Question 1

This Mohs section (Slide 1) is from the first stage excision of a tumor on the helix of an 80-year-old man. Frozen section biopsy of the lesion prior to Mohs (Slide 2) is also submitted for your information.

Which of the following is the best answer?

A. There is residual pilomatrix carcinoma.

B. There is residual pilomatricoma.

C. There is residual basal cell carcinoma.

D. There is residual sebaceous carcinoma.

Discussion

Question 1

Correct Answer:

A. There is residual pilomatrix carcinoma.

Main Histologic Features:

- Pilomatrix carcinoma is typically composed of irregularly shaped, infiltrative proliferations of large anaplastic, hyperchromatic basaloid cells with prominent nucleoli, nuclear pleomorphism, and numerous mitoses.
- Toward the center of the tumor, there may be transformation of basophilic cells into eosinophilic shadow cells (ghost cells), or large cystic centers containing necrotic debris.
- Both the clinical and histological distinctions between benign and malignant pilomatricoma are challenging given their overlapping features. There are some clues to differentiate pilomatrix carcinoma from benign pilomatricoma: asymmetry, poor circumscription, atypical basaloid cells, extensive areas of necrosis, infiltrative growth pattern and presence of ulceration.

Differential Diagnosis:

- Pilomatricoma
- Proliferating pilomatricoma
- Basal cell carcinoma with matrical differentiation
- Clear cell porocarcinoma

Clinical Concerns:

- Pilomatrix carcinoma commonly presents as an asymptomatic, firm, mobile, slow-growing, dermal or subcutaneous mass, ranging from 0.5 to 14.5 cm. It may have overlying bluish hue and/or ulceration. It can occur anywhere on the body but the majority of the lesions occur in the head and neck region (~ 60%). It usually affects middle-aged adults, with male predominance. Clinically it is often mistaken for other cutaneous neoplasms and epidermoid cyst.
- It is unknown whether pilomatrix carcinoma arises de novo or through malignant transformation of a pre-existing pilomatricoma. The majority of the cases have no prior history of pilomatricoma. Activating mutations of Wnt signaling pathway have been found in both benign and malignant pilomatricoma.
- Most studies recommend wide local excision with margins ranging from 4 to 30 mm. Mohs micrographic surgery has been used in several cases.
- The recurrence rate is fairly high (50-60%) in the lesions treated with simple excision, even when histological margins are clear. Reported rate for distant metastases is about 10%, usually to the lung and regional lymph nodes and rarely to bones and viscera.

References:

1. Lever's Histopathology of the skin. 11th Ed. Edited by Elder DE, 2014; Wolters Kluwer.
2. Jones C et al. Pilomatrix carcinoma: 12-year experience and review of the literature. J Cutan Pathol. 2018 Jan;45(1):33-38.
3. Papadakis M, et al. Pilomatrix carcinoma: More malignant biological behavior than was considered in the past. Mol Clin Oncol. 2017 Mar;6(3):415-418Discussion

Question 2

A 50-year-old renal transplant patient presents for Mohs surgery for a poorly differentiated SCC presenting as a friable ulcerated tumor on the distal shin. There are two new papules noted distally and frozen section biopsies are taken for your review. FYI the original permanent section biopsy from the larger tumor demonstrates similar features (slide not shown).

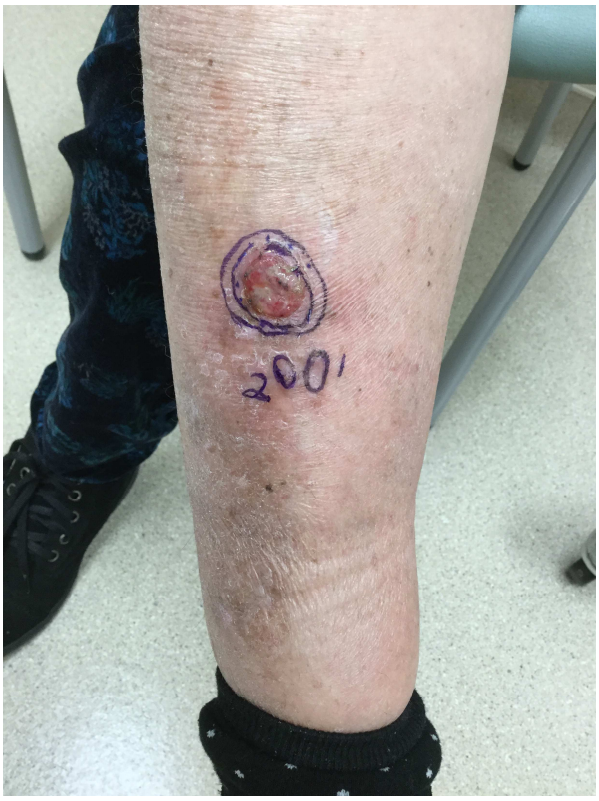
Please select the best possible answer from the following statements:

A. Biopsy shows poorly differentiated SCC indicating two primary cancers. Proceed to Mohs to obtain clear margins.

B. Biopsy shows poorly differentiated SCC, indicating satellite/in-transit metastases. Discuss sentinel lymph node biopsy and post-op radiation therapy with the patient. Proceed to Mohs to obtain clear margins or coordinate with surgical oncology for wide local excision and possible SLNB.

C. Biopsy shows malignant neoplasm but definitive diagnosis needs to be investigated.

D. None of the above.



Discussion

Question 2

Correct answer:

B. Biopsy shows poorly differentiated SCC, indicating satellite/in-transit metastases. Discuss sentinel lymph node biopsy and post-op radiation therapy with the patient. Proceed to Mohs to obtain clear margins or coordinate with surgical oncology for wide local excision and possible SLNB.

Main Histopathologic Features:

- Cutaneous SCC with satellite or in-transit metastasis is a diagnosis made on the clinicopathological correlation.
- The proposed diagnostic criteria (clinical and histological criteria) for in-transit metastasis of SCC are best illustrated by Ma JH et al (Dermatol Surg 2016; 42:1285-1292)

TABLE 3. Diagnostic Criteria for In-Transit Squamous Cell Carcinoma

Clinical criteria
Metastasis should lie separate from scars of previous treatment (excluding donor site for flaps)
Metastasis should lie between the initial tumor and possible draining lymph nodes
Histological criteria
Deposit should lie separate from scars of previous treatment (excluding flaps)
Deposit should not have epidermal origin
Tumor should not be present exclusively in perineural locations
Metastasis should bear at least focal histological similarity to initial tumor

Differential Diagnosis:

- Satellite/in-transit metastases of cutaneous SCC vs. separate lesions of SCC

Clinical Concerns:

- Satellite and in-transit metastasis from cutaneous SCC is an uncommon form of lymphatic metastasis that tends to occur more in immunocompromised individuals.
- There is a paucity of studies on this topic. The definition of satellite and in-transit metastasis, as defined in malignant melanoma, refers to clinically evident cutaneous and/or subcutaneous metastases occurring within 2 cm (satellite) or greater than 2 cm from the primary SCC, in the region between the primary and the first echelon of regional lymph nodes. Occasionally, satellite or in-transit metastases may occur distal to the primary tumor.
- Prognosis is poor with 5-year survival of approximately 13%. Management is a combination of surgery and adjuvant radiotherapy. For selected cases with unresectable tumor not amenable to radiotherapy and those with distant metastases, chemotherapy agents, targeted therapy inhibiting epidermal growth factor receptor, and anti-PD-1 immunotherapy are used off-label.

References:

1. Ma JH et al. In-transit metastasis from squamous cell carcinoma. Dermatol Surg 2016; 42:1285-1292.
2. Carucci JA et al. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics management, and outcome in a series of 21 patients. Dermatol Surg 2004;30:651-655.
3. Gershenwald JE et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Nov;67(6):472-492.
4. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Management of advanced and high-stage tumors. J Am Acad Dermatol. 2018 Feb;78(2):249-261.

Question 3

A 77-year-old male with a history of 8 squamous cell carcinomas (SCCs) of the lower extremities (LE) arising within the past 2 years presents with a 1.5cm pink plaque on the right pretibial region that has developed over the past 4 months.

The lesion is biopsied and processed in the Mohs lab as a vertically-cut frozen section.

Select the most likely diagnosis and best course of action:

A. Inflamed Seborrheic Keratosis; Clinical observation.

B. Regressing Keratoacanthoma (KA); Clinical observation.

C. Well-Differentiated SCC; Proceed with Mohs micrographic surgery (MMS).

D. Poorly-Differentiated Infundibulocystic SCC; Proceed with MMS.

Discussion

Question 3

Correct Answer:

C. Well-Differentiated SCC; Proceed with Mohs micrographic surgery (MMS).

Main Histologic Features:

- An endophytic proliferation with islands of atypical, well-differentiated squamous cells that extend into the dermis is visualized. These features may be representative of a conventional, well-differentiated, SCC, or an early proliferative keratoacanthoma.

Differential Diagnosis:

- Early proliferative Keratoacanthoma
- Infundibular SCC
- Crateriform Verruca
- Inflamed Seborrheic Keratosis

Clinical/Histologic Concerns:

- Cutaneous SCCs of the LE are likely to represent a distinct subset of SCC, with unique histologic features and implications for management.
- These tumors are more likely to develop on the anterior versus posterior aspect of the leg and appear to behave relatively indolently as compared to the general population of SCC.
- Patients developing disproportionate numbers of SCC on the LE are most often female, and develop a ratio of SCCs:BCCs similar to that seen in immune-suppressed organ transplant recipients.
- Some authors have recently reclassified endo and exophytic tumors into distinct histologic subtypes: KA, KA with conventional SCC component, crateriform Bowen's disease, crateriform SCC arising from solar keratosis, and crater form of infundibular SCC.
- As the regression rate of KA-like SCC (33.3%) is significantly lower than that of classical KA (98.1%), differentiating these tumors is clinically relevant.
- Although a conservative approach may be selected in certain settings, surgical resection remains standard of care for KA as these tumors are biologically unstable and occasionally evolve into conventional SCC.
- Genetic and molecular analysis may ultimately elucidate the observed behavioral differences among conventional SCC, SCC of the LE, and KA.

References:

1. Takai T, Misago N, Murata Y. Natural course of keratoacanthoma and related lesions after partial biopsy: Clinical analysis of 66 lesions. Jounral of Dermatology 2015;42:353-62.
2. Ogita A, Ansai S, Misago N, et al. Histopathological diagnosis of epithelial crateriform tumors: Keratoacanthoma and other epithelial crateriform tumors. Journal of Dermatology 2016;43:1321-31.
3. Munday WR, Leffell DJ, McNiff JM, Ko CJ. Histopathologic features of multiple cutaneous squamous cell carcinomas of the lower extremity. J Cutan Pathol 2016:43:759-65.

4. Solus JF, Murphy GF, Kraft S. Cutaneous Squamous Cell Carcinomas of the Lower Extremities Show Distinct Clinical and Pathologic Features. International Journal of Surgical Pathology. 2016;24(1):29-36.
5. Kim C, Ko CJ, Leffell DJ. Cutaneous squamous cell carcinomas of the lower extremity: A distinct subset of squamous cell carcinomas. J Am Acad Dermatol 2014;70:70-4.
6. Goldberg LH, Silapunt S, Beyrau KK, Peterson SR, et al. Kertoacanthoma as a postoperative complication of skin cancer excision. J Am Acad Dermatol 2004;50:753-8.
7. Ko CJ, Glusac EJ, McNiff JM, Rodic N, Leffell DJ. Squamous proliferations on the legs of women: Qualitative examination of histopathology, TP53 sequencing, and implications for diagnosis in a series of 30 cases. J Am Acad Dermatol 2017;77:1126-32.

Question 4

A 74-year-old female with a history of 6 SCCs of the LE over the past year presents with a 1.5cm SCC on the right LE.

The first stage of MMS is observed here.

Select the most likely diagnosis and best course of action:

A. No remaining tumor is visualized; Evaluate wound for management.

B. There is a focus of epidermal and superficial dermal squamous atypia; Take another layer.

C. Invasive SCC is present in the deep subcutis; Take another layer.

D. Specimen is inadequate; Request recuts from the histotechnician.

Discussion

Question 4

Correct Answer:

B. There is a focus of epidermal and superficial dermal squamous atypia; Take another layer.

Main Histologic Features:

- Quality Assurance:
  - Epidermis is present around entire section and deep-tissue is well-preserved without significant holes.
  - Staining is adequate.
- Oncologic Analysis:
  - Residual SCCIS is visualized opposite from blue-inked hash mark.
  - Features differentiating SCCIS from background stasis dermatitis and scattered seborrheic keratosis include well-differentiated cellular atypia, keratin pearls with concentric parakeratosis, and loss of granular layer.

Differential Diagnosis:

- No remaining tumor is visualized.

Clinical/Histologic Concerns:

- Histologic features of SCC arising on the LE are unique and may be difficult to differentiate from benign findings, particularly on frozen sections.
- While analysis of the Mohs debulk specimen in these tumors most commonly reveals classical features of well-differentiated SCC (95% of reported cases), margins are often obscured by chronic inflammation, fibrosis, and stasis changes (85% of cases).
- Peripheral margins of SCC arising on the LE are less likely to reveal actinic keratosis (13% of cases) as compared with SCC arising in the head/neck region (67% of cases), with a unique basal retiform proliferation observed in 80% of LE SCCs.
- Basal retiform proliferations are comprised of thin and elongated rete ridges and slightly enlarged keratinocytes with atypical nuclei, and appear to have a unique immunohistochemical profile as compared with actinic keratosis.
- Differentiating the benign histologic findings of commonly-encountered entities such as seborrheic keratosis and pseudoepitheliomatous hyperplasia, among others, from those of SCC arising on the LE may be surprisingly challenging, requiring a pragmatic approach incorporating judgment of clinical as well as histologic findings.

References:

1. Takai T, Misago N, Murata Y. Natural course of keratoacanthoma and related lesions after partial biopsy: Clinical analysis of 66 lesions. Journal of Dermatology 2015;42:353-62.
2. Ogita A, Ansai S, Misago N, et al. Histopathological diagnosis of epithelial crateriform tumors: Keratoacanthoma and other epithelial crateriform tumors. Journal of Dermatology 2016;43:1321-31.

3. Munday WR, Leffell DJ, McNiff JM, Ko CJ. Histopathologic features of multiple cutaneous squamous cell carcinomas of the lower extremity. J Cutan Pathol 2016:43:759-65.
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7. Ko CJ, Glusac EJ, McNiff JM, Rodic N, Leffell DJ. Squamous proliferations on the legs of women: Qualitative examination of histopathology, TP53 sequencing, and implications for diagnosis in a series of 30 cases. J Am Acad Dermatol 2017;77:1126-32.

Question 5

A 73-year-old Caucasian gentleman received Mohs surgery treatment of a micronodular basal cell carcinoma on the right temple.

Please review the 1st stage Mohs section and select the best next step:

A. Take another stage to clear the deep tumor.

B. Take another stage to clear the lateral margins.

C. The 1st stage is clear, proceed with reconstruction.

D. Order a recut slide for further evaluation.

E. Thaw the block and send for permanent sections with pathology review.

Discussion

Question 5

Correct Answer:

C. The 1st stage is clear, proceed with reconstruction (Favre-Racouchot)

Main Histologic Features of Favre-Racouchot:

- This slide includes the benign findings of Favre-Racouchot syndrome (nodular cutaneous elastosis with cysts and comedones) [1, 2].
- This condition is noted to have marked solar elastosis with numerous cysts and comedones.
- Cavity walls include 4-8 layers of cells of benign basal, spinous, granular and cornified layers without nuclear atypia nor parakeratosis.
- The cysts and comedones include multiple vellus hair shafts.

Histologic Differential Diagnosis:

- Microcystic adnexal carcinoma: Malignant tumor of follicular and eccrine origin composed of keratin-filled cysts and aggregates of basaloid cells in slender cords deeply infiltrating the dermis[3, 4]. Locally aggressive, deeply infiltrating, invading nerves, and rarely metastasizes.
- Syringoma: Benign tumors of eccrine origin composed of small, superficial dermal ducts with two layers of cuboidal epithelium and strands of cells among a dense stroma. The pattern has been described as “comma or tadpole-like”[4, 5]. Most frequently periorbital.
- Desmoplastic trichoepithelioma: Benign tumors of follicular origin composed of superficial, narrow strands of basaloid cells, keratin-filled cysts and desmoplastic stroma[6]. Horn cysts are frequently calcified.
- Micronodular basal cell carcinoma: Malignant tumor of follicular origin composed of islands of basaloid cells within dense fibrous and sclerotic stroma. Frequently with mitotic figures and rarely forming cysts.

Clinical Concerns:

- Actinic damage contributes to the occurrence of both Favre-Racouchot and nonmelanoma skin cancer. The presence of benign proliferations can confound or mask tumor detection[7].

References:

1. Favre, M. and J. Racouchot, *[Nodular cutaneous elasteidosis with cysts and comedones].* Ann Dermatol Syphiligr (Paris), 1951. 78(6): p. 681-702.
2. Sanchez-Yus, E., et al., *The histopathology of closed and open comedones of Favre-Racouchot disease.* Arch Dermatol, 1997. 133(6): p. 743-5.
3. Calderon-Castrat, X., et al., *Microcystic adnexal carcinoma mimicking basal cell carcinoma.* JAAD Case Rep, 2017. 3(6): p. 492-494.
4. Boos, M.D., et al., *Benign subclinical syringomatous proliferations adjacent to a microcystic adnexal carcinoma: a tumor mimic with significant patient implications.* Am J Dermatopathol, 2014. 36(2): p. 174-8.
5. Kim, J., et al., *Eccrine squamous syringometaplasia of underlying syringoma associated with Tegafur/Gimeracil/Oteracil (TS-1).* Acta Derm Venereol, 2015. 95(8): p. 999-1000.

6. Wang, Q., et al., *Desmoplastic trichoepithelioma: A clinicopathological study of three cases and a review of the literature.* Oncol Lett, 2015. 10(4): p. 2468-2476.
7. Leeuwis-Fedorovich, N.E., M. Starink, and A.C. van der Wal, *Multifocal squamous cell carcinoma arising in a Favre-Racouchot lesion - report of two cases and review of the literature.* J Dermatol Case Rep, 2015. 9(4): p. 103-6.

Question 6

A 74-year-old Caucasian woman received Mohs surgery treatment of an infiltrative basal cell carcinoma of the right ala. Perineural basal cell carcinoma was diagnosed on the first stage. This slide from the second Mohs stage includes superficial basal cell carcinoma on the lateral margin and a small basaloid proliferation in the center of the slide.

Please evaluate the basaloid proliferation in the center of this slide and determine the best next step:

A. Defer surgery until immunostaining can confirm keratinocytes on the deep margin.

B. Take another stage to clear the deep tumor and lateral margins.

C. Take another stage to clear only the lateral margins.

D. Order a recut slide for further evaluation.

Discussion

Question 6

Correct Answer:

C. Take another stage to clear only the lateral margins (Superficial BCC and single deep hair bulb).

Main Histologic Features of Transected Nasal Hair Follicles:

- The anatomic location of this section introduces a potential confounder with a tangential nasal hair bulb arising deep in the nasalis muscle. Tangential sections of the hair bulb can mimic basal cell carcinoma[1, 2]. While multiple hairs within the plane of section often provide context for diagnosis of hairs, the progression of Mohs layers into the base of the internal nasal mucosa occasionally presents spatial challenges to accurate interpretation.
- The superficial structures of internal nasal mucosa appear in deeper Mohs sections of the nasal ala and tip.
- Deeper cuts do not assist with diagnosis as the hair is oriented away from the center of the block and deeper cuts move away from the hair shaft.
- The tangential sections of hair bulbs and the hair papilla can resemble the cuffing of keratinocytic tumor around a nerve.

Histologic Differential Diagnosis:

- Perineural basal cell carcinoma: Pleomorphic basaloid cells within or surrounding a nerve fiber. Associated with a worse prognosis. Extirpating perineural tumor is important for cure but also potentially disfiguring because of extensive subclinical spread[3]. Eosinophils might be a clue to a malignant diagnosis[4].
- Reexcision perineural fibrosis: Also called reactive neuroepithelial aggregates, this benign proliferation of perineural epithelial cells in previously biopsied areas is challenging to differentiate from perineural basal cell carcinoma[5].
- Perineural inflammation: Dense lymphocytic perineural inflammation can both portend and mask keratinocytic tumor. Lymphocytes are uniform in cell size and contain basophilic nuclei without atypia[6].
- Peritumoral fibrosis: Surrounding basal cell carcinoma, concentric layers of fibrous tissue with slender fibroblasts with tapering ends and surrounding bundles of collagen can resemble nerves[7].

Clinical Concerns:

- Deeper layers with muscle and fat can be technically challenging to process with frozen sections.
- Even with ideal sections, perineural tumor can be difficult to differentiate from mimics.
- Normal anatomy can present histologic challenges to interpretation of Mohs sections.

References:

1. Leshin, B. and W.L. White, Folliculocentric basaloid proliferation. The bulge (der Wulst) revisited. Arch Dermatol, 1990. 126(7): p. 900-6.
2. Krunic, A.L., et al., The use of antidesmoglein stains in Mohs micrographic surgery. A potential aid for the differentiation of basal cell carcinoma from horizontal sections of

the hair follicle and folliculocentric basaloid proliferation. Dermatol Surg, 1997. 23(6): p. 463-8.
3. Ratner, D., et al., Perineural spread of basal cell carcinomas treated with Mohs micrographic surgery. Cancer, 2000. 88(7): p. 1605-13.
4. McCalmont, T.H. and J. Ye, Eosinophils as a clue to the diagnosis of microcystic adnexal carcinoma. J Cutan Pathol, 2011. 38(11): p. 849, 850-2.
5. Bechert, C.J. and J.B. Stern, Basal cell carcinoma with perineural invasion: reexcision perineural invasion? J Cutan Pathol, 2010. 37(3): p. 376-9.
6. Shimizu, I. and V.D. Thomas, Evaluation of nerves in Mohs micrographic surgery: histologic mimickers of perineural invasion and nervous tissue on frozen section. Dermatol Surg, 2014. 40(5): p. 497-504.Hassanein, A.M., et al., Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: potential pitfall in Mohs micrographic surgery. Dermatol Surg, 2005. 31(9 Pt 1): p. 1101-6.

Question 7

A 54 year-old woman presented in consultation for a same-day, Mohs-assisted excision of a biopsy-proven infiltrative basal cell carcinoma on the vertex scalp.

Appropriate next steps may include:

A. Proceeding with the Mohs-assisted excision.

B. Submitting blocks from the Mohs-assisted excision for permanent processing and review.

C. Requesting a dermatopathology review of the initial biopsy slides.

D. All of the above.

Discussion

Question 7

Correct answer:

D. All of the above.

This case highlights metastatic breast cancer misdiagnosed as basal cell carcinoma. Though 40% of basal cell carcinomas will present with mixed histologic subtypes,[1] the absence of nodular basal cell carcinoma and the presence of only an infiltrative tumor was unusual. This aggressive histology, notable for the single-filing of cells in the dermis, prompted the Mohs surgeon to question the presenting diagnosis. The surgeon obtained an informal intraoperative dermpath consultation that supported the suspicion for a cutaneous metastasis. The Mohs-assisted excision was halted and the block from the first stage was submitted for permanent sections revealing metastatic breast cancer. The patient's past medical history was significant for breast cancer.

Histologic features of metastatic breast cancer include single filing of cells (most common in lobular breast cancer), the formation of abortive glandular structures, dermal fibroplasia, cellular atypia and rare signet ring cells. Immunostains verifying tumor lineage are critical in the workup of cutaneous metastases. Commonly employed stains include CK7, GCDFP-15, estrogen receptor (ER), progesterone receptor (PR), HER2/neu, mammoglobin, and carcinoembryonic antigen (CEA). Metastases may be differentiated from primary carcinomas/adenocarcinomas of the skin with the help of p63 and/or CK5/6 immunostains (negative in metastatic breast cancer and positive in cutaneous primaries).[2] On frozen sections alone, however, the distinction between an infiltrative, primary cutaneous carcinoma and a cancer metastasis is very difficult.

Overall, 1% of internal malignancies will metastasize the skin [3] with lung cancer (25%), colon cancer and melanoma frequently observed in men and breast cancer (69%), lung cancer and colon cancer frequently observed in women. Metastases commonly occur on the scalp, with recent work supporting that variations in T-cell populations within the skin predict the location of metastases. [4]

The treatment of metastatic breast cancer requires systemic therapy with the inclusion of radiation and surgery based on the extent of disease and clinical context. The surgical excision of focal metastases, so-called metastasectomies, may be employed to lower the overall tumor burden or to provide symptomatic relief. Though metastasectomies show a survival benefit in metastatic melanoma, the survival benefits of metastasectomies in breast cancer have yet to be determined.[5,6]

References:

1. Cohen PR, Schulze KE, Nelson BR. Basal cell carcinoma with mixed histology: a possible pathogenesis for recurrent skin cancer. *Dermatol Surg*. 2006 Apr;32(4):542-51.
2. http://www.pathologyoutlines.com/topic/skintumornonmelanocyticmetastaticcarcinoma.html
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6. Joyce KM. Surgical Management of Melanoma. In: Ward WH, Farma JM, editors. Cutaneous Melanoma: Etiology and Therapy [Internet]. Brisbane (AU): Codon Publications; 2017 Dec 21. Chapter

Question 8

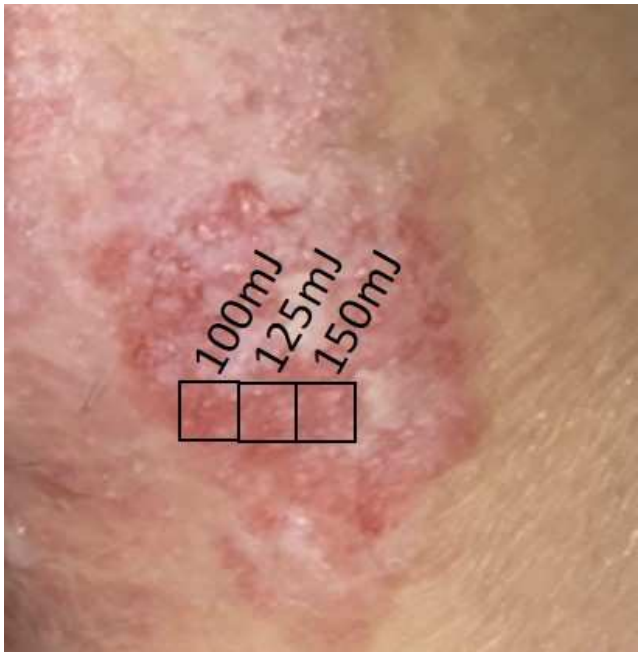
An 82-year-old woman presented for the evaluation and management of extramammary Paget's disease (EMPD) confined to the skin. Laser ablation and Mohs-assisted excision, both followed by topical imiquimod cream, were discussed. Fractionated carbon dioxide laser test spots followed by frozen section biopsies were performed to determine the appropriate laser fluence and to rule-out invasive disease. The scouting biopsies were grossed with the following ink code: red 100 mJ, yellow 125 mJ, blue 150 mJ.

The patient asks if the scouting biopsies show high-risk disease. Based on histology, you respond:

A. The biopsies indicate that your disease is low risk: there is neither tumor in the hair follicles nor invasion.

B. The biopsies indicate that your disease is low risk: although there is tumor in the hair follicles, invasion is not identified.

C. The biopsies indicate that your disease is high risk: there is both tumor in the hair follicles and invasion.



Discussion

Question 8

Correct answer:

B. The biopsies indicate that your disease is low risk: although there is tumor in the hair follicles, invasion is not identified.

Primary extramammary Paget's disease (EMPD) is a rare adenocarcinoma that arises from pleuripotent stem cells of the epidermis. The most common sites of involvement include (in decreasing order) the vulva, the perianal area, perineum, scrotum, penis, and axillae. 1Prognosis may be stratified by depth of invasion: in-situ disease and tumors less than 1 mm invasion are defined as "low risk" with tumors >1 mm invasion are defined as "high risk." 2 This disease is notoriously difficult to treat, with some suggesting a multifocal growth pattern. Recurrence rates of 20% - 60% with wide-local excision and 8 – 28% with Mohs-assisted excisions have been reported, though no prospective, head to head trials exist. 3 Additional treatment modalities include topical imiquimod, radiation therapy, and photodynamic therapy, each with varying success.

Histologically, EMPD is characterized by a proliferation of epithelioid cells with ample cytoplasm demonstrating Pagetoid growth. This proliferation may arise with or without epidermal acanthosis and hyperkeratosis. On H&E stains alone, primary EMPD is identical to epidermotropic metastases from underlying gastrointestinal or genitourinary malignancies, termed secondary EMPD. Immunohistochemical stains for primary EMPD include CK7, the most commonly used immunostain for margin assessment, and CEA. PAS stains may also be helpful. Of note, secondary EMPD stains positively for both CK7 and CK20.2

In this case, sections show EMPD involving the epidermis and the follicular epithelium (adnexal involvement). Invasion is absent. The patient presented here has suffered a difficult and frustrating clinical course. She is status-post nine surgical resections of in-situ disease between 2002 and 2007, resection of invasive disease of the anus and rectum in 2017, and placement of a colostomy in 2017. In fall 2017, she recurred with histology revealing only in-situ disease of the perianal, vulvar, and vaginal skin. Initially, she was treated with imiquimod cream which was discontinued due to pain. She was reassured during her consultation that her scouting biopsies revealed low-risk disease confined to the epidermis. The extent and location of disease precluded a Mohs-assisted excision. Her current treatment regimen includes serial laser ablation to decrease the tumor burden in combination with topical imiquimod as tolerated to contain, not cure, this multiply-recurrent disease.

References:

1. Hartman R, Chu J, Patel R, Meehan S, Stein JA. Extramammary Paget disease. Dermatol Online J. 2011 Oct 15;17(10):4.
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3. Bae JM, Choi YY, Kim H, Oh BH, Roh MR, Nam K, Chung KY. Mohs micrographic surgery for extramammary Paget disease: a pooled analysis of individual patient data.J Am Acad Dermatol. 2013 Apr;68(4):632-7.

Question 9

A 67-year-old woman presents for treatment of an acral lentiginous melanoma in situ on the left plantar foot. Both H&E and MART-1 immunostains are performed during Mohs surgery. The first layer is unequivocally positive, so you take a second layer. The slide is from the second layer.

What is your next step?

A. Stop. The margin is clear. Only normal skin is appreciated.

B. The peripheral margin is positive due to melanoma in situ. Take an additional layer.

C. The peripheral margin is positive due to melanoma in situ. Invasive melanoma is also present. Take an additional layer.

D. The findings are equivocal. Stop. Show the case to a colleague.

Discussion

Question 9

Correct Answer:

C. The peripheral margin is positive due to melanoma in situ. Take an additional layer.

Main Histologic Features of Acral Lentiginous Melanoma in Situ:

- The early stage of acral lentiginous melanoma in situ can be quite subtle.[1] It is characterized by a proliferation of irregularly spaced, slightly atypical melanocytes along the dermal-epidermal junction.[2]
- Over time, junctional nests form and alternate irregularly with solitary melanocytes. [2] These nests are often found at the tips of the epidermal ridges.[1]
- It is common to see "skip areas" where parts of the epidermis are devoid of melanocytes.[2]
- Pagetoid cells may be present. These are usually irregularly distributed and multi-focal.[2]
- The epidermis often displays hyperkeratosis, acanthosis, and hypergranulosis.[1]
- There is commonly an inflammatory infiltrate in the dermis.[2]

Differential Diagnosis:

- Incidental acral junctional melanocytic nevus: Distinguishing between an incidental acral junctional nevus and the edge of an acral lentiginous melanoma in situ may be challenging during Mohs surgery. Diagnostic criteria overlap as both may show a lentiginous pattern, junctional nests and pagetoid scatter.[2] It is therefore recommended to take an additional layer and remove any junctional melanocytic proliferation when performing Mohs surgery for melanoma.

Clinical Concerns:

- According to the American Academy of Dermatology guidelines, surgical excision with clear histologic margins is the primary treatment modality for cutaneous melanoma.[3] The goal is to minimize local recurrence due to persistent disease.
- Melanoma antigen recognized by autologous cytotoxic T-cells (MART-1), a cytoplasmic stain, is one of the most widely used antibodies during Mohs surgery for melanoma.[4,5]
- Two large studies have shown that Mohs surgery with the MART-1 stain achieves local recurrence rates for primary tumors of less than 0.5%.[4,5]
- Previously published criteria for positive margins when using the MART-1 immunostain include "(1) nests of at least 3 atypical melanocytes, (2) melanocytes above the dermoepidermal junction, (3) confluence of more than 9 adjacent melanocytes, (4) "vertical stacking" of melanocytes, (5) melanocytic hyperplasia significantly different in one area as compared with the rest of the margin, and (6) presence of nests of atypical cells in the dermis."[4].
- When performing Mohs surgery for acral lentiginous melanoma in situ, it is important to be aware of the subtle histological features found in early disease. These features may also be found at the trailing edge of a more advanced tumor. As a result, the threshold for taking an additional layer may be lowered when this subtype of melanoma compared to other types.

References:

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3. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. *J Am Acad Dermatol.* 2011;65(5):1032-1047.
4. Valentin-Nogueras SM, Brodland DG, Zitelli JA, Gonzalez-Sepulveda L, Nazario CM. Mohs Micrographic Surgery Using MART-1 Immunostain in the Treatment of Invasive Melanoma and Melanoma In Situ. *Dermatol Surg.* 2016;42(6):733-744.
5. Etzkorn JR, Sobanko JF, Elenitsas R, et al. Low recurrence rates for in situ and invasive melanomas using Mohs micrographic surgery with melanoma antigen recognized by T cells 1 (MART-1) immunostaining: tissue processing methodology to optimize pathologic staging and margin assessment. *J Am Acad Dermatol.* 2015;72(5):840-850.

Question 10

A 55-year-old man presents for treatment of a melanoma in situ on the left cheek. Both H&E and MART-1 immunostains are performed during Mohs surgery. The slide is from the first layer.

What is your next step?

A. Stop. The margin is clear. Only normal skin is appreciated.

B. Stop. The findings represent a solar lentigo.

C. The peripheral margin is positive due to melanoma in situ. Take an additional layer.

D. Although the findings are suggestive of an intra-dermal nevus, you take an additional layer.

Discussion

Question 10

Correct Answer:

D. Although the findings are suggestive of an intra-dermal nevus, you take an additional layer.

Main Histologic Features of Intradermal nevi:

- Melanocytic nevi can be divided into junctional, intradermal, and compound types. These can further be divided into numerous subtypes. [1,2]
- Intradermal nevi are classically comprised of well-formed nests in the superficial dermis and as strands and cords in the deeper dermis. Single melanocytes may also be present.
- Intradermal nevi with congenital features display nests of melanocytes that appear to envelop adnexal structures.
- There is no melanocytic atypia and mitoses are usually absent.

Differential Diagnosis:

- Invasive melanoma: Some features suggestive of invasive melanoma include nests or sheets of atypical melanocytes without maturation. Mitoses are occasionally be present. Melanoma in situ is commonly present in the epidermis.[2]
- Metastatic melanoma: Although multiple subtypes exist, metastatic melanoma is classically characterized by sheets of atypical melanocytes located in the dermis. Histological features may be misleading as metastatic melanoma may also mimic a benign nevus, displaying symmetry and circumscription. [2]

Clinical Concerns:

- Incidental nevi can be found on Mohs sections during Mohs for melanoma or non-melanoma skin cancer.
- As it can be challenging differentiate between benign and atypical nests, it is conceivable to remove incidental nevi to avoid missing invasive or metastatic melanoma. In fact, presence of atypical cells in the dermis are part of published criteria for calling a margin positive during Mohs surgery for melanoma with the MART-1 antibody.[3]
- An additional reason to remove incidental nevi is to prevent the development of recurrent nevi which may mimic melanoma (pseudo-melanoma) on histopathology.

References:

1. Calonje E, Brenn T, Lazar A, McKee PH. *McKee's Pathology of the Skin.* 4th ed: Elsevier; 2012.
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