37 Pitfalls in Dermatopathology: When Things Are Not What They Seem To Be

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2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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This session focuses on histological mimickers: skin malignancies that resemble reactive conditions or benign neoplasms, benign conditions that masquerade as malignancies and tumors that are prone to be mistaken for other types of cutaneous malignancies. Pitfalls in the diagnosis of cutaneous neoplasms that may result in diagnostic errors with significant clinical impact will also be presented. Participants will have the opportunity to improve their diagnostic acumen and clinical skills by increasing their awareness of dermatopathology entities that are prone to be misdiagnosed.

- Recognize a variety of dermatopathology cases that are prone to be misdiagnosed.
- Identify histological features that are useful in preventing pitfalls in diagnosis.
- Determine appropriate ancillary studies that help arrive at the correct diagnosis.

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Pitfalls in dermatopathology: When things are not what they seem to be

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I HAVE NO CONFLICTS OF INTEREST RELATED TO THIS PRESENTATION
Most diseases of the skin can be correctly diagnosed by integrating the clinical and histological features of a certain lesion. There are however, certain entities in which the clinical appearance as well as the impression obtained from a superficial histologic examination are misleading due to approximation of a completely different entity and may result in an erroneous diagnosis. These pitfalls in diagnosis are most significant when they involve tumors with a malignant potential in which a misdiagnosis is likely to have serious medical consequences. Awareness of histological mimickers may prompt the pathologist to allocate additional time for evaluating the histology of a problematic lesion which often allows the detection of subtle changes that permit a correct diagnosis. These entities prone to misdiagnosis can be divided into skin malignancies that resemble reactive conditions or benign neoplasms, benign conditions that masquerade as malignancies and tumors that may be mistaken for other types of cutaneous malignancies.

A. Malignant entities mimicking reactive or benign neoplastic lesions

1. Epithelioid sarcoma
   Epithelioid sarcoma affects predominantly young adults between 23 and 40 years of age and demonstrates a male predominance. Typical presentation is that of a slow growing painless nodule within the dermis or subcutis of distal extremities. Superficially located tumors can eventually ulcerate whereas deeper lesions extend along tendon sheaths or aponeuroses. (1-3) Microscopically, the tumor is composed of nodules, some exhibiting central degeneration or necrosis. Chronic inflammatory cells are usually present at the periphery of the tumor nodules. Tumor cells are of medium to large size, with polygonal shape, distinct cytoplasmic borders, abundant eosinophilic cytoplasm and large vesicular nuclei. There is only mild nuclear pleomorphism and mitotic figures are usually sparse. The tumor is positive for keratin, EMA and vimentin. In addition, about 50% of cases express CD34. Immunohistochemical stains for S100, Factor VIII and CD31 are usually negative. The presence of a dermal nodule with central degeneration, composed of rather bland cells may at cursory examination mimic to identity an infectious or a palisading granuloma such as granuloma annulare or rheumatoid nodule. In contrast to these reactive processes, at closer scrutiny, the cells of epithelioid sarcoma tend to be larger, exhibit more eosinophilic cytoplasm and show distinct cell borders. In addition epithelioid sarcomas express cytokeratin and EMA which is not a feature or reactive granulomas.

2. Desmoplastic melanoma
   Desmoplastic melanoma is a variant of malignant melanoma defined histologically by spindle, slender melanocytes embedded into a fibrous stroma. The tumor deeply infiltrates dermis and often subcutis and exhibits perineural invasion however, the melanocytes do not show overt cytologic atypia. (4) At superficial examination, the lesion may resemble a dermal scar, a sclerotic blue nevus, a dermatofibroma or even a leiomyoma. (4) Subtle diagnostic clues (which are not always encountered) are the presence of a junctional melanocytic proliferation, lymphocytic aggregates, cytologic atypia, perineural invasion and mitotic figures; however a high index of suspicion is required for a correct diagnosis. (4-5)
3. Metastatic breast carcinoma

Breast carcinoma is the most common cutaneous metastatic disease in women, more often involving the anterior chest. (6-7) Described histologic patterns include interstitial, intralymphatic, epidermotropic and duct-forming. (8-9) Out of these various patterns, the interstitial one which is seen more common in the lobular variant of breast carcinoma, is the most likely to be misdiagnosed because it often shows only mild cytologic atypia and may resemble the interstitial variant of granuloma annulare, dermatofibroma or xanthelasma. Clues to the correct diagnosis include a "busy" dermis, subtle cytologic atypia and single file cellular infiltrate. (10)

4. Malignant melanoma is situ with lichenoid inflammation

A lichenoid tissue reaction occurs not infrequent in melanomas and when it is extensive may obscure the presence of a junctional melanocytic proliferation. (11) Compounding the problem is the fact that some of these lesions are clinically amelanotic (12-13) and the biopsy is performed to rule out a lichen planus-like keratosis (LPLK), basal cell carcinoma or Bowen disease. In these cases, a superficial histologic examination finds a prominent lichenoid infiltrate and confirms falsely the clinical suspicion of LPLK overlooking the melanocytic nature of the lesion. Clues favoring a melanocytic lesion over LPLK are absence of a precursor lesion such as solar lentigo or seborrheic keratosis, effacement of the epidermis and heavily sun damaged skin. (11) Correct diagnosis can be achieved only by a high index of suspicion. Careful scrutiny of the biopsy and additional stains will often identify a subtle melanocytic proliferation that went unnoticed at first inspection.

5. Nevoid melanoma

 Nevroid melanoma is an uncommon variant of melanoma that closely resembles a benign nevus on histology. Confusing histological features include symmetrical silhouette, circumscription, maturation and an inconspicuous junctional component. Clues to the diagnosis of melanoma include presence of dermal mitotic figures, especially deeply located and atypical mitoses, a sheet-like growth pattern, prominent nucleoli at the base of the lesion and lack of complete maturation. (10) New molecular techniques such as comparative genomic hybridization and FISH can aid in establishing a correct diagnosis. (14)

6. Blue-nevus like metastatic melanoma

These are special variants of melanoma metastases that are clinically and histologically indistinguishable from benign blue nevi. Subtle histologic differences that may suggest a diagnosis of melanoma include presence of mitoses and slight nuclear atypia. (15) Again, new ancillary FISH testing can aid in establishing a correct diagnosis. (16)

B. Benign entities mimicking malignant tumors

1. Lupus panniculitis

Lupus panniculitis (lupus profundus) is known to mimic both clinically and histologically lesions of subcutaneous panniculitis-like T-cell lymphoma (SCPTCL).
Clinically lupus panniculitis presents with subcutaneous plaques predominantly on extremities. Histology shows a lobular panniculitis with broadened fibrotic septa and hyaline changes that extend into the lobules. Useful features that allow separation from SCPTCL are the presence of epidermal and dermal changes of lupus, presence of lymphoid follicles adjacent to septa, a mixed cell infiltrate with prominent plasma cells and polyclonal TCR gene rearrangements.

2. Nodular scabies

Scabies is caused by infestation with the mite Sarcoptes scabiei. There are three clinical forms of the disease: papulovesicular, nodular and Norwegian. The nodular form occurs in about 7% of cases and affects mainly children and young adults. The patients develop pruritic nodules that may persist for up to one year and involve mainly lower trunk, proximal lower extremities and genital areas. This form is believed to represent a delayed hypersensitivity reaction similar to other arthropod bites. Histological examination shows a dense superficial and deep infiltrate composed of lymphocytes, histiocytes, plasma cells and eosinophils. Large, atypical mononuclear cells are often noted and in long standing lesions there is positivity for CD 30 antigen. (18) Also, mites are rarely found in sections from nodular scabies. These features may lead to an erroneous diagnosis of lymphomatoid papulosis (LyP) in lesions of nodular scabies. (19) Clues to the correct diagnosis are represented by the character of the CD30 staining which is scattered in scabies (and in other reactive lesions that exhibit CD30 staining) and arranged in clusters in LyP. Also, performing serial sections in a suspected case of scabies can increase the proportion of positive mite identification.

3. Congenital nevus mimicking melanoma in situ

Intraepidermal spread of melanocytes in a pagetoid pattern that mimics melanoma in situ is a phenomenon described in congenital nevi. It was initially described in congenital nevi biopsied within the first three month of life. (20) Later this pattern was also found in older patients as well. Pagetoid spread appears to be more common in the superficial type of congenital nevi where is encountered in about one third of the cases. (21) As opposed to melanoma, in congenital nevi the intraepidermal spread is orderly, there is no associated lymphocytic infiltrate and the atypia is minimal.

4. Proliferative nodule in a congenital nevus

Proliferative nodules are cellular nodules of melanocytes that develop in large congenital nevi. These lesions do not behave aggressively however their histology is very worrisome for a melanoma developing in a congenital nevus. Features that favor a proliferative nodule include absence of atypical mitoses or necrosis and an architecture that blends with the surrounding nevus. (22-23) New molecular techniques such as comparative genomic hybridization can aid in establishing a correct diagnosis. (24)

5. Atypical fibrous histiocytoma

This tumor also known as dermatofibroma with "monster" cells has clinical features similar to conventional dermatofibroma. Histologic examination shows markedly atypical cells, some multinucleated admixed with bland cells. (19) Mitotic figures including atypical forms are also encountered. (25) This lesion can be easily
misdiagnosed as atypical fibroxanthoma or malignant fibrous histiocytoma. Pertinent clues to the correct diagnosis include overlying epidermal hyperplasia, circumscription and peripheral collagen trapping. (25)

6. Aneurysmal fibrous histiocytoma
   This is a variant of dermatofibroma which is characterized by blood-filled spaces lined by histiocytes. (26) Clinically the lesion may resemble a vascular tumor and on superficial histologic examination the impression may be that of a malignant vascular neoplasm such as angiosarcoma or Kaposi sarcoma. (19, 26)

7. Atypical fibroxanthoma
   Atypical fibroxanthoma is a tumor characterized by marked cellular pleomorphism but with a benign or intermediate prognosis. (19) The lesions typically present as solitary nodules on the head and neck of the elderly. Recurrences occur in about 5% of the cases and rare cases are described to metastasize. Histologically AFX is a tumor characterized by a mixture of spindle cells, large epithelioid cells and multinucleate giant cells with atypia and pleomorphism. Histologic variants include spindle cell, osteoclast-like giant cells, clear cell, with chondroid or osteoid differentiation, pigmented and granular. AFX is a diagnosis of exclusion and immunohistochemical stains should be routinely preformed to rule out melanoma and squamous cell carcinoma.

8. Hypertrophic lichen planus
   This variant of lichen planus is characterized by marked epidermal hyperplasia that can have an irregular contour and therefore mimics an invasive squamous cell carcinoma. The clue to the diagnosis relies on the presence of a lichenoid infiltrate at the tips of the rete ridges with dyskeratosis and recognizing the benign cytology of the lesion. (19, 27)

9. Exophytic (verrucous) herpes simplex virus infection
   The most common symptomatic presentation of herpes simplex virus (HSV) includes painful, sometimes umbilicated, vesicles on an erythematous base which can progress to pustules and/or ulcerations. In the case of immunosuppressed patients such as transplant recipients, patients with lymphoma and acquired immunodeficiency syndrome (AIDS), the HSV infection often presents in an atypical fashion including verrucous, exophytic, pustular or ulcerative lesions. The verrucous or exophytic atypical presentations often mimic a squamous cell carcinoma. (28) Clinical suspicion and recognition of viral cytopathic changes is necessary for a correct diagnosis. (29)

10. Deep fungal infection
    Marked pseudoepitheliomatous hyperplasia is classically associated with a variety of fungal infections. (19) In these cases the epidermal hyperplasia mimics a well differentiated squamous cell carcinoma and the correct diagnosis may be difficult especially in superficial shave biopsies. Accurate diagnosis relies on a high index of suspicion which will trigger special stains for microorganisms or microbiology culture studies.
11. Desmoplastic trichilemmoma
This lesion presents as a dome shaped papule on the face. Histologically, in addition to the classical features of trichilemmoma (clear cells with peripheral palisading) there are thin strands of epithelial cells embedded into a desmoplastic stroma. When this pattern occurs towards the base of the lesion it mimics a squamous cell carcinoma. (30)

C. Malignancies that may be confused with other cancers:

1. Pigmented variant of Paget’s disease
Pigmented Paget’s disease is a rare variant of Paget's disease characterized by intraepidermal pagetoid cells of epithelial origin containing prominent melanin pigment. Clinical impression is often that of a pigmented lesion. Histologically, especially on a superficial shave biopsy this entity can be confused easily with melanoma in situ. (31)

2. Merkel cell carcinoma
Merkel cell carcinoma (MCC) is a rare and highly malignant neoplasm. Although in the majority of the cases it is easily recognized and the diagnosis is straightforward, there are particular instances in which MCC may be mistaken for other neoplasms.
- Occasionally cases of MCC show focal peripheral palisading, a mucinous stroma and stromal retraction mimicking a basal cell carcinoma. (32) The key to avoiding this pitfall is to recognize the typical nuclear features of MCC.
- Cases of MCC with prominent intraepidermal pagetoid spread may be confused with small cell melanoma. (32)
- Cases of MCC with a diffuse pattern may resemble lymphoma. This initial misdiagnosis may be falsely confirmed if only a limited lymphoma panel is performed as MCC are often positive for CD56 and TdT. (33)

3. Cellular neurothekeoma
Cellular neurothekeoma (CNTK) is a benign lesion most commonly presenting in the first two decades of life and demonstrating a female predominance. Most occur on the head and neck area or upper limbs; however, cases have been reported in other sites. CNTKs often present as solitary, superficial, slow-growing, and relatively asymptomatic papules or nodules usually less than two centimeters in diameter. Clinical impression includes basal cell carcinoma, cyst, nevus, dermatofibroma, adnexal neoplasm, neurofibroma or melanoma. Microscopically, the tumor demonstrates a micronodular architecture and is composed of nests and fascicles of spindle to epithelioid cells with pale eosinophilic cytoplasm, poorly defined cell borders, ovoid nuclei with fine chromatin and variable amounts of sclerotic collagen. Occasionally the tumor exhibits atypical features including cytologic atypia, elevated mitotic count, deep infiltration and vascular invasion. Due to the nested architecture, the initial impression is often that of a melanocytic neoplasm, either nevus or melanoma. Correct diagnosis relies on demonstrating the characteristic immunohistochemical profile positive for NKI/C3, CD10, MITF and PGP9.5 and negative for melanocytic markers S100, Mart1 and HMB45. (34-35)
4. Extraskeletal Ewing Sarcoma

This is a rare tumor composed of small undifferentiated cells with hyperchromatic nuclei and high nuclear to cytoplasmic ratio. It is currently accepted that primitive neuroectodermal tumors and Ewing sarcoma (ES) form a continuum. The tumor occurs usually in the deeper soft tissues. Superficial locations are very rare. ES is positive for CD99 in a characteristic membranous pattern and demonstrates recurrent translocations involving the Ewing gene on chromosome 22. Due to the undifferentiated nature of ES, the differential diagnosis includes other small blue cell tumors. Tumors entering the differential diagnosis of ES include Merkel cell carcinoma, metastatic small cell carcinoma from distant sites such as lung, basal cell carcinoma, high-grade lymphoma such as Burkitt and small cell variant of melanoma. A positive diagnosis is often not possible based on histology alone and a number of ancillary immunohistochemical stains are usually employed to refine the diagnosis. Common stains performed either simultaneous or in a staggered fashion include neuroendocrine markers (chromogranin and synaptophysin) positive in MCC and small cell carcinoma, CK20 for MCC, lymphocytic markers (LCA, CD3, CD20 etc) for lymphomas, epithelial markers for BCC, MCC and small cell carcinoma, TTF1 for pulmonary small cell carcinoma and melanocytic markers (S100, Mart-1 and HMB45) for small cell melanoma.

References


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