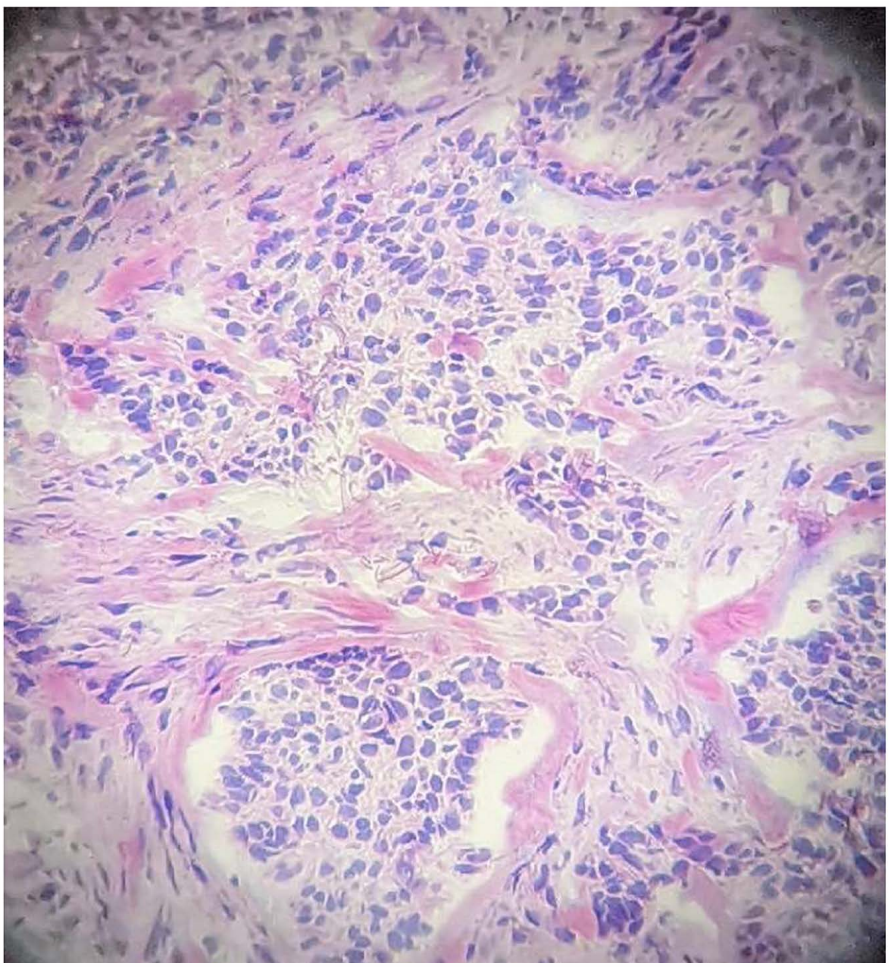
Question 5

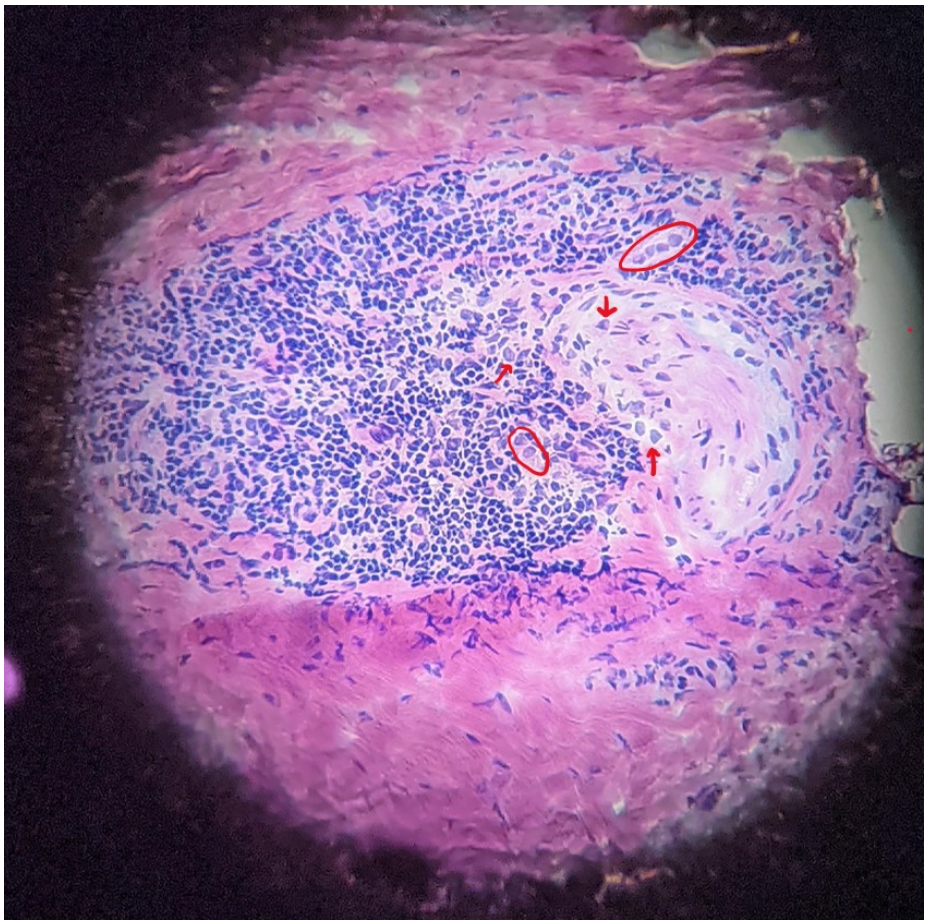
Correct Answer:

A. Take a 2nd stage at the deep margin









Main Histologic Features:

- There is infiltrative BCC within scar tissue at the deep margin
- The main histologic finding is incidental perineural invasion (arrows)

Differential Diagnosis:

- Infiltrative BCC within scar
- Morpheaform (sclerosing) BCC

Clinical Concerns:

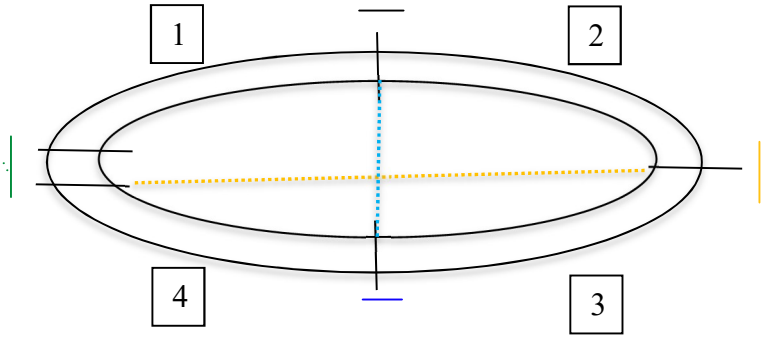
- BCC with perineural invasion is rare but can be seen in aggressive histologic variants of BCC including infiltrative BCC, morpheaform BCC, micronodular BCC, basosquamous carcinoma, and recurrent tumors.
- PNI is a risk factor for recurrence after MMS but management beyond surgery is not clearly defined.
- In the instance of incidental and limited PNI, as seen in this case, adjuvant RT is not indicated.

References:

1. McKee Pathology of the Skin 4th Ed, J. Eduardo Calonje, Thomas Breen, Alexander Lazar, and Phillip McKee, Elsevier 2011
2. Pyne JH, et al. Basal cell carcinoma with perineural invasion: a prospective study examining subtype, tumor surface diameter, invasion depth, and anatomic site in 3005 consecutive cases. J Cutan Pathol. 2020 Nov;47(11):1033-1038.
3. Collins MK, et al. Approaches to perineural, lymphovascular, and single-cell disease. Dermatol Surg. 2019 Dec;45 Suppl2:S118-S128.
4. Adams A, et al. Keratinocyte cancer with incidental perineural invasion: a registry analysis of management and 5-year outcomes. Australas J Dermatol. 2020 Aug;61(3):226-230.

Question 6

A 61-year-old patient is referred for Mohs surgery for a biopsy-proven porocarcinoma. The Mohs histotech grossed and inked the specimen (Figure 1). You review a slide that's labeled as 1st stage, 1st section. This slide demonstrates:



A. Invasive porocarcinoma

B. Basal cell carcinoma

C. Incorrect map labeling

D. A and C

E. B and C

Discussion

Question 6

Correct Answer:

E. Basal cell carcinoma and incorrect map labeling

Main Histologic Features:

- There is a rounded collection of basaloid keratinocytes arranged in a peripheral palisade within a myxoid stroma at the black hashmark
- Even though this slide is labeled as the 1st stage, 1st section, the hashmarks do not align with the map which shows that the 1st section should be inked with green at one peripheral edge and black at the other peripheral margin. Instead, this specimen shows black at one peripheral margin and yellow at the other end, corresponding to where section 2 is numbered on the map.

Differential Diagnosis:

- Nodular BCC
- Porocarcinoma

Clinical Concerns:

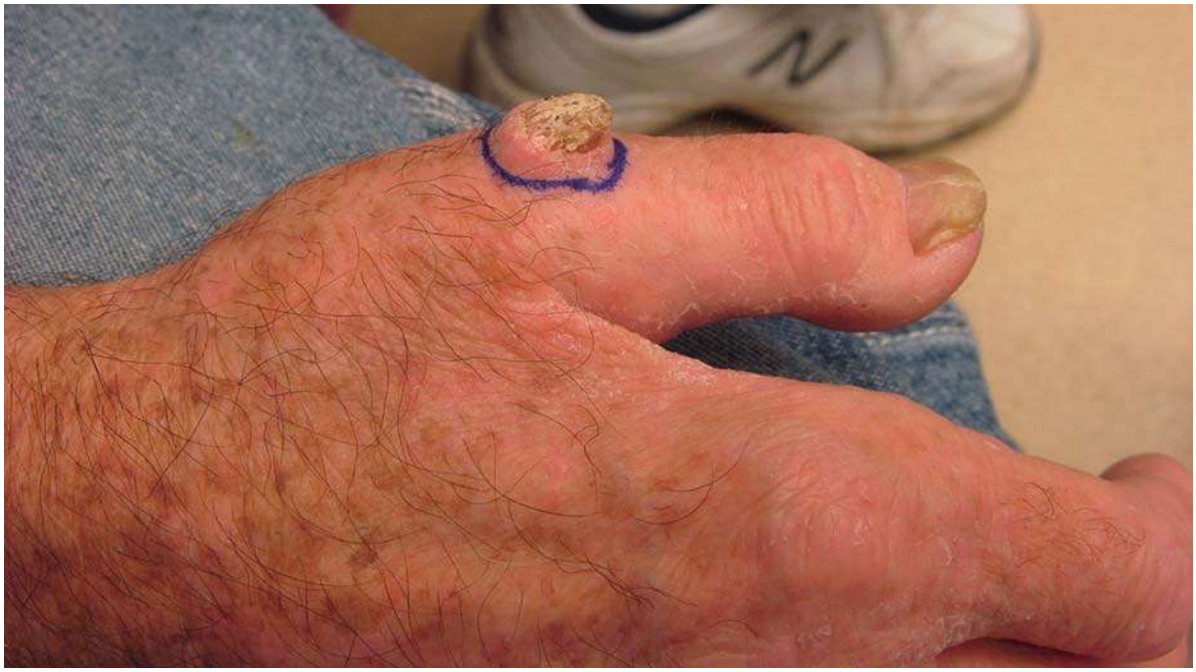
- Incidental nodular BCC should be recognized and differentiated from invasive porocarcinoma which is characterized by an infiltrative and anastomotic growth pattern, small cells with nuclear pleomorphism and conspicuous mitotic activity, ductal differentiation and/or intracytoplasmic lumen formation, and lack peripheral palisading and myxoid stroma.
- Mohs surgeons should be cognizant of discrepancies and attuned to the possibilities of Mohs laboratory errors including wrong patient/wrong slide, incorrectly labeled slides, and incorrectly labeled maps

References:

1. McKee Pathology of the Skin 4th Ed, J. Eduardo Calonje, Thomas Breen, Alexander Lazar, and Phillip McKee, Elsevier 2011

Question 7

A 60-year-old white male with history of non-melanoma skin cancer, uncontrolled diabetes mellitus type I, end-stage renal disease s/p transplantation with rejection, and rheumatoid arthritis (RA) presented for Mohs surgery for squamous cell carcinoma of the right dorsal thumb overlying the metacarpophalangeal joint which had been fractured without splinting or casting 3 months prior.



Review the section of the 1st stage of Mohs surgery, and select the best next step:

A. Stage 1 is clear; proceed to closure.

B. Stage 1 is positive for SCC in the deep margin; proceed to stage 2.

C. Submit the block to dermatopathology to evaluate for perineural/ intravascular invasion.

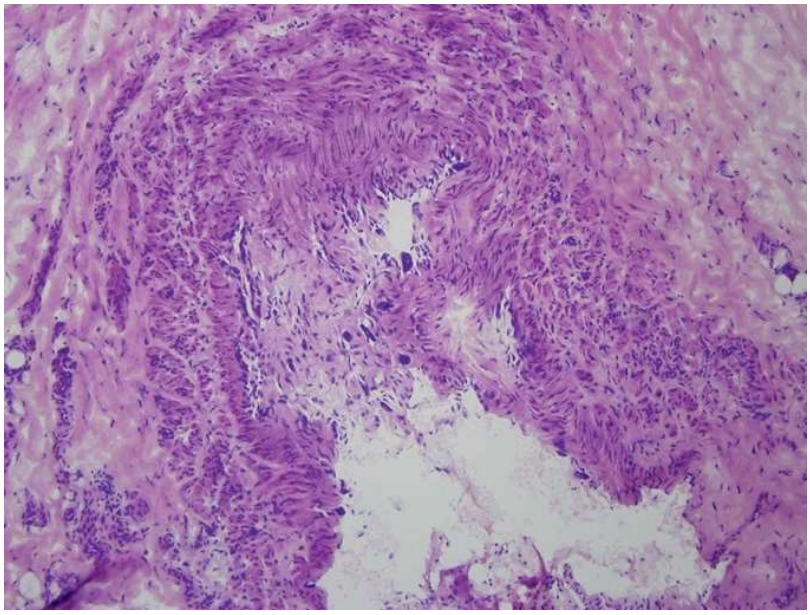
D. Request consult with radiation oncology for perineural/intravascular invasion.

Discussion

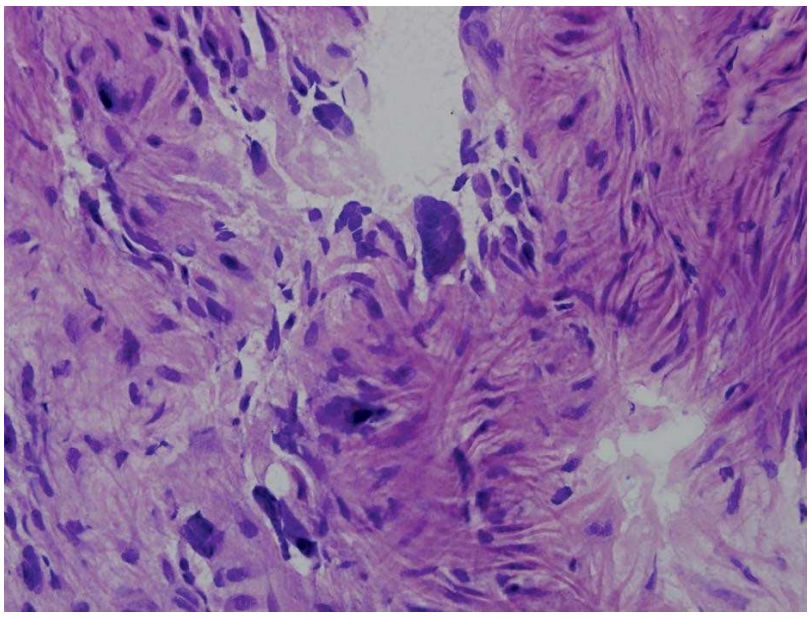
Question 7

Correct Answer:

C. Submit the block to dermatopathology for further assessment for perineural/intravascular invasion. (Intravascular epithelioid cells consistent with intravascular histiocytosis.)



Frozen section



Frozen section

Main Histologic Features:

- Large epithelioid cells within large, dilated vessels of the reticular dermis and subcutaneous fat.
- Cells not cytologically atypical, with an oval nucleus and with abundant granular eosinophilic cytoplasm.
- Multi-nucleated giant cells around and within the large vessels.

Differential Diagnosis:

- Intravascular histiocytosis (IVH)
- Reactive angioendotheliomatous (RAE)
- Intravascular lymphoma
- Cytomegalovirus (CMV)

Clinical Concerns:

- IVH is a rare benign condition.
    - Associated with RA often in proximity to involved joints
    - May be found in association with Merkel cell carcinoma and melanoma
    - May be an early form of RAE, also a rare and benign condition, which can be associated with a wide variety of systemic diseases, hematologic disorders, vascular abnormalities and infections
- Intravascular lymphoma could present with fevers, night sweats, weight loss, neurological symptoms and skin findings requiring further work up.
- CMV can cause severe even life-threatening disease in patients with immunosuppression.

References:

1. Fancher, Whitney, Longley, Jack, Wood, Gary, Swanson, Andrew. Incidental Intravascular Histiocytosis During Mohs Surgery. Dermatol Surg. 2016;42(12):1386-1388.
2. Aung PP, Ballester LY, Goldberg LJ, Bhawan J. Incidental simultaneous finding of intravascular histiocytosis and reactive angioendotheliomatosis: a case report. Am J Dermatopathol 2015;37:401–4.
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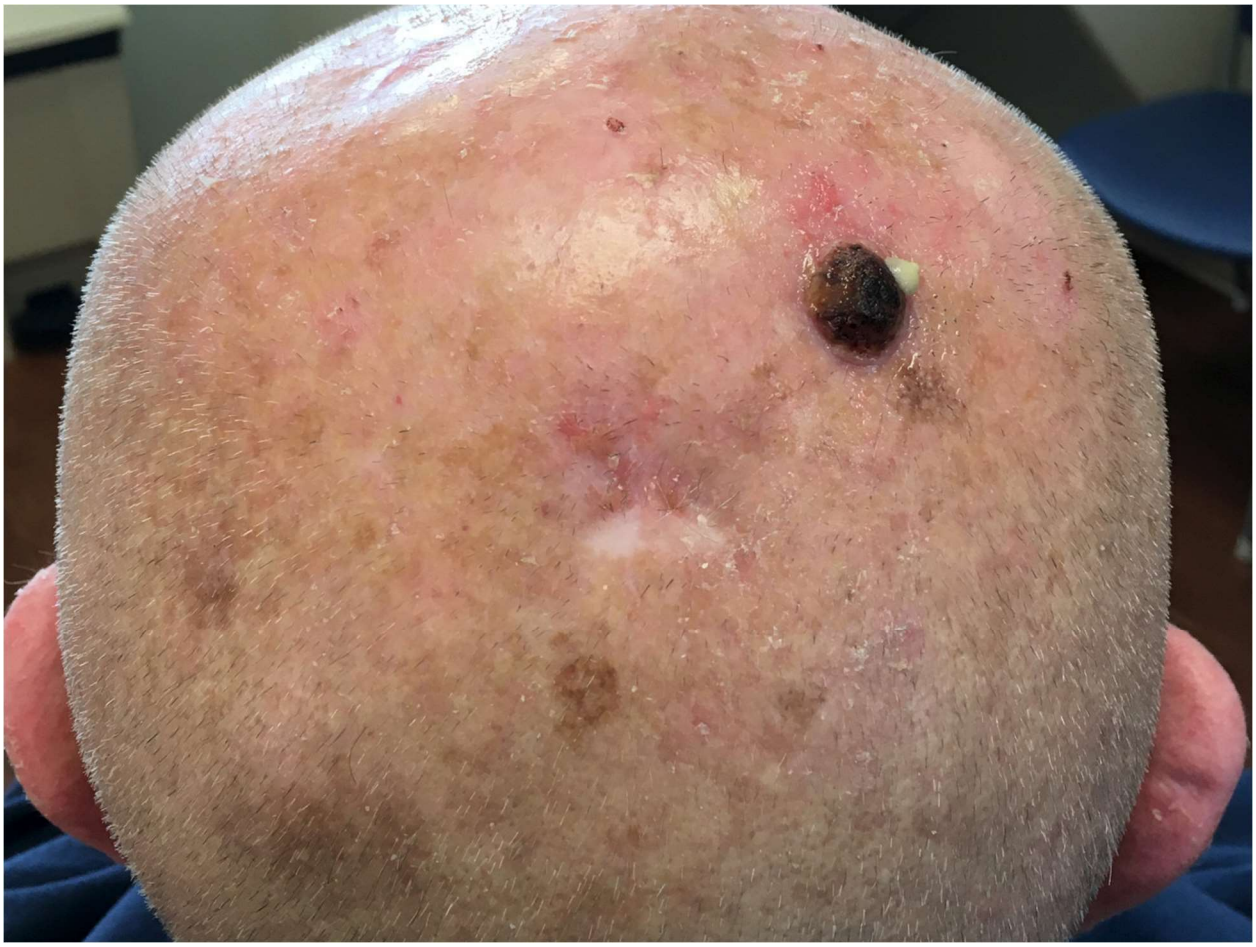
Question 8

An 83-year-old white male with history of non-melanoma skin cancer presented for Mohs surgery for squamous cell carcinoma of the right posterior scalp vertex.



Review the 1st stage Mohs section, and select the best next step:

A. Send the first stage to dermatopathology for further assessment.

B. Consider field therapy for diffuse actinic keratoses rather than proceeding with additional stages of Mohs surgery.

C. Proceed to take stage 2 for residual carcinoma/carcinoma in situ.

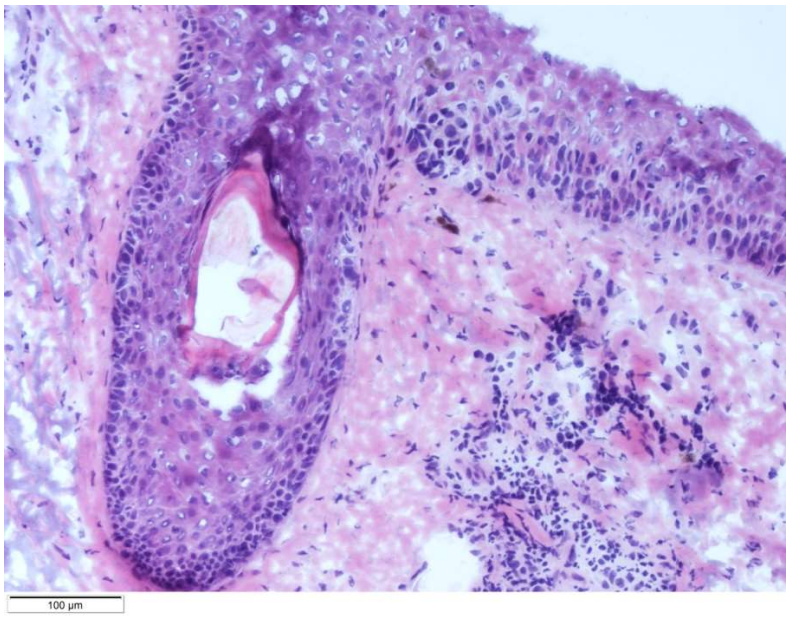
D. Proceed with most functionally and cosmetically appropriate closure.

Discussion

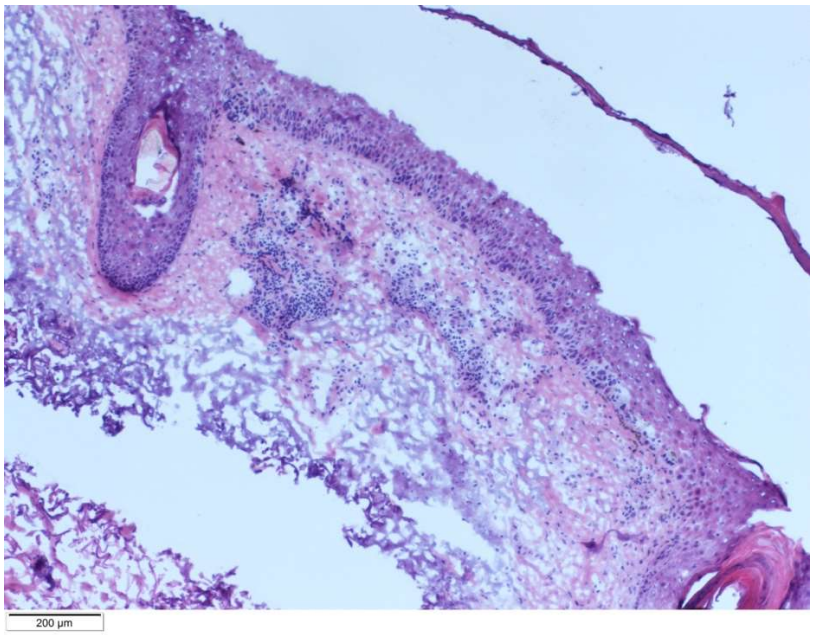
Question 8

Correct Answer:

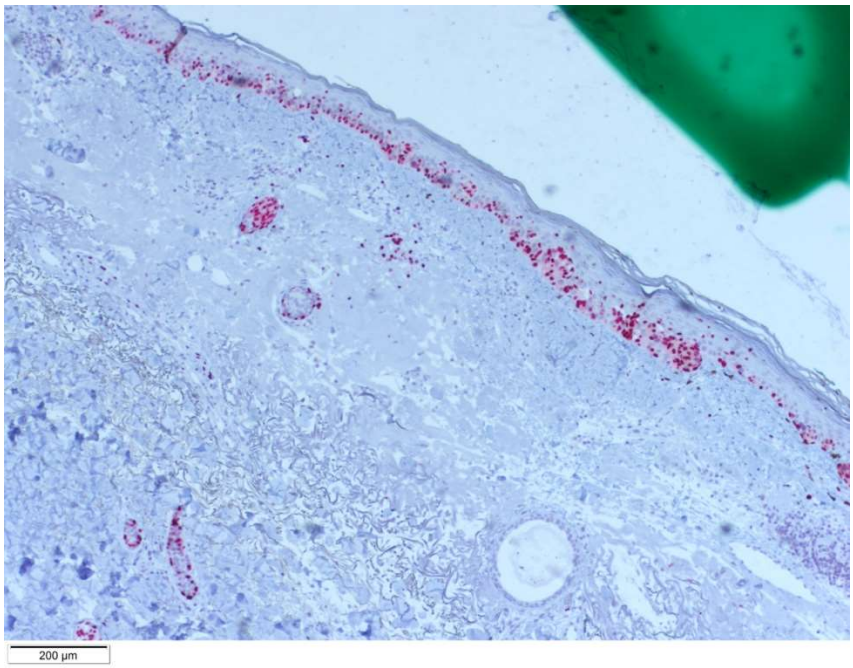
A. Send the first stage to dermatopathology for further assessment.



Frozen section



Frozen section



Permanent section with Sox10 at 4X

Main Histologic Features:

- Proliferation of atypical melanocytes present as nests and single units tending to confluence in the epidermis.
- Atypical melanocytes extending above the epidermis in a pagetoid array.
- Lymphocytic inflammation with epithelioid cells and zones of subtle superficial fibrosis in the dermis.
- These findings are confirmed on permanent sections with Sox10, and Breslow depth is measured at 0.4 mm.

Differential Diagnosis:

- Melanoma in situ
- Invasive melanoma
- Solar melanocytic hyperplasia
- Solar lentigines
- Melanocytic hyperplasia secondary to previous biopsy
- Bowenoid squamous cell carcinoma in situ
- Bowenoid actinic keratoses
- Actinic damage

Clinical Concerns:

- On chronically sun-damaged skin it can be difficult to discern early melanoma from normal sun-damaged skin.
- Intraepidermal pagetoid spread of atypical cells on standard frozen section histology can be seen with melanoma, non-melanoma skin cancers and precancerous lesions exacerbated by the tangential cuts of Mohs surgery.
- Appropriate removal or biopsy of lesions suspicious for melanoma is necessary for staging and to recommend the appropriate treatment. Special consideration is needed if incidentally encountered during Mohs surgery for a different primary skin cancer.
- If diagnosis and staging of melanoma found incidentally as part of surgery for a different primary skin cancer is delayed or neglected, immediate flap closure at the site can lead to false negative sentinel lymph node biopsy in the future.

- Use of dermoscopy before Mohs for non-melanoma skin cancer can be effective and may provide additional benefits on chronically sun damaged skin with pigmented lesions in the field, facilitating identification of pigmented lesions needing biopsy and avoiding pitfalls of recognition on standard frozen sections.
- Though in experienced centers diagnosis and thickness of melanoma can be established on frozen section, there are pitfalls especially with regressing melanomas. It is recommended that this approach be performed only in centers processing a large number of these cases.

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1. Hendi A, Brodland DG, Zitelli JA. Melanocytes in Long-standing Sun-Exposed Skin: Quantitative Analysis Using the MART-1 Immunostain. *Arch Dermatol.* 2006;142(7):871–876.
2. Satter EK, Metcalf J, Lountzis N, Elston DM. Tumors composed of malignant epithelial and melanocytic populations: a case series and review of the literature. J Cutan Pathol 2009;36:211–9.
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Question 9

A 73-year-old female presents for Mohs micrographic surgery for an incompletely excised invasive squamous cell carcinoma on the back. The pathology report notes the tumor is poorly differentiated with perineural invasion. A standard Mohs layer with a 5mm margin around the prior linear repair is performed.

Review the section from the 1st stage (H&E stain), and select the most likely diagnosis and best next step:

A. Positive for invasive squamous cell carcinoma; take another layer.

B. Positive for perineural squamous cell carcinoma; take another layer.

C. Apparently negative for tumor; perform AE1/ AE3 cytokeratin immunostain in addition to hematoxylin-eosin stain to confirm due to concern for inflammation masking tumor.

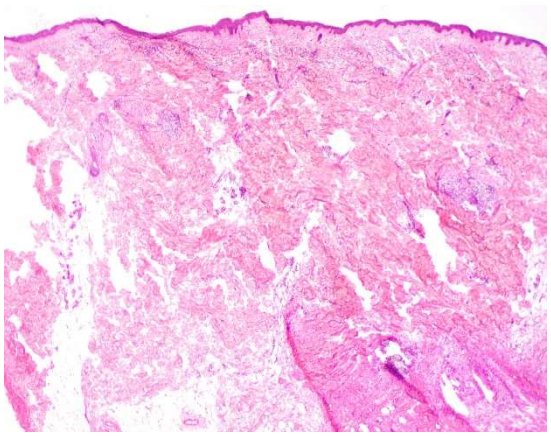
D. Apparently negative for tumor; excise additional margin and send for permanent sections due to concern for inflammation masking tumor.

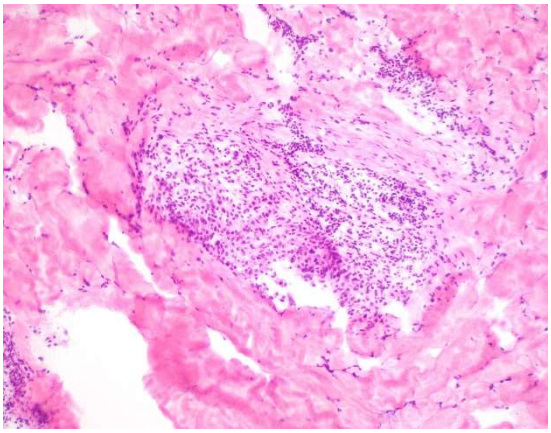
Discussion

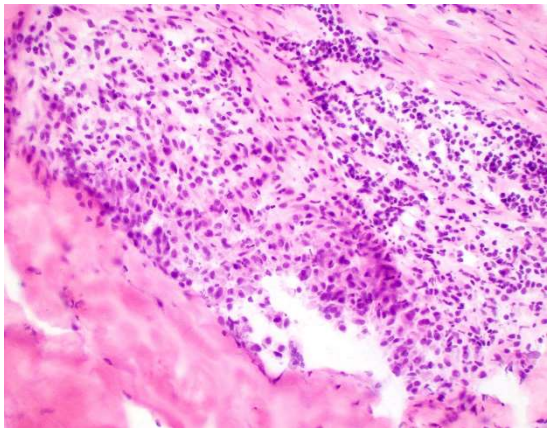
Question 9

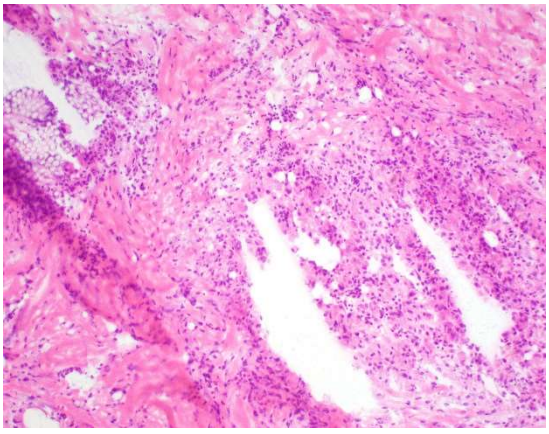
Correct Answer:

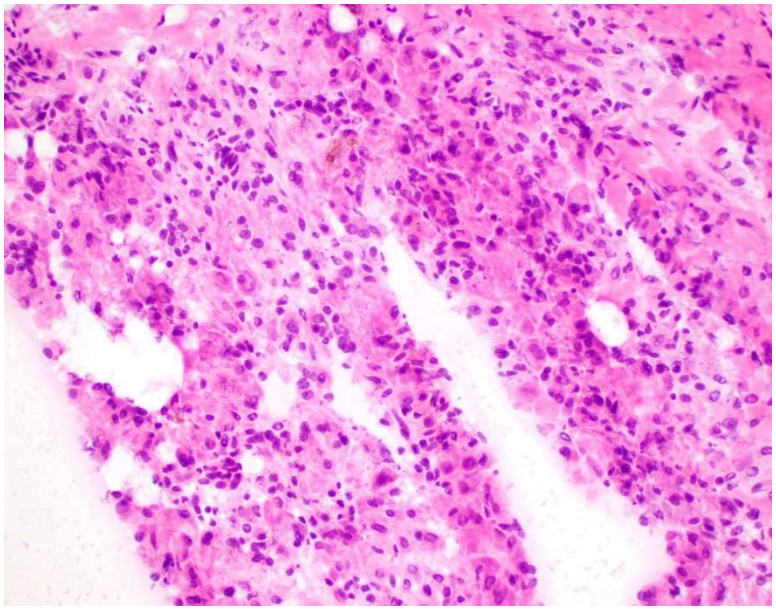
C. Apparently negative for tumor; perform AE1/ AE3 cytokeratin immunostain in addition to hematoxylin-eosin stain to confirm due to concern for inflammation masking tumor.











Main Histologic Features:

- Granulomatous response with histiocytes and giant cells around foreign material.
- Giant cells are of foreign-body type in which the nuclei are in haphazard array.
- No definitive evidence of either invasive or perineural squamous cell carcinoma.

Differential Diagnosis:

- Foreign body granulomatous inflammatory response
- Foreign body granulomatous response and squamous cell carcinoma

Clinical Concerns:

- An inflammatory response is commonly present in histologic sections of cutaneous neoplasms.
    - May be a host response to the tumor.
        - Can aid in the identification of subtle infiltrative or perineural tumor.
    - May be secondary to unrelated factor (e.g. ulceration, infection, foreign material or CLL).
        - Can make slide interpretation more challenging.
- There is clinical concern by many surgeons that dense inflammation present in H&E stained Mohs sections can mask underlying tumor.
    - May lead to both false negative and false positive interpretation.
        - Recurrences
        - Unnecessary additional surgery
- Currently available data on the topic is limited and mixed.
    - Cumulative data suggests dense inflammation may obscure SCC present at margins of Mohs sections leading to higher local recurrence rates if not excised.
    - There are no consensus guidelines for how to manage these cases.
        - How to proceed made on case by case basis depending on: tumor type, characteristics and location, the type and extent of inflammation and surgeon experience.
        - Options include: stopping surgery, cutting further into the block, taking an additional stage, performing cytokeratin immunostains in addition to H&E and sending tissue out for permanent sections.
        - In the absence of visible tumor, removal of additional tissue to clear inflammation may unnecessarily result in increased expense and patient morbidity.
        - Use of IHC in addition to H&E staining enhances margin interpretation and control when dense inflammation is encountered and may prevent unnecessary surgery.
            - Data supports higher sensitivity and lower local recurrence rates for high risk SCC evaluated with both H&E and AE1/AE3 cytokeratin immunostains than tumors evaluated by H&E alone.
            - Negative in this case.

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1. Aizman L, Miller CJ, Perez AM, Lukowiak TM, Cohen OG, Bean E, Hitchner MK, Etzkorn JR, Shin TM, Higgins II HW, Giordano CN, Cohen JV, Miura JT, Sobanko JF. Low Recurrence rates for challenging squamous cell carcinomas using Mohs micrographic surgery with AE1AE3 cytokeratin immunostaining. *J Am Acad Dermatol* (2020), doi: https://doi.org/10.1016/j.jaad.2020.06.1012.
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5. Lee KC, Higgins HW II, Dufresne RG Jr. Tumor recurrence after Mohs micrographic surgery. *J Am Acad Dermatol* 2014;70:385-6.

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Question 10

A 76-year-old female underwent Mohs micrographic surgery with MART-1 immunostain for a melanoma in situ of the left superior cheek.

Review slides from the 3rd stage (H&E and MART-1 immunostain), and select the most likely diagnosis and most appropriate next step:

A. Positive for melanoma in situ; take another Mohs layer.

B. Positive for invasive melanoma; take another Mohs layer.

C. Positive for melanoma in situ with underlying invasive melanoma; take another Mohs layer.

D. Positive for invasive melanoma; excise an additional margin for paraffin sections, delay closure.

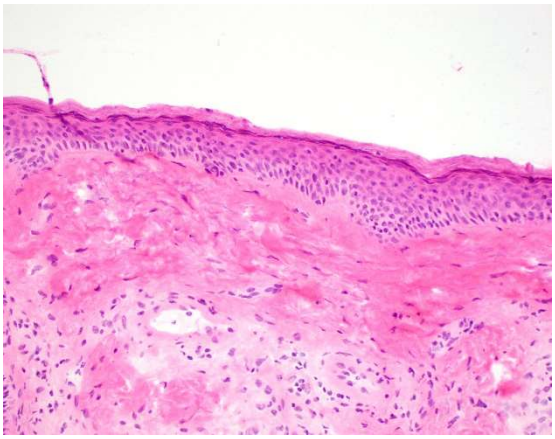
E. Negative for tumor; perform closure.

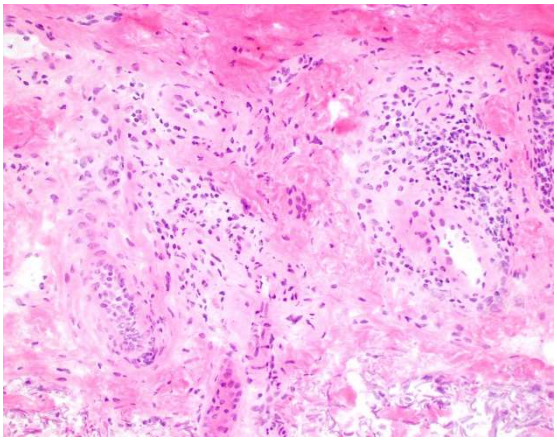
Discussion

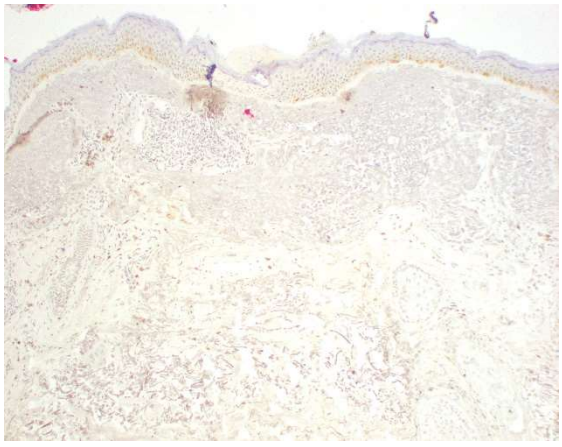
Question 10

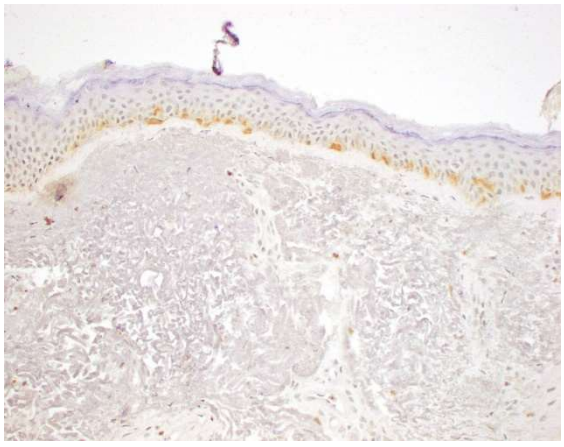
Correct Answer:

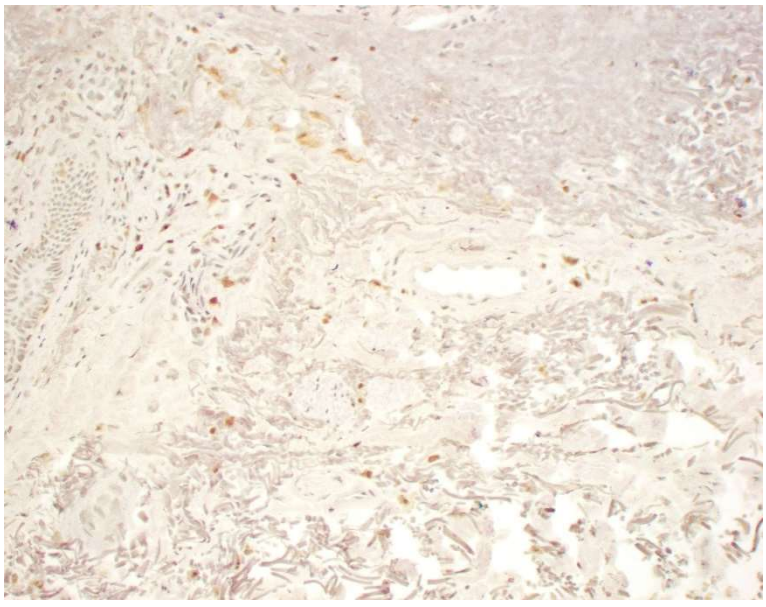
E. Negative for tumor; perform closure.











Main Histologic Features:

- The slide stained with MART-1 depicts normal to slightly increased melanocyte density and distribution in the basal layer of the epidermis.
- Evenly distributed within the dermis are larger hyperchromatic cells that stain strongly for MART-1.
- Although these cells stain for MART-1, a melanocytic derivation and therefore invasive melanoma is unlikely for the following reasons:
    - The cells are dispersed evenly without nesting and in the corresponding hemotoxylin and eosin-stained sections their cytologic features are bland.
    - Superficial invasion is typically seen beneath confluent junctional nests with a host response and these features are not present.
    - In contrast to melanocytes, cells staining in dermis are smudgy with indistinct nuclear outline.

Differential Diagnosis:

- Invasive melanoma: Asymmetrical proliferation of nested/sheets of melanocytes with poorly demarcated border.
- Dermal melanocytic nevus: Symmetric proliferation of nested melanocytes demonstrating maturation and well demarcated border.
- Non-specific non-melanocytic MART-1 staining cells.

Clinical Concerns:

- Melanocyte Antigen Recognized by T-Cells (MART-1) is very sensitive for melanocytes with minimal background staining; however, scattered nonspecific MART-1 staining patterns may be seen in the dermis in about half of cases.
- Three patterns recognized:
    - Inflammatory pattern
    - Follicular pattern
    - Dendritic pattern
- Etiology unclear but felt to represent nonmelanocytic inflammatory cells or cells damaged by an inflammatory process.
- More likely present in slides with increased background chromogen coloration and adjacent to torn edges of tissue.
- It is important to distinguish normal MART-1 staining patterns to prevent “over-calling” and taking additional tissue, which can lead to increased cost and patient morbidity.

References:

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