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SOFT TISSUE TUMORS  
SHOWING  
FIBROUS / FIBROHISTIOCYTIC DIFFERENTIATION

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**Bullet points**

- Cellular and atypical variants of fibrous histiocytoma are often mistaken for sarcoma
- Morphologically benign examples of fibrous histiocytoma, most often the cellular or atypical variants, may metastasize.
- Atypical fibroxanthoma is likely unrelated to so-called 'MFH' and almost never metastasizes.
- Cellular neurothekeoma appears to be fibroblastic/myofibroblastic and, despite sometimes worrisome morphology, seems to be consistently benign.
- Digital fibromyxoma and myxoinflammatory fibroblastic sarcoma are 'newer' lesions which merit wider recognition.

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**Differential Diagnosis**

Cellular benign FH is confused often with leiomyosarcoma or dermatofibrosarcoma protuberans. The former, however, has plumper eosinophilic spindle cells with cigar shaped nuclei, a more uniform fascicular pattern, at least focal cytologic atypia and shows diffuse positivity for desmin and alpha-smooth-muscle actin. The latter lacks epidermal changes or cytological polymorphism and has a prominent storiform pattern; the neoplastic spindle cells have paler, poorly defined, cytoplasm and usually show both extensive involvement of the subcutaneous tissue and diffuse positivity for CD34.

**ATYPICAL (PSEUDOSARCOMATOUS) FIBROUS HISTIOCYTOMA**

**Clinical Features**

This variant of fibrous histiocytoma,<sup>13-17</sup> also known as dermatofibroma with monster cells, represents less than 2% of all fibrous histiocytomas, and may easily be mistaken for a malignant lesion. In the same manner as ordinary FH, it presents as a small nodule (usually less than 2 cm) on the limbs, or less commonly the trunk, over a wide age range but most often in middle-aged adults of either sex. The recurrence rate is low, even after incomplete excision. However, recent data from a large series<sup>17</sup> have shown that these lesions also may rarely metastasize, although this is not reliably predictable on morphologic grounds and inevitably is exaggerated in consultation material.

**Histologic Appearances**

Histologically, tumors can be polypoid or dome-shaped and they share features with ordinary fibrous histiocytoma, namely epidermal hyperplasia and a polymorphic population of spindle-shaped and histiocyte-like cells intermixed with giant cells, foamy macrophages and lymphocytes. Hemosiderin deposition is a frequent finding and a very small proportion of cases overlap histologically with aneurysmal or cellular benign fibrous histiocytoma. On medium or high power examination, a proportion of the cells in the tumor show prominent pleomorphism with large hyperchromatic irregular nuclei and prominent nucleoli. The extent of pleomorphism is variable. Commonly, lipid-laden cells and siderophages also show these changes. In addition, large multinucleate cells showing intense (probably degenerative) nuclear hyperchromasia are common. Mitotic figures usually are few in number but may be quite numerous and, in my experience, 30% of cases contain atypical mitotic figures.<sup>17</sup>

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**Introduction**

The goal of this symposium, as outlined by the moderator, is to focus on lesions involving dermis and/or superficial subcutis, of the type which often present as skin biopsies in routine dermatopathology practice, which have been either the subject of conceptual shift, or been associated with unexpected clinical outcome or which are a frequent source of difficulty, as reflected in consultation material. This has inevitably resulted in an eclectic list of lesions (outlined below), without necessarily any strict inter-relationship. It has also provided an opportunity to include one or two relatively 'newer' tumor types with which participants may not be so familiar.

Before reviewing specific tumor entities, it is best to remind ourselves what the term 'fibrohistiocytic' connotes in present-day pathology practice. The term "fibrohistiocytic" was originally introduced to describe a group of tumors composed of cells that on light microscopy were thought to have morphologic features of fibroblasts and histiocytes. In the early 1960s this theory appeared to be confirmed by tissue culture evidence of amoeboid growth and phagocytic activity in tumor cells. However, these features do not provide specific evidence of histiocytic differentiation. Over the years the introduction of newer techniques, such as electron microscopy and immunohistochemistry, provided conflicting results which, on balance, firmly deny the histiocytic nature of this group of tumors. It is clear that the word "fibrohistiocytic" is best used as a descriptive term, with no histogenetic implications, to encompass a heterogeneous group of tumors which share similarities in terms of cytomorphology and a frequently storiform growth pattern.<sup>1-6</sup> Whether or not cutaneous fibrous histiocytomas are neoplastic or reactive has also been controversial, but the bulk of evidence (at least for all but the spontaneously regressing lesions) would favor a neoplastic process, perhaps evolving from an otherwise self-limiting clonal proliferation. While cutaneous "fibrohistiocytic" lesions appear to be morphologically related to one another, albeit many are probably fibroblastic/myofibroblastic in nature, there is no longer any real justification for grouping together the more deep-seated "MFH" family, as was codified in the 2002 WHO classification.

**CELLULAR BENIGN FIBROUS HISTIOCYTOMA**

**Clinical Features**

This distinctive variant accounts for approximately 5% of cutaneous fibrous histiocytomas and combines a high local recurrence rate and worrying histologic features.<sup>7</sup> As

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**Differential Diagnosis**

Diagnosis is not difficult if attention is paid to the typical cytoarchitectural features of ordinary fibrous histiocytoma. The main differential diagnosis is with atypical fibroxanthoma, which occurs in a completely different clinical setting (i.e., sun-exposed skin, especially face and scalp of elderly patients), and usually shows epidermal ulceration, prominent pleomorphism throughout the lesion and numerous typical and atypical mitotic figures. Non-mesenchymal sarcomatous cutaneous tumors, such as melanoma and squamous cell carcinoma, can usually be identified if attention is paid to epidermal features and with the use of appropriate immunohistochemical stains.

**ATYPICAL FIBROXANTHOMA**

Atypical fibroxanthomas (AFX) is the term used since the beginning of the 1960s to describe a histologically highly pleomorphic cutaneous neoplasm that almost always pursues a benign clinical course.<sup>18,19</sup> As with all the so-called "fibrohistiocytic" tumors, the histogenesis of this lesion always has been controversial. Over the years the "histiocytic" theory has become less tenable due to non-specific electron microscopic and immunohistochemical findings and other potential candidates such as myofibroblasts, fibroblasts and undifferentiated mesenchymal cells have been proposed. As a result of this, and also due to the demise of pleomorphic malignant fibrous histiocytoma as a specific entity, it is apparent that this tumor no longer can be considered simply a superficial non-metastasizing variant of MFH. With the advent of new techniques, especially immunohistochemistry, it has become clear that AFX is a diagnosis of exclusion and that many cases classified as such in the past, especially those with metastasis,<sup>20</sup> probably represent examples of spindle cell squamous carcinoma or melanoma or other high grade sarcomas. Although the initial descriptions of AFX emphasized variants with a prominent spindle-cell population, over the years the presence of pleomorphism became the *sine qua non* for this diagnosis, thereby overlooking cases with mild pleomorphism and a prominent spindle cell population. This more monomorphic variant has been recognized as part of the spectrum of AFX and has been called spindle-cell non-pleomorphic AFX.<sup>21</sup> Most recent molecular data has affirmed that, in contrast to so-called 'MFH', AFX shows evidence of a UV-related pathogenesis<sup>22,23</sup> and, based on the usually benign clinical behaviour, these are most likely UV-induced pseudosarcomas, as proposed in the 1950s and 1960s.

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such, it features very prominently in consultation material. Similar cases have been reported in the past as benign fibrous histiocytoma with potential for local recurrence,<sup>8</sup> in a series of dermatofibromas extending into the subcutaneous tissue,<sup>9</sup> and also (perhaps less appropriately) under the term "atypical" fibrous histiocytoma.<sup>10</sup> Cellular benign fibrous histiocytoma is commonest in young adults, especially males, with a predilection for the limbs and head and neck region. Most lesions have been present only for a few months and they are usually bigger than common FH. The local recurrence rate is 20-30%, especially after incomplete excision.

More worryingly, several convincing cases with pulmonary metastasis have been documented recently<sup>11,12</sup> and I also have encountered several such cases (as well as additional examples of lymph node metastasis) among a total of almost 1000 examples of this 'entity' seen in consultation. How much significance we should attach to such 'outliers' remains uncertain. Clearly it would be both incorrect and an over-reaction to now regard all cellular fibrous histiocytomas as potentially malignant - but, since the cases which metastasized showed no evident morphologic clues to such behavior (at least initially), it seems inevitable that we will be caught out now and again by such treacherous neoplasms. However, repeated local recurrence should be viewed with concern in this context.

**Histologic Appearances**

Histologically, the most striking feature is the high cellularity of these tumors with a relatively more fascicular but partly storiform growth pattern. There is frequent involvement of the superficial subcutaneous tissue and, rarely, tumors are multinodular. Tumor cells typically have relatively abundant pale eosinophilic cytoplasm with a tapering nucleus. Normal mitotic figures are common and may number up to 10 per 10 HPF. In almost all lesions focal cytologic polymorphism (inflammatory cells, foam cells and giant cells) is seen but this may be very limited in extent. Epidermal hyperplasia is a frequent finding. Up to 12% of cases show central necrosis or infarction and, less commonly, ulceration is seen. Despite the unusual histologic features, identification of the lesion as a fibrous histiocytoma is not difficult if attention is paid to the epidermal changes, the presence of focal polymorphism and the somewhat hyalinized collagen bundles entrapped by tumor cells at the edge of the lesion. Occasionally there is overlap with the atypical and aneurysmal variants. Up to 60% of cases show focal positivity for alpha smooth-muscle actin in as many as 20-30% of the spindle-shaped cells. As many as 5% of cases may show some CD34 positivity, allowing possible confusion with DFSP.

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**Clinical Features**

AFX presents as a solitary, polypoid, ulcerated lesion in sun-damaged skin, especially of the head and neck and less commonly on the dorsum of the hands, of elderly patients. A short history of rapid lesional growth (often simulating a pyogenic granuloma) is common. Those cases reported in the past to occur in non-sun-exposed areas of young adults probably represent examples of atypical fibrous histiocytoma (see above). Behavior is usually benign and complete excision is generally curative. Local recurrence is uncommon and should raise at least a little doubt as to the diagnosis. If AFX is diagnosed using strict criteria (see below), metastasis is vanishingly rare.

**Histologic Appearances**

Histologic criteria for the diagnosis of AFX should be very strict and require the use of immunohistochemistry. Histologically, all lesions are unencapsulated dermal neoplasms, quite often surrounded by an epidermal collarette and trapping, but not destroying, adnexal structures. Growth tends to be expansile with only limited infiltration. In the neighboring dermis, solar elastosis is prominent. Ulceration is present in most cases and this makes evaluation for the presence of epidermal dysplasia or junctional activity to exclude epidermal origin difficult or impossible. Classical AFX is composed of highly pleomorphic histiocyte-like cells and very atypical giant cells interspersed with a variable number of spindle-shaped cells and inflammatory cells. Normal and abnormal mitotic figures are numerous. Most lesions have frequent small blood vessels and stromal hemorrhage is common. Some cases contain stromal osteoclastic giant cells and very rare examples may show clear cell morphology. The **spindle cell variant** of AFX is composed of fascicles of eosinophilic spindle cells with vesicular nuclei and one or two eosinophilic nucleoli,<sup>21</sup> thus often simulating malignant melanoma. Mitotic figures are common but cytologic pleomorphism is focal and can be absent. I do not accept deep (subcutaneous or further) invasion, necrosis or vascular or perineural invasion as features of AFX, although there may be focal very superficial invasion into fat. Such features, to me, indicate an unequivocal diagnosis of malignancy.

Immunohistochemistry is essential for confirming the diagnosis of AFX. Vimentin is diffusely positive in all cases and a few are positive focally for smooth-muscle actin, suggestive of fibroblastic or myofibroblastic differentiation. Keratin, S-100 protein and desmin are always negative, ruling out the main three differential diagnoses namely, spindle cell squamous cell

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carcinoma, spindle cell melanoma and leiomyosarcoma. Claims regarding the utility of CD10<sup>24</sup> and pro-collagen<sup>25</sup> in the diagnosis of AFX have yet to be widely substantiated, but the facts that both stain some examples of spindle cell squamous carcinoma and that CD10 expression is quite ubiquitous in mesenchymal lesions make their value in individual cases extremely limited, at least in my opinion.

#### CELLULAR NEUROTHEKEOMA

The concept (and diagnosis) of cellular neurothekeoma has been somewhat controversial, mainly because of confusion with regard to nomenclature and to the manner in which it was described. The lesion originally known simply as neurothekeoma (which is nowadays more usually called dermal nerve sheath myxoma) was a lobulated intradermal lesion which was entirely myxoid. Some time later, Rosati and colleagues from Italy coined the term 'cellular neurothekeoma' in describing three cases which shared this lobular configuration but which were more cellular.<sup>26</sup> Some years thereafter Barnhill and Mihm<sup>27</sup> reused the term cellular neurothekeoma in writing up a series of cellular lesions in which they stressed fascicularity and a resemblance to melanocytic lesions. It is the latter description which has generally been adopted but, in truth it turns out that these were simply different points along a morphologic continuum, probably unrelated to dermal nerve sheath myxoma.

#### Clinical Features

Cellular 'neurothekeoma', as described by Barnhill and Mihm in 1990, arises usually on the upper trunk or head and neck of children or young adults, with a predilection for females.<sup>28</sup> Most lesions are small, clinically non-specific, dermal nodules which generally measure less than 2 cm and are asymptomatic and, until recently, there seemed to be no tendency to recur. However it is now appreciated that, in addition to being histologically atypical in some cases (see below), very occasional cases can be larger, more deeply invasive and may very rarely recur, usually following incomplete excision on the face.<sup>28</sup> No convincing example with metastasis has been reported as yet.

#### Histologic Features

Cellular 'neurothekeoma' in its presently accepted form, differs from the cases described by Rosati and colleagues by being cellular throughout and by consisting principally of nests and fascicles of eosinophilic epithelioid or spindle-shaped cells with vesicular nuclei. These nests permeate the dermis in an infiltrative manner and share with dermal nerve sheath myxoma the

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entrapment of hyaline collagen bundles and is almost always CD34 negative, myxoinflammatory fibroblastic sarcoma (see below) which shows much more notable nuclear atypia (including bizarre mucin-containing pseudolipoblasts and large, usually mononuclear Reed-Sternberg-like cells), and myxofibrosarcoma which also shows more notable nuclear hyperchromasia and pleomorphism (especially if hypercellular), generally lacks areas with collagenous stroma in its morphologically low-grade form and is rare in the digits.

#### MYXOINFLAMMATORY FIBROBLASTIC SARCOMA

Myxoinflammatory fibroblastic sarcoma,<sup>35,36</sup> also known sometimes as inflammatory myxohyaline tumor, occurs principally (but not exclusively) in the distal extremities, particularly the hands, of adults over a wide age range. Because of their predilection for the digits, they may present as a very superficial lesion. I have also encountered histologically identical lesions more proximally in the limbs and on the trunk. It is characterized by frequent and repeated local recurrence, often necessitating some type of amputation, but metastasis appears (as yet) to be infrequent.

Macroscopically, these are poorly circumscribed, infiltrative or multinodular lesions, often involving tendosynovial structures, with variably myxoid and fibrous cut surfaces (albeit the latter tends to predominate). Histologically, these lesions often show at least some resemblance to myxofibrosarcoma, except for the presence of a) more solid fibrous areas, b) a more prominent mixed inflammatory infiltrate, and c) large polygonal or epithelioid cells with bizarre nuclei and inclusion-like nucleoli. These latter cells, which may appear "mummified" often resemble Reed-Sternberg cells or cells with viral inclusions. Foci with prominent myxoid stroma and large vacuolated mucin-containing pseudolipoblastic cells are a frequent feature. Immunohistochemistry plays no truly useful role in diagnosis, although there may be CD68 positivity and I have also found consistent fascin positivity and (less frequent) CD34 reactivity in the atypical lesional cells, albeit neither of these antigens has much specificity.

common presence of multinucleate cells and mitotic figures. However, in most cases, myxoid change is at most only focal (usually in the deeper parts of the lesion) and the overall appearances, at least superficially, are much more like a melanocytic neoplasm, except that there is no junctional or epidermal component. Extension into superficial subcutaneous fat is quite common. Immunohistochemically there are significant differences from conventional dermal nerve sheath myxoma in that cellular 'neurothekeoma' is consistently negative for S-100 protein but is commonly positive for NKI-C3 (a putative melanoma antigen) (100% of cases), neuron-specific enolase (NSE) (90% of cases) and quite often for SMA (57% of cases).<sup>28</sup>

For some time it was hard to reconcile how dermal nerve sheath myxoma and cellular neurothekeoma could be related in view of their apparently different morphology and immunophenotype and, as a consequence, the term neurothekeoma (at least transiently) was regarded with some suspicion. In fact we wrote a paper more than 10 years ago suggesting that these two 'entities' were unrelated and proposing that cellular neurothekeoma might possibly be an unusual epithelioid variant of pilar leiomyoma.<sup>29</sup> We<sup>30</sup> and others subsequently (and mistakenly!) proposed that these are truly related lesions, based principally on the evidence of morphologic hybrid lesions. The latter may either show abrupt transition from putative nerve sheath myxoma to cellular neurothekeoma or they may have the lobular architecture of dermal nerve sheath myxoma but with greatly increased cellularity and close cytologic resemblance to cellular neurothekeoma. In fact, it turns out that such 'hybrids' are consistently S-100 negative and, instead, they have the same immunophenotype as cellular neurothekeoma, of which they seem to be a myxoid variant – and, in truth, others had earlier reached a similar conclusion<sup>31</sup> but their proposal had not initially gained popularity. Furthermore, ultrastructural analysis of cellular neurothekeoma shows no evidence of nerve sheath differentiation and, instead, appears to show myofibroblastic features. Morphologically atypical variants of cellular neurothekeoma (accounting for perhaps 5% of cases) have subsequently been identified.<sup>28,32</sup> Atypical features include high mitotic rate, notable cytologic pleomorphism and deeper or vascular invasion. However available data so far suggest that these morphologically atypical cases are essentially benign and local recurrence is extremely uncommon.<sup>28</sup> Given their often very worrisome morphologic features, care should be taken to identify other more typical cytoarchitectural features as well as the characteristic immunophenotype in order to avoid a mistaken diagnosis of malignancy.

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#### Differential Diagnosis

The differential diagnosis of cellular neurothekeoma includes principally melanocytic lesions (Spitz nevus and malignant melanoma) which, aside from the absence of any junctional or epidermal component, are most easily excluded by their S-100 positivity. There may also be some morphologic overlap with juvenile xanthogranuloma or benign fibrous histiocytoma but the presence of a focally nested architecture, the relative lack of cytologic (as opposed to nuclear) polymorphism and the absence of lipidized cells is usually helpful.

#### DIGITAL FIBROMYXOMA

Digital fibromyxoma,<sup>33</sup> also known as digital myxoma or superficial acral fibromyxoma, is not uncommon but has received little attention in the literature and seems quite often to cause diagnostic confusion. These lesions show a very striking predilection for the toes and fingers, very often developing adjacent to the nail bed, and present most often as a solitary, slowly growing mass in middle-aged adults, with a moderate male predominance. However, the overall age range is wide, albeit young children are rarely, if ever affected. The majority of lesions measure less than 2 cm in maximum diameter and, although excision is often marginal or even incomplete, local recurrence is a feature of no more than 10% of cases and is non-destructive.

Histologically, these are poorly marginated dermal and subcutaneous lesions which, at low power, have a variably myxoid or collagenous stroma. Cellularity is variable but generally moderate to high and the lesional spindle cells have a uniform non-descript fibroblastic appearance with tapering, bipolar or stellate nuclei and pale indistinct cytoplasm. Typically there is no well-developed architectural pattern, although fascicular foci may be evident. There may be mild focal nuclear hyperchromasia/atypia but this is never striking and mitoses are scarce. In occasional cases, multinucleate giant cells, similar to those seen in pleomorphic fibroma or fibroepithelial stromal polyps, may be seen. Vascularity is variable but usually most prominent in the myxoid areas. As in many myxoid lesions, most cells are often quite numerous. Immunostains, if performed, usually show CD34 positivity, while S-100 protein, GFAP, SMA and desmin are negative. Some authors have described quite frequent EMA positivity,<sup>33</sup> but this is of dubious significance.

Differential diagnosis includes superficial angiomyxoma,<sup>34</sup> which is typically more lobulated, generally less cellular, lacks areas with fibrous stroma and is uncommon on the digits, myxoid neurofibroma, which is also less cellular, contains nerve bundles and is S-100 protein positive, fibrous histiocytoma, which is only rarely myxoid, typically more storiform, shows lateral

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Extrapolation of the diagnostic criteria of deeply located tumors to a superficially located tumor is questionable and resulted in confusing spectrum of terminology such as, cellular schwannoma, atypical schwannoma, and "borderline-transformed" schwannoma<sup>(20-26)</sup>.

In the superficial dermis these lesions are particularly difficult, because of the often-epithelioid cytology, nuclear atypia, mitotic figures and the associated lymphoid infiltrate imitating nodular amelanotic melanoma, which may or may not express melanosome-related antigens.

Unfortunately, so far, no comprehensive studies have been performed to address this issue satisfactorily. The pathologist is left to his best judgment to use clinicopathologic correlation to advise on the biologic behavior of the lesion<sup>(27)</sup>.

#### 4. Epithelial Sheath Neuroma and Dendritic Cell Neurofibromas with Pseudorosettes

These cases represent very new observations on developing entities. Epithelial sheath neuroma is a bizarre combination of epithelial sheath surrounding nerve bundles. The histogenesis is controversial<sup>(28)</sup>. The epithelial cells appear to be benign and unlikely represent a perineurial tumor spread. Despite the distinct appearance, the changes most likely represent a reactive or metaplastic process rather than a true de-novo neoplasm.

Dendritic cell neurofibroma is a better-defined entity composed of multinodular proliferation of small-lymphocyte-like cells and large cells with vesicular nuclei and dendritic extension<sup>(29)</sup>. The smaller cells have a rosette-like arrangement around the larger cells in a neurofibromatous background. The cells express S-100 protein, CD57, and epithelial membrane antigen. Because of the ganglion and rosette-like structures, the differential diagnosis can be extensive. While so far, there has not been a satisfiable explanation for this peculiar combination of changes, the morphologic findings appear to be quite consistently encountered<sup>(30)</sup>.

As this summary illustrates, several new morphologic subtypes of cutaneous neural tumors have been recognized. It is important to emphasize that despite the striking morphologic features, the clinical characterization of these lesions is still evolving, and the biologic potential of these lesions

## Problematic Cutaneous Neural Tumors

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As our recent attention in dermatopathology has shifted more to the superficial soft tissue neoplasms, the field of cutaneous neural neoplasms has also been considerably expanded. Much of the new information provided us with better characterization of existing tumors, but also with the diagnostic dilemma of dealing with a group of "newly" described entities. Many of these newly described lesions have no well-established clinical features, reproducible histologic features, or a predictable histologic behavior. While their recognition is important for diagnostic purposes, their significance remains questionable. The purpose of this presentation is to summarize some of the most important observations of selected entities of this field.

The developments in cutaneous neuropathology can be divided into three main categories:

- 1) Well-established entities with new information
- 2) Recently established entities with new developments
- 3) New observations on evolving entities.

Because of the time limitations, only the following selected examples will be discussed from each category.

#### I. Cellular Neurofibroma with Atypia

While the relationship between neurofibroma—neurofibromatosis—malignant peripheral nerve sheath tumor is well established, the relevance of cytologic atypia in solitary neurofibromas has not been well defined. A relatively recent study by Lin BT et al<sup>(1)</sup> tried to address this issue and found there was a subset of neurofibromas in which the cytologic atypia or hypercellularity alone

has not been fully established yet. While reclassification of these lesions may be necessary in the future, familiarity with these new developments remains important for better patient management.

was not indicative of malignancy. These tumors were characterized by the usual growth pattern of neurofibromas, but composed of cells with mild to severe cytologic atypia, hyperchromasia, bizarre giant cells, low mitotic activity (1<10 HPF) and focal degenerative changes. Despite the concerning morphologic changes in the tumors, the patients did well on conservative treatment.

This study suggests that a separated designation for neurofibromas with these features is justifiable and cytologic atypia alone may not be a marker of malignancy in neurofibromas. Consequently, patients with these lesions can be treated conservatively.

#### 2. Cellular Neurothekeoma

Although Rosati et al described this entity in 1986 and the clinicopathologic features have been well established, its histogenesis has remained controversial<sup>(2)</sup>. It has been postulated that cellular neurothekeoma represent the less-differentiated end of the nerve sheath myxoma spectrum, based on the occasional co-existence of myxoid and "cellular" features within the same lesions<sup>(3,4)</sup>. This has been further complicated by the observation of divergent mesenchymal differentiation within the tumor, such as smooth muscle, cartilaginous, osteoid and neuroendocrine<sup>(5-8)</sup>. While earlier immunohistochemical and electron-microscopic studies appeared to support the light microscopic observation of divergent mesenchymal differentiation<sup>(9-10)</sup>, numerous recent studies offered a wide range of speculations for its histogenesis<sup>(11-15)</sup>.

Although the original assumption on biologic behavior of cellular neurothekeoma was benign, it was recently challenged by a study of Busam et al<sup>(16)</sup>, who described a cytologically atypical, mitotically active variant of this lesion. A conservative excision is recommended for partially removed lesions, however Mohs surgery was also advocated<sup>(17-18)</sup>.

#### 3. Cellular Schwannoma:

Cellular Schwannoma is usually a tumor of deep soft tissues and the viscera; however, hypercellular variants of schwannomas rarely occur in the superficial dermis representing considerable diagnostic dilemma<sup>(19)</sup>. The diagnostic difficulty stem from the disagreement between experts regarding the acceptable mitotic rate and the tumor related degenerated features.

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DermPath Companion Meeting

USCAP 2007

Bullet points

John R. Goldblum, M.D.

- The utility of identifying lipoblasts in the diagnosis of well-differentiated lipomatous tumors
- Controversies in the nomenclature of well-differentiated lipomatous neoplasms
- Some of the more common lipomatous neoplasms that can be mistaken for a sarcoma

Lipomatous tumors are among the most commonly encountered tumors in soft tissue pathology. Although the vast majority of such lesions are lipomas and easily diagnosed, there are a number of lipomatous tumors (both benign and malignant) that are diagnostically challenging to the general surgical pathologist and the dermatopathologist. In fact, dermatopathologists very frequently encounter difficult lipomatous neoplasms, and it has been my own personal experience that a high proportion of consultation cases I review are unusual or difficult to diagnose lipomatous neoplasms excised by dermatologists and reviewed by dermatopathologists.

There are a number of benign lipomatous tumors that have unusual features which can make the pathologist believe one is evaluating a liposarcoma (or possibly even some other type of sarcoma). Similarly, there are some malignant lipomatous tumors (e.g. atypical lipomatous tumor/well-differentiated liposarcoma) that are easily mistaken for a lipoma. This presentation will focus on some of the more commonly encountered problems in the diagnosis of lipomatous neoplasms (particularly well-differentiated lipomatous neoplasms) to the general surgical pathologist/dermatopathologist.

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#### Lipoblasts: are they necessary for a diagnosis of liposarcoma?

Virtually any time one discusses lipomatous tumors, the topic of lipoblasts is discussed. As a general rule, I do not look for lipoblasts for a number of reasons. First, lipoblasts are not required for a diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma. As discussed below, the identification of enlarged, atypical, hyperchromatic nuclei is the prerequisite for rendering a diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma. In fact, one may not be able to identify any definite lipoblasts in an atypical lipomatous tumor/well-differentiated liposarcoma, even if one is meticulous about searching for these cells. Second, lipoblasts can actually be identified in benign lipomatous tumors. For example, I have seen a number of examples of pleomorphic lipoma with unequivocal lipoblasts. Therefore, the recognition of a lipoblast does not necessarily mean that a given tumor is malignant. Finally, and probably most important, there is simply too much interobserver variability in the recognition of lipoblasts. In my opinion, "lipoblasts are in the eye of the beholder," and there are a number of cells that are essentially histologically indistinguishable from lipoblasts which are not ("pseudolipoblasts"). For example, one can encounter lipoblast-like cells in atrophic fat which are essentially indistinguishable from the most perfect lipoblasts one might encounter in a myxoid liposarcoma. One can also encounter lipoblast-like cells in lipomas with fat necrosis or hibernomas. In addition, I have seen a number of examples of neoplasms that infiltrate the surrounding subcutaneous tissue, isolating individual cells which are indistinguishable from lipoblasts. Therefore, one should not have to rely on the identification of lipoblasts to separate a benign from malignant well-differentiated lipomatous neoplasm.

## Soft Tissue Tumors with Lipocytic Differentiation

### American Society of Dermatopathology

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#### The nomenclature of well-differentiated lipomatous neoplasms

Unfortunately, the nomenclature of well-differentiated lipomatous tumors has been fraught with confusion. Before 1979, differentiated lipomatous tumors characterized by atypical stromal cells intermingled with mature fat and variable numbers of lipoblasts were all designated as well-differentiated liposarcomas, whether they were found in the subcutaneous tissue, the deep soft tissues of the extremity, or the retroperitoneum.<sup>1</sup> However, in 1979, Evans et al proposed a change in nomenclature because of the variability of clinical behavior depending on site.<sup>2</sup> These authors evaluated 30 well-differentiated lipomatous lesions, all of which were histologically similar but varied according to site. Nine cases were found within the subcutaneous tissue, and none of these cases recurred, dedifferentiated, metastasized, or resulted in patient death. Of 13 lesions in the deep soft tissue (intramuscular) of the extremities, 9 cases (69%) recurred, although similar to the subcutaneous lesions, none dedifferentiated, metastasized, or resulted in patient death. Of the 8 retroperitoneal lesions, 5 recurred (62%), and although none of the cases dedifferentiated or metastasized, 3 patients (37%) died of their disease. Based upon these data, Evans et al proposed that the lesions in the subcutaneous tissue be called "atypical lipoma," and the intramuscular extremity lesions be called "atypical intramuscular lipoma," given their lack of associated morbidity or mortality. However, he proposed that the term "well-differentiated liposarcoma" be retained for histologically identical lesions of the retroperitoneum, given their propensity to recur and occasionally result in patient death.

In 1987, Azumi and colleagues performed a similar study on 69 well-differentiated lipomatous lesions.<sup>3</sup> Similar to Evans' study, none of the 17 subcutaneous lesions recurred, dedifferentiated, metastasized, or resulted in patient death. Although 29% (7/31 cases) of the deep soft tissue lesions recurred, none resulted in significant morbidity or mortality. Of 21 retroperitoneal lesions, 14 recurred (67%) and 5 dedifferentiated (23%). Although none of the

cases metastasized, 9 patients (43%) died of disease. Thus, these authors proposed that the subcutaneous and deep soft tissue lesions be called "atypical lipoma" and opted to retain the term "well-differentiated liposarcoma" for the retroperitoneal lesions.

In 1992, Weiss and Rao re-analyzed a large group of well-differentiated lipomatous tumors with a minimum follow-up of 2 years, and found that behavior was strongly influenced by location, with retroperitoneal lesions having the worst prognosis, deep soft tissue lesions having the best prognosis, and inguinal lesions having a prognosis in between.<sup>4</sup> Although their data on retroperitoneal lesions is similar to the other studies (recurrence rate: 91%; dedifferentiation: 17%; metastasis: 17%; death due to disease: 33%), 3 of 46 cases from the deep soft tissue of the extremities (6%) showed areas of dedifferentiation. These authors concluded that dedifferentiation is not a site-dependent, but rather a time-dependent phenomenon, and is observed in locations with a high likelihood of clinical persistence of disease. Thus, they recommend the use of the term "well-differentiated liposarcoma" for lesions in all locations, except those located in the subcutis, which are usually easily cured at initial excision and do not have the opportunity to dedifferentiate. They proposed the term "atypical lipoma" for these subcutaneous lesions. Finally, there are some who propose calling all of these neoplasms, regardless of location, "atypical lipomatous tumors," since they are histologically indistinguishable and vary only with respect to location/depth. Therefore, one's preferred nomenclature depends upon whether one is a "lumper" or a "splitter." In the end, what is of paramount importance is the communication that occurs between the pathologist and the clinician in terms of the necessity for complete excision of a given neoplasm.

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clinicopathologic setting and the superficial nature of the lesion, this tumor can be distinguished from ALT/WDL or pleomorphic liposarcoma.

In 1975, Enzinger and Harvey described a lesion (spindle cell lipoma) with a similar clinicopathologic setting as that seen in pleomorphic lipoma, but characterized histologically by a mixture of lipocytes and uniform bland spindle cells within a myxoid stroma and accompanied by dense collagen.<sup>6</sup> Spindle cell lipoma is probably part of a spectrum with pleomorphic lipoma, given the similar clinicopathologic setting and overlapping histologic features. Up to 25% of cases of pleomorphic lipomas show areas indistinguishable from spindle cell lipoma. Furthermore, both spindle cell lipoma and pleomorphic lipoma typically stain diffusely for CD34.<sup>7</sup> The spindle cells are often deposited in a prominent myxoid stroma composed primarily of hyaluronic acid, and in those cases in which the lipomatous component is inconspicuous, differentiation from other myxoid tumors, including myxoid sarcomas, may be difficult. Similar to pleomorphic lipomas, spindle cell lipomas are treated with local excision, and virtually never recur.

Cytogenetic studies have also linked spindle cell and pleomorphic lipoma, both of which generally show monosomy 16 or partial loss of the long arm of chromosome 16 in association with unbalanced alterations of the long arm of chromosome 13.<sup>8</sup> These cytogenetic alterations differ from those found in ALT/WDL (giant marker and ring chromosomes derived from the q13-15 region of chromosome 12), supporting the concept that these are histogenetically different lipomatous tumors. Other benign lipomatous tumors also reveal characteristic cytogenetic abnormalities. The most common cytogenetic aberration identified in solitary lipomas is a translocation between 12q13-15 and various other chromosomes.<sup>9</sup> Hibernomas consistently reveal abnormalities involving chromosomes 11q and 10q22, and lipoblastomas consistently reveal deletions of the short arm of chromosome 8.<sup>8</sup>

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### Problematic benign lipomatous tumors

The vast majority of benign lipomatous tumors are straightforward and do not cause the pathologist any difficulty. However, there are a number of benign lipomatous tumors that, on occasion, can have histologic features which might suggest one is dealing with a sarcoma. Although dermatopathologists do not typically encounter such lesions, the **intramuscular lipoma** can be an exceedingly difficult diagnosis to make with certainty. In general, the larger and deeper the well-differentiated lipomatous neoplasm, the more likely the lesion is to be malignant. However, there are large and deep benign lipomatous tumors - i.e. the intramuscular lipoma. As implied by the name, these lesions arise as large intramuscular masses, typically in the deep soft tissue of the thigh or buttocks. In general, these lesions need to be extensively sampled (at least one section per cm of tumor) in order to exclude the possibility of an atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL). The interdigitation of mature adipose tissue and skeletal muscle is a strong indication that one is dealing with an intramuscular lipoma, as opposed to an ALT/WDL, since the latter entity generally pushes aside the skeletal muscle to the periphery of the lesion. One must be wary of atrophic skeletal muscle fibers, which can closely mimic the enlarged, hyperchromatic nuclei diagnostic of ALT/WDL.

**Angiolipomas** are relatively common lesions and often occur in "crops" in one general anatomic location. These lesions are composed of an intimate admixture of mature adipocytes and slit-like blood vessels, some of which contain fibrin thrombi. The classic angiolipoma is not difficult to diagnose, but on occasion one may encounter a cellular variant of angiolipoma that can be worrisome for an angiosarcoma. I have seen such lesions arise in the soft tissue near the breast, where one already has a heightened awareness of angiosarcoma. These lesions are generally small and very well circumscribed, and the vascular structures do not infiltrate into the surrounding soft tissue as one would expect for an angiosarcoma. Less cellular zones of classic

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angiolipoma are also a useful finding. **Chondroid lipoma** is fortunately an exceedingly uncommon neoplasm, but this lesion can cause difficulty in diagnosis, since it can be mistaken for either a myxoid liposarcoma or a myxoid chondrosarcoma. Grossly, these lesions have a yellow-brown appearance similar to classic lipoma. The presence of cartilage-like areas can either be focal or occupy most of the lesion and in the latter circumstance can cause confusion with respect to another type of sarcoma.

In my experience, the most common difficulty arises in diagnosing **pleomorphic/spindle cell sarcoma**. In 1981, Shmookler and Enzinger described 48 cases of a lipomatous lesion characterized by mature adipose tissue admixed with bizarre, pleomorphic, multinucleated giant cells.<sup>5</sup> Many of these bizarre cells had a floret-like arrangement of nuclei, and were often associated with interlacing bundles of dense collagen. 83% of these lesions occurred in males, with a mean age of 57 years, and 78% of the cases occurred either on the shoulder, neck or back. None of the cases recurred, confirming the clinical benignancy of this lesion. Thus, pleomorphic lipoma is a unique variant of lipoma occurring in a particular clinicopathologic setting; that is, a well-circumscribed lesion in the subcutis of a middle-aged or elderly male in the shoulder, neck or back region.

Grossly, pleomorphic lipomas are typically well circumscribed and are sharply demarcated from the adjacent mature adipose tissue. Although the average size of this tumor is close to 4.0 cm, they may be significantly larger (up to 12 cm). Histologically, this lesion is characterized by multinucleated floret cells with a wreath-like arrangement of hyperchromatic nuclei. These cells are admixed with mature lipocytes and dense, birefringent collagen fibers. Occasionally, there is a prominent myxoid stroma composed primarily of hyaluronic acid. Lipoblast-like cells have been described in up to 50% of cases. Thus, this tumor does have overlapping features with well-differentiated liposarcoma. However, given the characteristic

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### VASCULAR TUMORS OF THE SKIN

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### BENIGN VASCULAR NEOPLASMS

Regardless of their particular histologic appearances, hemangiomas may be observed throughout life and assume relatively uniform macroscopic characteristics (1-3). They are bluish-red, non-ulcerated, relatively well-circumscribed, variably-fluctuant masses that may be macular, plaque-like, or protuberant in nature and commonly blanch when manually compressed by the examiner. The sizes of hemangiomas vary considerably, from 1 to 2 mm to more than 20 cm in greatest dimension. Large areas of the skin surface may be affected by those lesions that are part of the Sturge-Weber syndrome, and these also tend to be confined to one side of the body. Hemangiomas are not uncommonly congenital proliferations, and if so, they usually regress spontaneously with maturation of the host (1,3). Patients with **Kimura's disease** (tentatively included as a form of cutaneous hemangioma) often have multifocal nodular and violaceous lesions of the skin, peripheral eosinophilia, and enlargement of those lymph nodes draining the affected cutaneous area (4). Another distinctive subtype-- "**targetoid hemosiderotic**" (also known as "**hobnail**") **hemangioma**-- is named for its clinical appearance, which may simulate that of an archery target at some stage of lesional evolution (5-7).

Despite the fact that all cutaneous hemangiomas are benign, some variants-- such as lobular capillary hemangioma and infiltrating hemangioma-- may be floridly multifocal and difficult to approach surgically (8). Recurrence of such lesions therefore does not necessarily indicate progression to a biologically aggressive neoplasm.

#### Histologic Findings:

In the past few years, several microscopic variants of hemangioma of the skin have been recognized. These include the well-known capillary and cavernous subtypes-- composed of small-bore and large ectatic vascular spaces, respectively-- as well as mixed capillary-cavernous/venous hemangiomas (1), lobular capillary hemangiomas ("pyogenic granulomas") (9), "cellular" capillary hemangiomas (1), acquired tufted hemangiomas (10), glomeruloid hemangiomas (11), verrucous hemangiomas (12), infiltrating hemangiomas (13), targetoid/hobnail hemangiomas (6,7), epithelioid ("histiocytoid") hemangiomas (14,15), and Kimura's tumor/disease (4,15).

The lesion now known as **epithelioid hemangioma** (15) has been the subject of considerable terminological debate in recent years. Alternative designations for this tumor include "**angiolymphoid hyperplasia with eosinophilia**" (25) and "**histiocytoid hemangioma** (14). The salient feature of epithelioid hemangiomas is the plump, cuboidal appearance of the endothelial cells that line constituent blood vessels. The latter channels have the dimensions of capillaries or venules, and their lumina are indistinct because of the space occupied by proliferating endothelia. Nuclear contours in the tumor cells are round or slightly indented, chromatin is dispersed, and nucleoli are indistinct (15). These characteristics led Rosai et al. to focus on a morphologic similarity between the nuclei of such neoplasms and those of histiocytes (14). Angiolymphoid hyperplasia with eosinophilia is nothing more than an inflamed version of epithelioid hemangioma, in which the stroma between constituent dermal blood vessels is rich in lymphocytes and eosinophils (25).

Like other morphologic variants of hemangioma, a basically lobular substructure is observed in epithelioid hemangiomas as well. Nevertheless, a unique finding in the latter neoplasms is their potential association with large arteries or veins in the skin, such that the tumoral blood vessels appear to emerge from pre-existing vascular adventitia like a swarm of bees.

Considerable attention also has been given to the possible synonymy between epithelioid hemangioma and **Kimura's disease/tumor** (4). However points of convincing clinicopathologic dissimilarity do exist between these two neoplasms. Kimura's tumor features a striking stromal lymphoid infiltrate-- complete with germinal centers-- and is centered more deeply in the skin. Moreover, constituent vessels are more elongated than those of epithelioid hemangioma, and tumor cell nuclei do not have the complex contours of those in the latter lesion. As already mentioned, Kimura's disease often includes the presence of regional lymphadenopathy and eosinophilia in the peripheral blood, whereas epithelioid hemangiomas are unassociated with these findings (15).

### BORDERLINE ENDOTHELIAL TUMORS

#### Papillary Endovascular (Lymph)-Angioendotheliomas

Clinical Features: Papillary endovascular angioendotheliomas (PEA) were first described by Dabska in 1969 (26), and have subsequently become known using her name as an eponym (i.e., Dabska's tumor). A more recent paper (27) has suggested that a more correct

The basic structure of all of these proliferations is that of *organized formation of complete intercellular lumina*, mantled by pericytic cuffs of variable thickness and lined by bland endothelial cells with a spectrum of appearances (16). Another feature common to all the hemangiomas (possibly excepting "infiltrating" and "targetoid" lesions) is a *lobular configuration* (9,16). Discrete groups of lesional blood vessels and investing pericytes are separated from one another by fibrous stroma, and they contain a central "feeder" vessel in each lobule. Indeed, the **lobular capillary hemangioma** (LCH) is the prototypical example of this morphologic arrangement. Although the latter tumor is most commonly superficial and polypoid-- often with overlying ulceration-- it also may be seen deep in the dermis or subcutis (8). Examples of LCH that are traumatized may show regenerative nuclear atypia and mitotic activity in constituent endothelial cells (17); indeed, we have seen lesions such as this that were misdiagnosed as vascular sarcomas because of these features. However, attention to the fact that the lobular character of the tumor is retained in these circumstances should help to avoid erroneous interpretations.

"**Cellular**" **capillary hemangioma** is simply regarded as a variant form of LCH in which the boundaries between adjacent lobules are indistinct, and the lumina formed by constituent endothelial cells are extremely small. In our opinion, this lesion is synonymous with the "angioblastoma" of Nakagawa (18). Another alternative designation-- that of "juvenile hemangioendothelioma"-- is unacceptable for diagnostic use, because hemangioendotheliomas in general are regarded as potentially-malignant neoplasms.

**Verrucous hemangioma** is a variant of cavernous hemangioma that is typified by overlying epidermal papillomatosis, parakeratosis, and hyperkeratosis (12). Keratinocytic rete ridges extend downward in this tumor to "embrace" or surround lesional blood vessels, much in the same manner as that observed in angiokeratoma (see below).

**Acquired tufted hemangioma** is another subtype of LCH, in which the lobules of tumor cells project into ectatic but pre-existing dermal veins and lymphatics (10,19). This arrangement yields a low-power appearance which has been likened to "cannon balls in the dermis" by Wilson-Jones and Orkin (19). In light of this description, it is likely that some examples of "intravenous pyogenic granuloma" described by Cooper et al. (20) would be regarded as acquired tufted hemangiomas currently.

designation for this neoplasm is that of papillary intralymphatic angioendothelioma. It is apparently seen only in children and adolescents, as a fluctuant, ill-defined reddish plaque or nodule that ranges in size up to 5 cm. A zone of dermal edema may surround such neoplasms (26,28). "Metastases" of PEA to regional lymph nodes were reported in the seminal series of cases, but other authors have since suggested the alternative interpretation that the nodal implants actually represented tumor "satellites" as part of a field neoplasia phenomenon (29). Nevertheless, PEA does have a marked propensity to recur locally after surgical excision, justifying its inclusion as a "borderline" proliferation (26,30).

Histologic Findings: The microscopic features of PEA are distinctive. As its name suggests, this tumor is confined to pre-existing vascular spaces in the corium, most of which have the properties of dilated lymphatic channels. Also in similarity to deep lymphangiomas of the skin, PEA features contiguous dermal fibrosis and intralesional aggregates of lymphocytes. The latter cells are also evident in intimate admixture with plump endothelial cell clusters inside of the affected vessels (26,27).

The papillae of PEA are composed of polyhedral cells with round nuclei, dispersed chromatin, and small nucleoli. As just mentioned, mature lymphocytes commonly mantle the peripheral aspects of the papillary formations, and they contain internal, globular, intercellular eosinophilic deposits of basement membrane material. These inclusions may be labeled with the periodic acid-Schiff stain or with immunostains for laminin and collagen type IV (17).

Adjacent blood vessels in PEA that do not contain papillae are nonetheless lined by atypical endothelial cells, with hyperchromatic nuclei. Small areas of racemose vascular proliferation also may be apparent in the dermis, as seen in well-differentiated angiosarcomas. Mitotic activity is present but limited in scope.

#### Epithelioid Hemangioendotheliomas

Clinical Attributes: Epithelioid hemangioendotheliomas (EH) are subcutaneous lesions that only uncommonly involve the dermis. As such, they present as firm tan-pink nodules and plaques measuring several cm in maximum diameter. Adult patients are primarily affected, with a slight predilection for women. The trunk and extremities are the usual sites of origin (31-33). Some patients with EH of the skin will concurrently have histologically-identical tumors in the lung (where they were known in the past as "intravascular bronchoalveolar

**Glomeruloid hemangioma** is a newly described variant in which proliferating vascular channels take on the size of dermal venules, and are grouped together in discrete clusters such that they passively resemble glomeruli of the kidney on low-power microscopy (21). The significance of such tumors resides in their association with the "POEMS" syndrome, a constellation of disorders (polyneuropathy, organomegaly, endocrinopathies, monoclonal gammopathies, and skin lesions) that is usually linked to an underlying lymphoproliferative disease or plasma cell dyscrasia (11,21).

**Infiltrating hemangioma** is again composed of venule-sized channels, but this lesion differs from the others described thus far because it shows no circumscription. A disorganized proliferation of randomly-arranged (but complete) luminal profiles is seen throughout the dermis and subcutis in this variant, and it may involve underlying fascia and muscle as well. Viscera, bones, and multiple soft tissue sites are affected in some cases, justifying diagnostic use of the term "angiomatosis" (13).

The **targetoid hemosiderotic ("hobnail") hemangioma**, as well as another closely allied variant-- **microvenular hemangioma**-- are probably related to the infiltrating variant just cited (5-7,22). Nonetheless, the first two of these lesions show a greater penchant for formation of incomplete and interanastomosing vascular spaces that "dissect" through dermal collagen and subcuticular tissue (5). Small papillary projections of bland endothelial cells also may project into the lumina of targetoid hemangiomas (6,7). These histologic features often cause considerable concern regarding the potential diagnosis of a vascular sarcoma. Nonetheless, the advancing boundaries of targetoid hemangiomas are relatively well-defined (unlike those of endothelial malignancies), and an organized rim of dense hemosiderin deposition is often apparent peripherally (5). Other lesions with closely-similar microscopic features include the so-called "**benign lymphangioendothelioma**" (23) and "**multinucleate angioreticulohistiocytoma**" (24). However, the latter tumors do differ from targetoid hemangioma. Benign lymphangioendothelioma contains proteinaceous lymphatic fluid rather than luminal erythrocytes, lacks stromal hemosiderin deposits, has a more regimented superficial constituency by vertically-aligned vascular spaces, and may be invested by lymphoid infiltrates. Angioreticulohistiocytoma contains multinucleated stromal cells that border vascular spaces, and in some foci, may appear to line them.

tumors" [IVBATs]) and the liver (32). Under these conditions, it is impossible to determine whether the visceral and cutaneous lesions are independent primary neoplasms, or whether they represent metastases of one another. EH recurs in up to 40% of cases, and approximately 15% metastasize to distant extracutaneous locations (34). Histologic Features: EH is typified by disorganized sheets and cords of large polyhedral tumor cells with amphiphilic cytoplasm, prominent cytoplasmic vacuoles, and round but eccentric nuclei. Chromatin is vesicular and small nucleoli are often seen. The neoplastic cells make no attempt to form complete intercellular vascular lumina, as seen in epithelioid hemangiomas (17). However, like the latter tumor, EH has a proclivity for growth around pre-existing large blood vessels. Mitotic activity and necrosis may be apparent, but they are relatively inconspicuous when present. The background stroma is variably fibrous or myxoid in character (32).

Two diagnostic errors are common in the evaluation of EH. First, one may focus on the cord-like arrays of polygonal cells in some cases, leading to a misinterpretation of metastatic carcinoma. Secondly, those lesions with extensive cytoplasmic vacuolization may erroneously be labeled as adipocytic in nature. The application of electron microscopy or immunohistochemical studies for epithelial and endothelial determinants (see above) is useful in resolving such uncertainties.

#### Spindle-Cell "Hemangioendothelioma" (Hemangioma)

Clinical Characteristics: Spindle-cell "hemangioendothelioma" (SCH)—now regarded as a benign entity (spindle-cell hemangioma [35]) is a tumor entity that is seemingly confined to the skin and subcutis (36,37). It is included in this section with other hemangioendotheliomas mainly because of historical context. This lesion has a long period of evolution-- up to 30 years-- and therefore usually presents in young adulthood (36). It has a marked tendency for multifocality, and a predilection for the skin of the extremities. It also may arise in the setting of Maffucci's syndrome, in which multiple enchondromas of bone are also observed (36-38).

SCH is a multinodular, red-violet, fluctuant lesion that may attain a size of several centimeters. Its original "borderline" status stemmed from the fact that local recurrence after surgical excision was thought to be a common event, being seen in up to 70% of cases (36). However, reanalysis of this point has made it appear likely that such "recurrences" are

actually a reflection of multifocality (35). Only one documented instance of distant metastasis by SCH has been reported to date, and this case was unusual in that the patient had received radiation therapy (36). Another controversy surrounding this lesion centers on whether it is, indeed, a neoplasm at all. Some authors instead prefer the view that SCH represents a reactive endothelial proliferation (39,40).

**Histologic Features:** SCH has a distinctive microscopic appearance that represents an "amalgamation" of the attributes of cavernous hemangioma and Kaposi's sarcoma (33,36). One observes an intimate admixture of large, ectatic vascular spaces in the dermis-- which often contain luminal thrombi and may harbor calcifications as well-- with spindle-cell foci showing extravasation of erythrocytes and intracytoplasmic vacuoles. The latter finding is shared with **epithelioid** hemangioendothelioma, as described above. Nuclei of the tumor cells in both components of SCH are relatively bland, and mitotic activity is limited. The peripheral borders of the proliferation are poorly-defined, and small "satellite" lesions may be observed within several millimeters on either side of the main mass (37). Permeation into the subcutis or deeper soft tissues is relatively common. Small areas featuring racemose, interanastomosing, "dissecting" vascular channels may be noted as well.

#### Kaposiform Hemangioendothelioma

**Clinical Features:** Kaposiform hemangioendothelioma (KHE) is a neoplasm that is most commonly observed in children and adolescents, although examples also have been reported in adult patients as well (41-44). There is no apparent gender predilection. This cutaneous tumor may take the form of rapidly-enlarging red-violet plaques, nodules, or grouped telangiectasias, and may reach a maximum size of several cm. Lesions in the skin may be accompanied by concomitant KHEs in the deep soft tissues, and an association with lymphangiomatosis is also common (41,44). Another peculiar clinical linkage of KHE is with the Kasabach-Merritt phenomenon (peripheral consumption of platelets and other formed blood elements), producing a potentially life-threatening coagulopathy (41).

The preferred therapy for this lesion is complete surgical excision, when possible. However, administration of interferon, steroids, and other agents may be necessary for unresectable KHEs (44). Death may occur as a result of the cited complications of these neoplasms, and their aggressive local growth may produce considerable morbidity, but metastasis has not been documented.

Interestingly, several common threads have emerged that bind all of the variants of KS together. One factor is the HLA-DR5 allele, which is greatly overrepresented in KS patients when compared with the population at large (55). The second is seropositivity for the cytomegalovirus (CMV) (56). In reference to that observation, some authors have advanced the hypothesis that KS is not a neoplasm at all, but instead represents an unusual tissue reaction to the latter infectious agent (57). We do not subscribe to the latter view. It has been shown that KS cells express an activated oncogene, termed "K+FG" (58). Moreover, the features of this proliferation in transfection studies are most consistent with those of a true neoplasm, and the pattern of visceral involvement seen in advanced cases is unlike that of any known viral disease. Lastly, genomic sequences of human *Herpes* virus type 8 (HHV8) have been detected in Kaposi's sarcoma by molecular analyses (59). It would therefore appear tenable to conclude that KS may result from the effects of HIV-CMV-HHV8 co-infection in susceptible (HLA-DR5-positive?) individuals, allowing viral agents to express a latent potential for cellular transformation and oncogenesis (59,60).

Classical KS is an indolent process that only infrequently causes death of the patient directly. African, transplant-associated, and HIV-related variants evolve more rapidly and are often fatal (50).

**Histologic Features:** The reason that KS was included in this section is that its histologic spindle-cell pattern is most well-known to pathologists. Nevertheless, all subtypes of the tumor will be described here for the sake of convenience.

Clinically "early" KS most often takes a macular or "patch" form (54). Microscopically, this variant is extremely subtle. One often sees only a limited proliferation of small, attenuated, interanastomosing but bland blood vessels in the periappendageal reticular corium, together with an excess of nondescript spindle cells throughout the dermal connective tissue. In addition, small pre-existing blood vessels are often invested by a lymphoplasmacytic infiltrate. The "promontory" sign, wherein neovascular channels are formed around native vessels-- yielding profiles that simulate the promontory of a cliff-- is a helpful diagnostic finding (54). Small groupings of venule-like blood vessels are also interspersed randomly throughout the dermis in some cases, and extravasated erythrocytes are inconspicuous if present at all (50). McNutt et al. have also called attention to the fact that endothelia within "new" (neoplastic) blood vessels of KS are often apoptotic in the

**Histologic Features:** KHE is typified by an amalgamation of histologic findings that one might expect in lymphangiomas, hemangioma variants, other forms of hemangioendothelioma, and Kaposi's sarcoma. As such, one observes a proliferation of fusiform or compact polygonal endothelial cells, arranged in sheets or irregular nodules in the dermis and subcutis. These also line interconnecting slit-like vascular channels or rounded capillary-type vessels, and some of the lumina in such structures contain microthrombi. Cytoplasmic hyaline droplets, extravasated erythrocytes, and stromal hemosiderin are seen in a proportion of KHEs. Nuclear atypia is slight, and mitotic activity is variable but generally limited. In contrast to true Kaposi's sarcoma, which is the principal differential diagnostic consideration, there is no molecular evidence of infection with the human *Herpes* virus type 8 in KHE (or, for that matter, any of the other hemangioendotheliomas) (45).

#### Other Hemangioendotheliomas

Two other cutaneous hemangioendotheliomas are now recognized--"retiform" hemangioendothelioma (RHE) and "composite" hemangioendothelioma (CHE). The first has a strong clinicopathologic resemblance to Dabska's tumor, except that it may occur in adults. The principal feature of RHE is the elongated and sinusoidal nature of its vascular channels, such that they resemble the rete testis on scanning microscopy. Its behavior is "borderline," with frequent recurrence but uncommon metastasis (44,47).

As its name suggests, CHE demonstrates microscopic features that represent a potential admixture of those seen in epithelioid, spindle-cell, and retiform hemangioendotheliomas (48). In addition, CHE may contain foci that simulate angiosarcoma or variants of lymphangioma. Again, it is a biologically-borderline proliferation.

#### OVERTLY MALIGNANT ENDOTHELIAL NEOPLASMS

Those mesenchymal neoplasms that demonstrate a reproducible tendency for recurrence *and* distant metastasis are rightly considered to be overtly malignant. In specific regard to cutaneous vascular tumors, there are only two that truly fulfill those criteria; namely, Kaposi's sarcoma and angiosarcoma.

#### Kaposi's Sarcoma

patch-stage (61). This observation is unique, and would not be expected in benign vascular proliferations.

"Plaque" stage KS features the appearance of more organized aggregates of spindle cells, forming small fascicles in admixture with capillary-sized neovascular channels, extravasated erythrocytes, and stromal hemosiderin granules (50,62). The groupings of neoplastic cells are most often diffusely dispersed throughout the dermis, but they sometimes assume a pseudolobular configuration (50). Another useful diagnostic clue that appears at this phase of tumor evolution is the presence of hyaline globules in the neoplastic endothelial cells. These represent phagocytosed erythrocytes, as documented by the peroxidase reaction, and they also may be stained with the periodic acid-Schiff-diastase method (49). Hyaline globules are not sufficient unto themselves for a diagnosis of KS, because they can rarely be seen in non-neoplastic vascular proliferations of the skin (62). However, they are helpful when interpreted in the proper context. Finally, small papillary projections of tumor cells may be observed within ectatic neovascular spaces in this stage of KS, together with racemose, "dissecting" luminal profiles throughout the dermis.

The truly spindle-cell stage of KS is its "nodular" phase, where fusiform elements comprise the bulk of the proliferating cell population. Their nuclei are only modestly hyperchromatic, with indistinct nucleoli, and cytoplasm is scant and amphophilic. A notable diagnostic feature is the presence of cytoplasmic vacuoles in the spindle cells, probably representing a primitive attempt at vascular lumen formation (50). Another helpful microscopic finding is that the fusiform cells of KS appear to "spare" dermal zones that surround pre-existing vessels, leaving hypocellular cuffs around the latter structures (63). Extravasated erythrocytes and stromal hemosiderin deposition are maximal in scope in the nodular stage of KS, and hyaline globules often are numerous in the neoplastic cells.

Another continuing controversy regarding KS focuses on the "nature" of the proliferating elements in its spindle-cell form. There is no question that patch stage and plaque stage disease features reproducible immunoreactivity for endothelial markers, but these determinants are only occasionally detected in the spindle cell variant. Some authors contend that KS is a modified lymphatic endothelial tumor (64), whereas others have concluded that it is not endothelial at all (65). I prefer the premise that KS begins as a vascular endothelial neoplasm that undergoes reproducible clonal evolution, to yield a

**Clinical Findings:** The clinical characteristics of Kaposi's sarcoma (KS) are by now all-too-familiar to most physicians, because of the tremendous increase in the incidence of this tumor occasioned by the advent of the AIDS epidemic in the 1980's. Prior to that time, KS was a relatively rarely encountered lesion outside of the Mediterranean basin and Africa (49).

This neoplasm occurs in four well-defined clinical settings (49-51). **Classical Kaposi's sarcoma** is a disease that predominantly affects elderly men of Middle-Eastern or Italian heritage, and which manifests itself as multiple, coalescent, red-brown macules and plaques on the distal lower extremities. A subset of patients has lesions that resemble deep lymphangiomas, accompanied by lymphedema of the extremities. Nodular, sometimes-ulcerated tumors of the skin and viscera eventually supervene in this variant, but only after a prolonged period of time. **African KS** is seen in young black patients from restricted portions of the African continent. Women are almost as frequently afflicted as men, and their mean age is less than that of classical KS patients by two to three decades. The disorder is more rapidly progressive in African KS, with relatively early appearance of nodular lesions and involvement of lymph nodes and internal organs. **KS associated with iatrogenic immunosuppression** shares clinical features with both the classical and African subtypes, and primarily affects recipients of allogeneic organ transplants. **AIDS-related KS** is precipitated by infection with the HIV. At the outset of the AIDS pandemic, it was first noted in young homosexual men (52), with lesser numbers of cases in intravenous drug abusers and recipients of infected blood products.

Although the other manifestations of AIDS have become more evenly-distributed among all infected patient populations, KS has remained largely confined to gay males. In fact, its incidence has already begun to decline, even though the number of HIV-infected individuals continues to rise on a worldwide scale. The reasons for these epidemiologic peculiarities are unknown at the present time (53).

AIDS-related KS has a deceptively innocuous appearance at its onset, taking the form of ill-defined macular "patches" that often resemble ecchymoses (54). In contrast to the topographic confinement of the classical variant, KS in AIDS patients may affect virtually any skin field and also is seen in the mucosae (52). Visceral involvement also appears rapidly, in likeness to that seen in the African form.

cellular population that predominantly resembles myofibroblasts but retains immunoreactivity for HHV8-latent nuclear antigen-1 (66,67).

Differential diagnosis includes leiomyosarcoma, spindle-cell melanoma, spindle-cell squamous carcinoma, malignant peripheral nerve sheath tumor, and spindle-cell angiosarcoma. All but the last of these possibilities are easily excludable by attention to histologic detail or application of special studies.

**Spindle-cell angiosarcoma** (SCA) is a rare lesion (see below), the microscopic attributes of which are nearly identical to those of nodular KS (33). Nevertheless, the clinical features of the two conditions usually differ substantially, as detailed below. SCA also exhibits a much higher degree of nuclear atypia and mitotic activity. Moreover, immunostains for thrombomodulin, FLI-1, CD31, and CD34 are typically positive in SCA but not in spindle-cell KS, and only the latter tumor contains genomic sequences of HHV8 and immunoreactivity for the latent nuclear antigen-1 of that virus (33,68).

#### Angiosarcoma

**Clinical Features:** Angiosarcoma of the skin is characteristically seen in one of several well-defined clinical contexts. These encompass idiopathic proliferations on the scalp or face of elderly patients; occurrence in a field of prior therapeutic irradiation after a "lag" period of 5 or more years; and development in an area of chronic cutaneous lymphedema (the so-called **Stewart-Treves syndrome**) (69). An exceedingly small minority of tumors do arise outside of the situations just cited, as lesions of the extremities or trunk in individuals with no apparent predisposing conditions.

Angiosarcomas likewise show a variety of macroscopic presentations. They may be large, multinodular, ill-defined, violaceous, bloody, and sometimes-ulcerated masses; vague ecchymosis-like macular lesions; ligneous, "brawny" alterations in the skin that simulate erysipelas; and multifocal, seemingly-discrete bluish-red nodules that imitate cavernous hemangiomas (17).

The behavior of angiosarcoma is uniformly aggressive. Those patients whose neoplasms are less than 10 cm in maximum dimension may derive some benefit from radical surgical excision and postoperative irradiation, but almost all affected individuals will eventually die of unmanageable local tumor growth or distant metastases (70).

**Histologic Findings:** In classical form, angiosarcoma is a disorganized proliferation of polyhedral atypical endothelial cells with hyperchromatic nuclei and scant amphophilic cytoplasm. The tumor cells mantle racemose, interconnecting, "sieve-like" vascular channels in the skin that "dissect" through dermal collagen and deeper tissues and contain luminal red blood cells (71-74). Cutaneous appendages are variably entrapped or destroyed by the proliferation; hemosiderin and chronic inflammatory cells may be interspersed throughout the lesion. Large tumors may ulcerate the overlying epidermis multifocally. Micropapillae of neoplastic cells are frequently seen projecting into the neovascular channels of angiosarcomas, and the supporting (stromal) blood vessels also may show nuclear atypia in endothelial cells. Mitotic activity is variable in scope but always present. Necrosis may or may not be observed.

Several well-documented microscopic variants of angiosarcoma have been recognized. These include the spindle-cell subtype, as described above, a solid "epithelioid" form (75), "minimal-deviation" (hemangioma-like) angiosarcoma (76), a granular-cell variant (77), and a pleomorphic subtype with the potential to simulate atypical fibroxanthoma or malignant fibrous histiocytoma (69). Akiyama et al. also have reported two cases in which benign melanocytes and melanophages were intermixed with the neoplastic endothelial cells in the dermis (78).

Among these histologic forms, several merit further comment because they may be the sources of diagnostic error. Minimal-deviation angiosarcoma (MDAS) shows minimal cytologic atypia of constituent endothelial cells, and forms more complete (tubular) vascular lumina in the upper dermis than those seen in other variants (76). Nonetheless, specimens including the deep dermis and subcutis inevitably reveal the racemose "dissecting" endothelial profiles that are characteristic. The danger here is in the interpretation of shallow punch biopsies or shave biopsies, such that MDAS may be mistaken for "targetoid" or "microvenular" hemangiomas. As described above, the latter hemangioma subtypes have a permeative pattern of growth in the dermis which mimics the superficial aspect of MDAS. Thus, all tumors demonstrating an atypical, disorganized pattern of neovasogenesis should be excised totally.

Epithelioid angiosarcoma is composed entirely or predominantly of plump polyhedral cells that imitate true epithelia (75). These occupy much of the lumen in vascular spaces

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formed by such lesions, and therefore the latter channels often contain few discernible erythrocytes and are not readily recognized as endothelial in nature.

Simulants of spindle-cell AS have been discussed above in connection with KS. Epithelioid vascular tumors may simulate true epithelial neoplasms (particularly "pseudovascular" or "angiomatoid" squamous carcinomas [79]), melanoma and clear-cell sarcoma, epithelioid sarcoma, epithelioid leiomyosarcoma, and large-cell lymphoma (17). Pleomorphic variants of angiosarcoma can be confused with atypical fibroxanthoma, primary or metastatic undifferentiated carcinomas, melanoma, and malignant fibrous histiocytoma. In these contexts, immunohistologic analysis is the most useful diagnostic tool. Endothelial tumors are reactive for vimentin, CD31 & CD34 antigens, FLI-1, and thrombomodulin. Even though epithelioid vascular neoplasms may occasionally label for keratin (80), as a general category, endothelial tumors lack epithelial membrane antigen, desmin, muscle-specific actin, and p63 & S100 proteins, in contrast to the alternative diagnostic entities cited above.

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