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WHAT'S NEW IN PATHOLOGY?

Issue 13 || August 2020

THE LATEST NEWS IN DERMPATH

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The 4th Edition WHO Classification of Skin Tumours and the 8th Edition AJCC Cancer Staging Manual have introduced changes to our practices. Highlights are described below.

Keratinocytic/Epidermal Tumors

- Keratoacanthoma is reclassified as a subtype of squamous cell carcinoma.
- 80% of Merkel cell carcinomas have clonal integration of Merkel cell polyomavirus (MCPyV). The remaining 20% have mutations in TP53 and a UV radiation signature mutation profile. **MCPyV is a surrogate immunohistochemical marker for viral genomic integration, and limited data suggest that it could distinguish primary cutaneous tumors from extracutaneous metastases with 98% specificity (PMID 21453956)**.

Melanocytic Tumors

- **There have been extensive updates to melanoma staging:**
  - **Breslow depth is rounded to the nearest tenth of a millimeter (e.g. 0.76 mm = 0.8 mm).**
  - **Mitoses no longer distinguish pT1a vs. pT1b.**
  - **Changes to Breslow depth cut-offs:**
    - **pT1a: < 0.8 mm thickness without ulceration.**
    - **pT1b: < 0.8 mm thickness with ulceration or 0.8 - 1.0 mm thickness with or without ulceration.**
  - Regional lymph node pN categories:
    - pN1a: 1 nodal metastasis, clinically occult (no in transit, satellite or microsatellite metastasis).
    - pN1b: 1 nodal metastasis, clinically detected (no in transit, satellite or microsatellite metastasis).
    - pN1c: negative for nodal metastasis (positive in transit, satellite or microsatellite metastasis).
    - pN2a: 2 to 3 nodal metastases, clinically occult (no in transit, satellite or microsatellite metastasis).
    - pN2b: 2 to 3 nodal metastases, clinically detected (no in transit, satellite or microsatellite metastasis).
    - pN2c: 1 nodal metastasis, clinically occult or detected (positive for in transit, satellite or microsatellite metastasis).
    - pN3a: 4 or more nodal metastases, clinically occult (no in transit, satellite or microsatellite metastasis).
    - pN3b: 4 or more nodal metastases, clinically detected (no in transit, satellite or microsatellite metastasis).
    - pN3c: 2 or more nodal metastases (positive for in transit, satellite or microsatellite metastasis).
- BAP1 tumor predisposition syndrome:
  - Germinal BAP1 mutations (autosomal dominant inheritance) are associated with an increased risk of renal cell carcinoma, mesothelioma, basal cell carcinoma, and uveal and cutaneous melanomas.
  - In their second decades, patients can develop multiple BAP1-inactivated nevi which are dome-shaped papules that show morphologic overlap with Spitzoid tumors and a loss of nuclear BAP1 immunohistochemical expression.

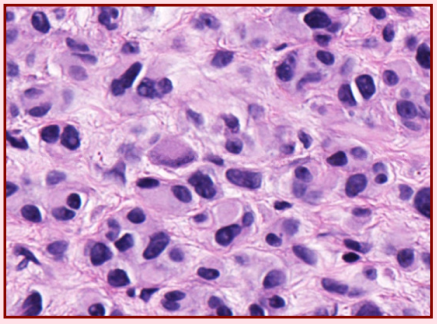

Figure 1: BAP1-inactivated nevi are comprised of epithelioid melanocytes with abundant cytoplasm and large nuclei.

- **BAP1-inactivated nevi:**
  - These recently classified neoplasms can arise in individuals with or without an undelrying BAP1 syndrome, and often as a portion of a combined nevus (Figure 1).
  - They generally have either a BRAF or NRAS activating mutation (present in the precursor common nevus), in addition to inactivation of both BAP1 alleles.
  - This is analogous to deep penetrating nevi which have an activating mutation (e.g. involving BRAF) in addition to secondary Wnt pathway activation by gain-of-function mutations in CTNNB1 (β-catenin) or loss of APC.
- **BAP1-inactivated nevi with features overlapping melanoma**:
  - Features include asymmetry, expansive nests compressing the nevoid component, necrosis, non-traumatic epidermal ulceration, nuclear pleomorphism or more than a rare mitotic figure.
  - It is appropriate to call these BAP1-inactivated melanocytomas.
  - **Ancillary testing (e.g. single nucleotide polymorphism chromosomal microarray) can help predict the behavior of these ambiguous lesions.**

- **Spitz nevi, atypical Spitz tumor (AST) and malignant Spitz tumor (MST):**
  - Now recognized as a spectrum of tumors characterized by enlarged, epithelioid or spindled melanocytes mimicking those of melanoma; however, genetically distinct from melanomas, blue nevi, deep penetrating nevi and BAP1-inactivated nevi.
  - Spitz nevi are generally < 6 mm, symmetric, circumscribed, wedge-shaped, exhibit dermal maturation and have little or no mitotic activity.
  - MST shows non-traumatic ulceration, confluent nesting, > 6 dermal mitoses/mm^2, atypical mitoses and necrosis.
  - AST is a term reserved for biologically indeterminate lesions that exceed criteria for Spitz nevus but fall short of MST.
  - Without ancillary testing, it can be difficult to distinguish between AST, MST and rare conventional melanomas with Spitzoid features.
  - In contrast with conventional melanomas with Spitzoid features, both MST and AST generally lack BRAF and NRAS activating mutations and possess mutually exclusive kinase fusions involving ROS1, ALK, BRAF, NTRK1, NTRK3, MET and RET.
  - **FISH or single nucleotide polymorphism chromosomal microarray can help predict the behavior of ambiguous lesions.**

Tumors Of Hematopoietic And Lymphoid Origin

- Primary cutaneous marginal zone lymphoma (PCMZL) is now recognized as having two distinct subtypes.
  - The IgM+/CXCR3+ non-class-switched subset resembles extracutaneous MALT lymphomas with sheets of monomorphous B-cells.
  - A class-switched CXCR3- subset shows significant overlap with cutaneous lymphoid hyperplasia including a predominance of T-cells.
  - Demonstration of a light chain restriction by immunohistochemistry can aid in the distinction.
  - There is discussion as to whether class-switched PCMZL should be reclassified as a lymphoproliferative disorder in lieu of lymphoma given its appearance and indolent behavior.
- **Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder is no longer classified as a lymphoma in light of its indolent behavior. Clinicopathologic correlation is required in order to establish this diagnosis.**
- New lymphomatoid papulosis (LyP) subtypes have been added. Clinical correlation is required to distinguish them from the lymphomas they histologically resemble.
  - Type D resembles primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma.
  - Type E resembles an angiodestructive lymphoma.
  - LyP with *DUSP22-IRF4* rearrangement resembles transformed mycosis fungoides and has small, epidermotropic cells and larger intradermal cells with cerebriform nuclei. This variant is often CD4-/CD8+ or CD4-/CD8-.

Soft Tissue Tumors

- **Atypical smooth muscle tumor:** the preferred nomenclature for an intradermal smooth muscle neoplasm with mitoses, nucleomegaly or nuclear hyperchromasia. These tumors have essentially no risk of metastasis when confined to the dermis.
- **Lesions extending into the subcutis have low metastatic potential and should be designated as leiomyosarcoma.**
- **The distinction between atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS), which has a low metastatic potential, similarly requires examination of the entire lesion. In contrast to PDS, AFX should not involve the subcutis, and should not show perineural invasion, lymphovascular invasion, or necrosis** (Figure 2).
- Radiation-induced angiosarcomas show MYC amplification by FISH while atypical vascular lesions do not.
- A majority of epithelioid fibrous histiocytomas have an ALK rearrangement and stain with ALK by immunohistochemistry, which can help distinguish them from other fibrohistiocytic neoplasms, cellular neurothekeoma and myoepithelioma.
- A majority of superficial acral fibromyxomas show loss of RB1 expression and combined with the CD34+/S100- immunophenotype can help distinguish them from other cutaneous tumors with myxoid stroma including neurofibroma, superficial angiomyxoma and myxoid dermatofibrosarcoma.

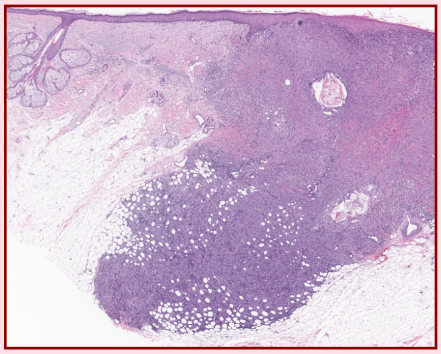

Figure 2: This PDS with extension into the fat was histologically indistinguishable from AFX in the initial shave.

Meet the Author

Our dermatopathology section editor, Robert E. LeBlanc, M.D. directs the dermatopathology fellowship program at Dartmouth-Hitchcock Medical Center, where he serves as an Assistant Professor and residency committee member in the Department of Pathology and Laboratory Medicine. He is passionate about patient safety and medical education. Robert is also a member of the American Society for Dermatopathology ethics committee as well as the fellowship program director committee. He has mentored dozens of medical students and trainees in pathology and dermatology, referees flagship dermatology and dermatopathology journals, and has lectured extensively on cutaneous lymphomas, melanoma and high risk non-melanoma skin cancers.