Benign (nonmelanotic) epidermal tumors or tumor-like lesions: acquired digital fibrokeratoma, clear cell papulosis, cutaneous horn, fibroepithelial polyp, hair follicle nevus, large cell acanthoma, melanoacanthoma, pseudoepitheliomatous hyperplasia, seborrheic keratosis, verrucous hyperplasia

Cysts: apocrine cystadenoma, bronchogenic cyst, cystadenoma, dermoid cyst, hidrocystoma, keratinous cyst, pigmented follicular cyst, sebaceous cyst, vellous hair cyst

Adnexal tumors: general

Apocrine glands: general, apocrine tubular adenoma, hidradenoma papilliferum

Eccrine sweat glands: acrosyringeal adenomatosis, aggressive digital papillary adenoma, chondroid syringoma, clear cell acanthoma, cutaneous lymphadenoma, eccrine acrospiroma, eccrine cylindroma, eccrine poroma, eccrine spiradenoma, intraepidermal epithelioma, mucinous carcinoma, myoepithelioma, papillary eccrine adenoma, papillary syringadenoma, sclerosing sweat duct carcinoma, sweat gland carcinoma, syringoma

Hair follicles: folliculofibroma, inverted follicular keratosis, keratinous cyst, keratoacanthoma, pilar tumor, pilomatrixoma, trichilemmoma, trichoepithelioma, trichofolliculoma, warty dyskeratoma

Sebaceous glands: nevus sebaceous of Jadassohn, sebaceous adenoma, sebaceous carcinoma, senile sebaceous hyperplasia

Premalignant/in situ: carcinoma in situ-general, actinic keratosis, bowenoid papulosis, Bowen’s disease, Paget’s disease

Carcinoma (non adnexal): adenoid cystic carcinoma, adenoid squamous cell, adenosquamous, basal cell, lymphoepithelioma-like, Merkel cell, metastatic, mucoclonidemoid, small cell, spindle squamous cell, squamous cell, verrucous carcinoma, staging

Lymphoma and related disorders: general, acute lymphoblastic, anaplastic large cell, angiocentric, blastic NK leukemia / lymphoma, diffuse large B cell, follicular, Hodgkin’s, HTLV-1, intravascular, Jessner’s lymphocytic infiltration of skin, leukemia, lymphoid hyperplasia, lymphomatoid papulosis, mantle zone, mast cell disorders, mycosis fungoides, NK/T cell, peripheral T cell, primary cutaneous (general), Wöringer-Kolopp disease

Vascular tumors: acquired angioma, angiokeratoma, angiosarcoma, bacillary angiomatosis, benign hemangioendothelioma, benign lymphangioendothelioma, glomus, hemangioma, hemangioendothelioma and subtypes, intravascular papillary endothelial hyperplasia, Kaposi’s sarcoma
Kimura’s disease, lymphangioma, pyogenic granuloma, reactive angioendotheliomatosis, vascular leiomyoma, verruga peruana

Other tumors of skin: angiofibroma, atypical fibrous histiocytoma, atypical fibroxanthoma, benign cystic teratoma, benign fibrous histiocytoma (superficial), collagenous fibroma, connective tissue nevus, deep benign fibrous histiocytoma, dermatofibrosarcoma protubersans, dermamyofibroma, endometriosis, epithelial sheath neuroma, granular cell tumor, hamartoma of scalp, histiocytoma, inclusion body fibromatosis, inflammatory pseudotumor, keloid, Langerhans cell histiocytosis, leiomyoma, leiomyosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, meningioma, meningioma-like tumor of skin, multicentric reticulohistiocytosis, neurofibroma, neurothekeoma, palisaded encapsulated neuroma, perineurioma, pleomorphic fibroma, schwannoma, sclerosing fibroma, sinus histiocytosis with massive lymphadenopathy, striated muscle hamartoma, supernumerary digit, xanthoma, xanthogranuloma

Primary references

AJCC Cancer Staging Manual (6th Ed)
American Journal of Surgical Pathology (AJSP), January 2003 to February 2005
Archives of Pathology and Laboratory Medicine (Archives), Jan 2005 to February 2005 (must do cutaneous)
Human Pathology (Hum Path), Feb 2004 to December 2004 (must do cutaneous)
Modern Pathology (Mod Path), Jan 2003 to January 2005 (must do cutaneous)
Rosai, J: Ackerman's Surgical Pathology (9th Ed); 2004
Sternberg, S: Diagnostic Surgical Pathology (4th Ed); Lippincott Williams & Wilkins, 2004

Journal search terms: skin, epidermis, dermis, cutaneous

Benign nonmelanotic epidermal tumors / tumor-like lesions

Acquired digital fibrokeratoma
Definition: collagenous protrusions covered by hyperkeratotic epithelium, often at interphalangeal joints; dermis lacks adnexae.

Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - acquired digital fibrokeratoma #1; #2; #3; #4

Clear cell papulosis
Children 0-3 years
Gross: small white maculopapular lesions
Micro: large pale cells (Toker’s cells), single or in clusters
Positive stains: CEA, EMA, low molecular weight keratin
DD: Paget's disease

Cutaneous horn
Also called cornu cutaneum
Usually caused by actinic keratosis, also verruca, seborrheic keratosis, inverted follicular keratosis, squamous cell carcinoma
Gross: protruding skin lesion composed of keratin and resembling a horn
Micro: usually epidermal type keratin (with granular layer); occasionally has trichilemmoma-like features (no granular layer but deep red granules)

Fibroepithelial polyp
Also called acrochordon, squamous papilloma, skin tag, soft fibroma
Common, non-neoplastic, no clinical significance
Ages 40+ years; usually face, neck, trunk, intertriginous areas
Associated with diabetes, intestinal polyposis; increase during pregnancy
May be a common endpoint of various processes, including seborrheic keratosis or warts

**Gross:** soft, flesh-colored, baglike tumor, attached to skin by slender stalk  
**Micro:** papillary, fibrovascular cores covered by squamous epithelium; may have ischemic necrosis due to torsion

**Hair follicle nevus - Skin-Nonmelanocytic tumor chapter**

**Case reports:** 2 year old boy with nose nodule (Pediatr Dermatol 2008;25:60), 26 year old man with small soft nodules on his nose since childhood (Eur J Dermatol 2008;18:185), in a distribution following Blaskho's lines (J Am Acad Dermatol 2002;46:S125)

**Dermoscopy:** many uniform hair follicles and an interfollicular pseudo-pigment network in the nodules

**Micro:** well-differentiated hair follicles and sebaceous glands; no cartilage (seen in accessory tragus), central cysts or a central canal (seen in trichofolliculoma)

**EM:** follicular germ cells present; active fibroblasts around the follicles merge with colloid substance (J Dermatol 2001;28:324)

**Large cell acanthoma**

**Gross:** light-tan to dark brown macule  
**Micro:** atrophic, acanthotic or verrucous epidermis; hyperpigmented basal layer with rounded contour of rete ridges; larger than usual keratinocytes (large nuclei and cytoplasm) compared to adjacent normal epidermis; no atypia

**Melanoacanthoma**

**Micro:** resembles seborrheic keratosis but with prominent, dendritic melanocytes with abundant melanin granules; melanocytes are scattered throughout the lesion; no atypia

**Pseudoepitheliomatous hyperplasia**

**Micro:** deep tongues of epithelial cells that may appear invasive but are thin, elongated, anastomosing and surrounded by inflammatory cells (acute/subacute); also dermal fibrosis and vascular proliferation; no/rare atypia  
**DD:** squamous cell carcinoma (thicker strands, atypia, usually no prominent inflammatory infiltrate)

**Seborrheic keratosis**

**Gross:** exophytic, sharply demarcated, pigmented lesions that protrude above surface of skin, appear to be stuck to skin, single or multiple, soft, tan-black  
**Micro:** basal keratinocyte proliferations
Patterns: acanthotic – most common, rounded verrucous surface; thick layer of basal cells mixed with horn cysts (contain keratin) and pseudohorn cysts (downgrowth of keratin into tumor mass); no prominent granular layer; some cells contain melanin due to transfer from neighboring melanocytes

irritated – pronounced squamous metaplasia with abundant eosinophilic cytoplasm and whorled squamous eddies; often atypia and mitotic figures; resembles carcinoma

inverted follicular keratosis – irritated seborrheic keratosis that grows downward and involves hair follicles

Also hyperkeratotic, adenoid, acantholytic and desmoplastic patterns

Positive stains: low molecular weight keratin

Negative stains: high molecular weight keratin (usually), HPV

DD: squamous cell carcinoma (particularly desmoplastic pattern)

Verrucous hyperplasia

Papillomatosis associated with hyperkeratosis

Benign

Nonspecific change, associated with various entities

Epidermal nevus: if present since birth or early childhood; higher risk for basal cell carcinoma or adnexal tumors

Nevus sebaceus of Jadassohn: associated with malformed adnexal structures (see below)

Verruca vulgaris: exophytic growth with marked hyperkeratosis, focal parakeratosis, papillomatosis resembling church spires, prominent granular layer, koilocytosis, dilated vessels within papillary dermis

Cysts

Apocrine cystadenoma

Usually face, solitary or multiple

Lined by sweat duct-like epithelium which may have apocrine features

Bronchogenic cyst

Lesion of suprasternal notch, discovered shortly after birth

Probably derived from branchial clefts, not bronchi

Micro: lined by bronchial (pseudostratified, ciliated columnar) epithelium

Cystadenoma

Also called cutaneous ciliated cyst

Usually extremities of teenage girls

May have mullerian derivation, although rarely described in males

Micro: cylindrical cells with cilia

Dermoid cyst

Resemble keratinous cysts of epidermal type, but also have hair adnexae

Usually face of children along embryonic closure lines

Hidrocystoma

Usually face, solitary or multiple

Lined by two rows of sweat duct-like epithelium which may have apocrine features

Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - #1; #2; #3

Keratinous cyst

See below
Pigmented follicular cyst
Hyperpigmented lesion with epidermal-type keratinization, contains laminated keratin, pigmented hair shafts, some growing hair follicles

Steatocystoma
Solitary (simplex, often scrotal) or disseminated (steatocytoma multiplex, autosomal dominant, dermal nodules 1-3 mm of upper arms, axilla, scrotum and presternal skin)
Gross: cysts contain clear fluid
Micro: cyst with elaborate inner folding of cyst wall with undulations of thin layer of stratified squamous epithelium resembling ductal portion of sebaceous gland; also lobules of sebaceous glands and small hair follicles

Vellous hair cyst
Children and young adults
Small, multiple cysts over chest wall and extremities
Micro: cyst lined by flattened, follicular sheath epithelium; contains numerous vellous hairs and soft keratinous material in lumen

Adnexal tumors
Adnexal tumors-general
Usually differentiate only along one adnexal line, but there may be divergent differentiation within 1 or more tumors within the same patient
Algorithms (from Sternberg)

Cystic lesions:
(a) glandular lesions are hidrocystoma (two rows of cells) or cutaneous ciliated cyst (cylindrical cells with cilia)
(b) lesions with squamous keratinization are trichilemmal cysts, pilomatricoma, steatocystoma (sebaceous lobules in wall), vellous hair cyst (hair shafts in lumen), epidermoid cyst (contains lamellated keratin), dermoid cyst (adnexal structures in wall), trichofolliculoma (radiating immature hairs) or warty dyskeratoma (acantholytic dyskeratosis)

Basaloid tumors:
Trichoepithelioma / trichoblastoma (ribbons of basaloid cells, cysts and fibroblastic stroma), trichofolliculoma (mature and immature hair follicles), cylindroma (jigsaw-puzzle appearance with thickened basement membrane), spiradenoma (basaloid cells with 2 cell types), sebaceous adenoma or carcinoma, eccrine poroma (large nodules connected to epidermis), eccrine acrospiroma (large dermal nodules), pilomatrixoma (ghost cells)

Squamous lesions:
(a) solid lobules of eosinophilic cells are pilar sheath acanthoma (connected to crater-like cavity) or acrospiroma (not connected to crater-like cavity)
(b) lobules with clear cells are acrospiroma (luminal differentiation), trichilemmoma (epidermal connection, peripheral palisading, thick basement membrane) or sebaceous tumors
(c) lobules of squamous cells with central keratinization are proliferative trichilemmal tumor

Glandular tumors:
(a) apocrine differentiation: papillary hydadenoma (papillary fronds, vulvar/perianal) or tubular apocrine adenoma (epidermal connection)
(b) syringoma: small ducts with 2 rows of cells
(c) papillary eccrine adenoma: cystic ducts and papillary fronds
(d) papillated ducts open to epidermis: papillary syringadenoma (scalp) or nipple adenomatosis (nipple)
(e) mixed tumor (chondroid syringoma): chondromyxoid stroma and tubular or anastomosing glands
(f) sebaceous hyperplasia (lobular arrangement around a central duct), adenoma or carcinoma

Adnexal tumors-apocrine glands
Adnexal tumors of apocrine glands - general
Eccrine sweat gland tumors may exhibit apocrine differentiation
Pure apocrine tumors are rare

Apocrine tubular adenoma
Micro: lobular pattern of dermal and subcutaneous tubular apocrine structures with epidermal connection; resembles papillary syringadenoma

Hidradenoma papilliferum
Also called papillary hydadenoma
Perianal or vulvar
Micro: papillary fronds, ducts lined by apocrine type cells which show decapitation secretion and fibrous stroma

Adnexal tumors-eccrine sweat glands
Acrosyringial adenomatosis
Also called eccrine syringofibroadenoma
Gradual and symmetric spread of papular lesions over large areas of body
Micro: diffuse proliferation of acrosyringial-related cells in epidermis and dermis

Aggressive digital papillary adenoma
Usually digits
Recurs locally
Malignant counterpart has poor glandular differentiation, necrosis, atypia, invasion; metastasizes to lung in many cases

**Micro:** tubuloalveolar and ductal structures, also areas of papillary projections protruding into lumina (may resemble breast carcinoma)

**Chondroid syringoma**
Also known as mixed tumor of skin
Usually benign
Face, head, neck, extremities, trunk or back
May have areas of apocrine, follicular and sebaceous differentiation

**Gross:** nodular, circumscribed, nonulcerated
**Micro:** myoepithelial and epithelial type cells, some with abundant hyaline cytoplasm, in chondromyxoid stroma; may have eosinophilic globules with radiating fibrillary structures around their lumina, similar to mammary collagenous spherulosis

**Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - #1; #2; #3; #4**

**Positive stains:** *inner epithelial layer* - keratin, EMA, CEA; *outer myoepithelial layer* – vimentin, S100, NSE; variable smooth muscle actin, GFAP

**Apocrine mixed tumors**
Epithelial component is branching tubular structures with two cell layers; inner layer is columnar with eosinophilic cytoplasm, "decapitation" type secretion, often squamous metaplasia and basal nuclei

**Clear cell acanthoma**
Legs of females, may be multiple

**Acanthoma:** benign tumor of epidermal keratinocytes
**Gross:** moist flat plaque
**Micro:** intraepithelial tumor of clear keratinocytes with dermal inflammation and abrupt transition to normal epidermis; may have melanocytic proliferation, psoriasiform acanthosis, parakeratosis

**Positive stains:** glycogen
**DD:** seborrheic keratosis

**Cutaneous lymphadenoma**
May be related to eccrine spiradenoma

**Micro:** multiple rounded lobules of basaloid cells with some peripheral palisading, focal keratinization, occasional duct formation, mixed with small lymphocytes

**Eccrine acrospiroma**
Also called solid-cystic or nodular hidradenoma
Arises from sweat gland distal excretory duct
**Gross:** nodules with cystic foci high in dermis
**Micro:** nests/lobules of cells resembling eccrine poroma with either clear cytoplasm or prominent squamous metaplasia; may have marked vascularity; small and large lumina are lined by cuboidal ductal cells or columnar secretory cells; cystic spaces may be due to degeneration of tumor cells

**Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - #1; #2; #3; #4; #5**

**Positive stains:** keratin, EMA, CEA, S100, vimentin
**DD:** glomus tumor (different staining pattern)

**Eccrine cylindroma**
Also called turban tumor, particularly when a large, multicentric scalp tumor
Somewhat common; solitary, small, slow growing adenoma, 90% in head and neck
Usually ages 40+ years, 90% women
Rarely associated with similar tumors in major salivary glands
Familial form (turban tumor syndrome, Brooke-Spiegler syndrome): autosomal dominant, multiple tumors of children / teenagers that may also involve trunk and extremities, or in association with spiradenoma, trichoepithelioma, milia or membranous variant of basal cell adenoma of salivary glands; due to mutations in CYLD gene at #16q12-13
Rarely undergoes malignant transformation

**Spiradenocylindromas:** features of cylindroma and eccrine spiradenoma; usually painful
**Gross:** pink-red dome-shaped nodule with smooth surface
**Micro:** compact nests of basaloid cells that fit together like a jigsaw puzzle, surrounded by thick basement membrane
**Micro images: #1; #2; #3; #4**

**Molecular:** mutation in CYLD gene in #16 associated with multiple cylindromas
**EM:** differentiation towards intradermal coiled duct region of eccrine sweat glands

**Eccrine poroma**
Palms and soles, also other sites
Benign, although eccrine porocarcinomas also exist
May be a subtype of eccrine acrospiroma
**Gross:** "moat and hillock" pattern
**Micro:** cords and nests of small keratinocytes attached to the epidermis; nests are sharply delimitated from adjacent epidermis; also ducts and sharply delimitated islands of squamous epithelium; either intraepidermal ("hydroacanthoma
simplex”), intradermal (“dermal duct tumor”) or mixed (most common); dermis has reactive vessels and inflammatory infiltrate; also heavily pigmented variants

**Micro images:** #1; #2; #3; #4

**Positive stains:** EMA

**EM:** features of eccrine gland acrosyringium

**DD:** basal cell carcinoma, seborrheic keratosis, acrosyringeal adenomatosis

### Malignant eccrine poroma

Also called porocarcinoma

Most common sweat gland carcinoma

Usually lower extremities, may be pedunculated

Recurs locally, also metastasizes to regional lymph nodes

**Micro:** malignant eosinophilic and clear cells in lobular masses or islands with cystic cavities due to extensive necrosis; eosinophilic cells are polyhedral or fusiform with variable cytoplasm, hyperchromatic nuclei, distinct nucleoli, indistinct cell boundaries; clear cells are large and polyhedral with abundant clear cytoplasm and distinct cell borders; resembles eccrine poroma, but with obvious atypia and frequent mitotic figures; also epidermotropism resembling Paget’s disease; variable squamous differentiation, clear cell change and pigmentation

Either horizontal pattern (intraepidermal, like superficial spreading melanoma) or nodular (into dermis, like nodular melanoma)

**DD for horizontal pattern:** intraepidermal poroma (no atypia), seborrheic keratosis (no atypia), Bowen’s disease (more atypical keratinocytes, more severe architectural abnormalities), Paget’s disease (large cells, clear cytoplasm, mucin+)

**DD for nodular pattern:** squamous cell carcinoma (prominent keratinization, keratin pearls, no cystic cavities), sebaceous carcinoma (clear cells with bubbly cytoplasm), proliferating trichilemmal tumors (solid and cystic, well demarcated with palisading of peripheral layer), metastatic renal cell or other clear cell tumors, balloon cell melanoma

### Eccrine spiradenoma

Extremely painful lesions, anywhere in body

Rarely transforms to high grade malignancy

**Micro:** sharply circumscribed, lobular adenomas; very cellular; cells have scant cytoplasm; high vascularity; variable T cells

**Micro images:** contributed by Dr. Amy Lynn, Toledo, Ohio - [image](#)

**EM:** epithelial and myoepithelial cells

**DD:** synovial sarcoma, metastatic carcinoma, thymoma, cutaneous lymphadenoma

### Intraepidermal epithelioma of Borst-Jadassohn

Heterogeneous group of disorders, including irritated seborrheic keratosis, eccrine poroma and other intraepidermal sweat gland tumors

### Mucinous carcinoma

Also called adenocystic carcinoma

Scalp of elderly patients

**Micro:** resembles mammary colloid carcinoma with lakes of mucin containing small tumor cell clusters; may also have an infiltrating ductal pattern

**DD:** metastatic carcinoma

### Myoepithelioma

Tumors with myoepithelial cells but no epithelial cells

Usually benign lesions of extremities, but should be completely excised

May recur locally, rarely metastasize

Usually male, mean age 22 years (range 10-63 years)

Part of a continuum with mixed tumors (ductal structures but few myoepithelial cells)

Mitotic activity may predict more aggressive tumor

**Gross:** mean 1 cm, range 0.5 to 2.5 cm

**Micro:** well circumscribed dermal lesions, not connected to epidermis, may extend into superficial subcutis; either composed of (a) solid proliferation of ovoid, spindled, histiocytoid or epithelioid cells with abundant eosinophilic syncytial cytoplasm and little stroma; or (b) reticular architecture with epithelioid, plasmacytoid or spindle cells in myxoid or hyalinized stroma; cells have ovoid/spindled nuclei, mild pleomorphism, small necrotic areas, fatty metaplasia, minimal mitotic figures (0-6/10 HPF), no ductal differentiation

**Positive stains:** required for diagnosis by Fletcher - (a) EMA+ or keratin+ and (b) S100 and (c) GFAP (50%) or muscle markers calponin, smooth muscle actin (57%) or muscle specific actin (HBF)

**DD:** benign mixed tumor, epithelioid benign fibrous histiocytoma (lower limbs, circumscribed, polypoid, plump and often binucleate epithelioid cells, may entrap dermal collagen, keratin-, myogenic markers-, S100-), Spitz nevus (large epithelioid melanocytes with prominent nucleoli, junctional component, downward maturation, HMB45+, S100+, EMA-, keratin-, myogenic markers-), epithelioid sarcoma (distal extremities of young adults, infiltrates along fibrous septa and fascial planes, discontinuous growth, S100-, GFAP-), cellular neurothekeoma (nested architecture, sclerotic dermal collagen, NKI-C3+, S100-, EMA-, keratin-), leiomyoma

**References:** [Hum Path 2004;35:14](#)

### Myoepithelial carcinoma

Severe cytologic atypia and high mitotic rate

**Papillary eccrine adenoma**

[Top](#)
Usually distal extremities of blacks
Recur locally, don't metastasize
**Micro:** eccrine duct-like structures, often dilated and with intraluminal papillomatosis
**EM:** differentiation towards secretory epithelium of sweat glands
**DD:** low grade eccrine carcinoma

**Papillary syringadenoma**
Warty tumor of scalp, neck and face
Any age
Slow growing or a recent change in an apparent birthmark
1/3 have adjacent nevus sebaceous, 10% have adjacent basal cell carcinoma
**Eccrine syringofibroadenoma:** with prominent fibrous stroma
**Syringocystadenocarcinoma papilliferum:** malignant counterpart
**Micro:** glandular papillary proliferation connected to skin surface, dense plasma cell infiltrate
**Positive stains:** plasma cells are IgA+, IgG+

**Sclerosing sweat duct carcinoma**
Also called microcystic adnexal carcinoma
Slow growing nodule or plaque, usually on upper lip or face
Commonly recurs, metastasizes very rare
**Micro:** cords and nests of bland keratinocytes, keratin cysts and ductal differentiation; dense collagenous stroma; is invasive, may extend into subcutis or perineurial spaces; resembles syringoma; rarely is sebaceous differentiation

**Sweat gland carcinoma**
Uncommon
Usually adults
Difficult to diagnose; may be life threatening
**Low grade:** microcystic carcinoma, adenoid cystic carcinoma, mucinous carcinoma, extramammary Paget's disease, mucoepidermoid carcinoma
**Intermediate grade:** ductal adenocarcinoma, aggressive digital papillary adenocarcinoma, acrosyringocarcinoma
**High grade:** porocarcinoma, clear cell acrosyringocarcinoma
**Unknown grade:** signet ring cell carcinoma, papillary syringadenocarcinoma
Includes malignant eccrine poroma (most common), mucinous carcinoma, sclerosing sweat duct carcinoma; also malignant chondroid syringoma (malignant mixed tumor), malignant myoepithelioma, malignant dermal cylindroma, malignant syringoma (syringoid eccrine carcinoma), malignant eccrine carcinoma, adnexal carcinoma; mucinous syringometaplasia
Benign sweat gland tumors can also undergo malignant transformation to high grade carcinoma
**Micro:** may resemble breast carcinoma, renal cell carcinoma, basal cell carcinoma
**Positive stains:** GCDFP-15, estrogen receptor, keratin, EMA, CEA
**Negative stains:** actin
**DD:** metastatic breast carcinoma, renal cell carcinoma

**Syringoma**
Multiple, yellow, papulonodular lesions on lower eyelids of women
Also face and neck, vulva, dorsal proximal and middle phalanges of hand or eruptive forms (below)
Appears to derive from sweat duct ridge
**Micro:** upper dermal clusters of small ducts lined by two layer thick epithelium, occasionally with comma shaped extensions; may have clear cells (due to glycogen); not infiltrative, no atypia, no mitotic figures, no local destruction
**Micro images:** contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clínica Ponferrada, Spain - #1; #2
**EM:** eccrine origin
**DD:** basal cell carcinoma

**Eruptive syringoma**
Neck, anterior trunk, axilla, shoulder, anterior surfaces of arms, abdomen or pubic areas of young men or women
May be reactive, not neoplastic
**Syringomatous carcinoma**
Infiltrative epithelial tumors resembling syringomas
**Micro:** tubules, keratinizing cystic structures, islands and cords within desmoplastic stroma; involve epidermis and diffusely infiltrates dermis
**DD:** syringoma (usually multiple, limited to upper dermis, not infiltrative, no atypia, no mitoses, no local destruction), syringomatous carcinoma of salivary glands (in oral mucosa not skin)

**Adnexal tumors-hair follicles**
See also cysts (above)

**Folliculofibroma**
Associated with Birt-Hogg-Dube’ (BHD) syndrome (autosomal dominant, multiple folliculomas on head and neck, acroacroids and trichodiscomas; also renal cell carcinoma [various types], renal oncocytoma and oncocytic hybrid tumors, lung cysts and spontaneous pneumothorax)
Human gene at 17p11.2 encodes folliculin, normally expressed in skin and adnexae; frameshift mutations occur in BHD causing premature protein termination
Tumor considered a hamartoma of hair follicle
**Gross:** skin papules
**Micro:** thin epidermal strands originating from a central hair follicle with prominent connective tissue

**References:** [Mod Path 2004;17:998 (mRNA expression of Birt-Hogg-Dube’ mRNA)]

**Inverted follicular keratosis**
Eyelid or face of elderly
May be irritated seborrheic keratosis, irritated verruca vulgaris or keratotic lesion of infundibular region of hair follicle
**Gross:** single nodule or papule projecting above skin surface
**Micro:** well circumscribed with squamous eddies containing an inverted papillomatous and acanthotic component; no inflammation

**Keratinous cyst**
Most probably arise from infundibular portion of hair follicles
Clinically called (incorrectly) sebaceous cyst
Lesions of palm, sole or other sites may contain HPV 57 or 60
Cysts contain keratin and lipid debris from sebaceous secretions
Cysts may be painful if ruptured

**Epidermal (epidermoid) type:** also called infundibular cyst; lined by keratinized epithelium with distinct granular layer, contain lamellated keratin but no calcification; may have seborrheic keratosis-like changes in cyst wall
**Trichilemmal (pilar) type:** also called isthmus-catagen cyst; often on scalp, has trichilemmal-type keratinization (sudden keratinization without a granular layer), uneven boundary between keratinized and non-keratinized cells; non-lamellated keratin within the cyst, often with nucleated cells, often calcified

**Micro images:** Trichilemmal type #1; #2; #3

**Keratoacanthoma**
May represent proliferation of infundibular portion of hair follicle (since keratinization occurs without a granular cell layer), or a subtype of well differentiated squamous cell carcinoma
80% males, usually sun exposed skin of face; younger age group than squamous cell carcinoma of skin
Familial cases may be multiple
Appears to be different from squamous cell carcinoma based on different telomerase, p53 and COX2 activity ([Mod Path 2004;17:468](#))
Usually arises from normal skin, grows rapidly for 4-8 weeks, then regresses over 6 months to leave a depressed, annular scar
Rarely metastasizes, usually in immunosuppressed patients
Also associated with inflammatory dermatoses, congenital lesions, genetic diseases, scars

**Gryzbowski type:** numerous eruptive lesions
**Ferguson-Smith type:** multiple ulcerating tumors with atypical distribution
**Gross:** flesh colored, dome shaped lesion with central, keratin-filled crater
**Micro:** early (evolving) phase is composed of well circumscribed solid lobules of large, pale squamous cells with little keratinization, distorted follicular infundibulum, mild atypia; **stable phase** has central crater filled with keratin but no granular layer, larger more irregular infiltrating squamous nests and islands, accompanied by marked inflammatory infiltration with lichenoid features and eosinophils but no plasma cells; may be deeply infiltrative, with microabscesses of neutrophils and eosinophils approaching periphery, perineural invasion; **regressing (resolving) phase** has keratin filled crater, mature epithelium without atypia, flattening of cup-shape, horizontal fibrosis in dermis, reduction of inflammation, transdermal elimination of elastic fibers

**Note:** overhanging edges, keratin-filled crater and hemispheric shape are most important features in differentiating from squamous cell carcinoma

**Variants:**
- **actinic**-arises from actinic keratosis and has marked atypia; **follicular**-plaque with numerous vertical strands of squamous epithelium resembling keratoacanthoma; **giant**-10-15 cm, may cover most of a member
- **Micro images:** (1) a: early lesion with central keratin-filled crater and overhanging lips; b: telomerase negative; c: p53 (basal staining); d: COX2 negative; (2) stable phase with large irregular infiltrating squamous cell nests and islands; (3) regressing phase with scalloped epithelial remnants and perforating strands of elastin fibers

**Negative stains:** p53 (usually)
**DD:** well differentiated squamous cell carcinoma

**Subungual keratoacanthoma**
May arise from nail matrix
Rapidly growing mass in tip of finger or toe
Associated with lytic, cup shaped defect of distal digit

**Pilar tumor**
Also called proliferating trichilemmal cyst
Neoplastic version of trichilemmal cyst
Women, base of neck and scalp
Usually benign, may recur locally, metastases are very rare and seen only with obvious malignant cytologic features resembling a focal trichilemmal carcinoma or a sarcomatoid carcinoma
**Gross:** pure tumors are multinodular, may be huge; may coexist with trichilemmal cyst
**Micro**: solid with pushing borders and lobulated contour, usually involves epidermis but may open into skin surface; bands of squamous epithelium with trichilemmal-type keratinization; may have prominent atypia, focal stromal invasion

**Molecular**: nondiploid DNA

### Pilomatrixoma

**Top**

Also called pilomatrixicoma, calcified epithelioma of Malherbe

Benign tumor arising from hair matrix

Usually children and young adults in head, neck or upper extremities

**Gross**: nodular, subepidermal

**Micro**: solid nests of basaloid cells undergoing abrupt trichilemmal-type keratinization; ghost cells, often foreign body reaction, calcification or ossification with extramedullary hematopoiesis; occasional transepidermal perforation

**Micro images**: contributed by Dr. Amy Lynn, Toledo, Ohio - image

contributed by Dr. Asmaa Gaber Abdou and Dr. Mona Kandil, Menofiya University, Egypt - #1; #2; #3; #4; #5; #6; #7; #8; #9

**DD**: basal cell carcinoma

**Aggressive pilomatrixoma**: atypical histology, locally invasive with local recurrence

**Malignant pilomatrixoma**: cytologic atypia, infiltrative border, transitions to squamous cells; clear cells, necrosis, mitotic figures, variable sarcomatoid features; commonly recur locally, may metastasize

### Trichilemmoma

**Top**

Also called tricholemmoma

**Benign**

**Cowden’s syndrome**: multiple trichilemmomas, multiple hamartomas in skin, oral mucosa, breast, thyroid and intestines, as well as malignancies at these sites

**Micro**: lobular or plate-like growth of pale pink, glassy cells that resemble infundibulum (upper portion of hair follicle); often palisading at periphery, thickened basement membrane, occasional central keratinization; desmoplastic variant simulates malignancy

**Micro images**: #1; #2; #3; #4; #5

### Trichilemmal (tricholemmal) carcinoma

**Top**

Indolent, with only rare metastases

**Micro**: lobular growth of clear tumor cells with trichilemmal-type keratinization, numerous mitotic figures, invasion of reticular dermis, ulceration

### Trichoepithelioma

**Top**

Chronic hair follicle tumors

Often in children, may be familial

Autosomal dominant related tumors are multiple, semitransparent, dome-shaped papules on face, scalp, neck, upper trunk

**Gross**: often multiple, may be huge, no ulceration

**Micro**: basaloid cells (like cylindroma) that form primitive hair follicle-germ structures with fibromyxoid stroma; cells are often in fronds, may have 2 or more layers of basaloid cells, may have papillary mesenchymal bodies

**Micro images**: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - #1; #2; #3; #4

**DD**: basal cell carcinoma

### Desmoplastic trichoepithelioma

**Top**

Benign, resembles basal cell carcinoma-morphea type

Usually solitary tumor

**Micro**: extensive fibrous stroma surrounds epithelial islands

**Negative stains**: stromalysin-3 (positive in most basal cell carcinomas)

### Trichofolliculoma

**Top**

**Gross**: solitary and nodular

**Micro**: highly organoid hamartomatous lesions that recapitulate various phases of normal hair follicle; have central dilated follicle surrounded by proliferating epithelium with various phases of follicle formation; often Merkel cells present

**DD**: trichoepithelioma, basal cell carcinoma

### Warty dyskeratoma

**Top**

Also called isolated follicular keratosis

Small maculopapular lesion of sun-exposed skin

Either follicular counterpart of actinic keratosis or a follicular neoplasm

Not related to Darier’s disease

**Micro**: follicular acantholysis and dyskeratosis
Adnexal tumors-sebaceous glands
Nevus sebaceous of Jadassohn
- Type of epithelial nevus on scalp and face
- Congenital, enlarges over time
- May transform to basal cell carcinoma, trichoepithelioma or rarely squamous cell carcinoma
- Micro: hamartoma composed of large sebaceous glands, heterotopic apocrine glands, defective hair follicles, acanthosis and epithelial papillomatosis

Sebaceous adenoma
Micro: nodular lobulated growth with dark and light areas corresponding to generative cells (dark) and sebaceous cells (light) with cytoplasmic lipid vacuoles; not as organoid as sebaceous hyperplasia
DD: angiofibroma with sebaceous hyperplasia of tuberous sclerosis

Sebaceous carcinoma
- Rare
- Tumors of eyelids, caruncles and orbit are more aggressive than skin tumors
- Also associated with Muir-Torre syndrome (multiple cutaneous tumors with sebaceous and hair follicle differentiation and multiple internal malignancies; tumors have cystic growth pattern)
- Poor prognostic factors: necrosis
- Micro: sebaceous differentiation, but also marked atypia, mitotic figures, invasion
- Micro images: #1; #2; #3; #4; #5; #6; #7
- Positive stains: keratin, EMA, LeuM1, variable androgen receptors
- Negative stains: CEA, S100
- DD: basal cell carcinoma with sebaceous differentiation, squamous cell carcinoma with hydropic change

Senile sebaceous hyperplasia
- Most common sebaceous gland lesion
- Usually elderly patients on nose or cheeks
- Micro images: #1; #2

Premalignant or noninvasive Carcinoma in situ-general
Controversial
- Typical progression in cervix from mild to moderate to severe dysplasia to invasion may not apply to skin
- Actinic keratosis with only a single layer of atypical keratinocytes may be invasive, but Bowen's disease seldom does
- Mucosal variants in glans penis and vulva are associated with more aggressive behavior
- Micro: by definition requires full thickness keratinocyte atypia, although may be surrounded by normal keratinocytes; marked nuclear and architectural atypia, numerous mitotic figures, atypical mitotic figures, apoptotic cells; variable melanin, variable lymphocytic infiltrate; may have hemangiomatous vascular proliferation, amyloid globules, adnexal differentiation

Actinic keratosis
Also called solar keratosis, senile keratosis
Buildup of excessive keratin due to chronic exposure to sunlight
On sun-exposed sites (face, arms, dorsum of hands)
Called actinic cheilitis in lips
May become invasive with only a single layer of atypical keratinocytes

**Risk factors:** fair skin, ionizing radiation, hydrocarbon or arsenic exposure, renal transplant

**Treatment:** curettage, cryotherapy, topical chemotherapeutic agents

**Gross:** tan-brown, red or skin colored, circumscribed lesions, sandpaper texture, may have cutaneous horn (due to excessive production of parakeratotic scale)

**Micro:** basal cell and squamous layer atypia and disorderly maturation, hyperkeratosis, parakeratosis; may have atrophy of epidermal surface; usually no granular layer except at follicular orifices; elastosis and often chronic inflammation of dermis; follicular apparatus and intraepidermal sweat duct are spared; may have coexisting melanocytic atypia

**Variants:** acantholytic (lack of intercellular adhesion with clefts containing rounded, acantholytic cells), atrophic (epidermis has only 3-4 layers of keratinocytes), basaloid, bowenoid (full thickness atypia), epidermolytic (vacuolar changes of keratinocytes at upper spinous and granular layers with coarse keratohyalin granules), hyperkeratotic (with cutaneous horn), pagetoid, pigmented (resembles solar lentigo, which lacks atypia and has downward projections)

**Positive stains:** p53 (75%)

**Bowenoid papulosis**

Multiple pigmented papular lesions of anogenital area, resembling condyloma acuminatum
Young adults
May regress spontaneously
Almost never invasive

**Micro:** resembles carcinoma in situ, but with localized acanthosis similar to condylomas; low power view is “salt and pepper” due to dark nuclei and clear vacuolar cytoplasm; usually no adnexal involvement

**Positive stains:** HPV

**Molecular:** HPV type 16 is most common

**Bowen’s disease**
Usually on skin NOT exposed to sunlight, such as trunk
Called erythroplasia if at glans penis, vulva, oral cavity
Often considered as carcinoma in situ or squamous intraepidermal neoplasia
**Gross:** slightly raised, large scaly erythematous plaque with irregular border; usually single patch or verrucous growth
**Micro:** atypia is prominent and throughout epidermis; includes nuclear hyperchromasia and multinucleation, individual cell dyskeratosis, increased mitotic figures, atypical mitotic figures; also cytoplasmic vacuoles, markedly altered maturation, but usually still some surface keratinization; may extend into eccrine sweat glands (not considered invasive disease); intercellular bridges present; rarely pagetoid cells or ground glass cytoplasm
**Micro images:** contributed by Dr. Amy Lynn, Toledo, Ohio - image #1; #2
**Positive stains:** p53, HPV, high molecular weight cytokeratin
**Molecular:** aneuploid
**DD:** Bowenoid actinic keratosis (circumscribed, in sun-exposed areas with clinical appearance of actinic keratosis), chronic arsenic ingestion

**Paget’s disease (extramammary)**
May originate from intraepidermal portion of sweat glands or primitive basal cells with ability to differentiation towards glandular elements
Labia majora, scrotum and perineum are most common sites
Due to underlying carcinoma in 10-20% of cases of vulvar disease
**Treatment:** complete surgical excision
**Gross:** erythematous, eczematous or ring-shaped; often multicentric, extensive, pigmented
**Micro:** malignant cells in epidermis with differentiation towards local glandular structures; almost always simultaneous involvement of eccrine glands or hair follicles; dermal invasion is less common (rare in vulva, more common in perianal region); cells are large, pale, vacuolated and usually just above basal layer of epidermis; single, clusters or glandular formations; may have cleft-like spaces between Paget’s cells and neighboring keratinocytes; no intercellular bridges, no dyskeratosis
**Positive stains:** mucin, EMA, CEA, PAS, low molecular weight cytokeratin (CAM 5.2, CK7); **vulva** - GCDFP-15 and androgen receptors; **perianal** - CK20
**EM:** cells with glandular differentiation, not melanocytes or keratinocytes
**DD:** pagetoid Bowen’s disease, pagetoid actinic keratosis, melanocytic lesions, metastatic epidermotropic carcinomas, clear cell papulosis

**Carcinoma (non-adnexal)**
**Adenoid cystic carcinoma**
**Micro:** cribriform and tubular structures in dermis
**DD:** metastases from salivary gland tumors, basal cell carcinoma

**Adenoid squamous cell carcinoma**
**top**
Also called pseudoglandular or acantholytic squamous cell carcinoma
Due to a desmosomal defect that causes lack of cell adhesion (acantholysis)
May resemble angiosarcoma
Usually sun-exposed skin, often associated with actinic keratosis with acantholysis
DD: adenocarcinoma (primary or metastatic), adenosquamous carcinoma

**Adenosquamous carcinoma**

**top**
Rare, aggressive
**Micro:** squamous differentiation and mucin production

**Basal cell carcinoma**

Most frequent form of skin cancer
Usually sun exposed skin (not mucosal surfaces), in proportion to number of pilosebaceous units present
Rosai claims these tumors attempt to differentiate toward pilosebaceous units, but often this is not readily apparent
Often multiple tumors
Usually older adults
Slow and indolent, untreated cases may invade subcutis, skeletal muscle and bone; facial tumors may invade skull, nares, orbit or temporal bone; only 100 metastatic cases described, often associated with basal cell nevus syndrome or basosquamous histology, on sunlight-protected skin
Metastases are rare; 60% to regional lymph nodes, also lung, liver, bone

**Risk factors:** fair skin, blue eyes, immunosuppression (higher incidence, more aggressive tumors), xeroderma pigmentosum
Also associated with nevus sebaceus of Jadassohn, chronic venous stasis of lower leg, arsenic, Xrays, skin injury, chickenpox scars, tattoos, hair transplant scars, immunosuppression
Less common in children or young adults, sunlight-protected skin; rarely coexists with benign nevus

**Basal cell carcinoma (continued)**
Basal cell nevus syndrome: also called Gorlin’s syndrome; autosomal dominant, young patients with multiple basal cell carcinomas (with more varied histologic types than normal, often superficial and multicentric, often with osteoid), palmar pits (in situ basal cell carcinomas), dural calcification, keratinous cysts of jaws, skeletal abnormalities, occasional abnormalities of CNS, mesentery and endocrine organs; due to mutations in PTC (patched) gene on 9q22.3

Poor prognostic factors: dense fibrous stroma and loss of peripheral palisading; reduced expression of syndecan-1 and bcl2, greater expression of p53 and aneuploidy, basosquamous histology, perineural invasion, positive margins

Case report: malignant basomelanocytic tumor with subsequent metastatic melanoma (AJSP 2004;28:1393)

Treatment: excision with frozen section evaluation of margins, curettage, desiccation, radiation therapy; 1/3 with positive margins will recur

Gross: nodular, ulcerative, superficial, erythematous or sclerosing (morphea-like); often with telangiectasia (prominent, subepidermal vessels)

Micro: almost always epidermal attachment; nests or lobules of hyperchromatic but uniform basaloid cells with peripheral palisading, surrounded by loose stroma, often with myofibroblasts and mucinous changes; also cleft-like retraction spaces (due to stromal mucin); may appear pigmented due to dermal melanophages; variable Langerhans cells; occasional amyloid; rare spindled tumor cells, mitotic activity, atypical mitotic figures, bizarre tumor giant cells, atypical stromal cells, osseous metaplasia, collagen crystal-like structures, eccrine differentiation, thickened basement membrane or perineural invasion

Patterns are solid, cystic, adenoid, keratotic (resembles squamous cell carcinoma, but has apoprototic keratinocytes, no atypia, abundant stroma), pigmented, infiltrating, sclerosing (morphea-like, with slender, deeply infiltrating nests and abundant reactive stroma)

Micro images: contributed by Dr. Amy Lynn, Toledo, Ohio - superficial tumor

Positive stains: keratin, BerEP4, p53, bcl2

Negative stains: EMA, CEA, involucrin

Cytogenetics: +18, +9, +20, +7, +5; also loss of heterozygosity at 9q22.3 and trisomy 6

DD: basaloid proliferations associated with dermatofibromas, actinic keratosis or Bowen’s disease, trichoepithelioma (also basaloid but with follicle-like structures and no clefts)

References: Hum Path 2004;35:1549 (renal transplant patients)

Basosquamous (metatypical) carcinoma: basal cell carcinoma plus atypical squamous cells; more aggressive than classic basal cell carcinoma; may metastasize

Clear cell basal cell carcinoma: tumor cells with prominent cytoplasmic vacuoles or signet ring morphology

Fibroepithelial tumor: also called Pinkus’ tumor, fibroepithelioma; polyoid variant, often on back, with abundant stroma

Granular basal cell carcinoma: contains tumor cells resembling those in granular cell tumor; no clinical significance

Infundibulocystic basal cell carcinoma: has hair follicle differentiation

Superficial (multicentric) basal cell carcinoma: arises in skin of trunk and other sites with sparse fine hairs and thin epidermis; primarily grows laterally, has high recurrence rate, tumors may also regress; has multiple small tumor nests attached to undersurface of epidermis with associated stromal proliferation

Lymphoepithelioma-like carcinoma
top

May represent a primitive adnexal tumor
Micro: resembles upper respiratory tract tumor, with nests of high grade tumor cells in a syncytium, with a marked lymphocytic infiltrate; but also has features of sweat gland, follicular or apocrine differentiation

Negative stains: EBV

Merkel cell carcinoma

top
Also called neuroendocrine carcinoma of skin; originally called trabecular carcinoma
Usually adults or elderly; 60% women
Face and extremities
May be associated with squamous cell carcinoma (in situ or invasive), basal cell carcinoma, eccrine duct-like structures
Aggressive; regional nodal metastases are common; distant metastases to liver, lung, bones; also testis or other unusual sites
Rarely appears to arise initially in lymph node, probably due to regression of primary skin tumor
May derive from Merkel cell in epidermis, derived from neural crest, important for tactile sensation in lower animals
Treatment: wide local resection, regional lymph node resection; radiation therapy and chemotherapy as needed

Gross: nodular or ulcerated red-violet lesion

Gross images by anonymous contributor: hip lesion #1; #2; #3

Micro: dermal or subcutaneous centered tumor with monotonous round tumor cells and diffuse infiltration of subcutis; may have focal trabecular pattern; cells have scant eosinophilic cytoplasmic rim, round and vesicular nuclei with finely granular and dusty chromatin and multiple nucleoli; also apoptotic nuclei and frequent mitotic figures; may have vascular stroma with plump endothelial cells; epidermis is usually spared; rarely has leiomyosarcoma or atypical fibroxanthoma-like areas

FNA image by anonymous contributor: small blue cell tumor
(was CK20+ with perinuclear dot like staining, CD45-, TTF-; flow was CD56+, CD45-)

Positive stains: low molecular weight keratin, CK20 (perinuclear dot like staining), EMA, neurofilament, neuron-specific enolase, CD56 (J Cutan Pathol 2005;32:541); variable chromogranin, synaptophysin and CD117

Negative stains: TTF1, CD45/LCA

EM: dense core neurosecretory granules and tightly packed intermediate filaments; well developed desmosomes

Molecular: abnormalities in #1, #11, #12; 1p35-36 deletion

DD: lymphoma, metastatic small cell carcinoma of lung, basal cell carcinoma

Metastatic carcinoma to skin

Men: usually from lung (25%), colon, melanoma, kidney, upper aerodigestive tract
Women: usually from breast (69%), lung, melanoma, kidney, ovary
Most common sites of metastases to skin are chest, abdomen, head and neck; metastasis is often close to site of primary

Gross: multiple firm, nonulcerated nodules; may be solitary

Micro images: metastatic breast cancer is p63 negative (basal epidermis is p63+)

Negative stains: p63 is negative in metastatic adenocarcinoma vs. positive in cutaneous adnexal tumors (Mod Path 2005;18:137)

DD: sweat gland tumor (resembles renal cell carcinoma), dermatofibrosarcoma protuberans (resembles signet ring carcinoma), Merkel cell carcinoma (resembles neuroendocrine metastases)

Mucoepidermoid carcinoma

Very rare in skin (~ 30 cases reported)
Probable sweat gland origin
Resembles similar tumor of salivary gland
Usually low to intermediate grade
Case reports: 79 year old white woman with axillary mass (AJSP 2005;29:131)

Micro: circumscribed, not attached to surface; dermal lobules or cystic growth of low grade epidermoid, intermediate, mucinous cells and clear cells; peritumoral fibrosis is common

Positive stains: mucin, keratin, CK7, pCEA, EMA

Negative stains: CK20, GCDFP-15

DD: adenosquamous carcinoma (high grade tumor, often involves epidermis, adenocarcinoma component is well-differentiated), metastatic salivary gland tumor (usually high grade), mucinous metaplasia

Small cell neuroendocrine carcinoma

May be a variant of Merkel cell carcinoma or a metastases

Spindle squamous cell carcinoma

Also called metaplastic carcinoma
Sun exposed areas, particularly the lip
Carcinosarcoma: sharp segregation exists between epithelial and sarcoma-like areas
Sarcoma-like tumor of skin: cannot rule out a mesenchymal tumor

Micro: tumor is contiguous with basal layer of epidermis; usually at least focal squamous cell carcinoma
Positive stains: keratin, vimentin, p63 ([J Cutan Pathol 2006;33:413])
DD: melanoma, atypical fibroxanthoma

**Squamous cell carcinoma**

Common, derived from keratinocytes in epidermal layer

Usually men, associated with sun exposure (UV light may induce p53 mutations and diminish surveillance function of Langerhans cells in epidermis), PUVA treatment for psoriasis, arsenic, tars/oils, chronic ulcers, draining osteomyelitis, old burn scars, necrobiosis lipoidica, hidradenitis suppurativa, ionizing radiation

Risk factors: immunosuppression (post-transplant or HIV), xeroderma pigmentosa (disorder with diminished capacity for DNA repair after UV light exposure, due to gene at 9q22.3; associated with squamous cell, basal cell carcinoma and melanoma), lack of pigmentation in skin, actinic keratosis (precursor lesion), epidermodyplasia verruciformis; very rare in blacks

5% are node positive at diagnosis; metastatic rate is 5-10% in transplant patients, who do poorly with metastatic disease

Slow growing, locally invasive but rarely metastasizes outside nodes (but see above); most common site is lung

Metastases more likely in tumors that originate in scars or ulcers

**Prognosis:** excellent; metastases uncommon if tumor < 1.5 cm deep; 5% metastasize if 2 cm or more and definite dermal invasion

**Good prognostic factors:** low stage, no/superficial dermal invasion, small vertical tumor thickness (< 4 mm), well differentiated, short duration, location other than scalp, ears, lips, nose, eyelids or soft tissue (which readily invade subcutaneous tissue)

**Treatment:** surgical excision with adequate margins; also curettage, electrodesiccation, cryotherapy, radiation therapy

**Gross:** often white plaque (leukoplakia); may have induration, ulceration, hemorrhage

**Micro:** atypia at all levels of epidermis; 80% are well differentiated with keratin pearls, intercellular bridges and no/rare keratohyaline granules; invade dermis by definition; may contain non-neoplastic melanocytes that transfer melanin to tumor cells; occasionally clear cells, rarely signet ring cells

Spindle, adenoid and verrucous variants are described separately

Other variants are acantholytic (pseudoglandular, tumor clefts produced by acantholysis of tumor cells) and pseudoangiosarcomatous (clefts separate neoplastic lobules)

**Low grade (well differentiated):** cell differentiation, uniform cell size, intact intercellular bridges, no/rare mitotic figures, no/mild pleomorphism

**High grade (poorly differentiated):** little cell differentiation, pleomorphism with spindle cells, necrosis, marked mitotic activity, deep invasion

**Micro images:** (1) a: moderately differentiated (H&E); b: telomerase+; c: COX2+; d: p53+
Positive stains: high molecular weight keratin, EMA, involucrin, p53 (50%), variable CEA

Negative stains: Ber-EP4, usually CK7 and CK20 (head and neck tumors, Mod Path 2004;17:407)

DD: keratoacanthoma (for well differentiated tumors)

Verrucous carcinoma
top
Also known as epithelioma cuniculatum
Usually mucosal sites such as oral cavity, glans penis, vulva, cervix
Rarely on skin; usually sole of foot with frequent extention to bone; nodal metastases are rare

Gross: ulcerating, fungating or polypoid mass with sinus tracts opening onto skin surface

Micro: very well differentiated, ulcerating, fungating mass with deep sinus tracts; composed of lobules of mature squamous epithelium with minimal atypia; tumor lobules may invade and destroy bone; few mitotic figures, variable stromal response

Positive stains: HPV (frequently, usually 16, 6, 11)

DD: cysts, benign keratoses

Staging of skin carcinomas

Staging of melanomas is described in Skin - Melanocytic tumors chapter

Staging of eyelid tumors is described in the Eye chapter

Includes spindle cell variant of squamous cell carcinoma and adnexal carcinomas

Applies to clinical and pathologic staging

Primary tumor (T)

TX: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: carcinoma in situ
T1: tumor 2 cm or less in greatest dimension
T2: tumor more than 2 cm, but not more than 5 cm in greatest dimension
T3: tumor more than 5 cm in greatest dimension
T4: tumor invades deep extradermal structures (i.e. cartilage, skeletal muscle or bone)

Note: for multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g. T2 (5)

Regional lymph nodes (N)

NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: regional lymph node metastasis

Distant metastasis (M)
top
MX: distant metastasis cannot be assessed
M0: no distant metastasis
M1: distant metastasis

Stage grouping
top

Stage 0: Tis N0 M0
Stage I: T1 N0 M0
Stage II: T2-T3 N0 M0
Stage III: T4 N0 M0 or any T N1 M0
Stage IV: Any T, Any N, M1

**Lymphoma and related disorders**
See also Lymphoma chapters
Equal incidence of B and T cell disorders (noncutaneous lymphomas have B cell predominance)
May be primary to skin or part of systemic disease
Common primary cutaneous lymphomas are: T cell - mycosis fungoides; B cell - diffuse large B cell lymphoma, extranodal marginal zone lymphoma, follicular lymphoma
Note: lymphocytes in skin are significant, since not usually present, although may be due to dermatoses

**B cell lymphomas:** triangular architecture with base in subcutis, compact and nodular infiltrates with perivascular cuffing; epidermis not involved

**T cell lymphomas:** heterogenous; may have epidermal involvement; may have large reactive component mixed with tumor cells

**Epidermotropic:** mycosis fungoides, pagetoid reticulosis, mycosis fungoides associated follicular mucinosis, adult T cell leukemia / lymphoma

**Superficial dermal:** Sezary syndrome

**Dermal involvement:** lymphoid hyperplasia, inflammatory pseudotumor, follicular center cell lymphoma, marginal zone lymphoma, diffuse large B cell lymphoma, plasmacytoma, lymphomatoid papulosis, granulomatous slack skin disease, CD30+/- large T cell lymphoma, pleomorphic small/medium-sized T cell lymphoma, blastic NK cell lymphoma

**Subcutaneous:** subcutaneous panniculitis-like T cell lymphoma

**Angiocentric:** lymphomatoid granulomatosis, nasal type NK/T cell lymphoma

**Intravascular:** intravascular large B cell lymphoma

**Acute lymphoblastic lymphoma**
Most common type of cutaneous lymphoma in children; rare in adults
Aggressive behavior; T cell subtypes have best prognosis; stem cell transplantation may improve survival
Either B cell (CD19+, CD20+, CD79a+), T cell (surface CD3+) or nonB nonT (negative for B cell markers and CD3)
NonB nonT include (a) CD7+ stem cell lymphoma (CD7+, CD4-, CD56-, CD33 variable), (b) blastic NK lymphoma (CD56+, CD4-, CD33-, CD123-, CD7 variable), (c) myeloid/NK precursor cell leukemia (CD56+, CD4-, CD7+, CD33+), (d) CD4+ CD56+ hematodermic malignancy (CD4+, CD56+, CD123+, CD7 variable, CD33-) CD4+ CD56+ hematodermic malignancy frequently has skin lesions, an aggressive clinical course and poor prognosis

**References:** AJSP 2003;27:1366

**Anaplastic large cell lymphoma**
Usually elderly men
Either primary cutaneous, systemic ALK+ or systemic ALK negative
Primary cutaneous tumor has good prognosis
May have regressive phase

**Gross:** solitary or multiple lesions

**Micro:** large anaplastic tumor cells infiltrate dermis and subcutis, may resemble lymphomatoid papulosis, often pseudoepitheliomatous hyperplasia

**Variants:** lymphohistiocytic, sarcomatoid, Hodgkin's-like, small cell, monomorphic, myxoid, neutrophil-rich (associated with HIV+)
Positive stains: CD30 (diffuse membrane and paranuclear dot-like staining); usually T cell markers, NPM-ALK transcript
Molecular: t(2;5) generates NPM-ALK fusion transcript
DD: CD30+ non-neoplastic cutaneous infiltrates

Angiocentric lymphoma
Affects lungs, skin, CNS
Gross: multiple plaques, nodules or ulcerated nodules
Micro: perivascular to diffuse dermal infiltrate with vascular invasion in 50%, also perineural invasion, adnexal destruction, extensive necrosis; epidermis is uninvolved; infiltrate composed of atypical and normal appearing lymphocytes, plasma cells, histiocytes; atypical lymphocytes are high grade malignant cells
Positive stains: usually T cell

Blastic natural killer cell leukemia/lymphoma
Systemic disease, highly aggressive
Estimated 5 year survival is 0%; eventually becomes leukemia
Recommended to separate off CD4+ CD56+ CD123+ cases as “CD4+ CD56+ hematodermic malignancy”, which frequently has skin lesions and also has poor prognosis (AJSP 2003;27:1366)
Gross: usually multiple bruise-like deep red plaques/tumors
Micro: involves dermis and surrounding adnexa, subcutis but no epidermal involvement; grenz zone present; composed of monomorphous medium sized cells with fine chromatin resembling blasts of acute myelogenous leukemia (although AML is CD56-); may actually derive from common myeloid and NK precursor called plasmacytoid type 2 dendritic cell
Positive stains: usually CD4 and CD56, variable TdT and CD3
Negative stains: CD8, TIA1, EBV

Diffuse large B-cell lymphoma
Primary cutaneous cases, by definition, arise in skin with no known extracutaneous disease within 6 months of initial diagnosis
Represents 20% of primary cutaneous lymphomas; others are extranodal marginal zone lymphoma, follicular lymphoma, T cell lymphomas
Usually men (85%), mean age 64 years
Better outcome than other large B cell lymphomas, although similar to primary cutaneous follicular lymphoma - relapse common but estimated 5 year survival is 97%
CD10+ tumors in head and neck have increased risk of relapse
Can divide into follicular center type (CD10+, bcl6+, CD138- but without bcl2 translocations) and those with post-follicular center or activated B cell phenotype (CD10-, bcl2 usually negative); secondary cases are more like classic follicular lymphoma (AJSP 2003;27:356)
Treatment: surgery, localized radiotherapy; systemic chemotherapy only for generalized skin lesions or disseminated lesions
Case reports: t(14;18)(q32;q21) involving IgH and MALT1 (not bcl2, distinguish MALT1 from bcl2 by FISH (Hum Path 2003; 34:1212); two patients with T cell rich B cell lymphoma (Mod Path 2001;14:10)
Gross: solitary or grouped papules, plaques or tumors, usually in head, neck and trunk of older patients
Micro: either (a) mixed large and small B cells, (b) grade 3 follicular lymphomas (usually in head/neck and CD10+) or (c) monomorphous large cell (AJSP 2001;25:307)
Micro images: A: Grenz zone; B: occasional large cells; C: CD3+ reactive lymphocytes; D: CD20+ tumor cells

Positive stains: tumor cells - CD20; variable bcl2 and bcl6; reactive T cells - CD3, CD45RO (UCHL-1)

Negative stains: tumor cells - CD3 (positive in background cells), CD10 (usually)

Flow cytometry: reactive T cells are 65-90% of cells (Archives 1999;123:1236)

References: AJCP 2002;117:574 (study of 15 cases)

Leg

5-10% of primary cutaneous diffuse large B cell lymphomas cases

Usually elderly patients

May have poorer prognosis (AJSP 2003;27:1538), although somewhat controversial (Hum Path 2002;33:937)

Gross: solitary or grouped red/blue nodules

Micro: dense, diffuse large cells infiltrating entire dermis, usually thin grenz zone, cells resemble immunoblasts (large oval vesicular nuclei with prominent nucleoli) or centroblasts (large noncleaved nuclei, prominent nucleoli)

Follicular lymphoma-primary cutaneous

Mean age 64 years; localized papulonodular lesions, often in head, neck and trunk, with excellent prognosis

By definition, arises in skin with no known extracutaneous disease within 6 months of initial diagnosis; has follicular growth pattern and germinal center cytology (AJSP 2001;25:875)

In Scottish Highlands, cutaneous B cell lymphomas (all subtypes) are associated with Borrelia burgdorferi infection (Lyme disease, AJSP 2000;24:1279)

Indolent behavior, although cutaneous relapses are common; similar relapse rate as stage 1 nodal follicular lymphoma, but more likely to attain complete remission (AJSP 2002;26:733)

Gross: solitary or grouped papules, plaques or tumors

Micro: nodular, diffuse or floral-like pattern (32%, with IgD+ mantle zone) of centrocytes (cleaved follicular cells) and centrocytes (large transformed cells)

Positive stains: CD19, CD20, CD79a, bcl6+ and usually CD10+ centrocytes and centroblasts, usually bcl2+ in follicular and interfollicular/diffuse areas (AJSP 2001;25:732); similar to follicular lymphoma otherwise

Negative stains: CD5

Molecular: t(14;18)+ in only 20-30% by PCR (Mod Path 2001;14:913; Mod Path 2001;14:828, AJSP 2000;24:694); FISH may be more specific than PCR due to bystander cell positivity for t(14;18) (AJSP 2004;28:748)

DD: secondary follicular lymphoma, cutaneous MALT lymphoma (bcl2+, usually negative for bcl6 and CD10 although colonized follicles [CD21+] are bcl6+, AJSP 2001;25:732), lymphoid hyperplasia (bcl2 doesn’t stain germinal centers)

References: AJSP 2005;29:69

Hodgkin’s lymphoma of skin

Usually indicates stage IV disease

Rarely is primary in skin

Gross: nodules or papules distal to involved lymph nodes

Human T cell lymphoma 1 related lymphoma (HTLV-1)

Rapid clinical course

Micro: high grade, spares epidermis, may be angiocentric
Intravascular lymphoma
Also called angiotropic lymphoma, malignant angioendotheliomatosis
Usually diffuse large B cell (occasionally T cell) lymphoma
May present initially in cervix, prostate, other sites
Micro: large atypical tumor cells in lumen or wall of vessels

Jessner’s lymphocytic infiltration of skin
May be a variant of lymphoid hyperplasia
Related to discoid lupus erythematosus
Violaceous nodules of head and neck or trunk
Micro: lymphocytes and plasmacytoid monocytes, no distinct epidermal changes

Leukemia
Skin involvement (“leukemia cutis”) occurs in 5% with CML, 8% with CLL, 10% with monocytic leukemia
Usually is abnormal peripheral blood count at diagnosis
Skin involvement is rarely initial manifestation of recurrence (Am J Clin Pathol 2008;129:130)
Myeloid leukemia with monocytic differentiation more commonly involves the skin than other types of myeloid leukemia; may also have accompanying vasculitis (Am J Clin Pathol 1997;107:637) Aggressive behavior and short survival (J Am Acad Dermatol 1999;40:966)
Case reports: 68 year old woman with history of AML (Case of Week #140)
Treatment: systemic chemotherapy directed at eradicating the leukemic clone
Gross: multiple nodules/papules
Micro: in CLL, may be perivascular, periadnexal, nodular or bandlike dermal infiltrate; infiltrate in leukemic patients is often NOT neoplastic, but reactive
AML - dermis and superficial subcutaneous fat are diffusely infiltrated by a monotonous population of large cells with a high nuclear to cytoplasmic ratio, round to slightly irregular nuclear contours, finely dispersed chromatin and prominent nucleoli
Micro images: AML - #1; #2; #3; #4; CD45; CD43; CD117; CD68
Positive stains: myeloblasts - chloroacetate esterase (Leder stain), myeloperoxidase
References: eMedicine

Lymphoid hyperplasia
Usually on face of women
May be due to trauma or insect bites
Gross: solitary nodules or plaques
Micro: lymphocytic and histiocytic infiltrate with tingible body macrophages, plasma cells, eosinophils; often germinal cells or lymphoid follicles, hyperplastic vessels or epidermal hyperplasia; usually spares epidermis
Positive stains: both kappa and lambda light chain expression, both B and T cells
DD: MALT lymphoma (marginal zone cells, Dutcher bodies, sheets of plasma cells)

Lymphomatoid papulosis
Top
Rare, self-healing, recurrent papular eruption
Indolent clinical course, although 10% are associated with or evolve to anaplastic large cell lymphoma
May be self healing “benign” phase of anaplastic large cell lymphoma (per Rosai)
May resemble pityriasis lichenoides et varioliformis acuta, or have large ulcerated plaques and nodules
Treatment: regular follow-up
Micro: wedge shaped on low power with base of lymphocytes at epidermis and tip deep within reticular dermis; polymorphic superficial dermal infiltrate, usually perivascular, with thin epidermis; occasional atypical lymphoid cells
resembling Reed-Sternberg cells or "lumps of coal"; often obscures dermoepidermal junction with variable epidermotropism

**type A:** pleomorphic CD30+ lymphocytes with hyperchromatic nuclei that may mimic Reed-Sternberg cells; also mixed inflammatory infiltrate; CD3+, CD4+, CD8-, CD20-, CD30+, CD56-

**type B:** relatively small hyperchromatic lymphocytes with complex nuclear membranes; CD3+, CD4+, CD8-, CD20-, CD30-, CD56-

Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - type A - #1; #2; #3; CD30

Molecular: T cells are clonal, but this doesn't predict transformation to lymphoma

DD: arthropod bite

**Mantle zone lymphoma**

**top**

Chronic and protracted clinical course

**Micro:** extensive nodules in reticular dermis and subcutis of small lymphocytes with irregular nuclear membranes and clumped chromatin; forms wide mantle zones around germinal centers

Positive stains: B cell markers, bcl1

**Mast cell disorders**

**top**

Most cutaneous mast cell disorders have a good prognosis

**Mastocytosis:** monomorphic population of mast cells with rare eosinophils

**Urticaria pigmentosa:** common form of mastocytosis, numerous small yellow-brown papules, become hives when rubbed

**Micro:** variable dermal mast cell infiltration; variable eosinophils

Positive stains: toluidine blue and Giemsa demonstrate metachromasia (granules are purple-red), Leder chloroacetate esterase, CD117/c-kit

DD: normal skin or dermatoses (must search to find mast cells even with special stains)

**Mycosis fungoides**

Most common primary cutaneous T cell lymphoma

Usually elderly or other adults

May arise from progression of large plaque psoriasis

Usually protracted clinical course over years

By definition, are negative for HIV1, HIV2, HTLV

**Sezary syndrome:** peripheral blood involvement by cerebroid cells with PAS+ granules, lymphadenopathy, diffuse erythema and scaling of entire body surface; usually less epidermotropism; lymph nodes may have tumor cells or dermatopathic lymphadenitis (no atypical T cells, normal architecture, no clonality)

**Poor prognostic factors:** generalized plaques/tumors, diffuse erythema, lymphadenopathy

50% have nodal or visceral involvement that may resemble large cell lymphoma

Sepsis is a common terminal complication

**Treatment for skin limited disease:** total skin electron beam irradiation, topical chemotherapy, PUVA

Molecular: clonal proliferation of mature CD4+ epidermotrophic lymphocytes; low CD8/CD3 ratio in epidermal tumor cells (Mod Path 2003;16:857)

DD: drug reaction, inflammatory dermatoses (resemble early mycosis fungoides)

**Premycotic (patch) stage**

**top**

Usually indolent course

**Gross:** erythematous, scaly and pruritic skin

**Micro:** chronic non-specific dermatitis with psoriasiform changes in epidermis; often associated changes of lichen simplex chronicus due to repeated rubbing

**Mycotic stage**

**top**

**Gross:** infiltrative plaques

**Micro:** dermal polymorphous infiltrate of atypical lymphocytes with cerebriform nuclei alone or clustered in epidermis and in small sheets in dermis; also Pautrier's microabscesses, palisading along epidermal basal layer, tumor infiltrates around hair follicles, variable follicular mucinosis

Micro images: low CD8 expression (B) compared to inflammatory dermatoses (D)

**Tumorous stage**

**top**
Treatment: systemic chemotherapy

Micro: dense dermal infiltrates of atypical T cells with cerebroid nuclei (with thin sections); may have reactive B cell component also

Positive stains: CD4 (usually)

Negative stains: CD2, CD3, CD5, CD7

Molecular: T cell receptor gene clonality

DD: acute or chronic dermatitis with cerebroid cells

NK/T cell lymphoma, extranodal, nasal type

Aggressive tumors, usually in GI tract, less commonly in skin

More common in Asia and South American than Western countries

Estimated 5 year survival: 0%

Micro: may involve epidermis, dermis or subcutis; polymorphous lymphoid infiltrate with eosinophils, plasma cells, histiocytes; lymphocytes are usually large pleomorphic cells with vesicular nuclei and prominent nucleoli; also medium or small with irregular nuclei; usually angiocentric (52%) with necrosis (62%); apoptosis common; occasionally clear cytoplasm

Micro images: tumor from various sites, including skin - a: vascular infiltration/destruction; b: small cells with slightly irregular nuclei and inflammatory infiltrate; c: small and medium sized cells; d: large lymphoid cells with vesicular nuclei and distinct nucleoli; e: EBER+ by ISH

Positive stains: CD2, CD3epsilon, CD56, TIA, granzyme B, EBER by ISH

Negative stains: CD20

References: Mod Path 2004;17:1097 (skin and other sites)

Peripheral T cell lymphoma

50% of T cell lymphomas in Western countries; a large and heterogenous group of lymphomas

Median age 62 years

Usually present with advanced stage disease with nodal involvement and variable marrow or extranodal involvement

May have primarily skin involvement

Aggressive; recurrences, progressive disease and death due to disease are common

May resemble classic Hodgkin's lymphoma due to Reed-Sternberg like cells, and occasional cases are CD15+ and CD30+ (AJSP 2003;27:1513)

Positive stains: CD45 (usually), T cell markers on all cells; occasionally CD15+ and CD30+ in both Reed-Sternberg like cells and background cells

Negative stains: aberrant T cell expression (i.e. loss of some T cell markers)

Molecular: clonal rearrangement

DD: Hodgkin's lymphoma (background cells have normal morphology and normal T cell antigen expression; Reed-Sternberg like cells are negative for T cell antigens)

Primary cutaneous lymphoma

Primary cutaneous B cell lymphoma

< 20% of primary cutaneous lymphomas

Consists of follicular lymphoma, marginal zone lymphoma and diffuse large B cell lymphoma

Marginal zone lymphomas often associated with Borrelia burgdorferi infection

By definition, no evidence of extracutaneous disease is identified for 6 months after initial diagnosis

Similar morphology to nodal disease, but more indolent

Molecular: t(14;18) is rare in cutaneous follicular lymphoma, but is characteristic of nodal follicular lymphoma

References: Mod Path 2004;17:623 (mutational analysis)
Subcutaneous, blastic NK, NK/T cell or other cytotoxic T cell lymphoma (excluding mycosis fungoides)
These cases include patients with skin and non-skin disease at diagnosis, as well as skin only
All CD30 negative with medium/large cells or subcutaneous panniculitis-like
(a) subcutaneous panniculitis-like T cell lymphoma: indurated, erythematous and discolored plaques on extremities; alpha/beta CD8+ cytotoxic T cells, with almost exclusive involvement of subcutaneous tissue resembling lobular panniculitis; recommend to exclude cases with epidermal involvement from this category; tumor cells have pleomorphic nuclei and adipocyte rimming (not specific for this diagnosis); CD3+, CD8+, TIA1+, EBV-, estimated 5 year survival is 80% with systemic steroid therapy
(b) blastic NK cell lymphoma: usually multiple bruise-like deep-red plaques/tumors; involves dermis and surrounding adnexa, grenz zone present, subcutis but no epidermal involvement; monomorphous medium sized cells with fine chromatin resembling blasts of acute myelogenous leukemia (although AML is CD56-); may actually derive from common myeloid and NK precursor called plasmacytoid type 2 dendritic cell; CD3-, CD4+, CD8-, CD56+, TIA1+, betaF1+, EBV-; estimated 5 year survival is 0%; eventually become leukemia
(c) NK/T cell lymphoma, nasal type: multiple patches, plaques or nodules; may involve epidermis, dermis or subcutis; medium-large pleomorphic or blastic nuclei; CD3epsilon+, TIA1+, EBV+; estimated 5 year survival is 0%
(d) epidermotrophic CD8+ T cell lymphoma: multiple plaques and tumors, similar to disseminated pagetoid reticulosis; ulceration common; alpha/beta negative, CD8+ cytotoxic T cells, with predominant involvement of epidermis, also dermis, adnexae and subcutis; CD3+, CD8+; TIA1+, betaF1+; EBV-; estimated 5 year survival is 0%; must rule out mycosis fungoides
(e) cutaneous gamma/delta T cell lymphoma: multiple plaques and tumors, similar to disseminated pagetoid reticulosis; epidermal involvement with necrosis, interface dermatitis, adnexal involvement, gamma/delta T cells; CD4-, CD8-, CD56+, TIA1+, EBV-; estimated 5 year survival is 0%
(f) cutaneous alpha/beta pleomorphic T cell lymphoma: solitary or multiple plaques and tumors; often epidermal necrosis and adnexal involvement; alpha/beta T helper cells (CD8-) with expression of cytotoxic markers betaF1 and TIA1, different from subcutaneous panniculitis-like T cell lymphoma and epidermotrophic CD8+ T cell lymphoma; estimated 5 year survival is 0%
(g) cutaneous medium/large pleomorphic T cell lymphoma, not otherwise specified: multiple plaques and tumors, don’t fit other categories
References: AJSP 2004;28:719

Woringer-Kolopp disease
top
Also called pagetoid reticulosis
Indolent, T cell cutaneous proliferative disorder
Related to mycosis fungoides
Disseminated lesions are called Ketron-Goodman type of pagetoid reticulosis
Gross: solitary erythematous squamous patch
Micro: monomorphic intraepidermal infiltrate of mycosis fungoides-like cells, in Paget’s disease type pattern

Vascular tumors
Acquired (tufted) angioma
Also called Nakagawa’s angioblastoma; benign, juvenile or infantile hemangioendothelioma
May be the same entity as kaposiform hemangioendothelioma
Slowly enlarging multiple red plaques on shoulders and upper back of children or teenagers

**Micro:** multiple vascular lobules similar to pyogenic granuloma but more cellular, resembling cannonballs, and with semilunar vessel at periphery of lobule (versus central and open vessel in pyogenic granuloma); variable mitotic figures, no atypia

**Positive stains:** Ulex europaeus and factor VIII related antigen only in endothelium of larger vascular channels

**Angiokeratoma**

**Micro images:** contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clínica Ponferrada, Spain - #1; #2; #3

**Angiosarcoma**

Also called malignant hemangiendothelioma
Skin cases are in head and neck of elderly, not young patients, unless also associated with chronic lymphedema or radiotherapy (these lesions are often called lymphangiosarcomas)
Slow growing but highly aggressive with frequent recurrences that involve extensive areas of face and scalp; metastasize to regional lymph nodes, lungs, other organs

**Gross:** violet elevated nodules on flat lesion with ill defined margins; may be verrucoid

**Micro:** infiltrating, freely anastomosing channels lined by spindled to epithelioid endothelial cells with marked atypia, surrounding adnexae and dissecting dermal collagen; intracytoplasmic vacuoles represent lumina; also areas resembling Kaposi’s sarcoma and undifferentiated foci resembling melanoma or carcinoma; may have focal granular cell features; may extend into scalp aponeurosis

**EM:** features of endothelial cells

**Molecular:** not diploid by flow cytometry

**DD:** epithelioid variants resemble epithelioid hemangiendothelioma or epithelioid hemangioma; squamous cell carcinoma, epithelioid sarcoma, hamartoma of scalp with ectopic meningothelial elements

**Bacillary angiomatosis**

Due to infection by *Bartonella henselae*
May involve soft tissue, lymph nodes, internal organs
May coexist with Kaposi’s sarcoma
Reactive but mimics a neoplasm, and commonly presents as multiple cutaneous neoplasms in HIV patients

**Treatment:** antibiotics

**Micro:** lobules of capillaries with epithelioid endothelial cells; also fragmented neutrophils, granular purple extracellular bacteria

**Positive stains:** silver stains (bacteria)

**EM:** bacteria present

**DD:** verruga peruana, Kaposi’s sarcoma

**Benign (infantile) hemangiendothelioma**

**Micro:** lobular with marked hypercellularity; vascular lobules (of pyogenic granuloma) also present

**Benign lymphangiendothelioma**

Also called acquired progressive lymphangioma
Gross: bruise-like lesion
Micro: anastomosing vascular channels, but no atypia
DD: angiosarcoma, Kaposi’s sarcoma

Glomus tumor
Usually painful subungal tumors
Micro: dermal or subcutaneous tumors, either solid or vascular, composed of glomus cells, a modified smooth muscle cell with abundant cytoplasm and oval nucleus; either (a) solid variant - proliferation of glomus cells with no/rare vascular lumina or (b) vascular variant - abundant vascular lumina that may resemble cavernous hemangioma
Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clínica Ponferrada, Spain - #1; #2; #3; #4
DD: cavernous hemangioma, blue rubber bleb nevus syndrome (multiple tumors), acrospiroma

Hemangioma
Childhood tumors are often malformations, not neoplasms

Capillary hemangioma
Also called strawberry hemangioma
Children: usually regress by fibrosis
Adults: may slowly enlarge or thrombose
Micro: well formed vascular channels in dermis with endothelial lining and containing red blood cells; no atypia
DD: dermal vascular hyperplasia (with venous stasis), pyogenic granuloma, Kaposi’s sarcoma, angiosarcoma, hemangioendothelioma

Cavernous hemangioma
Markedly dilated dermal vessels, may elevate overlying epidermis, which may be atrophic
Associated with Maffucci’s syndrome, blue rubber bleb nevus syndrome, Kasabach-Merritt syndrome

Epithelioid hemangioma
Also called histiocytoid hemangioma, angiolymphoid hyperplasia with eosinophilia
All racial groups
Head and neck nodules, often periauricular
Benign in skin; may be reactive
Occasionally overlies soft tissue epithelioid hemangioendothelioma or occurs in bone
No/rare regional lymphadenopathy
Normal serum eosinophils, IgE
Gross: small, superficial, dermal papulonodules, frequently erythematous, with bleeding
Micro: proliferation of blood vessels with epithelioid endothelial cells exhibiting abundant eosinophilic cytoplasm with variable cytoplasmic vacuoles resembling intracytoplasmic lumina and variable atypia; usually heavy infiltrate of eosinophils and lymphocytes with germinal centers; may have lobular solid pattern
DD: epithelioid hemangioendothelioma (usually not cutaneous), epithelioid angiosarcoma (marked atypia), lobular pyogenic granuloma (no epithelioid endothelial cells), Kimura’s disease (usually Asians with elevated serum eosinophils and IgE, usually regional lymphadenopathy)

Glomeruloid hemangioma
Associated with Castleman’s disease and POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes)
Micro: dermal vascular spaces contain glomeruloid structures formed by capillaries; occasional cells have PAS+ eosinophilic globules
Micro images: contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clínica Ponferrada, Spain - #1; #2

Hobnail hemangioma
Endothelial cells protrude into vessel lumina
contributed by Drs. Asmaa Gaber Abdou and Nancy Asaad, Menofiya University, Egypt - lower lip of female - #1; #2; #3; #4

Juvenile hemangioma
Spontaneously involutes, not associated with Kasabach-Merritt phenomenon
Positive stains: GLUT1+, LewisY+
DD: kaposiform hemangioendothelioma (doesn’t involute, GLUT1-, LewisY-, often associated with Kasabach-Merritt phenomenon)

Microvenular hemangioma
Young to middle-aged adults; also pregnant women or women on oral contraceptives
Small, enlarging, purple-red nodules or plaques of extremities
Duration up to 4 years
Micro: transdermal proliferation of irregular branching venules with indistinct lumina, no atypia, no fat invasion (although may grow along collagenous septa of subcutis); variable dermal fibrosis and lymphocytes; resembles acquired (tufted) angioma, stasis change, sclerosing hemangioma
Positive stains: endothelial cells are strongly Ulex europaeus lectin 1+, weakly positive for factor VIII related antigen
DD: dermatofibroma, Kaposi’s sarcoma (irregularly anastomosing vascular spaces, plasma cells, hyaline globules, fascicles of spindle cells)

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 Positive stains: endothelial cells are strongly Ulex europaeus lectin 1+, weakly positive for factor VIII related antigen
 DD: dermatofibroma, Kaposi’s sarcoma (irregularly anastomosing vascular spaces, plasma cells, hyaline globules, fascicles of spindle cells)
Spindle cell hemangioma
Bland spindle cell proliferations between vascular lumina with extravasated erythrocytes (similar to Kaposi’s sarcoma), but also with vacuolated cells and epithelioid endothelial cells (unlike Kaposi’s sarcoma)

Hemangioendothelioma and subtypes
Epithelioid hemangioendothelioma
top
Superficial and soft tissues in adults
Micro: nests and cords of cells with abundant eosinophilic cytoplasm and prominent intracytoplasmic lumina
DD: carcinoma

Kaposiform hemangioendothelioma
top
Rare tumor of childhood (mean age 4 years, range 2 weeks to 20 years)
Some cases may have been called acquired tufted angioma
Intermediate malignancy; does not regress
50% are associated with Kasabach-Merritt phenomenon (profound thrombocytopenia and life-threatening hemorrhage); occasionally associated with lymphangiomatosis
Usually on extremities or head and neck
May affect skin or deep soft tissue
Metastases limited to regional perinodal soft tissue; mortality due to underlying Kasabach-Merritt phenomenon
Gross: skin lesions are slightly raised, blue-red
Micro: biphasic with vascular and lymphatic component; irregular, infiltrating nodules of compressed vessels, evoking a dense hyaline stromal response; vessels are tightly coiled and highly convoluted, and budded off larger vessels, resembling either capillary hemangioma or Kaposi’s sarcoma; scattered epithelioid or glomeruloid islands are associated with pericytes, hemosiderin and fibrin thrombi; also has lymphatic component with thin-walled vessels
Positive stains: CD31, CD34, FLI1+
Negative stains: GLUT1 (glucose transporter protein isoform 1), Lewis Y antigen, HHV8
DD: juvenile hemangioma (spontaneously involutes, not associated with Kasabach-Merritt phenomenon, GLUT1+, LewisY+)
References: AJSP 2004;28:559

Retiform hemangioendothelioma
top
Low grade variant of angiosarcoma
Usually distal extremities of young individuals
Weiss and Goldblum use term “hobnail hemangioendothelioma” for retiform and Dabska-type tumors, which they believe to be closely related
Rarely multiple (Am J Dermatopathol 1996;18:606)
2/3 recur, particularly without wide local excision; low rate of metastases, no tumor related deaths
Case reports: Case of the Week #107
Treatment: wide local excision;
Gross: lesion of reticular dermis and subcutaneous tissue
Micro: retiform (net-like, similar to rete testis) pattern of blood vessels that disperse through reticular dermis and subcutis; vessels lined by monomorphic hobnail endothelial cells with scant cytoplasm and rounded, naked-type nuclei; often prominent lymphocytic infiltrate; no epithelioid areas or cytoplasmic vacuoles (AJSP 1994;18:115)
Micro images: #1; #2; #3; #4; #5; CD31 #1; #2
Positive stains: endothelial cells - CD34 (strong), CD31, vWF
Negative stains: endothelial cells - keratin.
DD: angiosarcoma (may focally have low grade features, but also exhibits areas of marked atypia and pleomorphism; also dissects between individual collagen bundles and has mitotic activity), hobnail hemangioma (smaller, more superficial and more localized, with papillary dermal vessels that disappear into reticular dermis)

Spindle cell hemangioendothelioma
Dermis and subcutis
Frequent local recurrences, only rare metastases
Micro: thin-walled, large cavernous blood vessels and spindle cells

Intravascular papillary endothelial hyperplasia
Also called Masson’s hemangiomma
Often fingers and hemorrhoids
In skin, associated with preexisting pyogenic granuloma or hemangioma, vascular malformations or hemangiomas of blue rubber bleb nevus syndrome
Due to exuberant recanalization of a thrombus
May be secondary to trauma or superimposed on pyogenic granuloma or cavernous hemangioma
Slow growing, tender, blue-red, deep dermal to subcutaneous mass
Rarely recurs after excision
Micro: dilated vessel contains papillary proliferation of plump endothelial cells without atypia overlying fibrous tissue; fibrin deposition and thrombi present; variable pleomorphism and stratification, no/rare mitotic figures, no necrosis, no solid cellular areas
DD: angiosarcoma

Kaposi’s sarcoma
Derived from vasoformative mesenchymal multipotential cells
Low grade vascular neoplasm
Described by Kaposi in 1872
Note: HHV8 also present in primary effusion lymphoma, some cases of multicentric Castleman’s disease, reactive angioendotheliomatosis, plasmacytic lymphoma

**Classic Kaposi’s sarcoma**
Non-HIV associated
10% of all malignant tumors in equatorial (central) Africa, usually young adults and children
Also common in some Mediterranean regions among males; rare in US
Usually prolonged course; elderly patients may die of recurrent disease
Poor prognosis if over 50 years old and immunosuppression or in African cases

**HIV associated Kaposi’s sarcoma**
More common than classic form in US and Western world due to HIV (usually male homosexuals)
Similar to cases associated with organ transplant recipients, systemic Castleman’s disease, angioimmunoblastic lymphadenopathy, lymphoma, other malignancies
More rapid clinical course than classic disease
Frequent involvement of lymph nodes, lungs, GI tract

**Treatment:** radiotherapy, chemotherapy, excision

**Gross:** multiple blue/violet dermal nodules/plaques on feet and legs, progressing proximally; may be polypoid and resemble pyogenic granuloma; nodules may also be in subcutis, but these are clinically indolent

**Macular stage:** red-blue cutaneous discoloration, often lower extremity

**Micro:** spindle cells forming slits with extravasated red blood cells, hemosiderin laden macrophages, lymphocytes and fibrosis; minimal atypia; may have numerous eosinophilic, PAS+ hyaline bodies (may be ingested erythrocytes); moderate mitotic activity
Early changes may be limited to spindle cells in papillary dermis and vasculature around sweat glands, and not be diagnostic
Note: AIDS patients also have vascular lesions resembling angiosarcoma, epithelioid hemangiomia, lymphangiomia

**Macular stage:** thin-walled, angulated vessels throughout dermis, with hemosiderin and plasma cell infiltrate

**Patch stage:** angulated lumina that dissect dermal collagen; vessels may proliferate around well-developed round venules (premonitory sign); angiomatoid vascular spaces with red blood cells are surrounded by spindle cells in short fascicles

**Tumor stage:** solid nodules with extensive spindle cells and red blood cells in slit-like lumina; no/rare mitotic activity or atypia

**Lymphangiomia-like variant:** thin, angulated vessels with no red blood cells

**Positive stains:** Factor VIII related antigen, CD31, CD34, thrombomodulin, latent nuclear antigen-1 of HHV-8 (Kaposi sarcoma-associated herpes virus)

**Molecular:** diploid and clonal; HHV8 present in almost 100% of lesions (classic, HIV, or other types)

**DD:** arteriovenous malformation, acroangiodermatitis, cutaneous angiosarcoma, pyogenic granuloma, tufted angioma, bacillary angiomatosis, pigmented purpuric dermatosis, benign fibrous histiocytoma, spindle cell hemangioendothelioma (usually dermis and subcutis)
Kimura’s disease
Rare chronic inflammatory disorder of deep subcutaneous tissue, etiology unknown
Usually head and neck, often associated with regional lymphadenopathy or salivary gland involvement
Usually affects Asian males, but similar presentation in US (AJSP 2004;28:505)
Almost always affects nodal sites; often associated dermal involvement
Usually peripheral blood eosinophilia and elevated serum IgE
Benign and reactive
May recur, no/rare death from disease
Gross: large tumor-like lesions
Micro: lymph nodes have preserved architecture, but also follicular hyperplasia, prominent eosinophilic infiltrates, proliferation of postcapillary venules; marked fibrosis in advanced stage disease
DD: angiolymphoid hyperplasia with eosinophilia, hypersensitivity or drug reactions, infections

Lymphangioma
Usually infants or children age 5 years or less
Neck, axilla, breast, chest, buttock, thigh
Either superficial (lymphangioma circumscriptum, associated with surgery or radiotherapy for breast carcinoma), cystic (cystic hygroma) or deep (lymphangioma cavernosum)
Treatment: excision, but 25% recur
Micro: grouped translucent papules with thin vascular lumina that impinge on epidermis; often deep remnants in subcutaneous tissue

Pyogenic granuloma
Also called granuloma pyogenicum, lobular capillary hemangioma
Very common
Rapidly growing polypoid red mass surrounded by thickened epidermis, often in finger or lips
May be associated with keratinous cyst
Benign, often regresses spontaneously
May be disseminated, occur within port-wine stains, be in deep dermis / subcutis or be intravenous
Treatment: none, excision (may recur as multiple satellites)
Gross: fleshy cutaneous tumor
Micro: lobular pattern of vascular proliferation with inflammation and edema resembling granulation tissue; thin epidermis at top with variable ulceration; acanthosis and hyperkeratosis at sides; central branching vessel is called capillary or vascular lobule, with no/rare red blood cells, surrounded by endothelial cells; variable mitotic activity; deep lesions often lack edema and inflammation
Variants: classic polypoid, dermal, subcutaneous, intravenous, eruptive, with multiple satellites
DD: benign (infantile) hemangioendothelioma, venous stasis, acrodermatitis, reactive angioendotheliomatosis, verruga peruana, bacillary angiomatosis

Reactive angioendotheliomatosis
Usually occurs in skin, associated with systemic disease
Micro: multiple clusters of closely packed capillaries lined by endothelial cells without atypia; also striking proliferation of endothelial cells forming capillaries within preexisting dilated blood vessels; may have fibrin microthrombi, epithelioid endothelium
Positive stains: CD31, CD34, factor VIII related antigen

Vascular leiomyoma
Also called angioleiomyoma
Single, painful, deep-seated nodule
Micro: sharply circumscribed nodule of dermis or subcutis; solid or vascular; related to glomus tumors, but tumor cells are spindled and smooth muscle bundles are ill-defined; rarely arises in vessels

Verruga peruana
Endemic in Peru
Due to infection by Bartonella bacilliformis, a gram negative, flagellated, motile bacteria
Micro: vascular proliferative process with Rocha-Lima inclusions (large cytoplasmic inclusions of endothelial cells)

Other tumors of skin

Angiofibroma
See also Soft Tissue Part 1 - cellular angiofibroma
Also called fibrous papule of face
Usually on nose of middle-aged; also corona of penis and oral cavity
Associated with tuberous sclerosis
May be derived from dermal dendrocytes
Gross: solitary, dome-shaped, firm lesion
Micro: increased blood vessels with dilated lumina, fibroblastic stroma containing stellate or multinucleated cells similar to pleomorphic fibroma; numerous hair follicles surrounded by collagen fibers; normal or slightly acanthotic epidermis with vacuolated clear cells
contributed by Drs. Asmaa Gaber Abdou and Nancy Asaad, Menofiya University, Egypt

Atypical fibrous histiocytoma - skin-tumor chapter

Definition: cellular, circumscribed dermal lesion of spindled fibroblasts, myofibroblasts, histiocyte-like cells and often giant cells with marked nuclear pleomorphism and mitotic figures (often atypical), but no tumor cell necrosis and no vascular invasion
Rare variant of cutaneous fibrous histiocytoma, also called pseudosarcomatous fibrous histiocytoma, dermatofibroma with monster cells
First described in 1983 (J Cutan Pathol 1983;10:327)
May be misdiagnosed as sarcoma (Histopathology 1990;17:167)
Median age 38 years (range 5-79 years), no gender preference
Solitary lesions usually arise on extremities or trunk (Am J Dermatopathol 1986;8:467); also head and neck, vulva
Occasional local recurrence (14%) or distant metastasis (AJSP 2002;26:35)
Treatment: complete excision with negative margins
Gross: median 1.5 cm (0.4 to 8 cm), nodular or polypoid
Micro: involvement of dermis and superficial subcutaneous tissue by pleomorphic, plump, spindle or polyhedral cells with large hyperchromatic, irregular or bizarre nuclei; background of classic fibrous histiocytoma including spindle cells with storiform pattern and entrapped thick collagen bundles, especially at the periphery; variable multinucleated giant cells, often with bizarre nuclei and foamy or hemosiderin-rich cytoplasm; 0-15 mitotic figures/10 HPF, frequently atypical; necrosis occasionally present
Micro images: enlarged cells with hyperchromatic nuclei, but no/rare mitotic figures #1; #2; #3
Positive stains: vimentin, CD34 (occasionally)
Negative stains: CD68, S100, keratin (MNF116), EMA; <1% positive for MIB1 (Am J Dermatopathol 2004;26:367)
DD: pleomorphic sarcoma, pleomorphic fibroma, atypical fibroxanthoma (sun damaged areas of head and neck in elderly, presents as dome shaped or ulcerated nodule, tumor cells abut epidermis without a grenz zone [relatively normal collagen forming a boundary between normal epidermis and a dermal lesion], also marked actinic elastosis, no classic features of fibrous histiocytoma)
References: Am J Dermatopathol 1987;9:380

Atypical fibroxanthoma [AFX] - skin-tumor chapter
top
Definition: dermal variant of MFH-pleomorphic with low grade behavior
Also called intermediate fibrous histiocytoma
See also Ear chapter
Rapidly growing dome-shaped or polypoid nodule on sun-damaged areas of head and neck of elderly
Rarely presents as large mass in limb or trunk of younger individuals, or post radiation therapy
May clinically resemble carcinoma
Must exclude tumors with AFX like patterns, other lines of differentiation, significant involvement of subcutis, necrosis, vascular invasion or infiltrative margins

Poor prognostic indicators: history of immunosuppression, recurrence

Case reports: 81 year old woman with lower leg lesion (Dermatology Online Journal 14(1)), 63 year old man with metastatic tumor from eyebrow area to face (Archives 2006;130:735), 81 year old man with widespread peritoneal metastases (AJSP 2006;30:1041)

Treatment: local excision; rarely recurs or metastasizes

Gross:
- polypoid, ulcerated, usually small

Gross images:
- irregular polypoid tumor

Micro:
- bizarre tumor cells in hypercellular, spindly stroma with frequent mitotic figures, many atypical; also smaller fibroblastic, myofibroblastic and histocyte-like cells with pleomorphism and angulated nuclei; histologically identical to MFH-pleomorphic but centered in dermis; background stroma appears inflammatory or reactive; pushes aside surrounding pilosebaceous units and eccrine glands; typically does not involve epidermis or subcutaneous tissue; no grenz zone; lacks classic features of fibrous histiocytoma (entrapped hyalinized collagen bundles and epidermal hyperplasia); no necrosis, no vascular invasion, no infiltrative margins

variants:
- clear cell (J Cutan Pathol 2006;33:343), granular cell (Am J Dermatopathol 2007;29:84)

Atypical fibroxanthoma (AFX) - Skin-tumor chapter (continued)

top

Micro images:
- exophytic cellular nodule with ulceration; fascicles of atypical spindle cells; tumor is limited to dermis but otherwise resembles MFH-pleomorphic with marked cellularity, prominent pleomorphism, mitotic figures and clumped chromatid; marked cellularity and pleomorphism; characteristic bizarre cells; spindle variant has less pleomorphism; spindle and epithelioid cells with atypia; ulcerated tumor #1; #2; #3; #4; #5; nodular spindle cell tumor #1; #2; 81 year old woman with lower leg lesion: fig A: edge of lesion shows hyperchromatic cells next to elastotic dermis (arrow), fig B/C: atypical spindle cells and histiocytes, atypical mitotic figure (arrow), fig D: alpha-1-antichymotrypsin positive; figure 1: eyebrow primary, figures 2-4: facial metastasis (fig 4 is CD68); Factor XIIa: p53

contributed by Dr. Angel Fernandez-Florez, Hospital El Bierzo, Spain - #1; #2; #3; CD68; CD117; CD10; AE1-AE3

Positive stains:

Negative stains:
- keratin, EMA, S100 (although S100+ Langerhans cells may be present), HMB45 (rarely positive, J Cutan Pathol 2004;31:284), caldesmon

EM:
- myofibroblasts, fibroblasts and primitive mesenchymal cells

Molecular:
- diploid

DD:
- squamous cell carcinoma-spindle cell type; desmoplastic melanoma (may have focal AFX-type features and stain negative for melanocytic markers, Am J Dermatopathol 2007;29:551), atypical fibrous histiocytoma

References: eMedicine

Benign cystic teratoma

Rarely presents as skin nodule

Less common than dermoid cyst

Micro: tissue components from all 3 germinal layers

Benign fibrous histiocytoma (superficial) - skin-tumor

Definition: storiform pattern of bland spindle cells and foamy histiocytes centered in dermis with possible extension to subcutis, with variable hemosiderin, multinucleated giant cells, chronic inflammatory cells and pseudoepitheliomatous hyperplasia

Also called dermatofibroma (particularly if sclerotic and hypocellular), dermal fibrous histiocytoma

See also Bone, Eye-Conjunctiva, Eye-Orbit and Heart chapters
Very common benign, indolent tumor of adults, common site is legs of women 20-50 years old
May be associated with trauma
Line of differentiation is uncertain

**Case reports:** balloon cell fibrous histiocytoma (Am J Dermatopathol 2007;29:197)

**Treatment:** excision; local recurrence rare even with involved margins; rarely is locally aggressive or metastatic (more common for facial lesions, extension into subcutis or cellular and mitotically active)

**Gross:** tan-brown, firm, mobile, painless papule < 2 cm in dermis; size varies slightly with time, may dimple upon lateral compression
**Gross images:** inward dimpling is due to tumor binding to subcutis (arrow)

**Micro:** well defined but non-encapsulated; storiform pattern of spindled and bland fibroblasts and histioyte-like cells in mid-dermis and subcutaneous tissue with infiltrative margins but sparing epidermis; spindle cells have scant cytoplasm, thin elongated nuclei with pointed ends; nuclei almost touch each other unlike smooth muscle lesions; also foamy histiocytes with variable hemosiderin, some multinucleated giant cells, branching vessels, chronic inflammatory cells, pseudoepitheliomatous hyperplasia and epidermal hyperpigmentation; may be cellular but scant mitotic figures

**Micro images:** tumor is often more basophilic than surrounding dermis; basophilia is due to increased cellularity; sharp border between tumor and subcutis; some fat may be entrapped at edge of lesion (must differentiate from infiltration of DFSP); tumor cells are mostly fibrous in this focus; tumor cells in this focus are composed of histioyte-like cells and foam cells; randomly arranged foam cells, fibroblasts and histioyte-like cells, note that foam cells are somewhat specific for this lesion; foam cells with vacuolated cytoplasm; foam cells vary from none (top), mixed (middle) to predominating (bottom); fibroblastic cells with vacuolated cytoplasm in collagenous stroma; tumor with hyperplastic epithelium #1; #2; less common finding of predominantly foam cells and cholesterol clefts; hyperplastic epidermis and sclerotic stroma #1; #2; #3; epithelial hyperplasia-left side shows squamous/basaloid differentiation, right side shows follicular differentiation; spindle cell nodule; paucicellular dermal tumor; spindle cells in dense collagenous stroma; cellularity changes over time from subtle increase in fibroblasts (fig A) to cellular tumor (fig B/C) to sclerotic lesion (fig D-right side); vulvar tumor has uniform spindle cells confined to dermis; low Ki-67 compared to DFSP and AFX

**Positive stains:** vimentin, Factor XIIIa; also tenasin at dermoeipidermal junction (Hum Path 2001;32:50), calponin (65%); variable actin, desmin and myosin

**Negative stains:** CD68, CD34, bcl2; Ki-67 < 10% (Archives 2006;130:831)

**Molecular/cytogenetics:** often clonal

**DD:** Kaposi’s sarcoma, dermatofibrosarcoma protuberans, leiomyoma or leiomyosarcoma (confusion based primarily on immunostaining of fibrous histiocytomas), malignant fibrous histiocytoma, atypical fibroxanthoma, Rosai-Dorman disease

**References:** AJSP 2002;26:35

**Variants of benign fibrous histiocytoma (superficial)**

**Aneurysmal variant of benign fibrous histiocytoma - skin-tumor chapter**
Definition: rare variant with dermal spindle cells and lakes of blood, but no endothelium
First described in 1981 (Cancer 1981;47:2053)
Early lesion also called hemosiderin variant
Similar to sclerosing hemangioma variant (which has more prominent capillaries), but differs from lung lesion called sclerosing hemangioma
Usually extremities or trunk; often rapid growth and pain (J Clin Pathol 1996;49:313)
Tends to recur after excision; rarely metastasizes
Case reports: 48 year old woman with recurrent tumor (J Clin Pathol 2004;57:312), abdominal lesion (Dermatology 2007;214:82)
Gross: blue, black or dark red; cystic
Micro: storiform pattern of fibrohistiocytic cells (as in classic fibrous histiocytoma), also large cystic spaces filled with blood, but without an endothelial lining, often bizarre cells present; may have hemangiopericytoma-like vascular pattern; may have up to 10 MF/10 HPF
Micro images: non-endothelial lined clefts or lakes containing blood #1; #2; fibrohistiocytic cellular proliferation with numerous blood filled cysts #1; #2; cysts lack an endothelial lining; cysts have a squamous lining #1 (unusual finding); #2; hemangiopericytoma-like pattern #1; #2; large amounts of hemosiderin; hemosiderin plus marked sclerosis
Positive stains: vimentin, Factor XIIIa (in non cystic areas, J Dermatol 2002;29:744), NKI-C3 (60%), smooth muscle actin (45%)
Negative stains: CD31, CD34
EM: hemosiderin containing histiocyte-like cells, fibroblast-like cells and intermediate cells; no prominent proliferation of endothelial cells (Am J Dermatopathol 1995;17:179)
Cytogenetics: single case report of recurrent tumor with t(12;19) (Cancer Genet Cytogenet 2006;164:155)
DD: Kaposi’s sarcoma, angiosarcoma (APMIS 2006;114:744), melanoma
References: Histopathology 1995;26:323

Angiomatoid fibrous histiocytoma - skin-tumor chapter
Definition: uncommon variant with thick pseudocapsule, marked chronic inflammatory infiltrate and cystic areas of hemorrhage
First described in 1979 (Cancer 1979;44:2147)
Not a WHO diagnosis
Formerly called angiomatoid malignant fibrous histiocytoma
Teens/young adults, often on extremities in areas of lymphoid tissue (popliteal fossa, decubital fossa) or neck
Often fever, malaise, anorexia or paraproteinemia
Considered to have low to intermediate malignant potential; may recur locally (10%), distant metastases are rare (1%) 
May not actually be fibrohistiocytic - Rosai believes origin is vessel related myoid cells with inflammatory features
Case reports: mediastinal tumor (Ann Thorac Surg 2001;72:283), pleomorphic tumor with minimal angiomatoid or lymphoid features (J Cutan Pathol 2008 Apr 16 [Epub ahead of print]), cystic structures of sweat duct origin (Pathol Int 2007;57:513), 25 year old man with t(12;22) and intracerebral primary (AJSP 2008;32:478)
**Gross:** circumscribed, multinodular or multicystic hemorrhagic mass; median 2 cm, usually subcutaneous

**Micro:** thick fibrous pseudocapsule surrounds nodules of monomorphic bland spindle to ovoid eosinophilic cells, often highly cellular with hemorrhagic cyst like spaces, large aggregates of chronic inflammatory cells at edge of tumor in lymphoid follicles; may have moderate pleomorphism and mitotic activity

**Cytology:** histiocyte-like cells in clusters or dispersed, also eosinophilic mesenchymal fragments in bloody background with lymphocytes; tumor cells have moderate pleomorphism with abundant fragile cytoplasm and prominent nucleoli ([Diagn Cytopathol 2005;33:116](#))

**Micro images:** tumor with heavy chronic inflammatory infiltrate resembles a lymph node - consider angiomatoid fibrous histiocytoma in an apparent lymph node that is out of place in soft tissue; chronic inflammatory cells are accompanied by nodules of cells with round/oval nuclei that surround hemorrhagic cystic spaces #1; #2; cells surrounding cystic spaces are uniform with round/oval nuclei; some tumors have moderate pleomorphism; mediastinal tumor; various images #1; #2; #3

**Virtual slides:** angiomatoid fibrous histiocytoma

**Positive stains:** CD68, desmin (40-50%), EMA (40%), CD99 (45%), actin (14%)

**Negative stains:** Factor VIII, CD34, keratin

**Cytogenetics/molecular:** usually t(12:16)(q13:p11) [ATF1-FUS] or t(12:22)(q13;q12) [ATF1-EWSR1], which is also present in GI clear cell sarcoma; also EWSR1-CREB1 ([Genes Chromosomes Cancer 2007;46:1051, Clin Cancer Res 2007;13:7322](#))

**Cytogenetics/molecular images:** t(12;16) karyotype; diagram

**DD:** aneurysmal variant of benign fibrous histiocytoma (no thick pseudocapsule, no inflammatory cells, no significant pleomorphism)


**Atypical fibrous histiocytoma - skin-tumor chapter**

See above

**Cellular variant of benign fibrous histiocytoma - skin-tumor chapter**

**Definition:** more cellular than usual fibrous histiocytoma, elongated cells are arranged in storiform pattern or fascicles

5% of dermal fibrous histiocytomas

Young or middle-aged adults, 60% men

Extremities or head and neck are most common

20% recur; rare metastases ([AJSP 1996;20:1361](#))

**Gross:** up to 2.5 cm

**Micro:** fascicular or storiform but no “tight” storiform pattern, cells plumper than DFSP with eosinophilic cytoplasm and tapering nuclei; mean 3 mitotic figures/10 HPF but may be >10 MF/10 HPF, extension into subcutaneous fat in 1/3 cases; at least focal inflammatory cells, foam cells or giant cells; epidermal changes in 58%, focal central necrosis in 12%

**Micro images:** elongated cells are arranged in fascicles or storiform pattern; storiform growth; spindled tumor resembles a leiomyoma; deep tumor extension; more cellular than classic tumor; tumor cells are more histiocyte-like and foam cells are present; hyperplastic and acanthotic epithelium; DFSP (fig A-C) versus cellular fibrous histiocytoma (fig D-F) with H&E, CD34 and APOD (new marker)

**Positive stains:** vimentin, CD163, CD68 (83%, J Cutan Pathol 2006;33:353), CD63/NKI-C3 (50%), Factor XIIIa (48%), focal smooth muscle actin
Negative staining: CD34, CD117 (J Cutan Pathol 2007;34:857), desmin, S100, keratin

DD: dermatofibrosarcoma protuberans (tight storiform pattern, cells more spindly than cellular fibrous histiocytoma, CD34+ [strong], Factor XIIIa negative), leiomyosarcoma

References: AJSP 1994;18:668

Epithelioid variant of benign fibrous histiocytoma - skin-tumor chapter

Definition: variant with 50% or more of tumor cells having epithelioid morphology Uncommon, usually presents as small (1 cm or less), solitary, elevated nodule in extremities
Mean/median age 40-42 years (Br J Dermatol 1989;120:185), no gender preference
May arise from dermal microvascular unit (J Cutan Pathol 2003;30:415)

Case reports: Case of the Week #116, underlying a damaged artery (J Dermatol 2005;32:721)

Treatment: excision, only rarely recurs (Histopathology 1994;24:123)

Micro: circumscribed with uniform, medium to large angulated epithelioid cells (50% + of tumor cells) that are often perivascular; overlying epidermal effacement, minimal inflammation, no prominent giant cells

Micro images: histiocyte-like cells with abundant cytoplasm, no/rare spindle cells #1; #2; #3; epithelioid cells in hyalinized stroma; low power - #1; #2; high power - #3; #4; vimentin; Factor XIIIa+; CD68 negative; keratin negative; MelanA negative

Positive stains: Factor XIIIa, vimentin

Negative stains: keratin, S100, myogenic markers, CD68, CD163

DD: solitary epithelioid histiocytoma (dense eosinophilic and glassy cytoplasm, often with spiked cytoplasmic extensions, variable nuclear grooves and multinucleated cells, frequent lymphocytes and neutrophils, CD68+, CD163+ AJSP 2006;30:521), Rosai-Dorfman disease (multiple skin lesions and adenopathy, histiocytes are S100+ and pleomorphic with emperipolesis, also prominent B cells and plasma cells), granulomas (epithelioid histiocytes in well formed clusters, surrounded by lymphocytes), melanoma (tight clustering of atypical cells, S100+, HMB45+), epithelioid sarcoma (deep seated, granula-type clusters with necrosis, more atypia, keratin+, CD163-), histiocytic sarcoma (marked atypia and mitotic activity)

References: AJSP 1994;18:583

Juvenile xanthogranuloma - skin-tumor chapter

Definition: benign, usually self-limited, non-Langerhans cell histiocytic disorder of skin
Also called nevoxanthoendothelioma
See also Breast-nonmalignant, Eye-uvea and Liver-tumor chapters

Proliferative disorder of dendrocytes
Uncommon (< 0.5% of pediatric tumors in one study)
Usually infants (median age 5 months) with a congenital mark, although 10-30% occur in adults; male/female = 1.4:1
Skin of face or trunk, less commonly in subcutis, skeletal muscle, eye, peripheral nerve or testis
20% of patients have multiple lesions, usually males
May spontaneously regress leaving depressed area of skin with variable hyperpigmentation
In neonates, rarely associated with giant cell hepatitis and tumor in liver and viscera, requiring chemotherapy

**Case reports:** [Case of Week #5](#)

**Treatment:** conservative excision; multisystemic disease requires Langerhans cell histiocytosis-type chemotherapy ([Pediatr Blood Cancer 2008;51:130](#))

**Gross:** up to 2 cm, yellow-red, papulonodular

**Gross images:** [10 year old girl with 6 cm arm lesion](#)

**Micro:** dense dermal infiltrate of lymphocytes, histiocytes, Touton giant cells (usually), eosinophils and neutrophils, which may extend into subcutis; late - epidermis thins out, rete ridges become elongated; deep lesions - more cellular and monotonous with fewer Touton cells

**Cytology:** deep seated mass - vague, granulomatous aggregates with monotonous, CD68+ histiocytic cells ([Acta Cytol 2007;51:473](#))

**Micro images:** foam cells, Touton giant cells and scattered lymphocytes [#1; #2; adult patient; low power; medium power #1; #2; high power #1; #2 comparison of histiocytic giant cell types - Touton type- ring (wreath) of nuclei surrounding foamy cytoplasm with cytoplasm usually also visible around the nuclei; Langhans type- nuclei form a horseshoe arrangement, not necessary a distinct category from Touton type, foreign-body type- haphazard nuclear arrangement

**Positive stains:** CD68, HAM56, Factor XIIIa; also NKI-C3/CD63 (60%)  
**Negative stains:** S100, CD1a

**EM:** no Birbeck granules, may have cytoplasmic lipid

**DD:** Langerhans cell histiocytosis (more common, tumor cells have coffee bean nuclei/nuclear grooves, no Touton giant cells, are S100+ and CD1a+ and negative for CD68, HAM56 and Factor XIIIa, have Birbeck granules by EM), xanthomas (associated with hyperlipidemia, uniform collection of foam cells and variable Touton giant cells, but no other inflammatory cells)

**References:** [AJSP 2003;27:579](#), [AJSP 2005;29:21](#), [eMedicine #1; #2](#)

**Collagenous fibroma**

Also called desmoplastic fibroblastoma

Subcutaneous lesion, often with fascial involvement

**Micro:** bland stellate and spindled fibroblasts with collagenous or myxoid matrix

**Connective tissue nevus - Skin-Nonmelanocytic tumors chapter**

Rare connective tissue hamartomas derived from cells of mesodermal origin

**Case reports:** 8 year old girl with connective tissue nevus with zosteriform distribution ([Pediatr Dermatol 2007;24:439](#)), 25 year old man with 40 nodules/papules distributed in zosteriform pattern ([Am J Dermatopathol 2007;29:303](#))

**Deep benign fibrous histiocytoma- skin-tumor chapter**

**Definition:** benign fibrous histiocytoma of subcutaneous tissue, deep soft tissue or parenchymal organs, with no dermal involvement  
Rare, <1% of fibrohistiocytic tumors

Usually adult males > 25 years  
Head and neck and lower limb

**Gross:** well circumscribed with pseudo-capsule, typically 4 cm, variable hemorrhage

**Micro:** prominent storiform pattern of uniform spindle cells with ill defined eosinophilic cytoplasm and bland, elongated or plump vesicular nuclei with no atypia; often hemangiopericytoma-like vasculature; scattered lymphocytes, either multinucleated giant cells, osteoclastic giant cells or foam cells in 59%; usually less than 5 mitotic figures/10 HPF; stroma is myxoid or hyaline; borders are non-infiltrative, with no trapping of fat cells; necrosis or angiolymphatic invasion are rare

**Micro images:** circumscribed tumor with no trapped fat; cellular tumor; tumor with more fibrous stroma; foam cells help distinguish from DFSP; focal storiform pattern and cellular uniformity; hemangiopericytoma-like vascular pattern [#1; #2](#)

**Positive stains:** CD34 (40%), smooth muscle actin (38%)  
**Negative stains:** keratin, EMA, desmin, S100


Dermatofibrosarcoma protuberans (DFSP) - skin-tumor chapter

Part of WHO classification for skin tumors, not soft tissue tumors

Definition: low to intermediate grade malignancy, usually of dermis, with prominent storiform pattern of monomorphic fibroblast-like cells that invade into subcutis

Also called intermediate (borderline) fibrous histiocytoma

Slow growing, low-grade malignant neoplasm of trunk and various sites but not hands and feet

Rare, usually adults 20-40 years, more common in blacks in US (J Am Acad Dermatol 2007;56:968)

Can occur in infants (Arch Dermatol 2007;143:203) and children (J Plast Reconstr Aesthet Surg 2007 Dec 18 [Epub ahead of print])

May be a peculiar type of nerve sheath tumor since CD34 positive, or may derive from a subset of CD34 positive dermal dendritic cells

Locally aggressive, low rate of metastasis (after repeated failures at local control); may progress to fibrosarcoma or MFH

Giant cell fibroblastoma is considered the juvenile variant of DFSP as it has the same translocation (AJSP 2003;27:27)

Bednar's tumor: 5-10% of cases; pigmented variant due to dendritic cells with melanin, S100+ only in pigmented cells, HMB45 negative; associated with black patients


Dermatofibrosarcoma protuberans (DFSP) - skin-tumor chapter top


Clinical images: papulonodular thigh lesions

Gross: nodular, polypoid or plaque-like, centered in dermis, can occur in deep soft tissue; mean 5 cm, gray-white (brown/black if melanocytes present), may appear circumscribed; hemorrhage and necrosis are rare

Micro: non circumscribed, highly cellular, “tight” storiform pattern (cells radiating in spokes at right angles around a central point that often contains a vessel) that infiltrates deeply into subcutaneous tissue and entraps fat cells to form characteristic honeycomb pattern; some tumors show areas of fascicular growth; storiform pattern may be absent in early plaque stage; cells are monomorphic, thin and spindly with scant eosinophilic cytoplasm and hyperchromatic nuclei resembling neurofibroma; may have numerous mitotic figures, but not atypical ones; collagen usually non-polarizable and thin; only mild pleomorphism and focal atypia; may coexist with giant cell fibroblastoma; usually no significant pleomorphism, no/rare histiocytes, no histiocyte-like cells, no foam cells, no giant cells or other inflammatory cells

Variants: atrophic (depressed lesion), collagenous (with central thick collagen bundles), granular cell (S100 negative), myxoid (see below), palisading, pigmented, sclerosing
Cytology: homogeneous with isolated spindle cells, often tissue fragments with storiform pattern, fibrillary stromal fragments, naked nuclei; occasional slight to moderate atypia (Diagn Cytopathol 2004;30:261).

Micro images: small uniform cells radiating like pinwheels from central area that often has a blood vessel is characteristic; uniform cells with no significant pleomorphism, minimal intercellular collagen, no/rare foam cells or giant cells, which are characteristic of benign fibrous histiocytoma; fine strands of collagen are present; infiltration of fat causes tumor cells to surround fat cells #1; #2; #3; #4-residual fat cells are in linear arrangement resembling a string of pearls, which is characteristic of DFSP but not benign fibrous histiocytoma; DFSP with diminished storiform pattern but CD34+ (not shown); pigmented cells are not common; variants-with fibrosarcoma, myxoid, pigmented

Frozen sections: intradermal and extension into adipose tissue

Positive stains: CD34 (strong in 95%), vimentin; also actin (focal), ApoD (AJSP 2004;28:1063), bcl2, NKL-C3 (AJCP 1992;97:478), CD99 (J Cutan Pathol 2008 Jan 14 [Epub ahead of print])

Negative stains: Factor XIIIa (usually), keratin, EMA, S100, HMB45, desmin, CD117 (J Cutan Pathol 2007;34:857)

EM: stellate or spindle cells with long, slender, ramified cell processes joined by primitive junctions, often with subplasmalemmal densities; commonly multivesicular buds (Utractor Pathol 2006;30:283)

Molecular/cytogenetics: t(17,22)(q21;q13) [collagen type 1 alpha 1 gene and platelet derived growth factor beta chain gene, OMIM #607907] found in almost all cases using multiplex RT-PCR (Hum Path 2008;39:184); also supernumerary ring chromosomes derived from t(17;22) (Oncogene 2001;20:2965), rarely other translocations (Virchows Arch 2008 Feb 6 [Epub ahead of print])

DD: benign fibrous histiocytoma (also storiform but non-infiltrative, less cellular than DFSP, Factor XIIIa positive, CD34 negative), thymoma (storiform but different location, CD34 negative), MFH-pleomorphic or atypical fibroxanthoma (storiform pattern but also moderate/marked pleomorphism and nuclear atypia)

References: eMedicine

Indeterminate lesions between DFSP and dermatofibroma - skin-tumor chapter
top
Report of 10 tumors with features of both tumors, all Factor XIIIa+, CD34+, although in different cells (AJSP 2000;24:996)
Clinically, one recurrence at mean 22 months follow-up
Recommend complete excision

Myxoid variant of DFSP - skin-tumor chapter
top
Definition: DFSP with 50%+ myxoid stroma
Uncommon; median age 40 years, male and female
Extremities, head and neck, trunk, anogenital region
Associated with recurrent tumor
Similar prognosis as classic DFSP (AJSP 2007;31:1371)
Case reports: Case of the Week #132
Treatment: complete excision; occasional recurrences (Am J Dermatopathol 2007;29:443)
Gross: median 3 cm, white-tan-gray-yellow, firm to gelatinous
Micro: infiltrative, often hypocellular, sheet-like, bland spindle cells with pale eosinophilic cytoplasm, spindled nuclei, no pleomorphism; stroma is myxoid with prominent thin walled vessels; diffuse infiltration of fat; also cellular areas typical of DFSP
Micro images: various images; case of the week - #1; #2; #3; #4; #5
Virtual slides: myxoid DFSP
Positive stains: CD34
Negative stains: S100, muscle markers, CD99
DD: myxoid neurofibroma (wavy nuclei, often intratumoral axons, strong S100+), superficial angiomyxoma (myxoid stroma with numerous small vessels, may be CD34+, but does not infiltrate fat, tends to be less cellular), myxoid liposarcoma (vessels are more abundant, delicate and branching, lipoblasts are prominent)

**Sarcomas arising in DFSP - skin-tumor chapter**

Usually resembles fibrosarcoma; rarely MFH-pleomorphic

In cases with wide local excision and negative margins, 20% recur, metastatic rate varies from 0% ([AJSP 2000;24:1125](#)), to 10% ([AJSP 2006;30:436](#)).

Report as "DFSP with areas of fibrosarcoma", indicate extent of fibrosarcomatous change, nuclear grade, level of mitotic activity

**Case reports:** 42 year old woman with abdominal mass ([Archives 2006;130:882](#))

**Treatment:** wide local excision

**Micro:** in fibrosarcomatous areas, spindle cells intersect at acute angles, chromatin is coarser than usual, increased mitotic activity

**Micro images:** fibrosarcoma arising in DFSP - DFSP cells trap fat cells, fibrosarcoma cells are more uniform #1; #2; #3; fibrosarcoma cells are spindled, uniform and hyperchromatic and arranged in herringbone pattern

#1; #2; uncommon finding is myoid nodules containing cells with eosinophilic cytoplasm, present in DFSP or fibrosarcomatous areas, cells are actin+, CD34-, desmin-; H&E and FISH

pleomorphic sarcoma arising in DFSP - tumor cells are pleomorphic and have granular chromatin

**Dermatomyofibroma**

*top*

Also called cutaneous myofibroma

See [Soft Tissue chapter - Part 1](#)

**Endometriosis**

**Umbilical** or groin lesions in women of reproductive age, or elsewhere associated with surgical scar

**Micro:** endometrial glands, endometrial stroma and hemorrhage; may have marked decidual changes

**DD:** sweat gland tumor, metastatic adenocarcinoma

**Epithelial sheath neuroma**

Proliferation of nerve fibers coated by squamous epithelium

**Granular cell tumor of skin**

**Micro:** infiltrative tumor composed of large polyhedral cells with abundant granular cytoplasm and small, central nuclei; often pseudoepitheliomatous hyperplasia

**Positive stains:** PAS, S100

**Hamartoma of scalp with ectopic meningothelial elements**

Also called rudimentary meningocele

Related to meningioma of skin

**Micro:** whorls or dissecting pattern of meningothelial cells in dermis and subcutis; often psammoma bodies and cartilage; center of lesion may have long cleft

**Positive stains:** vimentin, EMA

**Negative stains:** CD31, factor VIII related antigen

**Histiocytoma - Skin-Tumor chapter**

Tumor of true histiocytic origin, not fibrohistiocytic

By definition, excludes Langerhans cell histiocytosis

Occurs in children, most tumors are benign
Micro: closely packed histiocytes with eosinophilic cytoplasm and variable lipid droplets, often inflammatory cells; minimal stroma; older lesions have fibrosis but no active fibroblastic proliferation

Negative stains: CD1a
EM: no Birbeck granules

Variants of histiocytoma

Solitary epithelioid histiocytoma - Skin-tumor chapter
Solitary or multifocal, often with articular involvement
May have malignant behavior
Formerly called reticulohistiocytoma
Micro: usually upper dermis; mononuclear and multinuclear epithelioid histiocytes with eosinophilic to glassy cytoplasm, often with spike-like cytoplasmic extensions; nuclei are round/oval with distinct nucleoli and variable nuclear grooves and multinucleation; frequent lymphocytes and neutrophils

Micro images: dermis contains multinucleated forms; dermal tumor contains mild atypia, and pushes against epidermis; giant cell reticulohistiocytoma

Positive stains: vimentin, CD163, Factor XIIIa (focal), CD68 (may be focal)
Negative stains: S100, keratin, MelanA
References: AJSP 2006;30:521

Generalized eruptive histiocytoma - Skin-tumor chapter
Definition: benign, papular, self-healing histiocytosis characterized by recurrent crops of small, firm, tan to red papules that appear in a symmetrical fashion on the face, trunk and arms, and may regress spontaneously
Rare, <50 cases described, most in adults
Part of spectrum of non-Langerhans cell histiocytosis
Case reports: successful treatment with PUVA (J Dtsch Dermatol Ges 2007;5:131)
Treatment: local excision, excellent prognosis
Positive stains: CD68, MAC387, alpha-1-antichymotrypsin, lysozyme
Negative stains: S100, CD1a
EM: no Birbeck granules

Inclusion body fibromatosis
See Soft Tissue Chapter-Part 1

Inflammatory pseudotumor
Probably does not represent an inflammatory myofibroblastic tumor
Gross: small, deep dermal nodule
Micro: central fibrosis and hyalinized vascular center with plasma cells and lymphoid follicles; usually spares epidermis

Keroloid
Abnormal dermal reaction to injury
Usually in blacks in earlobe
High rate of recurrence
Micro: wide bands of collagen with large, brightly eosinophilic, glassy fibers; also parallel fibroblasts and myofibroblasts; mucinous pools after steroid injection
DD: hyperplastic scar, keloidal dermatofibroma, complication of acne

Langerhans cell histiocytosis
Also called histiocytosis X
Langerhans cells are derived from bone marrow, circulate freely from skin to regional lymph nodes
Solitary or multiple lesions (papules, nodules, plaques)
In infants, resembles seborrheic keratosis
Micro: (1) diffuse dermal infiltrate of Langerhans cells (large, ovoid, pale pink cytoplasm, indented bland nuclei) or
(2) clusters of Langerhans cells which resemble granulomas or (3) dermal infiltrate of cells with more foamy cytoplasm

**Positive stains:** S100, CD1a

**EM:** Birbeck granules (resemble lollipops) next to nuclear membrane

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**Leiomyoma**

Divided into lesions of nipple or scrotum, pilar leiomyoma or solitary angioleiomyoma (vascular leiomyoma) usually in subcutis

May be very painful

**Familial cutaneous leiomyomatosis:** may be associated with renal cell carcinoma

**Micro:** intersecting smooth muscle fascicles; may have scattered bizarre hyperchromatic nuclei (symplastic leiomyoma); no atypia, no mitotic activity, no necrosis

**Pilar leiomyoma:** dermal intersecting fascicles of eosinophilic spindle cells with plump, cigar-shaped nuclei with dermal collagen bundles

**Micro images:** contributed by Angel Fernandez-Flores, MD, PhD, Hospital El Bierzo and Clinica Ponferrada, Spain - #1; #2; #3; #4

**Positive stains:** desmin, variable keratin and EMA

**Negative stains:** S100, GFAP

**DD:** myoepithelioma (desmin-, S100+)

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**Leiomyosarcoma**

Larger than leiomyomas

Recur, but only rarely metastasize

May be associated with HIV infection

**Micro:** cellular lesions of smooth muscle type cells with atypia, necrosis and mitotic activity; may have prominent vascular pattern, clear cell features, desmoplasia

**Malignant Fibrous Histiocytoma (MFH)**

See discussion in Soft Tissue Chapter-Parts 1 and 2 under MFH-giant cell type, MFH-inflammatory, MFH-pleomorphic, myxofibrosarcoma, benign fibrous histiocytoma-angiomaticoid subtype

**Malignant peripheral nerve sheath tumor (MPNST)**

More common in deep soft tissue but also present in skin

May be associated with neurofibromatosis type I

**Meningioma**

Nodule of scalp or vertebral axis

**Meningioma-like tumor of skin**

Whorled spindle cells, some arranged around blood vessels

**Neurofibroma**
Dermal tumors may cause proliferation of entrapped sweat glands or folliculosebaceous structures.
Diffuse variant involves scalp as a thick plaque.

**Variants:** localized or diffuse, intraneural, myxoid, pigmented, plexiform

**Neurothekeoma**
Also called nerve sheath myxoma.
Benign, despite atypia and mitotic figures; rarely recurs.
Children or teenagers with tumors of central face, arms and shoulders; 80% female.

**Myxoid variant of neurothekeoma**
**Micro:** encapsulated or sharply circumscribed, nests or cords of large epithelioid cells with mild/moderate atypia in myxoid or sclerotic background; tumor cells may be close to small nerves; variable mitotic figures.
**Positive stains:** usually NKI/C3 and microphthalmia transcription factor, type 4 collagen+, variable S100.
**Negative stains:** usually EMA, keratin.

**Cellular variant of neurothekeoma**
Top: head and neck of young women.
**Micro:** dermal or subcutaneous proliferation of nests and fascicles of tumor cells filling and expanding superficial and deep dermis; cells are epithelioid with abundant eosinophilic or amphophilic cytoplasm and overlapping cell membranes; nuclear are vesicular with dispersed chromatin; variable hyperchromatism; also spindled cells; no involvement of epidermis or junctional melanocytic proliferation; no mucinous stroma, no maturation, no circumscription.
**Micro images:** a: H&E shows dense dermal nests of epithelioid tumor cells; b: microphthalmia transcription factor+; c: NKI/C3+.
**Positive stains:** NKI/C3, smooth muscle actin, microphthalmia transcription factor, PGP 9.5, NSE, Leu7.
**Negative stains:** S100, HMB45.
**DD:** melanoma.
**References:** Mod Path 2004;17:230 (microphthalmia transcription factor and NKI/C3).

**Palisaded encapsulated neuroma**
Also called solitary circumscribed neuroma.
Common, usually due to trauma or surgery.
Small solitary papule, often in face.
Micro: spindle lesion with palisading, occasionally epithelioid cells
Positive stains: S100
DD: neurofibroma, leiomyoma

Perineurioma
Micro: may be epithelioid or sclerotic
Positive stains: EMA
DD: epithelioid histiocytoma, fibroma

Pleomorphic fibroma
Definition: polypoid or dome-shaped cutaneous nodule with sparse cellularity and cytologic atypia of fibroblasts
Not a WHO diagnosis
First described in 1989 (AJSP 1989;13:107)
Usually trunk, extremity or head (Clin Exp Dermatol 1998;23:22)
Case reports: 66 year old woman with subungual tumor (J Cutan Pathol 2003;30:569)
Micro: resembles fibroepithelial polyp but with enlarged, bizarre, smudged, hyperchromatic nuclei, thick collagen bundles and rare mitotic figures; may be sclerotic (Am J Dermatopathol 2002;24:54) or have myxoid foci (Am J Dermatopathol 1998;20:502)
Micro images: large pleomorphic cells separated by collagen; atypical cells have smudged chromatin, mitoses are absent/rare, compare to sarcomas with abnormal (but not degenerative) nuclei and frequent mitotic figures, some atypical; anal skin #1; #2; various images
Positive stains: vimentin, actin, CD34
Negative stains: S100
DD: atypical fibrous histiocytoma (more cellular, foam cells, hemosiderin laden macrophages, Am J Dermatopathol 1999;21:414), atypical fibroxanthoma (more cellular, more mitotic figures), giant cell fibroblastoma (young children)

Schwannoma
Relatively rare in skin
Variants: intraneural, plexiform, degenerative (with ancient change), granular cell tumor, congenital neural hamartoma

Sclerosing fibroma
Solitary lesions known as circumscribed storiform collagenoma
Some cases may represent folliculitis
May be associated with Cowden’s disease
Micro: well circumscribed hypocellular lesion with focal heavy collagen deposition
Positive stains: CD34

Sinus histiocytosis with massive lymphadenopathy
Also called Rosai-Dorfman disease
May involve skin
Usually prominent cervical lymphadenopathy

Striated muscle hamartoma
Also called rhabdomyosarcomatous mesenchymal hamartoma
Benign process in infants, usually on chin or near ala of nose
May be associated with other congenital anomalies
May be multiple
Micro: central core has bundles or individual skeletal muscle fibers; also other mesenchymal elements

Supernumerary digit
Acral neuroma, also called rudimentary polydactyly
On radial side of fifth digit
Micro: haphazard nerves with displaced Meissner bodies

Xanthoma
Non-neoplastic
Often periarticular; also trunk or extremities of males
Associated with hyperlipidemia (primary or secondary to diabetes, hypothyroidism, myeloma, lymphoma, leukemia, obstructive liver disease)

**Eruptive xanthoma:** abrupt onset of crops of yellow papules with erythematous halos on extremities, which wax and wane with triglyceride and cholesterol levels

**Plane xanthoma:** linear yellow lesions in skinfolds, including palmar creases; associated with primary biliary cirrhosis

**Tuberous/tendinous xanthoma:** yellow nodules on Achilles tendon and extensor tendons of fingers

**Verruciform xanthoma:** papillomatous, verruca-like change of overlying epidermis

**Xanthelasma:** soft yellow papules and plaques in eyelid; some cases lack lipid abnormalities

**Gross:** nodules

**Micro:** fat-laden histiocytes in dermis or subcutis; also tendons, synovium and bone

**Xanthogranuloma**

*Juvenile xanthogranuloma*

Also called nevoxanthoendothelioma

Proliferative disorder of dendrocytes

Uncommon (0.5% in one tumor registry), less common than Langerhans cell histiocytosis (3% incidence), the other principal histiocytic disorders of childhood

Usually infants (median age 5 months) with a congenital mark, although 10-30% occur in adults; male/female = 1.4:1

May spontaneously regress

Skin, often face or trunk, but may affect any site; less commonly in subcutis, skeletal muscle, eye, peripheral nerve, testis

20% have multiple lesions (>90% are males, usually age 6 years or less)

May be associated with glaucoma and amblyopia due to involvement of iris and ciliary body

Also associated with neurofibromatosis type I, Niemann-Pick disease, urticaria pigmentosa, CMV infection

Neonates may develop systemic disease and death due to hepatic failure (giant cell hepatitis and tumor in liver and viscera)

**Treatment:** excision; some lesions may involute spontaneously; relapse rate of 7%; systemic cases need multiagent chemotherapy

**Gross:** yellow-red, papulonodular lesions; solitary or multicentric, 1 mm to 2 cm

**Micro:** initially dense lymphohistiocytic proliferation of dermis with no/rare giant cells; then foamy and Touton giant cells (giant cells are often lacking in extracutaneous lesions) or other types of giant cells; also short fascicles of spindle cells; *late* - short fascicles of fibrohistiocytic cells and fibrosis; usually poorly circumscribed, thin epidermis with elongated rete ridges, preservation of adnexae, variable storiform pattern, lymphocytes, eosinophils, prominent vasculature; no/scattered mitotic figures, may have mild nuclear atypia

**Positive stains:** CD68, alpha-1-antichymotrypsin, lysozyme, vimentin, Factor XIIIa

**Negative stains:** S100, CD1a

**EM:** no Birbeck granules, may have cytoplasmic lipid

**DD:** Langerhans cell histiocytosis (nuclear grooves, S100+, CD1a+, Birbeck granules by EM), hyperlipidemia associated xanthomas (more uniform foamy histiocytes), reticulohistiocytoma (random distribution of multinucleated histiocytes with eosinophilic or ground glass cytoplasm), dermatofibroma (dense collagenous stroma, storiform growth pattern, pseudop epitheliomatous hyperplasia), lipoma, atheroma

**References:** *AJSP 2003;27:579, AJSP 2005;29:21*
Necrobiotic xanthogranulomas:
Destructive lesions of dermis and subcutis, often involving face and trunk, and accompanied by monoclonal gammopathy or cryoglobulins

Melanocytic Nevus

Definition
A localized, benign melanocytic proliferation of the skin.

Clinical Features

- Usually acquired (clinically apparent after first year of life)
- Most appear between second and sixth years
- Nearly all manifest by age 20 years
- Every Caucasian has variable number (average 20–30)\(^1\)
- Intradermal nevus:
  - common adult type of nevus
- Multiple lentigines in:
  - Peutz–Jeghers syndrome
  - centrofacial lentiginosis
  - Moynahan's syndrome
  - LEOPARD syndrome
  - Carney's syndrome
  - xeroderma pigmentosum\(^2\)

Pathogenesis

- Predictable evolution:
rarely upset by dramatic event, such as:
- spontaneous resolution
- activation
- malignant transformation

- proliferative activity roughly correlates with age

- Straddle fence between malformation and neoplasia:
  - cellular blue nevi and Spitz nevi:
    - morphologic and behavioral features consistent with true neoplastic process
  - usual compound nevi:
    - distinctive organoid configuration (with adnexal participation) suggesting developmental abnormality (may represent atavistic structures)
    - exhibit clonality and loss of heterozygosity (in favor of neoplastic nature)
  - ordinary compound mole may have dual origin from:
    - intraepidermal melanoblasts (some of which become intradermal)
    - deeper cells with features strongly suggesting differentiation toward specialized peripheral nerve structures (not necessarily schwannian related)
    - supported by ultrastructural, histochemical, immunohistochemical, and experimental studies

- Lentigo simplex:
  - generally regarded as first phase in evolution of common nevi ('nevi incipientes')
  - therefore a precursor of junctional nevus

- Percentage of nevi with junctional changes decreases as patient age increases

**Gross Pathology**

- Usually in skin:
  - most commonly head, neck, and trunk
- Also any mucosal membrane covered by squamous epithelium
- Every size, shape, and degree of pigmentation
- May be more or less hairy
- Junctional nevus:
  - flat or slightly elevated
  - nonhairy
  - fawn colored
- Intradermal nevus:
  - papillomatous, pedunculated, or flat
  - often hairy
- Clusters of benign nevus cells can be seen in capsule of lymph node:
  - most commonly axillary
  - do not penetrate node
  - should not be confused with metastatic malignant melanoma (particularly likely when specimen from axillary lymphadenectomy for cutaneous melanoma)

**Histopathology**

**Classification**

- Variously classified
- Location of melanocytes:
  - best system – definite relationship to likelihood of malignant transformation

**Junctional Nevus**
• Melanocytic proliferation restricted to basal portion of epidermis (‘junctional’ area)
• Characterized by melanocytic nests (‘theques’) on epidermal side of dermoepidermal junction (Fig. 1)

![Figure 1: Typical junctional nevus. Two large theques of melanocytes expand the basal layer of the epidermis.](image)

**Lentigo Simplex**

- Consists of proliferation of melanocytes in epidermal basal layer
- Differs from junctional nevus because melanocytes are individually arranged rather than in theques

**Intradermal Nevus**

- All melanocytes are in dermis
- Small nests or bundles of melanocytes:
  - in upper dermis
  - tend to concentrate around pilosebaceous units
- Degree of pigmentation and cellularity vary widely
- Lower half:
  - tends to be less cellular and less pigmented
  - composed of spindle cells with fibrillar cytoplasm arranged in bundles
  - sometimes structures resembling tactile (Wagner–Meissner) corpuscles
  - immunohistochemically different from neurofibromas, but may represent neural component of nevus (hard to dismiss these highly organoid structures as result of atrophy)
  - occasionally, a storiform pattern of growth, establishing link with dermal tumor known as storiform neurofibroma
- Multinucleated melanocytes:
  - scattered throughout nevus, particularly upper half
  - often characteristic ‘mulberry’ shape
- Ultrastructurally and immunohistochemically, cells surrounded by basement membrane components

**Compound Nevus**

- Combines features of junctional and intradermal nevi (i.e. epidermal and dermal components)
- Melanin deposition:
  - highly variable amount, as for other types of nevi
  - sometimes abundant (hypermelanotic nevus)
  - generally in superficial half, particularly intraepidermal portion
- Lymphocytes and other mononuclear cells:
as with other nevi, may be at base\textsuperscript{23}.
- tend to be in clusters (rather than bandlike quality more common in melanoma)

**Variations Depending on Site**

- Palms and soles:
  - nearly always junctional\textsuperscript{24}.
  - tend to remain junctional throughout life.
  - most intraepidermal melanocytes concentrated in skin furrows\textsuperscript{25}.
- Scalp:
  - often prominent neural component.
- Vulvar skin (vulvar or genital nevi):
  - tend to have larger, more irregularly shaped, and more irregular theques than elsewhere.
  - tend to be accompanied by lentiginous melanocytic hyperplasia.
  - can be misdiagnosed as malignant melanomas\textsuperscript{26}.

**Morphologic Variations in Typical Compound or Intradermal Nevi**

- Marked sclerosis (desmoplastic or sclerotic nevus)\textsuperscript{27}.
- Nodular myxoid changes\textsuperscript{28}.
- Amyloid deposition.
- Elastosis.
- Metaplastic bone in the stroma.
- Folliculitis and abscess formation.
- Association with keratinous cysts\textsuperscript{29} and psammoma bodies.
- Cytoplasmic vacuolization (sometimes resulting in lipoblast-like cells).
- Oncocytic changes\textsuperscript{30}.
- Eczematous or focal acantholytic keratotic changes in overlying epidermis\textsuperscript{31,32}.

**Diagnosis**

- Nevus (L. \textit{naevus}, birthmark):
  - can be properly applied to any circumscribed growth of skin of congenital origin.
  - usually used as synonym for mole (L. \textit{moles}, a shapeless mass) to designate localized benign abnormality of the melanocytic system.

**Malignant Melanoma**
Definition

Malignant cutaneous neoplasm derived from dermal melanocytes and whose prognosis is related to depth of dermal invasion (thickness).

Clinical Features

- Most:
  - in head and neck area
  - on lower extremities (particularly in females)
- Rarely:
  - subungual region (melanotic whitlow)
  - palms and soles
- Most:
  - white people:
    - particularly if:
      - fair complexion
      - red hair
      - tend to burn or develop freckles after exposure to sunlight
  - arise after puberty:
    - Also occur in:
      - children:
        - same microscopic pattern as adults (so usually distinguishable from Spitz nevi)
      - black people:
        - usually in:
          - palms
          - soles
          - nail beds
          - mucous membranes
        - May be:
          - multiple
            - distinguish from nevus activation
          - hereditary
            - often numerous atypical melanocytic lesions (dysplastic nevi)
          - associated with:
            - generalized melanosis
            - lesions resembling vitiligo
- Pathogenesis
  - Most:
    - associated with sunlight exposure
      - thought to be due to ultraviolet radiation
    - Immunologic factors probably play important but ill-understood role
Gross Pathology

Four Categories\textsuperscript{39–45}

- Melanoma arising in Hutchinson's freckle (lentigo maligna– melanoma)
- Superficially spreading melanoma
- Nodular melanoma
- Acral lentiginous melanoma

Histopathology

- If typical, easily identified by:
  - junctional activity
  - prominent melanin pigmentation
  - invasion of surrounding tissue
  - marked cytologic atypia
  - nuclear grooves, folds, and pseudoinclusion
  - large eosinophilic nucleoli
  - abundant mitotic figures (some atypical)\textsuperscript{53}

- Notorious for great variability: \textsuperscript{54,55}
  - cells may be:
    - epithelioid
    - spindle shaped (Fig. 2)

![Fig. 2: Malignant melanoma in region of Achilles tendon showing prominent spindling. This is a common finding in tumors at this site.](image)

- extremely bizarre
  - cell size can range from:
    - small (lymphocyte-like)\textsuperscript{56} to
    - giant multinucleated forms (Fig. 3)

![Fig. 3: Melanoma containing highly anaplastic tumor cells.](image)
Cytoplasm may be:
- eosinophilic
- basophilic
- foamy
- signet ring type
- rhabdoid
- oncocytic
- completely clear (balloon cell melanoma)

Melanin may be:
- abundant:
  - sometimes so massive as to obscure cellular details (animal type)
  - scanty
- absent (amelanotic melanoma)

Pattern of growth may be:
- pseudoglandular
- pseudopapillary
- peritheliomatous
- hemangiopericytoma-like resembling Spitz nevus (spitzoid melanoma)
- trabecular (Fig. 4)

Fig. 4: Prominent trabecular pattern of growth in melanoma.

Verrucous (nevoid or pseudonevoid melanoma) (Figs 5 and 6)

Fig. 5: Malignant melanoma with nevoid pattern of growth. Low-power view showing a polypoid configuration suggestive of a benign intradermal nevus. (Slide contributed by Dr Paul Duray, Bethesda, MD)
Fig. 6: Malignant melanoma with nevoid pattern of growth. High-power view showing only minimal atypicality of the tumor cells. This tumor recurred locally and eventually metastasized to regional lymph nodes. (Slide contributed by Dr Paul Duray, Bethesda, MD)

- may be:
  - marked fibroblastic response
  - myxoid changes\(^{68,69}\) (Fig. 7)

Fig. 7: Myxoid changes in malignant melanoma. This secondary alteration is more common at metastatic sites, but can also be seen in the primary lesion.

- metaplastic or neoplastic bone and cartilage\(^{70,71}\)
- osteoclast-like giant cells\(^{72,73}\)
- pseudopitheliomatous hyperplasia of overlying epidermis\(^{74}\)

- occasionally formations suggesting differentiation toward:
  - Schwann cells
  - tactile corpuscles
  - ganglion cells
  - other neuroid structures\(^{75–77}\)

- Sometimes lymph node and other metastases acquire appearance practically indistinguishable from that of malignant peripheral nerve sheath tumor\(^{78}\)

**Special Stains and Immunohistochemistry**
• Useful for distinguishing normal or neoplastic melanocytes from other cell types
• None of great use for distinguishing between benign and malignant melanocytic neoplasms
• Melanin stains:
  o silver based
    • rely on reducing properties of melanin granules
    • these argentaffin stains (Fontana–Masson is most widely used) are particularly useful for:
      • detecting finely dispersed granules not immediately apparent in H&E sections
      • demonstrating (when used with iron stain) that brown pigment in routine sections is melanin rather than hemosiderin

**Electron Microscopy**

• Contributes to confirmation of diagnosis through identification of:
  o melanosomes *(Figs 12–13)*

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**Fig. 12:** Electron microscopy of superficially spreading melanoma of right ear demonstrating junctional melanocytes among keratinocytes. (× 3850). Inset: Stage 3 melanosomes in neoplastic cells. (× 25,270)

**Fig. 13:** Stage 2 and stage 3 melanosomes with characteristic lattice arrangement in malignant melanoma of skin metastatic to lung (× 81,000)

• less specific premelanosomes

• Occasionally well-developed microvilli similar to those in adenocarcinoma cells