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Atlas of Essential Dermatopathology

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Preface

Atlas of Essential Dermatopathology is based on a sketchbook developed during Dermatopathology teaching signout at the Massachusetts General Hospital. While reviewing cases at the microscope, Dr. Duncan draws sketches to outline key diagnostic features. Many years ago she created a sketchbook that contained these teaching templates. As the years have progressed many trainees have made copies of the book. Dr. Szyfelbein Masterpol and Dr. Primiani provided the enthusiasm, motivation and ground work required to move this work from a book of hand drawn sketches and tables to a color atlas with outlines and histological images.

The content is based on the most frequently encountered processes in the MGH Dermatopathology Unit; it is not intended to be comprehensive but rather an outline and atlas of the essentials in diagnostic Dermatopathology. Each chapter is brief, a couple of pages, they are vignettes (literally something that would fit on a vine leaf), and focus on the main points. Tables of special stains, immunohistochemical markers and a glossary of terms are also included.

The goal of the book is to be a primer for trainees of all levels – students and residents alike – in dermatology and pathology.

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Contents

Part X Special Stains

Part I

Anatomy

1 Basic Anatomy

Epidermis

- Stratified squamous epithelium composed of layers of keratinocytes
  - From superficial to deep:
    - Stratum corneum
    - Stratum granulosum
    - Stratum spinosum
    - Stratum basale
- Intermingled cell types:
  - Melanocytes: at dermoepidermal junction
    - Transfer melanin → keratinocytes
  - Langerhans cells: CD1a + and Langerin + dendritic cells in stratum spinosum
    - Function in antigen presentation
  - Merkel cells: neuroendocrine cells in the stratum basale, associated with nerve endings from the dermis

Dermis

- Papillary dermis:
  - Dermal papillae complement rete ridges of epidermis
  - Fine, pale eosinophilic collagen fibers
  - Contains free nerve endings and Meissner's corpuscles
  - Separated from the reticular dermis by the superficial vascular plexus
- Reticular dermis:
  - Thick, deeply eosinophilic collagen fibers
  - Contains the deep vascular plexus, adnexal structures, nerve trunks, Pacinian corpuscles, glomus bodies

Subcutaneous Fat

- Separated into lobules by fibrous septae extending from the reticular dermis
- Contains anagen hair bulbs and medium sized arterioles and veins

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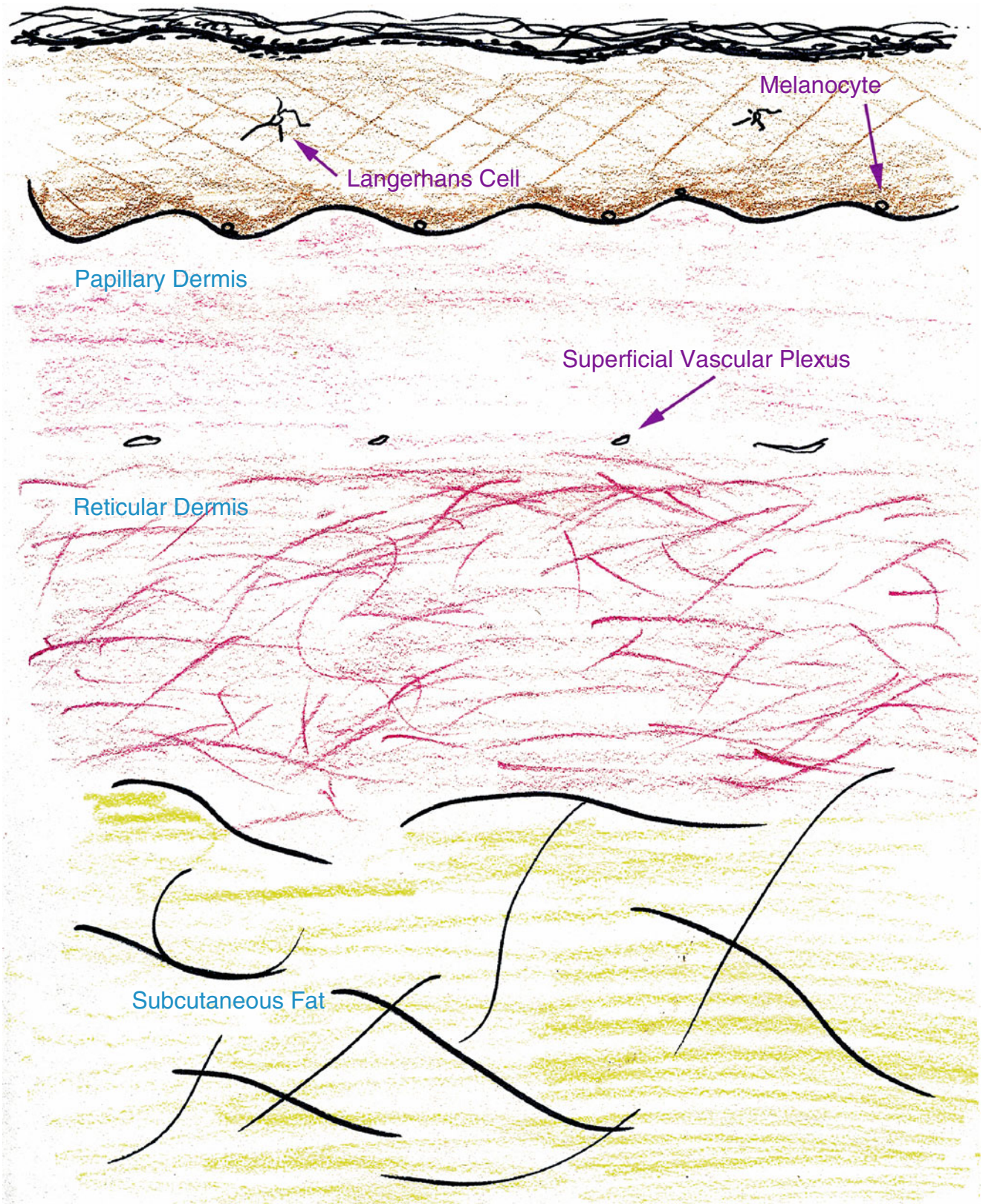

Fig. 1.1 The skin is composed of epidermis (*brown*), dermis (*pink*) and subcutaneous fat (*yellow*). Dendritic cells in the epidermis include Langerhans cells in the stratum spinosum and melanocytes at the base of the epidermis. The dermis is separated by the superficial vascular plexus into the papillary dermis and reticular dermis

2 Adnexal Anatomy

Eccrine Unit

- Eccrine Glands: palms, soles, forehead, axillae
  - Coiled, secretory component in deep dermis
    - Single layer of cuboidal epithelium, eosinophilic cytoplasm
    - Surrounded by myoepithelial cells
- Eccrine Ducts
  - Long duct, extends from glandular coil in deep dermis to exit through the epidermis as an acrosyringium
  - Two layers of epithelium, no myoepithelial cells

Pilosebaceous Apocrine Unit

- Hair Follicles
  - Types: terminal (diameter ≥0.06 mm), vellus (diameter ≤0.03 mm)
  - Zones (from superficial to deep):
    - Infundibulum = region above entry of sebaceous gland duct
    - Isthmus = extends from attachment of arrector pili muscle to entry of sebaceous gland duct
    - Hair bulb = dermal papillae and hair matrix
  - Phases: Anagen (growth), Catagen (involution), Telogen (resting phase)
  - Hair shaft = composed of cuticle, cortex, and medulla
  - Arrector pili = smooth muscle innervated by sympathetic nervous system
- Sebaceous Glands
  - Acinar pattern, multiple lobules
  - Inner layers of cells with vacuolated, lipid-filled cytoplasm
  - Outer rim of cuboidal basophilic germinative cells
  - Short duct with stratified squamous epithelium, enters into pilosebaceous unit
    - Rarely the sebaceous duct exits through the epidermis directly
- Apocrine Units: axillae, anogenital region, areola, eyelid
  - Coiled, secretory component in dermis
    - "Decapitation secretion", "snouts"
    - Single layer of cuboidal to columnar epithelial cells, eosinophilic cytoplasm
    - Surrounded by myoepithelial cells
  - Short duct opens into infundibulum of associated hair follicle

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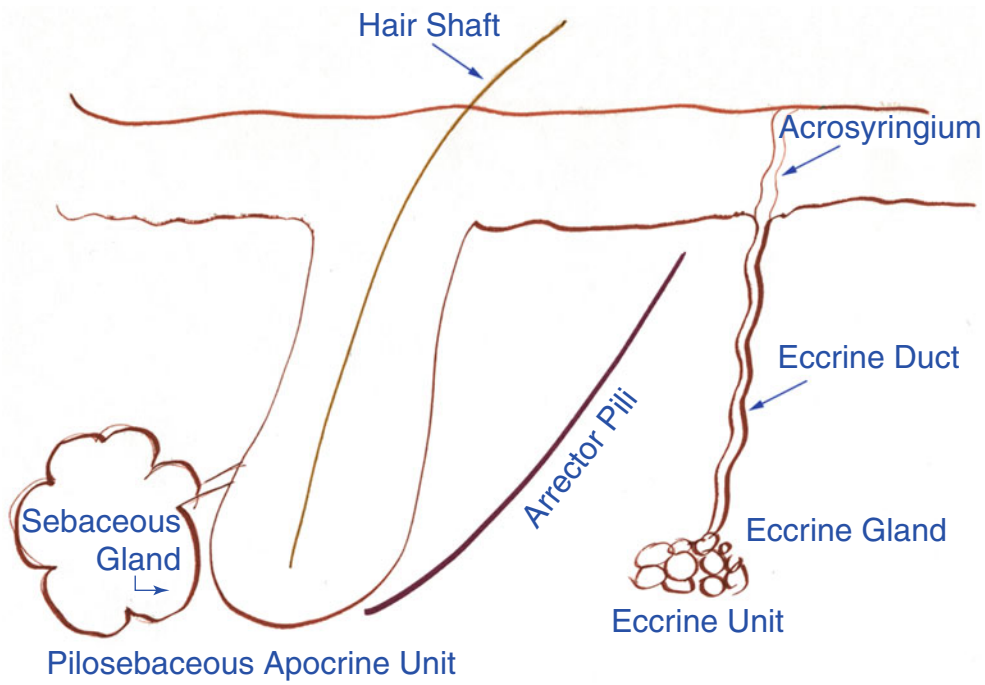

Fig. 2.1 The cutaneous adnexal structures include the pilosebaceous apocrine unit and the eccrine unit. Apocrine glands and sebaceous glands secrete their products into the hair follicle through short ducts. The sebaceous glands are often seen in association with hair follicles; apocrine glands are more inconspicuous. The smooth muscle arrector pili connects the pilosebaceous apparatus to the epidermis, contraction of the arrector pili produces goose bumps. The eccrine unit is distinct and separate from the pilosebaceous apocrine unit. The glands lay deep in the dermis, coiled like a garden hose, and are connected to the epidermis by a long straight eccrine duct. The coiled exit of the eccrine duct through the epidermis is termed the acrosyringium

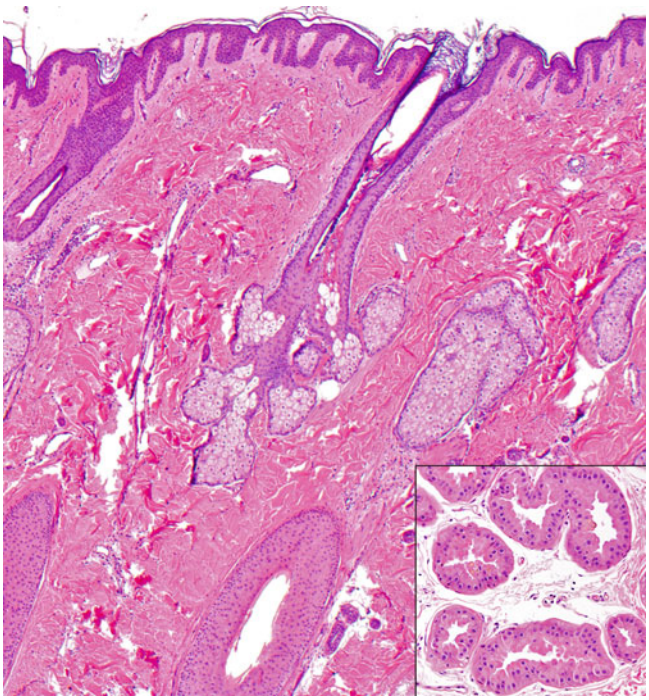

Fig. 2.2 Pilosebaceous Apocrine Unit. The sebaceous glands are associated with hair follicles. Apocrine glands are lined by plump epithelial cells with deep pink cytoplasm and surface blebs that are secreted by decapitation (*inset*)

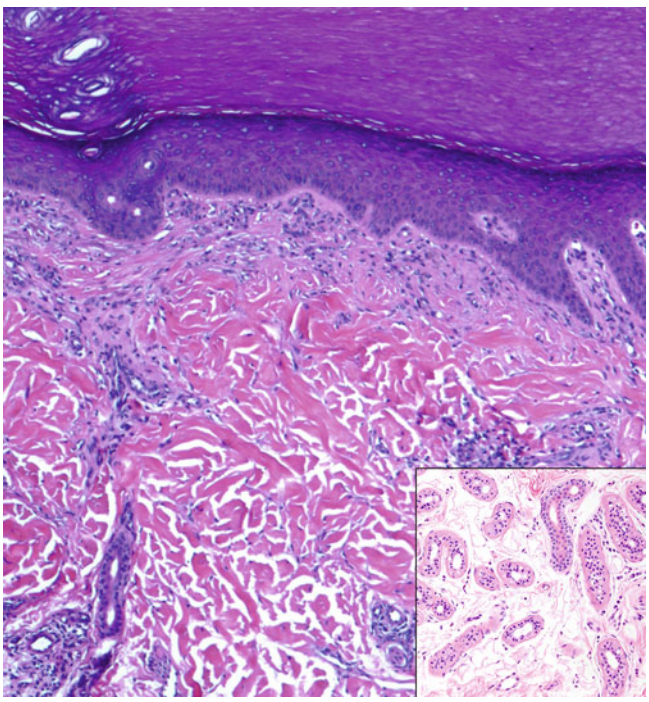

Fig. 2.3 Eccrine unit. The acrosyringium coils through the epidermis overlying the dermal eccrine duct. The glands are lined by secretory epithelium with pale pink cytoplasm; the ducts have less cytoplasm and are more brightly pink (*inset*)

3 Nail Anatomy

Nail
- Dense keratinized plate

Nail bed
- Stratified squamous epithelium

Eponychium
- Distal edge of proximal nail fold

Nail root
- Base of the nail that underlies proximal nail fold

Nail matrix
- Beneath the nail root
- Germinative epithelium that produces the nail plate

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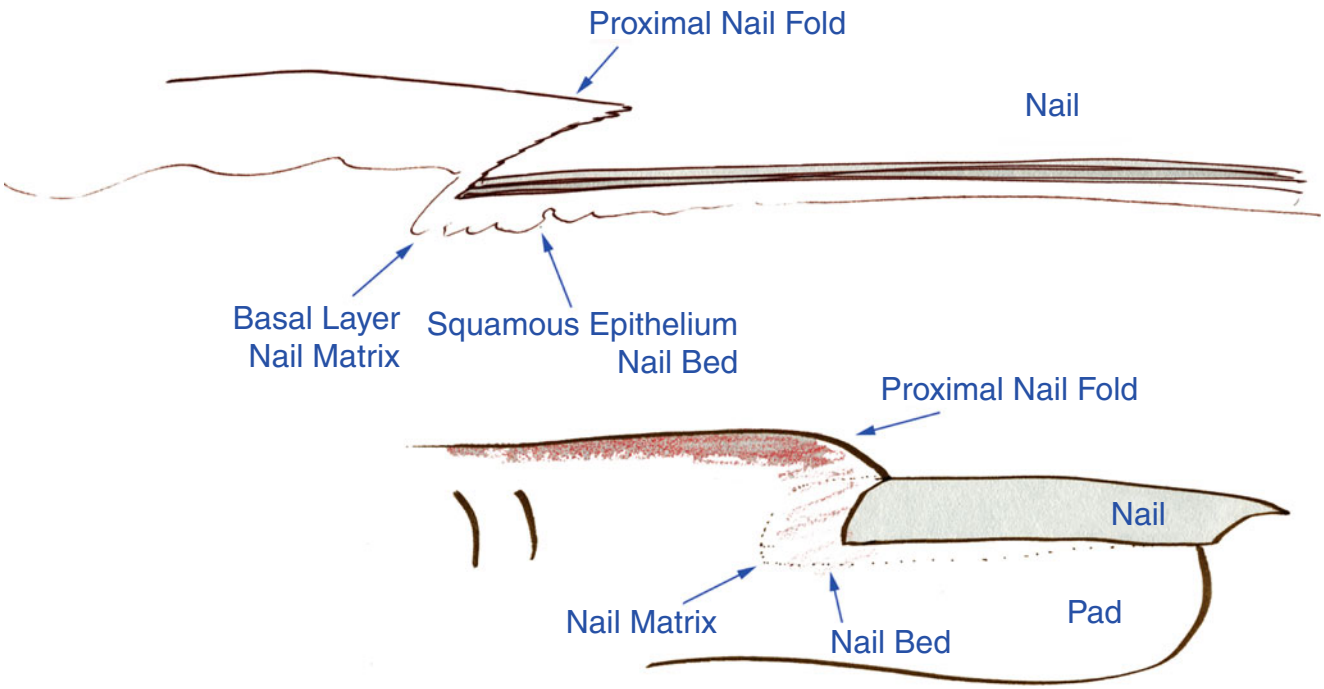

Fig. 3.1 Sketch of the Nail Unit. The nail matrix is at the base of the nail plate beneath the proximal nail fold; distal to the nail matrix is the nail bed

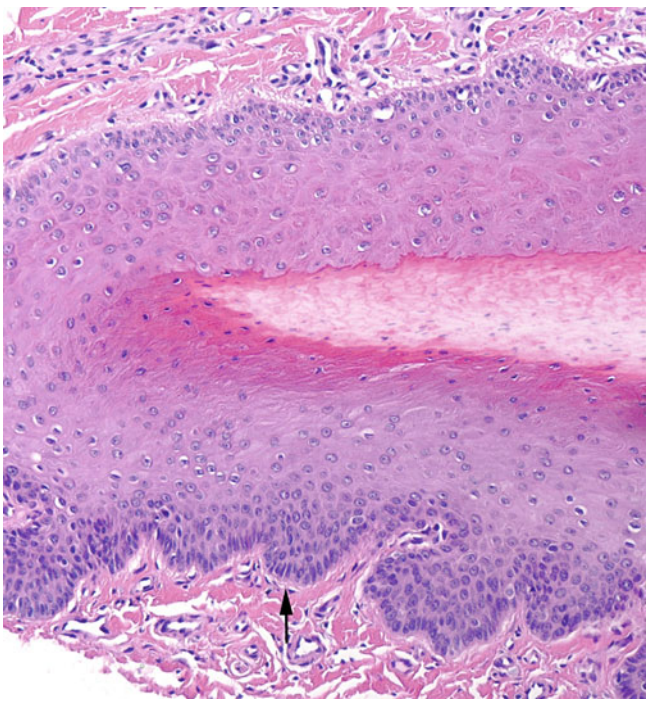

Fig. 3.2 Nail matrix. The basaloid germinal epithelium of the nail matrix produces the nail plate (*arrow*); damage to the nail matrix will lead to deformities of the nail plate

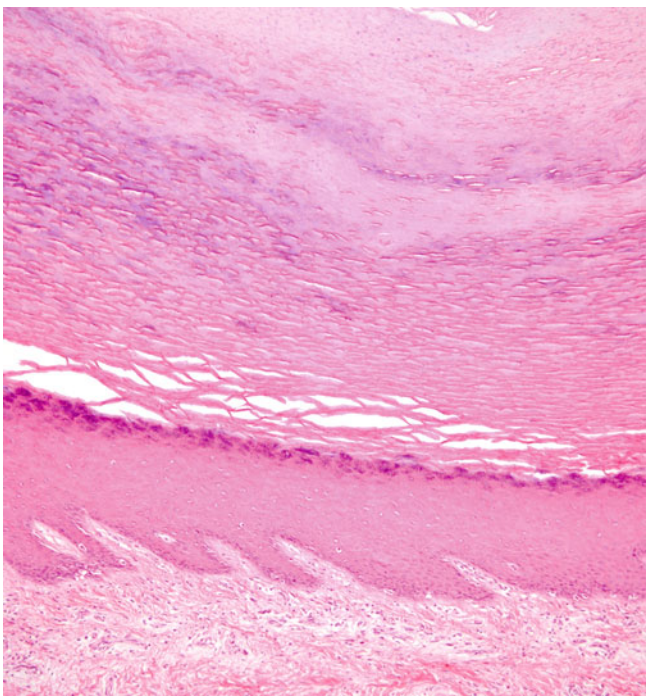

Fig. 3.3 Nail bed. The nail bed epithelium forms the underside of the nail plate

Part II

Infections

4 Parasites

Demodex
- Commonly seen in skin biopsies, especially those from sebaceous areas
- *D. folliculorum* – long and thin, aggregate in hair follicle infundibulum
- *D. brevis* – smaller, found singly in deeper sebaceous glands
- Common in hair follicles of the face

Tick Bites
- Chitinous body attached to skin, mouth parts embedded in dermis
- Dense superficial perivascular and interstitial mixed inflammatory infiltrate, can extend deep into subcutis

Scabies
- Mites, eggs, and larva found in burrows of stratum corneum
- Superficial and deep perivascular eosinophilic inflammatory infiltrate
- Common in interdigital and flexural sites

Spider Bites
- Dermal edema and hemorrhage
- Necrosis of blood vessel walls, thrombosis, and ulceration
- Variable superficial and deep perivascular lymphoid infiltrate with occasional eosinophils and neutrophils

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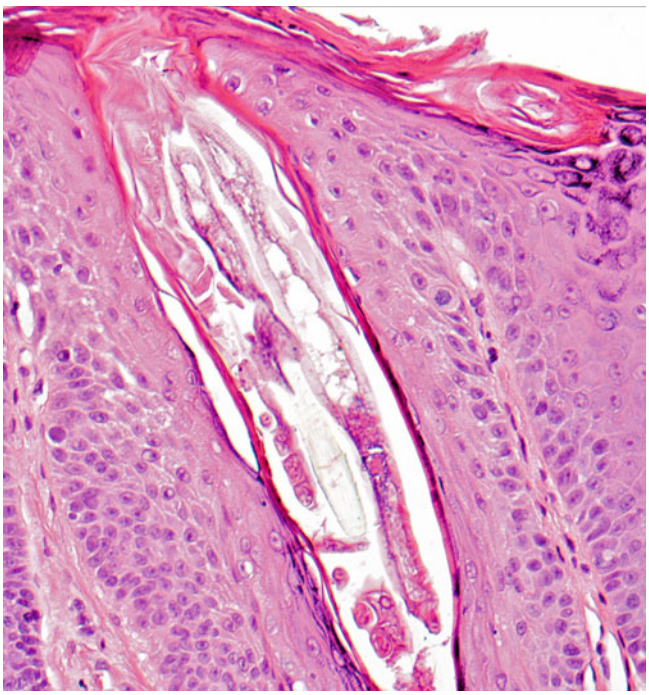

Fig. 4.1 Demodex. Located in the ostium of the hair follicle demodex mites are among the smallest of arthropods. These mites usually do not cause symptoms

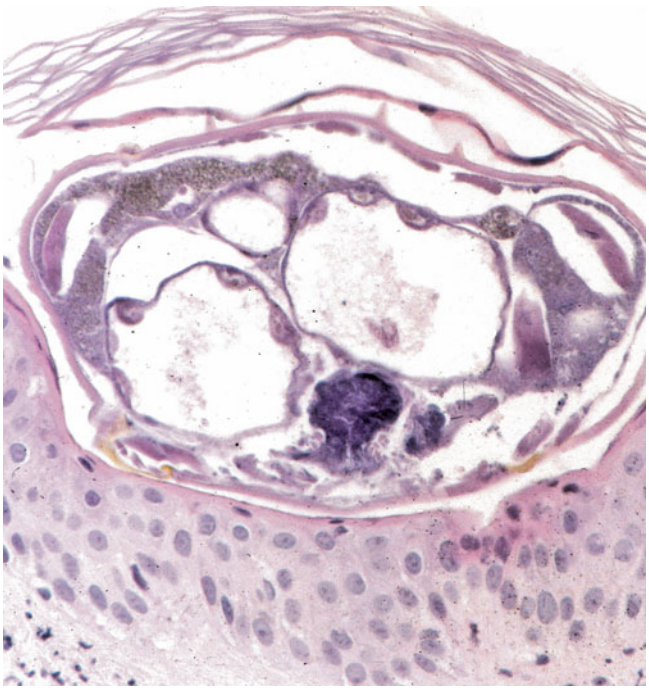

Fig. 4.3 Scabetic mite. The mite *Sarcoptes Scabiei* burrows under the stratum corneum and causes intense itching

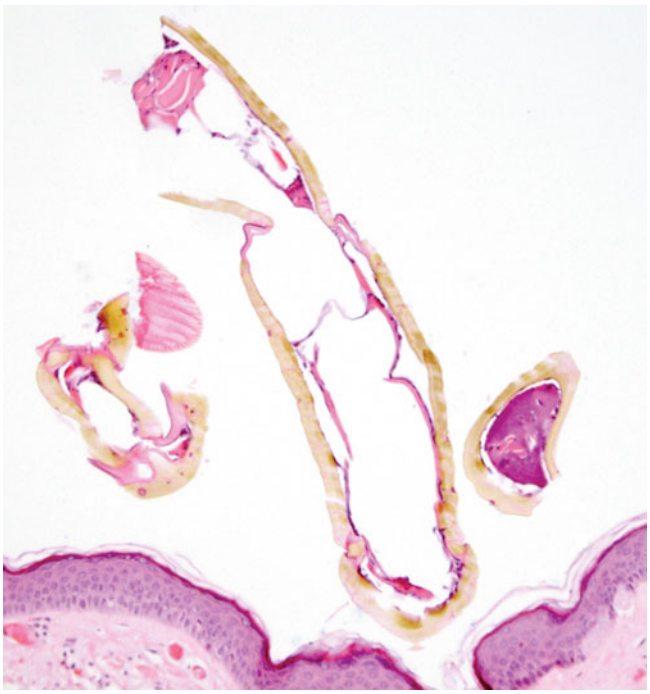

Fig. 4.2 Tick. The chitinous body of the tick hovers over the epidermis

Fig. 4.4 Brown recluse spider. Also known as the fiddleback spider, *Loxesceles reclusa* range from 6 to 20 mm and have a characteristic violin shaped marking on their dorsal cephalothorax (Image by Dr. Irwin Roth)

5 Verruca Vulgaris

Human Papilloma Virus (HPV) infection may lead to the formation of common warts (verruca vulgaris)

Histologic Features:

- Marked papillarity: acanthosis and elongation of rete ridges
- Intoeing of rete ridges at edges
- Columns of parakeratosis at rete peaks
- Hypergranulosis at valleys between rete ridges
- Dermal papillae with dilated, ectatic capillaries
- Viral cytopathic changes with keratohyaline granule clumping ("koilocytes") in upper epidermis

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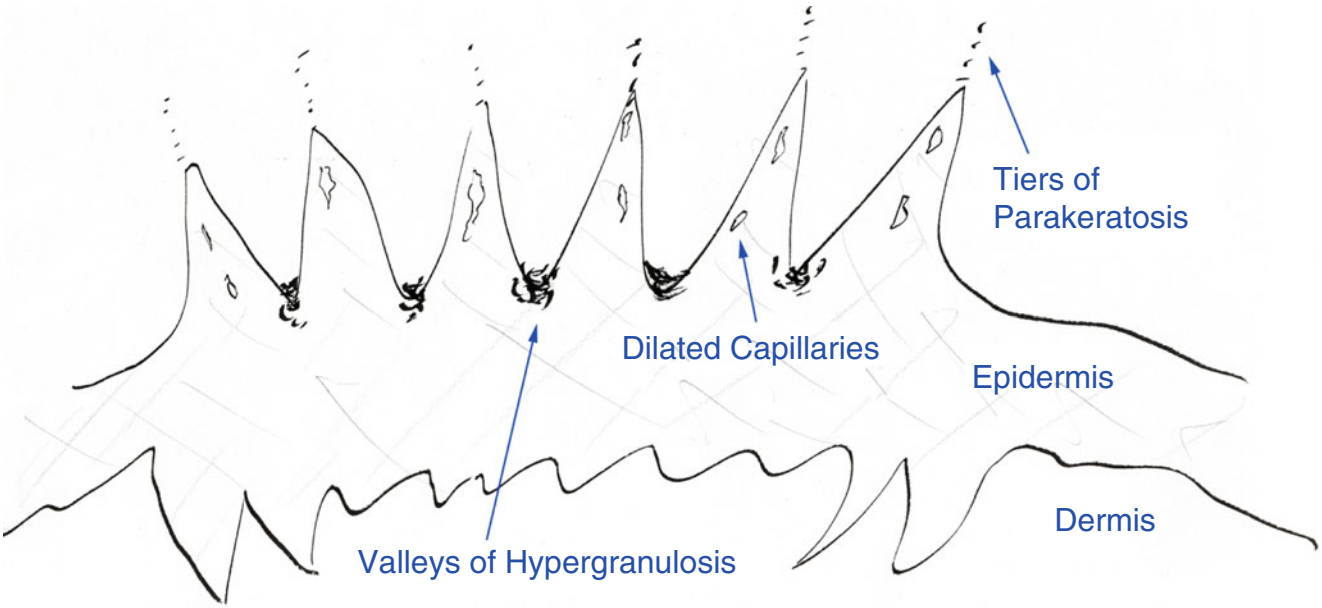

Fig. 5.1 Sketch of verruca vulgaris. The hyperkeratotic keratin forms tiers of parakeratosis alternating with valleys of keratinocytic hypergranulosis. Dilated capillaries are present in papillary dermis

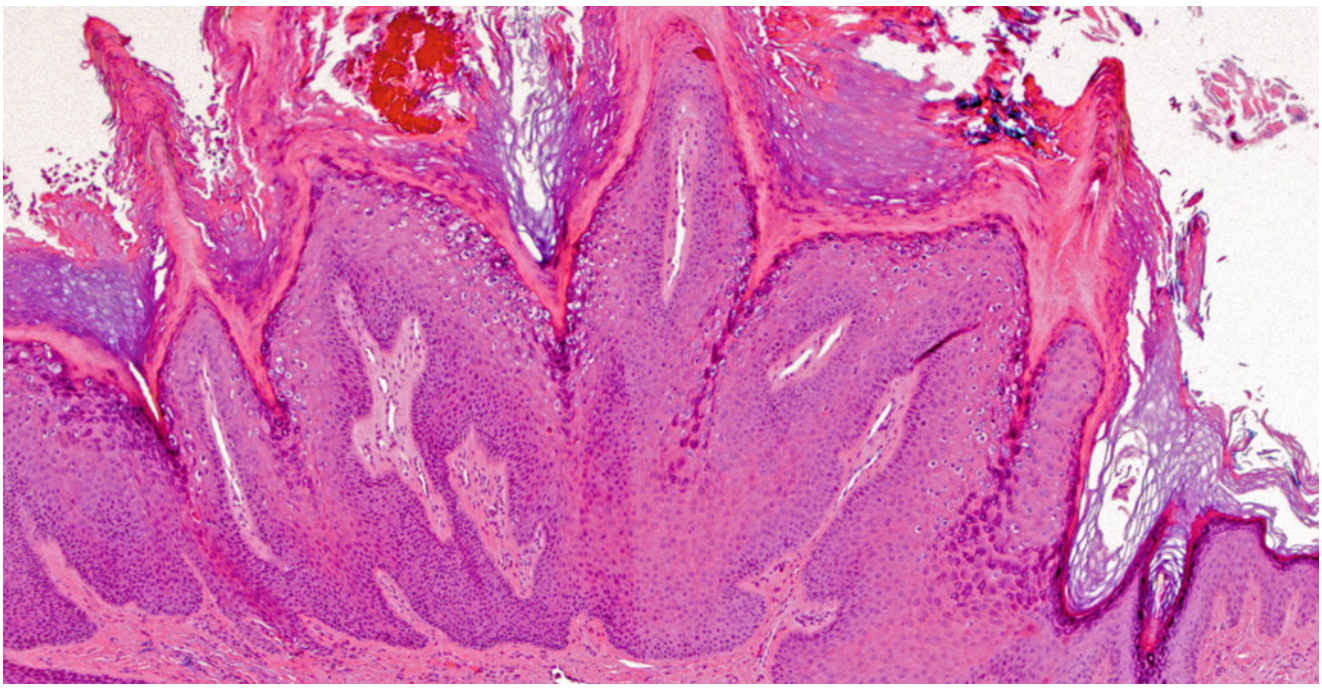

Fig. 5.2 Verruca vulgaris. A parakeratotic tier is present at the left of the image with underlying hypogranulosis. Hemorrhage is observed in the superficial stratum corneum and prominence of the granular cell layer is present in the valleys between the rete ridges

6 Herpes Simplex Virus

- Epidermal intracytoplasmic edema, acantholysis, vesicle formation, and/or necrosis
  - Acanthosis can be seen in chronic lesions
- Dermal lymphohistiocytic inflammatory infiltrate
- Follicular involvement and vasculitis can be seen
- Can detect viral particles by electron microscopy
- Multinucleated cells with ground-glass nuclear inclusions, nuclear molding, and margination of chromatin
  - Cowdry bodies = eosinophilic nuclear inclusions composed of nucleic acid and protein
    - Type A = with surrounding halo, "owl-eye"
    - Type B = fills nucleus

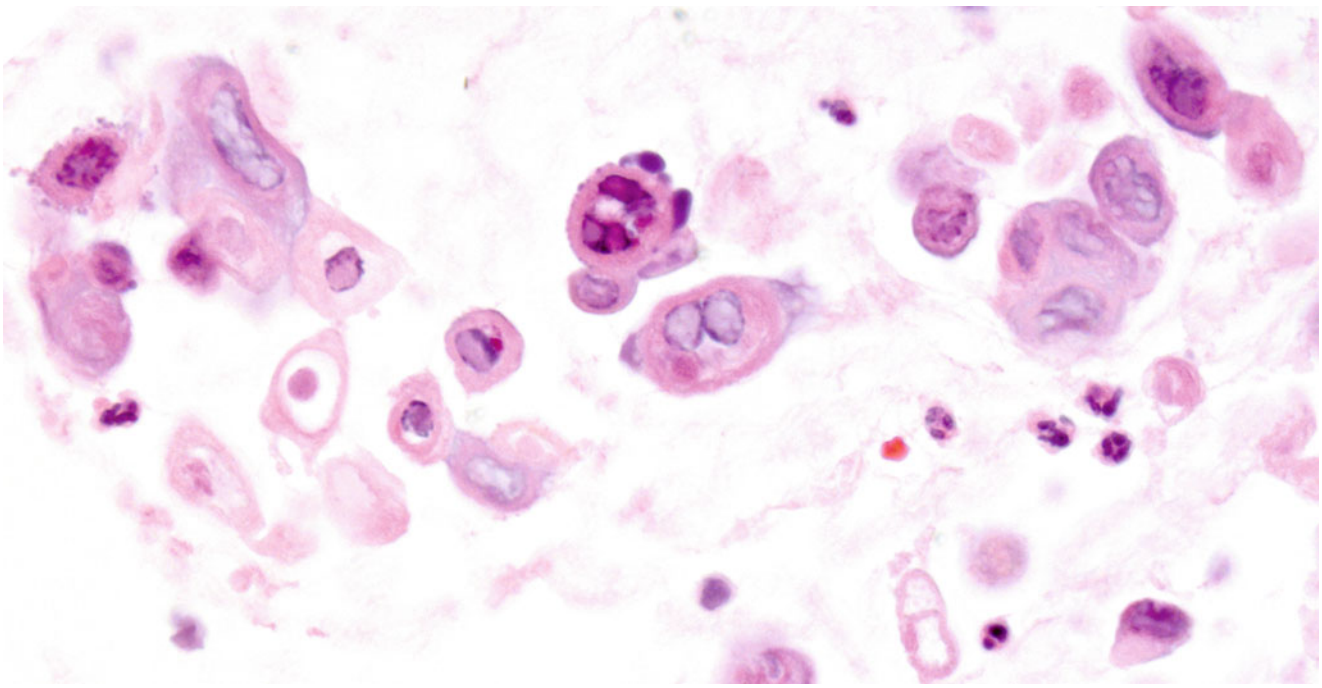

Fig. 6.1 Herpes Simplex. Epidermal keratinocytes infected with herpes virus display finely dispersed nuclear chromatin, nuclear inclusions and multinucleate cells

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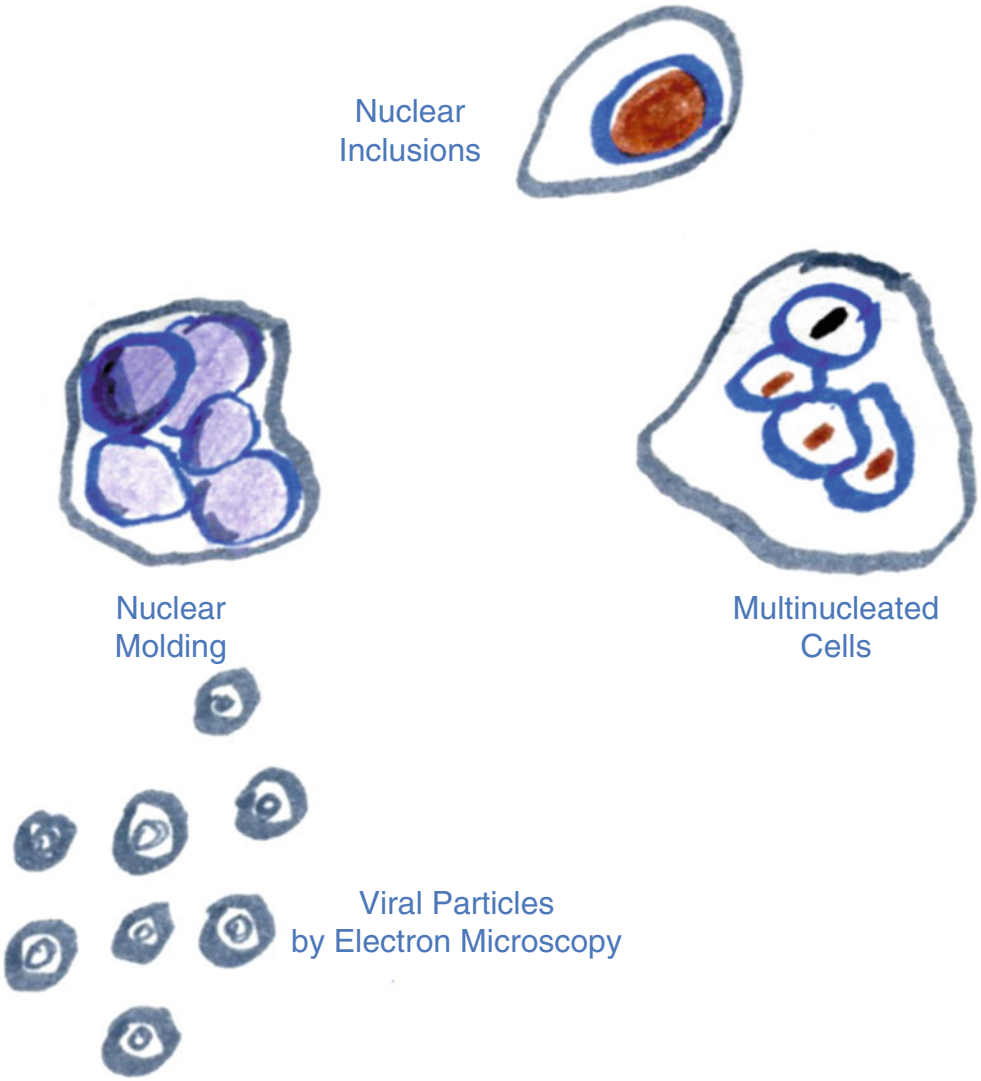

Fig. 6.2 Sketch of viral cytopathic effect of herpes virus infection. Keratinocytes may display bright pink intranuclear inclusions, dispersion of nuclear chromatin with molding of the nuclei to one another, and multinucleate cells. The viral particles have characteristic capsid and surrounding envelope

7 Superficial Fungal Infections

Dermatophytes (Microsporum, Trichophyton, Epidermophyton)

- Different clinical manifestations depending on the body site involved:
  - Tinea capitis, tinea corporis, tinea pedis, tinea unguium, tinea cruris, tinea barbae
- Histology:
  - Septate hyphae in stratum corneum (sandwiched between upper basket-weave layer and lower compact ortho- or parakeratotic layer)

Candida

- Histology:
  - Budding yeast and pseudohyphae

Pityrosporum ovale (Malassezia)

- Causes tinea versicolor or folliculitis
- Histology:
  - Short, stubby, unbranched hyphae and budding yeasts in stratum corneum, "spaghetti and meatballs" = T. versicolor
  - Dilated hair follicle filled with basophilic keratinaceous debris and spores in the dermis with inflammatory reaction = Pityrosporum folliculitis

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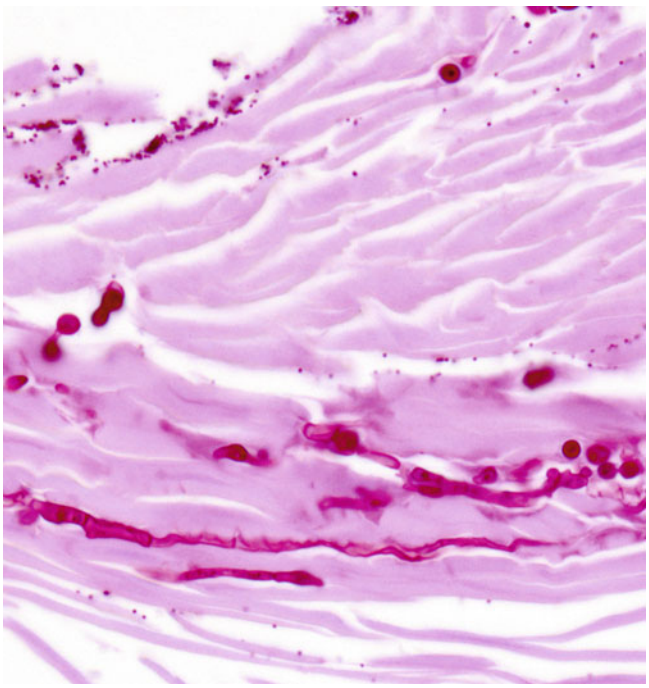

Fig. 7.1 Onychomycosis. Delicate septate hyphae (dermatophyte) and budding yeast (candida) are present in the keratin, staining magenta with periodic acid Schiff stain with diastase (PASD)

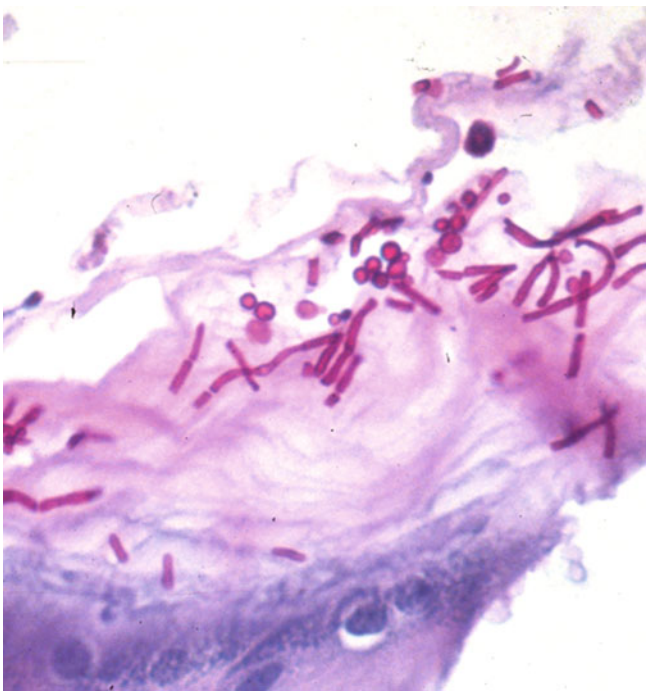

Fig. 7.3 Tinea versicolor. Infection with *Malassezia* is not really a "tinea"; the organism is not a dermatophyte. The yeasts admixed with delicate hyphae appear as "spaghetti and meatballs" in the stratum corneum on PASD stain

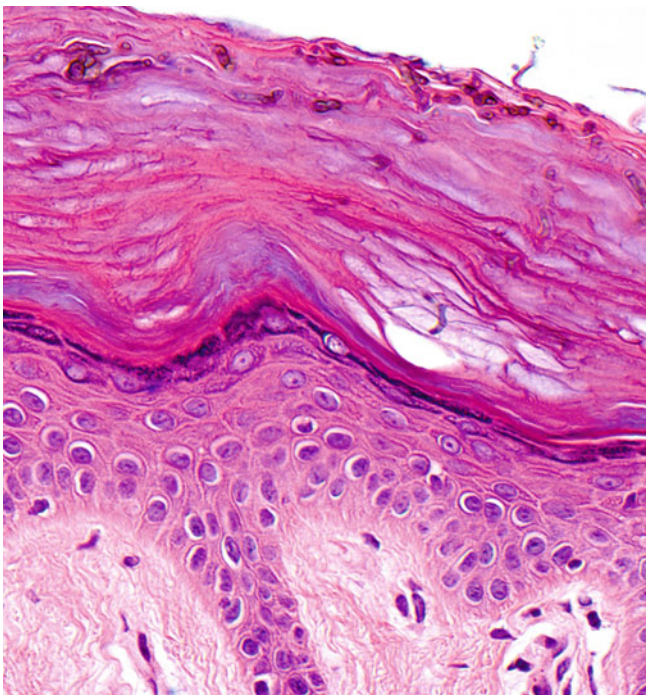

Fig. 7.2 Tinea nigra. The phaeohyphomycosis *Hortaea werneckii* hyphae in the superficial stratum corneum have brown pigmentation on hematoxylin and eosin stain (H&E)

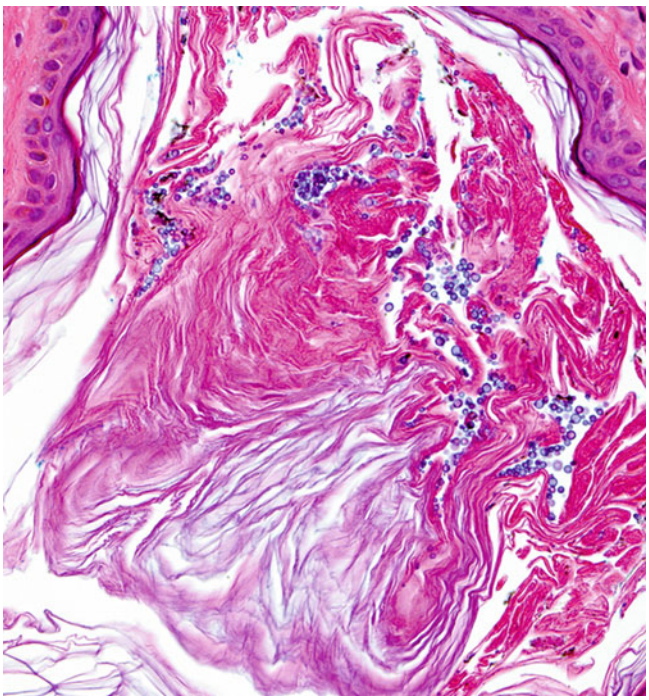

Fig. 7.4 Pityrosporum in follicular keratin. Pityrosporum are often present in the hair follicle keratin as small basophilic yeasts

8 Aspergillosis

Aspergillus is a fungal organism that typically occurs in immunocompromised patients. It has distinctive histomorphology, with acute angle branching and hyphal septation.

- Histology:
  - Vascular invasion and subsequent thrombosis are characteristic
  - Often pauci-inflammatory if immunocompromised or may have granulomatous inflammation and abscess formation
  - Fungal organisms may be visible on H&E but are highlighted by GMS and PAS-D stains
    - Septate hyphae with acute angle branching
    - Fruiting bodies, "aspergillum", are rarely seen in tissue
    - The fruiting body of aspergillus resembles an aspergillum used to sprinkle holy water

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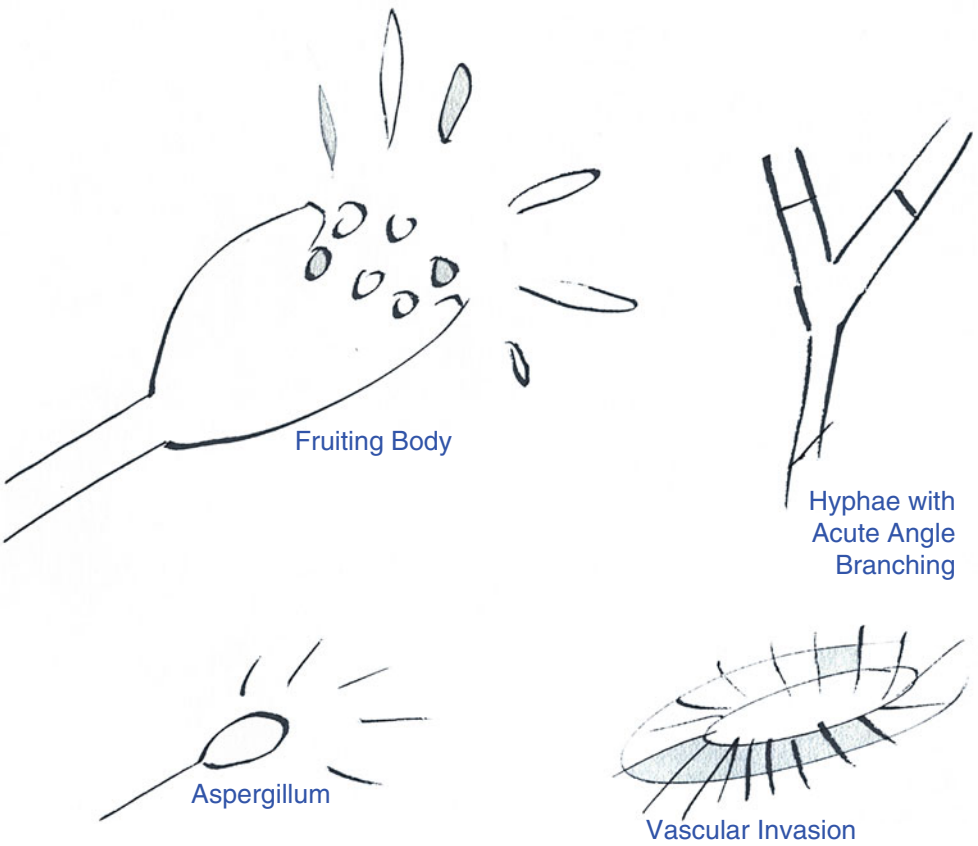

Fig. 8.1 Aspergillus. The organisms in tissue sections display acute angle branching and vascular invasion

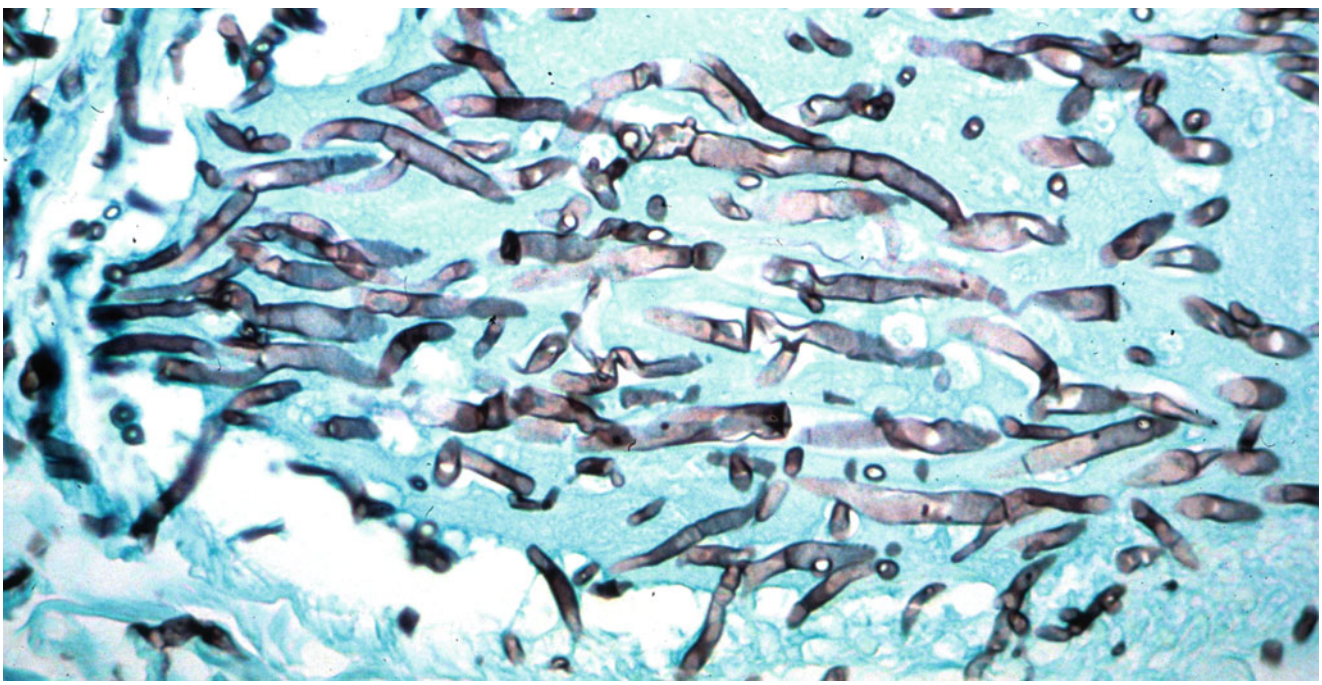

Fig. 8.2 Aspergillus on Gomori methenamine silver (GMS) stain with septate hyphae and branching at acute angles

9 Deep Fungal Infections

Zygomycoses (Rhizopus, Absidia, Mucor)
- Infection typically in immunosuppressed patients, including diabetics
- Thick, non-septate hyphae branch at right angles

Phaeohyphomycosis
- Typically in immunocompetent patients following trauma or in immunosuppressed patients
- Brown-black yeast and septate hyphae
  - Seen in stratum corneum or within abscess in subcutis

Chromomycosis
- Round, thick-walled, golden brown yeast forms (5–12 μm) resembling "copper pennies" (sclerotic bodies, Medlar bodies)

Coccidioidomycosis (endemic in the southwestern United States)
- Thick walled spherule (80–200 μm) with multiple endospores (2–30 μm)

Paracoccidioidomycosis (endemic in South America)
- Thick walled yeast with multiple daughter cells attached by narrow-based buds (6–60 μm), "captain's wheel"
  - Can be found intra- and/or extracellularly

Cryptococcosis
- Typically occurs in immunosuppressed patients
  - Localized infection can occur in immunocompetent patients
- Clusters of spores (3–8 μm) with clear capsule (5–10 μm), "soap bubbles"

Blastomycosis (endemic in Mississippi and Ohio River valleys and Southeastern U.S.)
- Thick-walled, round, multinucleated yeasts (8–30 μm) with single broad-based bud

Rhinosporidiosis
- Large, spherical sporangia (>300 μm) containing many endospores (up to 7 μm)

Lobomycosis (found in Central and South America)
- Thick-walled fungi (10 μm) arranged in chains

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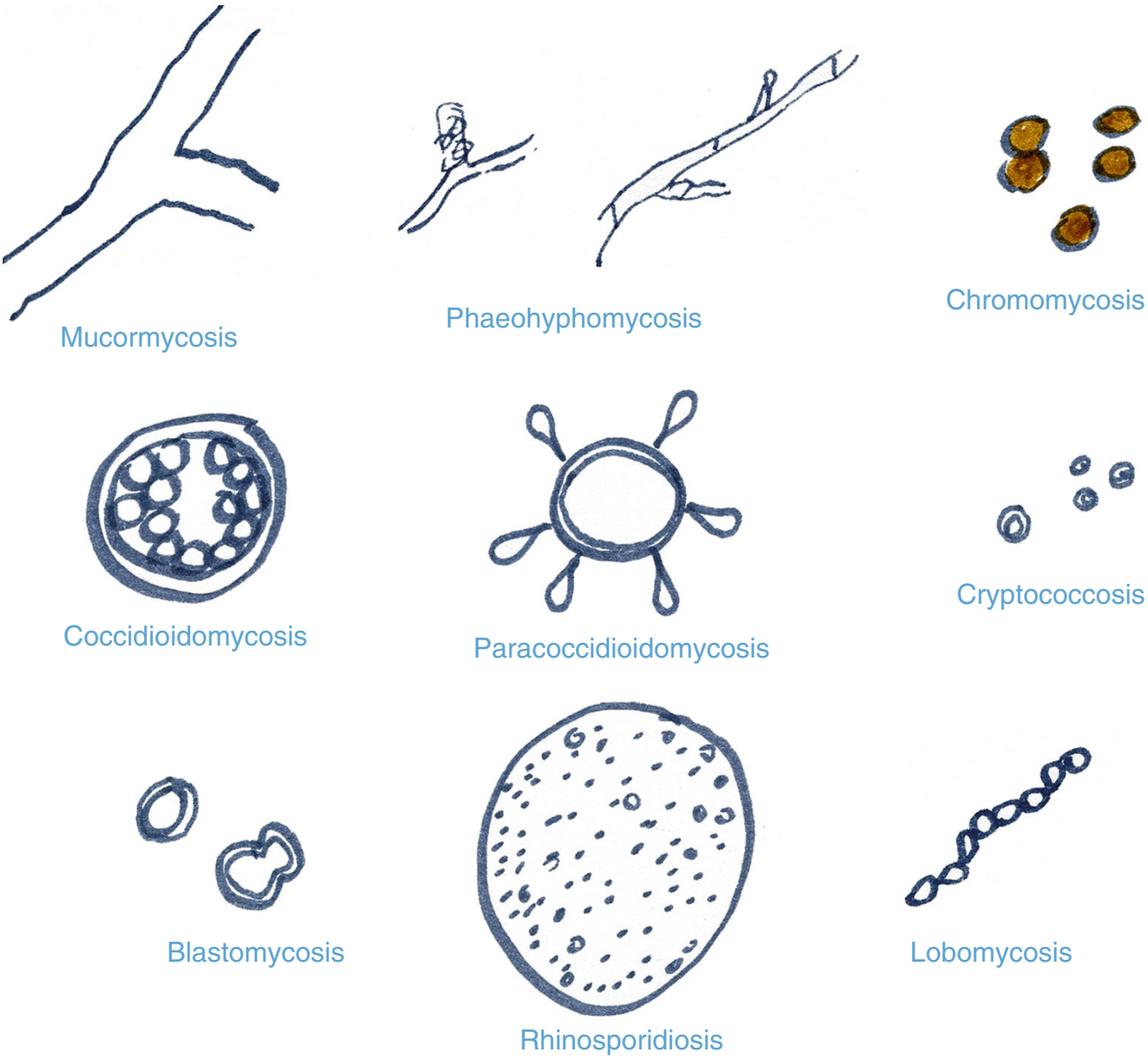

Fig. 9.1 The deep fungi that infect the skin have characteristic shapes and sizes

Part III

Inflammatory, Non-Infectious

10 Epidermolysis Bullosa

Epidermolysis bullosa encompasses a group of cutaneous blistering disorders that are characterized by mechanical fragility of the skin. The inherited forms of epidermolysis bullosa are designated either simplex, junctional or dystrophic based on the location of the cleavage plane. Electron microscopy or immunohistochemistry can help differentiate the ultrastructural level at which a subepidermal blister occurs.

Table 10.1 Subclassification of epidermolysis bullosa

	Simplex	Junctional	Dystrophic	Acquired
Level of blister formation	Intraepidermal (suprabasal)	Subepidermal	Subepidermal	Subepidermal
Ultrastructural site of blister formation	Within basal keratinocyte	Within lamina lucida	Deep to lamina densa	Deep to lamina densa
Targeted structure	Intermediate filaments, hemidesmosome	Anchoring filament, hemidesmosome	Anchoring fibril	Anchoring fibril
Targeted proteins	Keratin 5 and 14, plectin	Laminin 5, α6β4 integrin	Type VII collagen	Type VII collagen
Pathogenesis	Mutation	Mutation	Mutation	Antibodies
Other	Non-scarring		Scarring	

The location of the blister corresponds to the protein involved in the pathogenesis. Intraepidermal blisters are usually associated with erosions. Subepidermal blisters may lead to ulceration, with basement membrane zone damage and scarring

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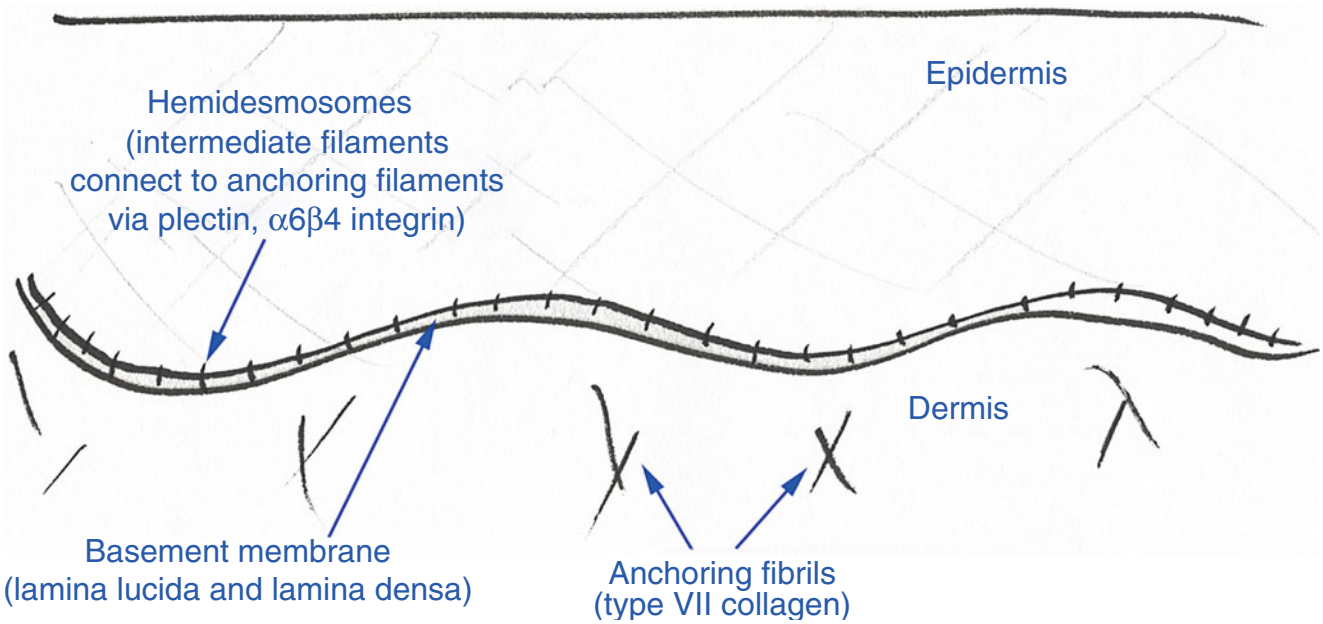

Fig. 10.1 Sketch of the structural elements of the epidermis and dermis affected in epidermolysis bullosa

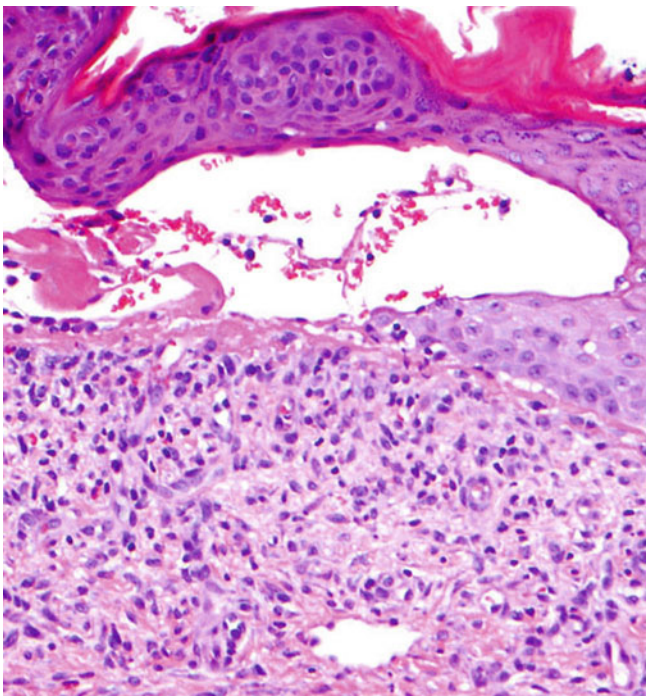

Fig. 10.2 Dystrophic epidermolysis bullosa. A pauci-inflammatory subepidermal blister with underlying dermal fibrosis, suggestive of a scar

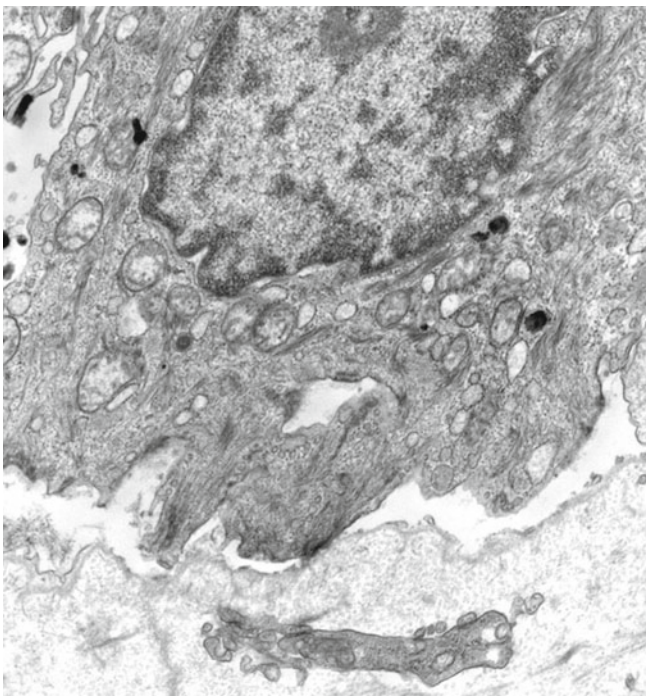

Fig. 10.3 Junctional epidermolysis bullosa. Electron microscopy reveals a split within the lamina lucida

11 Acantholytic Processes

Acantholysis occurs in the epidermis when there is dissolution or disruption of the intercellular attachments. The keratinocytes fall away from one another. Acantholysis may appear at any level of the epidermis: immediately above the basal layer of keratinocytes (suprabasal), full thickness, or in the superficial epidermis. Some forms of acantholytic dermatosis result from an autoimmune reaction, immunofluorescence testing may be helpful.

Table 11.1 Differential diagnosis of acantholytic processes

	Acantholytic dyskeratosis (corps ronds and grains)	Full thickness acantholysis (dilapidated brick wall)	Suprabasal acantholysis	Verrucous epidermal hyperplasia	Immuno-fluorescence
Darier's disease (Keratosis follicularis)	+				–
Hailey-Hailey disease (Benign familial pemphigus)		+			–
Grover's (TAD)	+	+	+		–
Pemphigus vulgaris			+		+ Chicken wire pattern, IgG and C3, Ab to desmoglein 3
Pemphigus vegetans			+	+	+ Chicken wire pattern, IgG and C3, Ab to desmoglein 3
Warty dyskeratoma	+			+	–
Neoplasia (AK, SCC)	+/–	+/–	+/–	+/–	–

TAD transient acantholytic dermatosis, *AK* actinic keratosis, *SCC* squamous cell carcinoma

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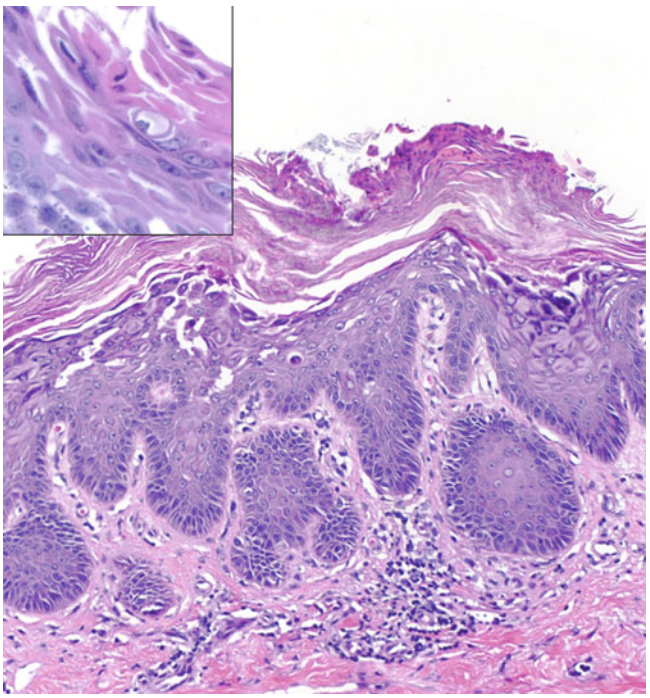

Fig. 11.1 Darier's disease. There is intraepidermal acantholytic dyskeratosis, hyperkeratosis, and corps ronds and grains (*inset*)

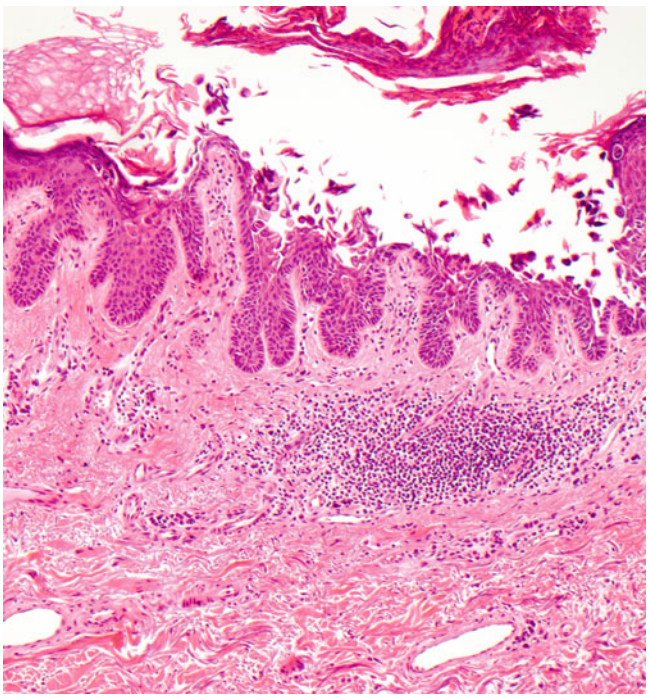

Fig. 11.3 Grover's disease. Two patterns of acantholysis, full thickness (*center*) and suprabasal (*right*)

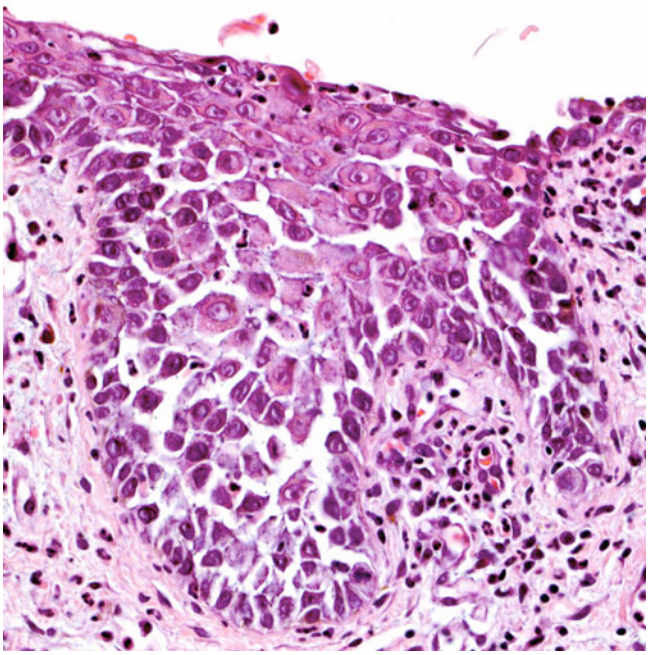

Fig. 11.2 Hailey-Hailey disease. There is intraepidermal acantholysis throughout stratum spinosum resembling a dilapidated brick wall

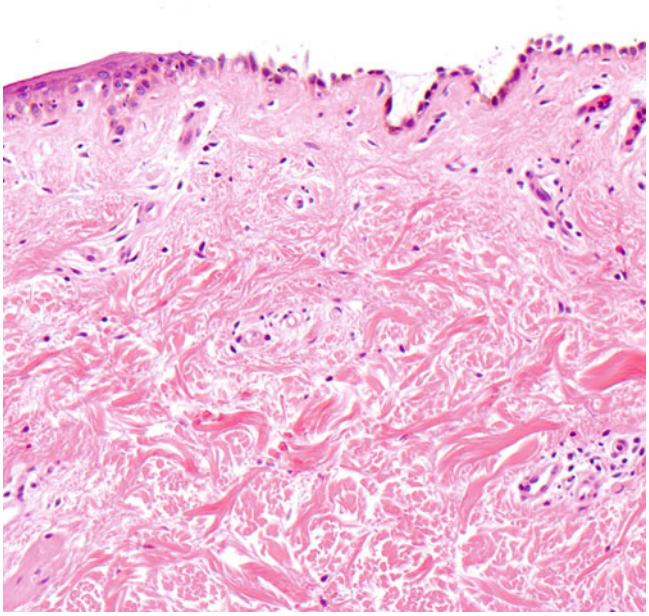

Fig. 11.4 Pemphigus vulgaris. There is suprabasal acantholysis with loss of the overlying epidermis

12 Autoimmune Blistering Dermatoses

The autoimmune blistering dermatoses result from antibodies directed against proteins in the epidermis or superficial dermis. Direct immunoflourescence testing is performed using reagents to detect antibodies deposited in a biopsy of the patient's skin.

Table 12.1 Differential diagnosis of autoimmune blistering dermatoses

	Blister location	Inflammatory infiltrate	Immunofluorescence	Pathogenesis
Pemphigus vulgaris	Intraepidermal	Eosinophilic spongiosis and mixed infiltrate	IgG and C3 on cell membranes, "Chicken-Wire" (Desmosomes)	Antibodies to desmoglein 3
Paraneoplastic pemphigus	Intraepidermal	Mixed, can be lichenoid	IgG and C3 on cell membranes and linear at DEJ (Desmosomes and hemidesmosomes)	Associated with internal malignancies, (most commonly lymphoproliferative disorders)
Bullous pemphigoid	Subepidermal	Eosinophils and Lymphocytes	Linear IgG and C3 at DEJ (Hemidesmosomes)	Antibodies to BPAg1 and 2
Bullous lupus erythematous	Subepidermal	Neutrophils	IgG, C3, and IgA deposits at BMZ and in upper dermis (Colloid bodies)	Antibodies to BMZ proteins
Dermatitis herpetiformis	Subepidermal	Neutrophils > Eosinophils	Patchy granular deposits of IgA in dermal papillae	Deposition of IgA in dermal papillae
Linear IgA disease	Subepidermal	Neutrophils > Eosinophils	Linear IgA at basement membrane	Antibodies to basement membrane proteins
Epidermolysis bullosa acquisita	Subepidermal	Minimal (if present, mixed infiltrate)	Linear IgG at basement membrane	Antibodies to Type VII collagen

DEJ dermoepidermal junction, *BMZ* basement membrane zone

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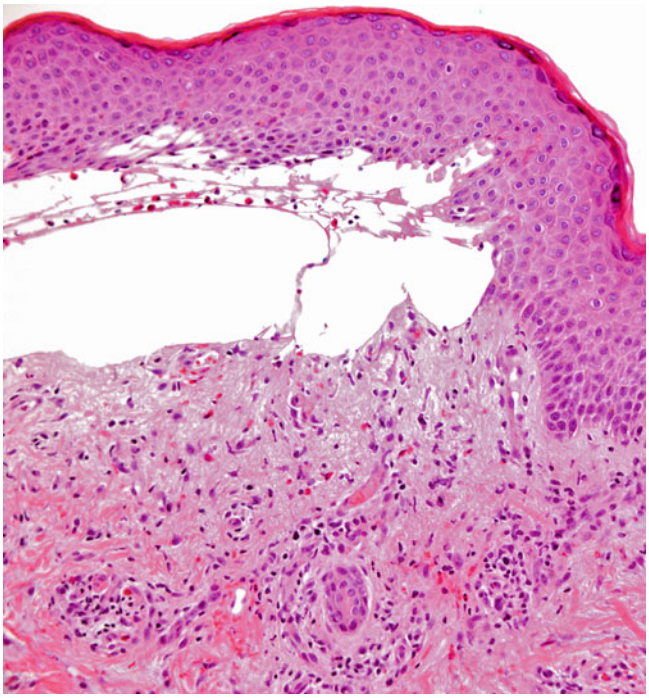

Fig. 12.1 Bullous pemphigoid. There is a subepidermal blister with a superficial dermal infiltrate of eosinophils and lymphocytes

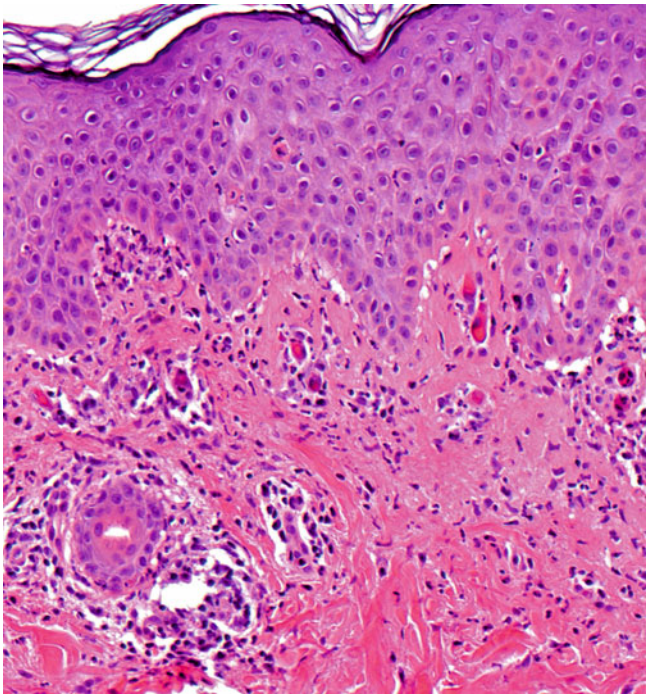

Fig. 12.3 Dermatitis herpetiformis. Aggregates of neutrophils and cellular debris are located intermittently along the tips of the papillary dermal pegs

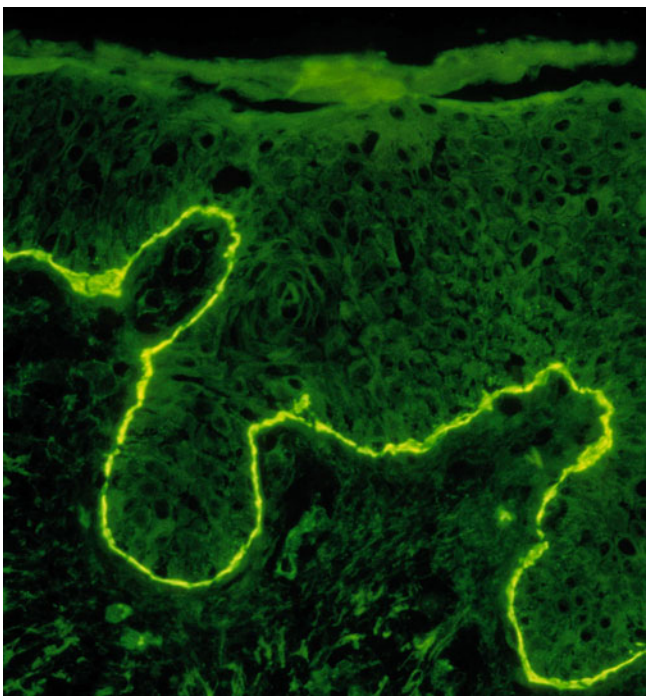

Fig. 12.2 Bullous pemphigoid. Direct immunofluorescence reveals a linear deposition of C3 along the dermal epidermal junction

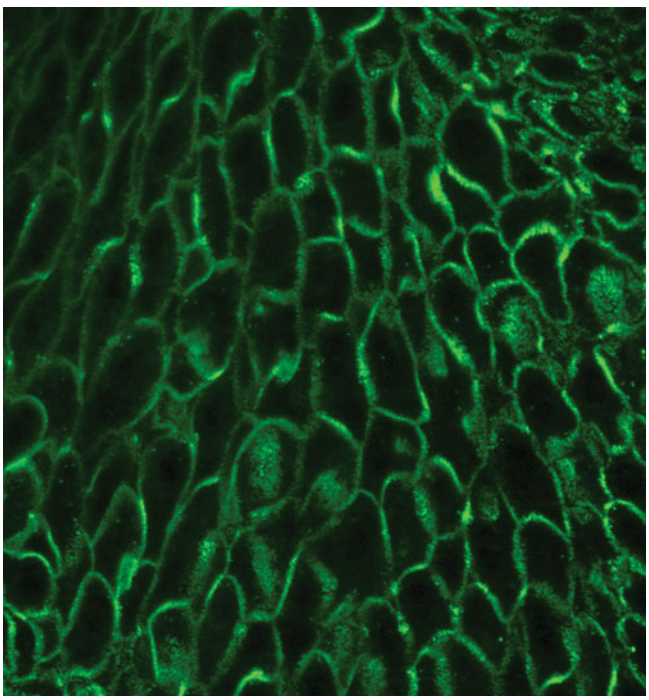

Fig. 12.4 Pemphigus vulgaris. Direct immunofluorescence reveals intercellular deposition of IgG

13 Porokeratosis

Clinical features

There are several variants

- Porokeratosis of mibelli – a plaque that develops in infancy or childhood
- Disseminated superficial actinic porokeratosis (DSAP) – thin papules on the legs of older women (the most common variant)
- Linear porokeratosis – follows the lines of Blaschko and occurs in infancy or childhood
- Punctate porokeratosis – tiny papules on the palms and soles appear after adolescence. A variant is porokeratosis palmaris et plantaris disseminata (PPPD) wherein lesions appear at other body sites

Histological features

- Characterized by the presence of coronoid lamellae
  - Column of parakeratosis, angled toward the center of the lesion, with a focal loss of the granular cell layer and dyskeratosis of the epidermal keratinocytes and thinning of the epidermis beneath the column.
- Center of the lesion can show atrophy with overlying hyperkeratosis and scattered dyskeratotic cells within the epidermis
- Lichenoid inflammatory infiltrate is often present

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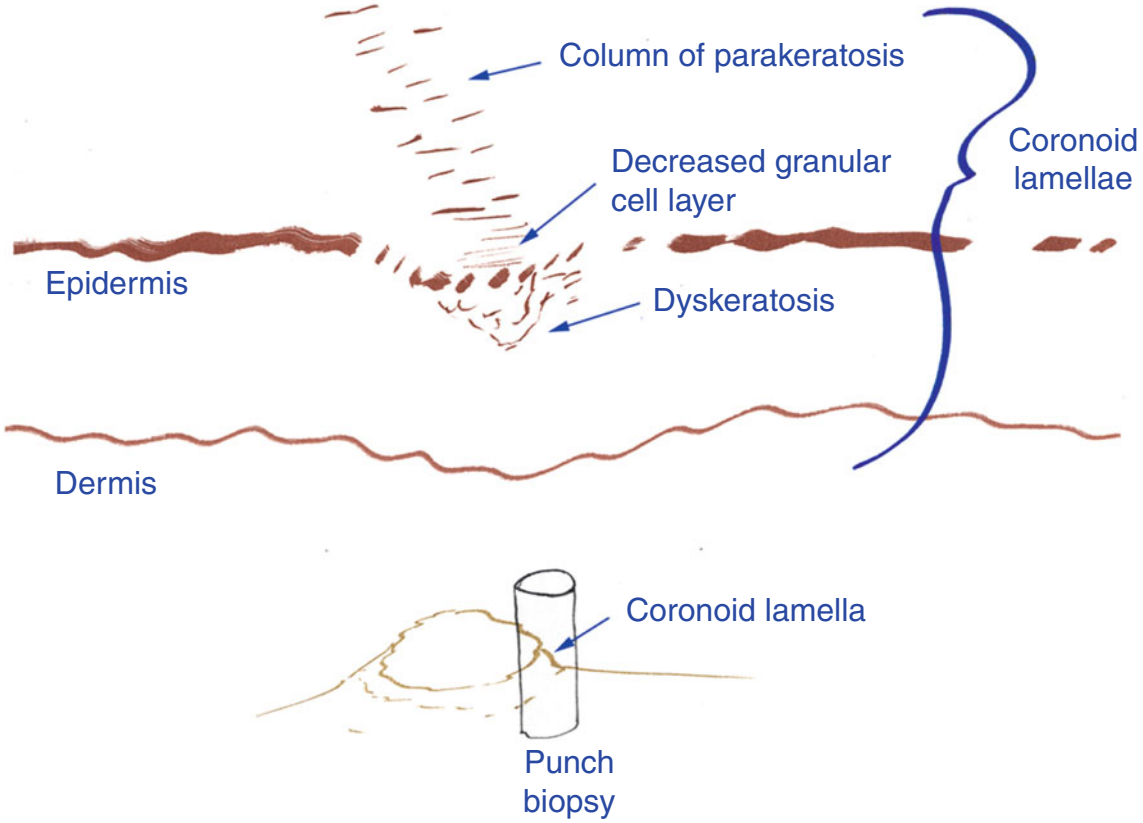

Fig. 13.1 The column of parakeratosis is usually angled toward the center of the lesion. It is important to biopsy the lesion at the margin in a manner that includes the hyperkeratotic column and the underlying epidermis

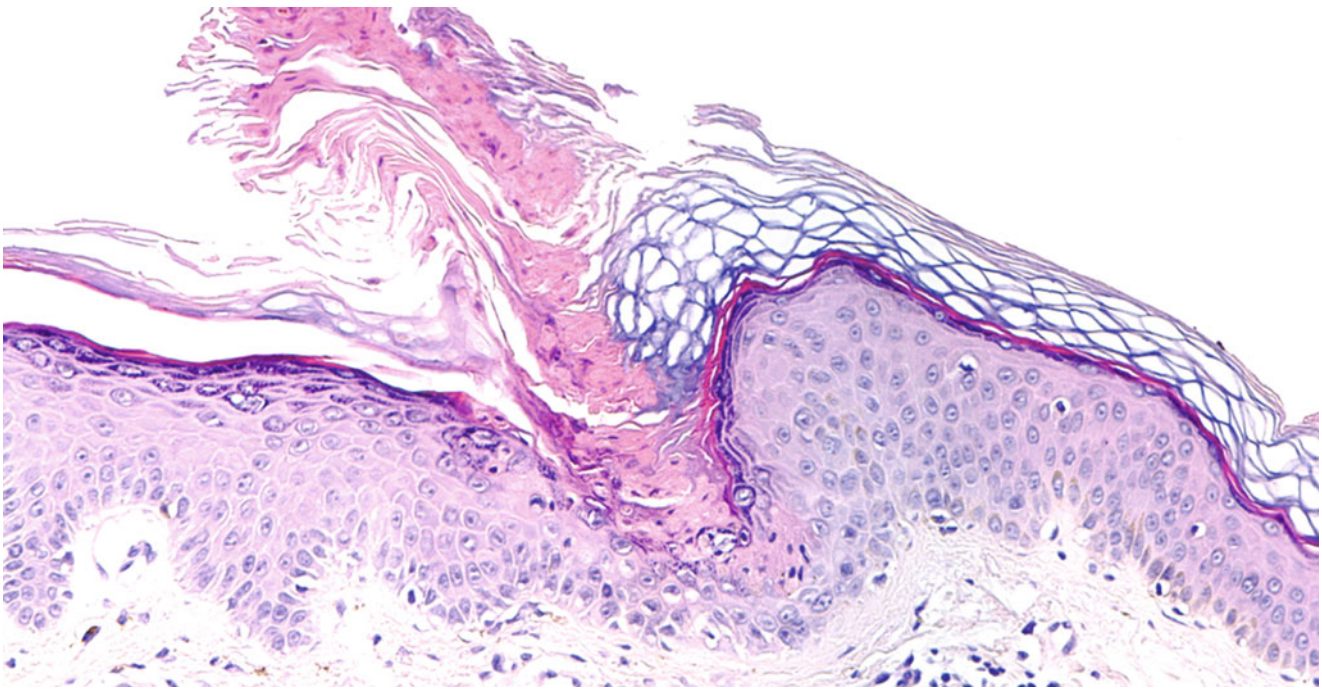

Fig. 13.2 The parakeratotic column is flanked by attenuated stratum corneum on the left and normal basket-weave stratum corneum on the right. The epidermis directly below the column has loss of the granular cell layer, dyskeratosis and epidermal thinning

14 Interface Dermatitis

Interface dermatitis is characterized by an inflammatory process, often with vacuolar changes, occurring at the interface of the epidermis and the dermis.

Table 14.1 The differential diagnosis of interface dermatitis

	EM	TEN	DM	LE	GVHD	PLC/PLEVA
Epidermal dyskeratosis, satellite cell necrosis	+	+	–/+	–/+	+	–/+
Colloid, civatte, cytoid bodies	+	+	+	+	+	+
Epidermal atrophy	+/–	–	+ (Grotton's papules have acanthosis)	+	+	–
Vacuolar interface changes	+/–	+/–	+/–	+	+	+
Epidermal lymphocyte exocytosis	+	+	–	+/–	+	+
Full thickness epidermal necrosis	–	+	–	–	–	–
Adnexal involvement	–	+ Follicular dyskeratosis	–	+ Follicular dyskeratosis, Periadnexal inflammation	+ Follicular dyskeratosis	–
Deep perivascular inflammation	–	–	–	+	–	–
Dermal eosinophils	+	+	–	–	–/+	–/+
Other		"Festooning" of naked dermal papillae	Loss of rete ridges	Interstitial mucin deposition		Erythrocyte extravasation

Satellite cell necrosis occurs when a dying keratinocyte is surrounded by lymphocytes. Colloid bodies are eosinophilic globules of cellular protein that are present in the epidermis or superficial dermis. *EM* erythema multiforme, *TEN* toxic epidermal necrolysis, *DM* dermatomyositis, *LE* lupus erythematous, *GVHD* graft versus host disease, *PLC* pityriasis lichenoides chronica, *PLEVA* pityriasis lichenoides et varioliformis acuta

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DOI 10.1007/978-1-4471-4471-7_14, © Springer-Verlag London 2013

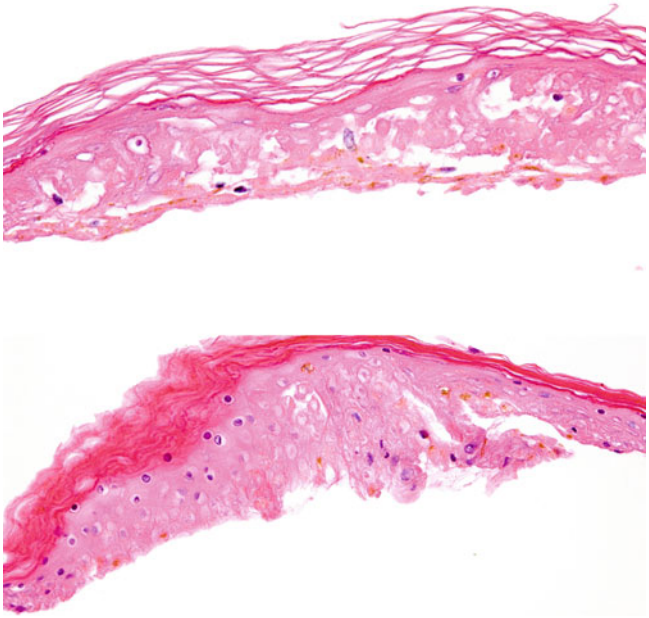

Fig. 14.1 Toxic epidermal necrolysis. There is full thickness epidermal necrosis and detachment of the epidermis from the underlying dermis

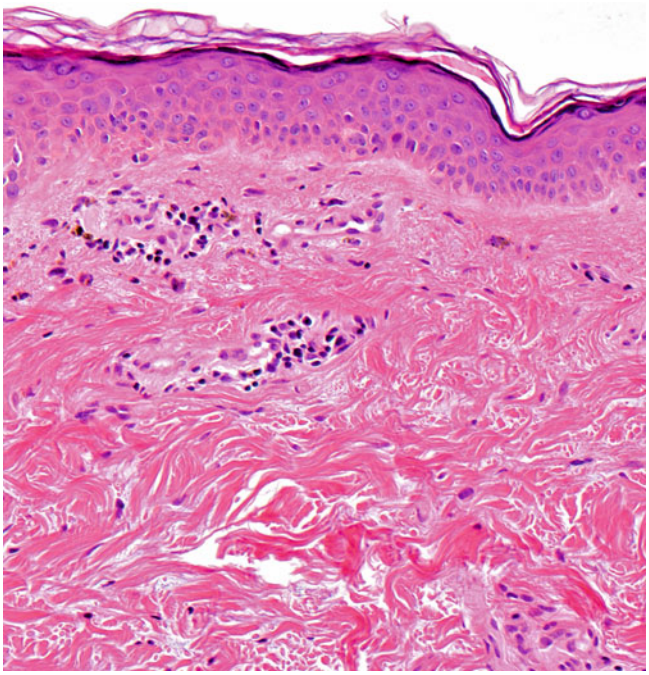

Fig. 14.2 Dermatomyositis. There is epidermal atrophy, vacuolar change at the dermal-epidermal junction and a sparse inflammatory infiltrate

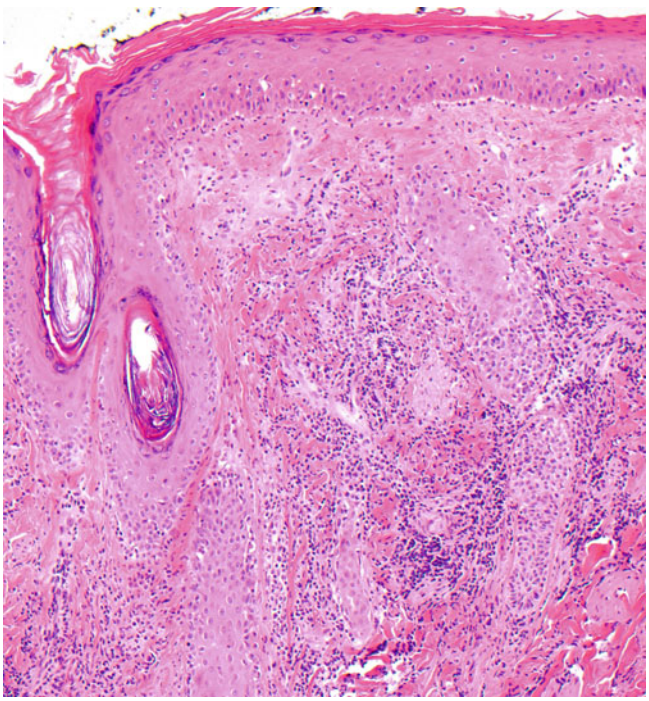

Fig. 14.3 Lupus erythematosus. Epidermal atrophy with follicular hyperkeratosis and an interface, perivascular and periadnexal inflammatory infiltrate are observed

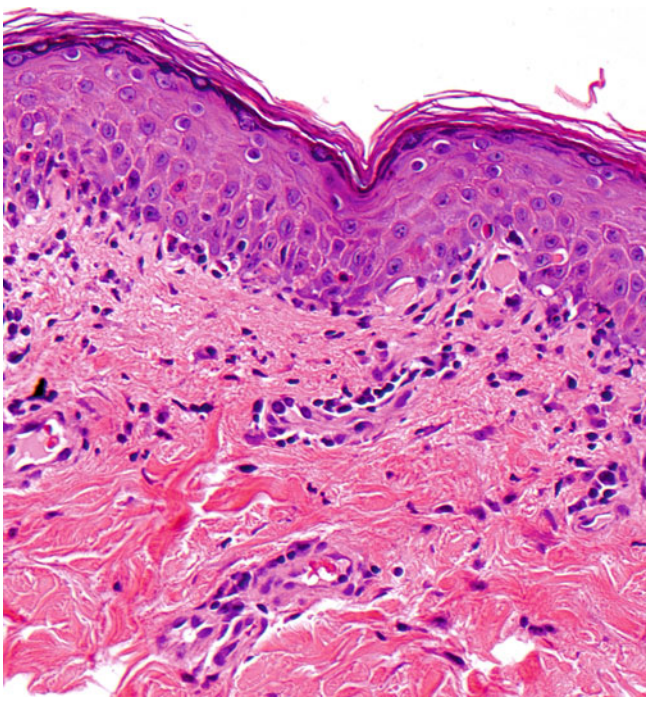

Fig. 14.4 Graft vs. Host disease. There is keratinocyte dyskeratosis and interface dermatitis

15 Lichenoid Dermatitis

Lichenoid dermatitis is characterized by a band like inflammatory infiltrate in the superficial dermis parallel to the epidermis. In some cases the infiltrate abutts and obscures the dermal epidermal junction.

Table 15.1 Differential diagnosis of lichenoid dermatitis

	Lichen planus	Lichenoid drug reaction	Fixed drug eruption	Lichen striatus	Lichen nitidus	Lichenoid keratosis	Lichen sclerosus
Hyperkeratosis	+	+	+	+	+	+	+
Parakeratosis	–	+ Focal	–/+	+	+	+ Focal	–/+
Hypergranulosis	+ Wedge shaped	+ Wedge shaped	–	–	–	+	+
Acanthosis	+ Irregular	+ Irregular	+/–	+/–	– Atrophy	+/–	–
Cytoid bodies	+	+	+	+ and dyskeratosis	+	+	–
Lichenoid infiltrate	+	+	+	–/+	+	+	+
Adnexal involvement	–	–	–/+	+	–	–	–
Dermal eosinophils	–	+	–/+	–	–	–/+	–
Hyalinized cell poor dermis	–	–	–	–	–	–	+

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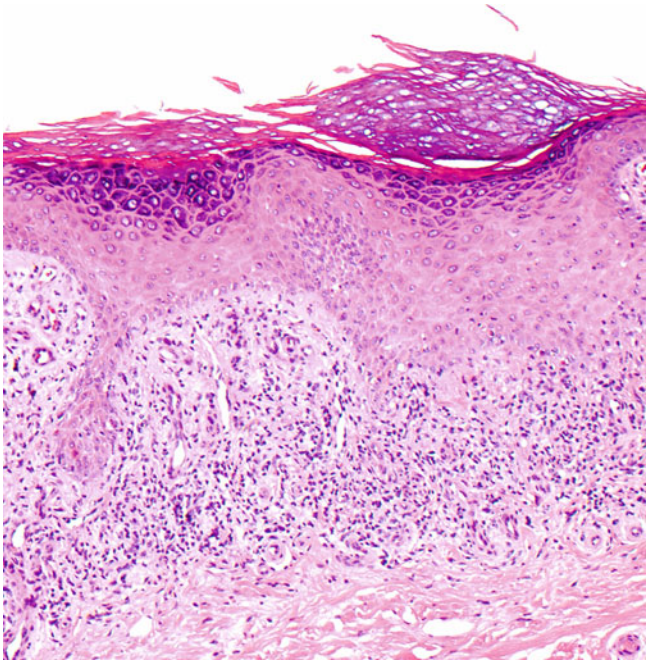

Fig. 15.1 Lichenoid dermatitis. There is wedge-shaped hypergranulosis with irregular epidermal hyperplasia and a band of inflammation along the epidermal base

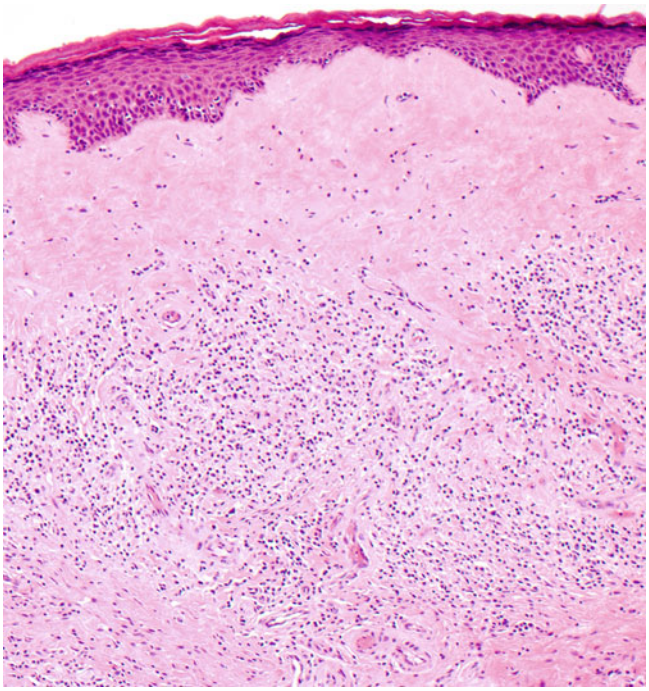

Fig. 15.3 Lichen sclerosus. There is eosinophilic homogenization of the subepidermal dermis with an underlying band of inflammation

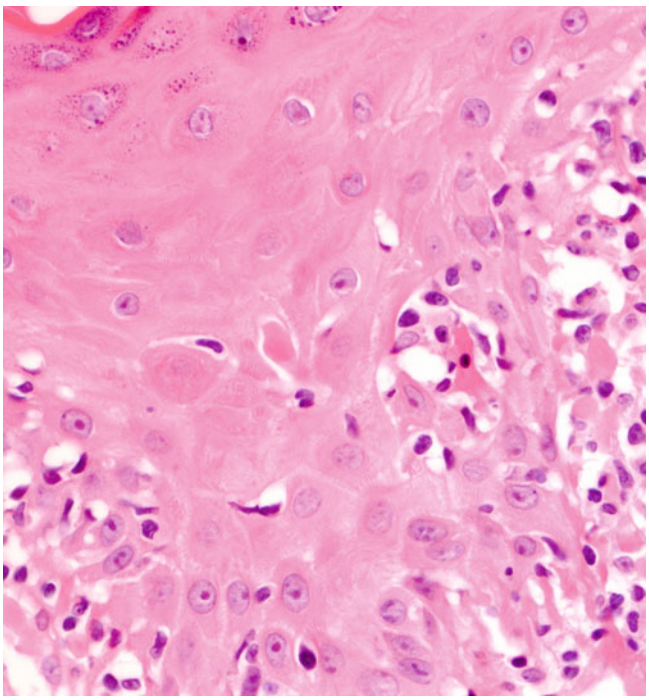

Fig. 15.2 Colloid bodies in lichen planus. The eosinophilic globules are extracellular and may be present in the epidermis or the superficial dermis, also known as Civatte bodies

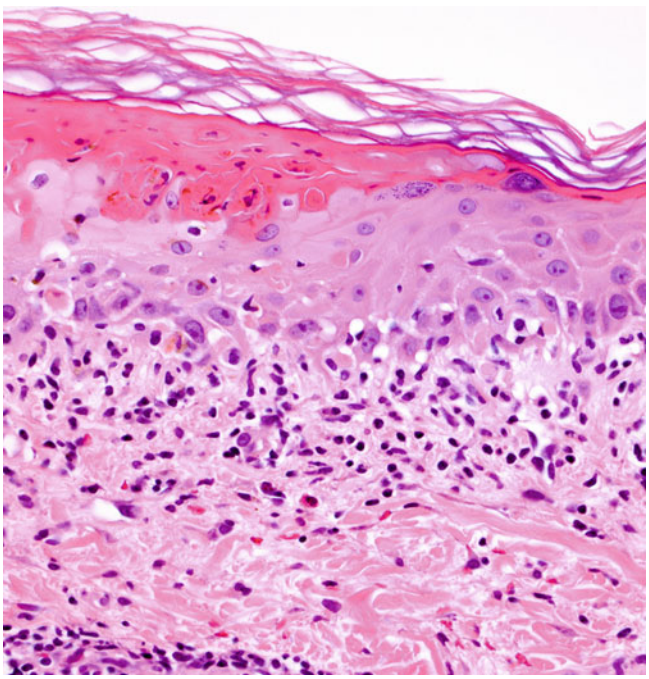

Fig. 15.4 Fixed drug reaction. There is extensive epidermal dyskeratosis and interface dermatitis that may have a dense lichenoid appearance

16 Psoriasiform Dermatitis

Psoriasiform dermatitis is characterized by a hyperplasia of the epidermis (acanthosis) that is regular, the rete are of roughly equal size to one another and the base of the epidermis is relatively flat. The rete ridges are often attenuated at the tips of the papillary dermis.

Table 16.1 Differential diagnosis of psoriasiform dermatitis

	Psoriasis	Lichen simplex chronicus/ prurigo nodularis	Pityriasis rubra pilaris
Parakeratosis pattern	Confluent	Focal	Checkerboard, "Notes on a scale" (alternating ortho- and parakeratosis); Perifollicular
Hypogranulosis	+	–	–/+
Hypergranulosis	–	+	+/–
Superficial perivascular lymphocytes	+	+	+
Papillary dermal fibrosis	–/+	+	–/+
Dermal eosinophils	–	+	–
Other	Intracorneal neutrophilic microabscesses	Nerve hyperplasia	Dilated follicles with perifollicular parakeratosis

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DOI 10.1007/978-1-4471-4471-7_16, © Springer-Verlag London 2013

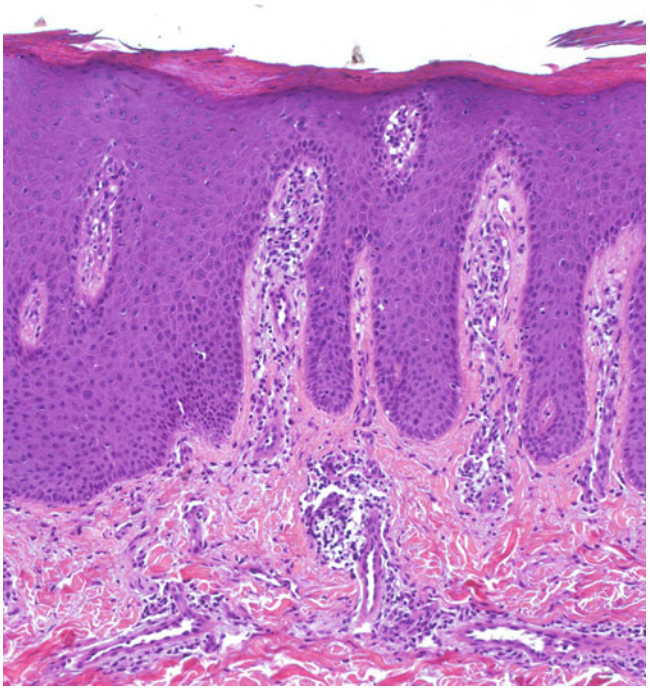

Fig. 16.1 Psoriasis. There is regular epidermal hyperplasia with attenuation of the epidermis at the tips of the papillary dermal pegs

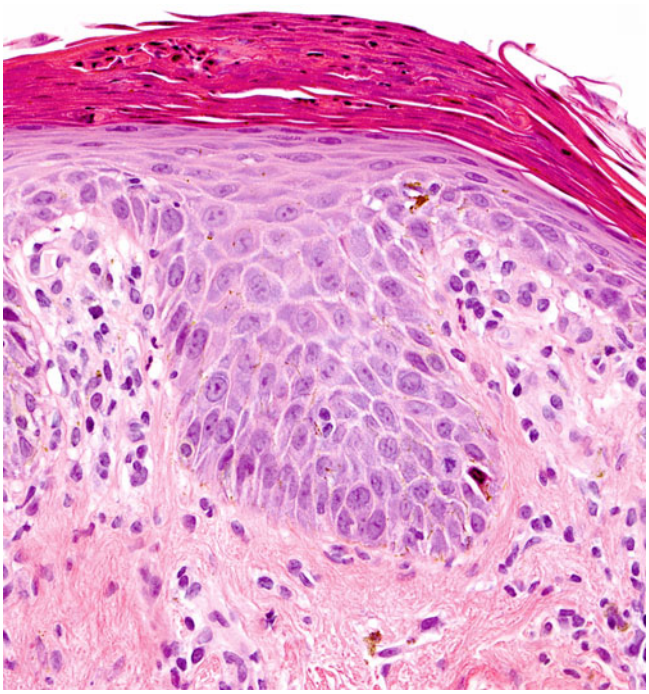

Fig. 16.3 Psoriasis. Neutrophils are observed in the epidermis and as microabscesses in the stratum corneum

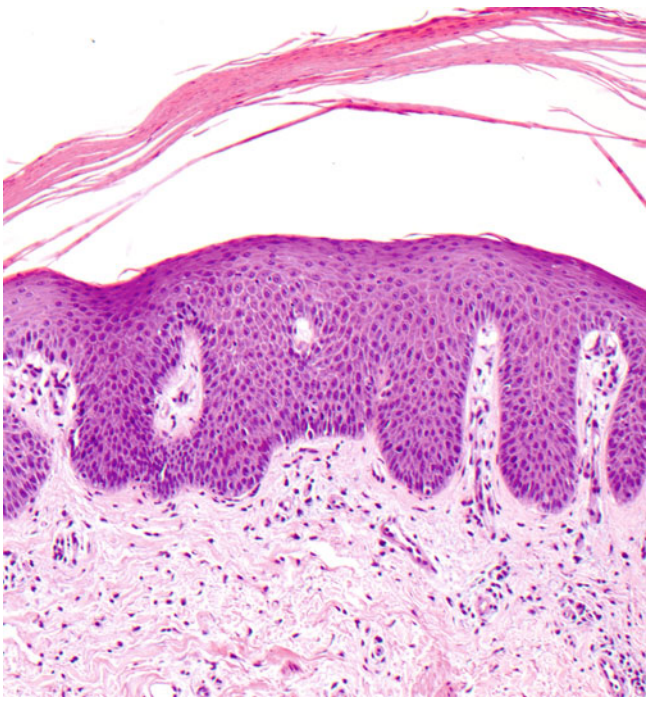

Fig. 16.2 Psoriasis. Diffuse parakeratosis with loss of the underlying epidermal granular cell layer is observed

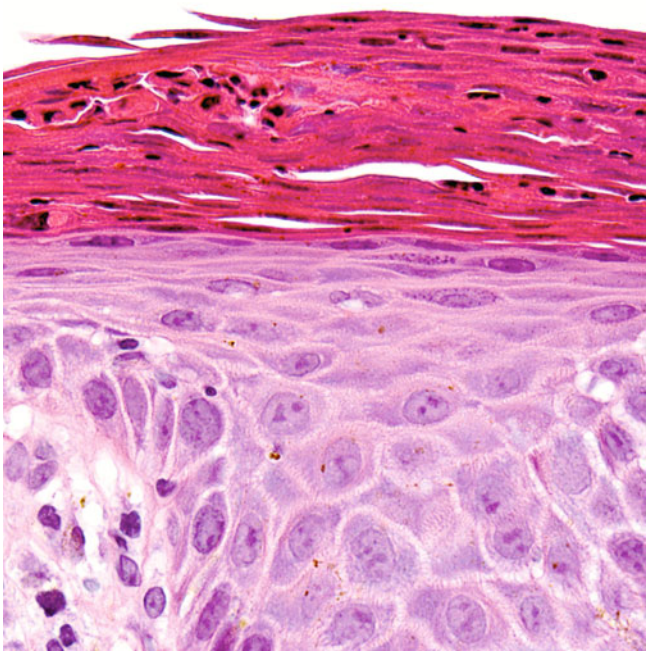

Fig. 16.4 Monro microabscesses. These collections of neutrophils in the stratum corneum are characteristic of psoriasis

17 Perforating Dermatoses

Reactive Perforating Collagenosis
- Transepidermal elimination of deeply basophilic degenerate collagen fibers
- Dermal chronic inflammatory infiltrate
- Trichrome positive

Elastosis Perforans Serpiginosa
- Epidermal intoeing with intraepidermal channel and microabscesses
- "Claw and ball"-like transepidermal elimination of elastotic material, keratin, and basophilic inflammatory debris
- Elastic stain reveals thickened dermal elastic fibers abutting and exiting the epidermis
- Variable granulomatous infiltrate

Perforating Folliculitis
- Hair follicle rupture with granulomatous dermal reaction
- Channel containing basophilic debris in follicle epithelium

Kyrle's Disease* (Hyperkeratosis Follicularis et Parafollicularis in Cutem Penetrans)
- Associated with chronic renal insufficiency and uremia
- Hyperkeratosis, acanthosis
- Epidermal invaginations with keratin and neutrophil-rich debris-laden plug
- Transepidermal elimination of keratotic material
- Absence of hair follicle or shaft fragments
- Variable dermal lymphohistiocytic inflammatory infiltrate

*Historically, Kyrle's disease occurred in renal disease and displayed one or more of these patterns, because of significant overlap – there are no longer considered to be distinct entities.

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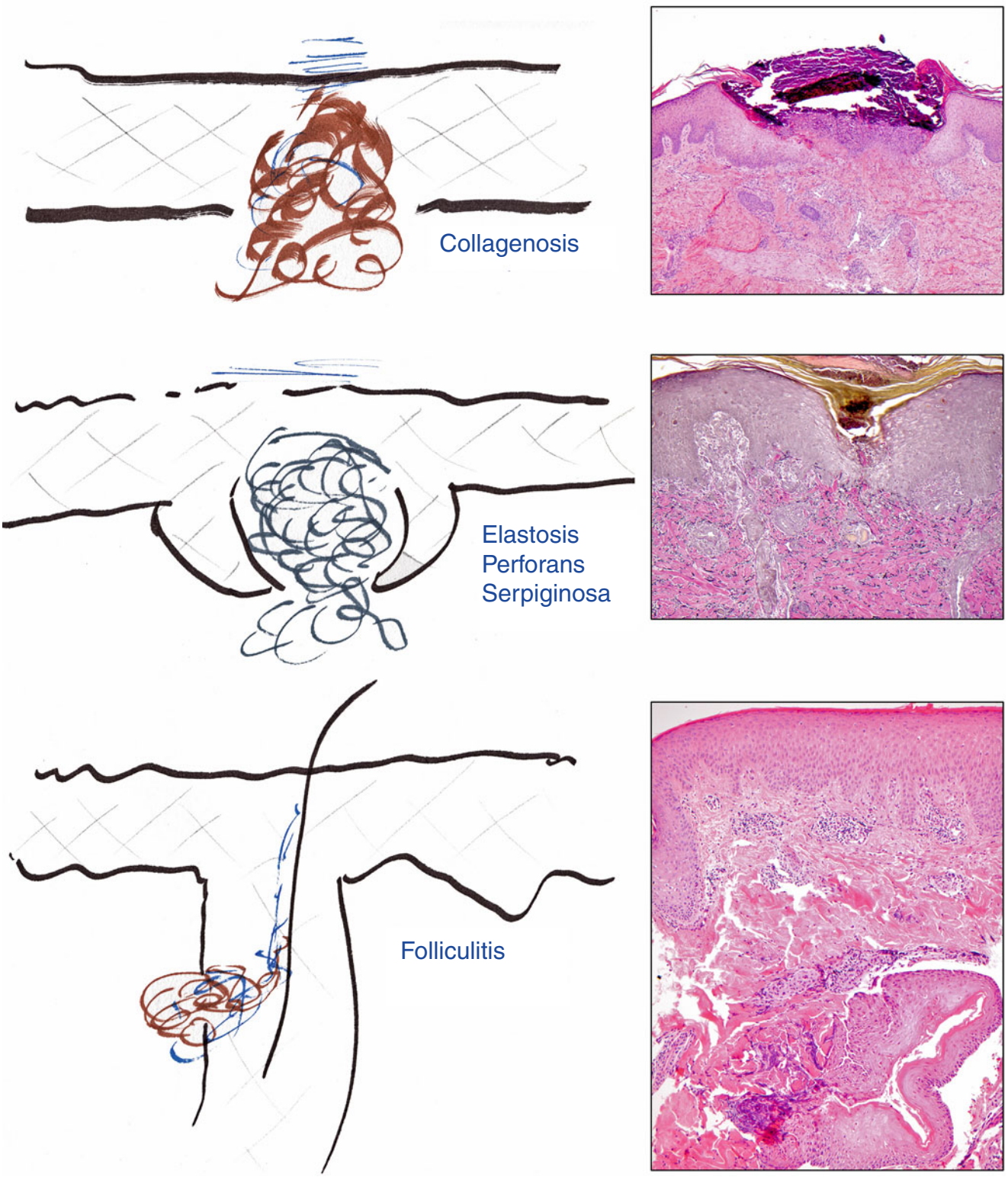

Fig. 17.1 The three patterns of perforating dermatoses include the extrusion of collagen through the epidermis, the entrapment of elastic fibers within the epidermis and the perforation of dermal connective tissue elements into the hair follicle epithelium

18 Non-infectious Palisading Granulomatous Dermatitis

There are many causes of granulomatous dermatitis, many are caused by infectious organisms. This chapter focuses on the three distinct types of non-infectious palisading dermatitis. Sarcoidosis is included as an example of non-infectious granulomatous dermatitis that is rarely palisading.

Table 18.1 Differential diagnosis of non-infectious palisading granulomatous dermatitis

	Hypocellular central zone	Multinucleate giant cells	Neutrophilic debris	Dermal location
Granuloma annulare (GA)	Mucin (hyaluronic acid)	+/–	–/+ (+ when drug associated)	S/M
Necrobiosis Lipoidica (Diabeticorum) (NLD)	Sclerotic collagen	+ +	–	S/D
Rheumatoid nodule	Zonal fibrin	–	+ +	D/F
Sarcoid	None	++	–	S/M/D

S superficial, *M* mid-dermal, *D* deep dermal, *F* fat

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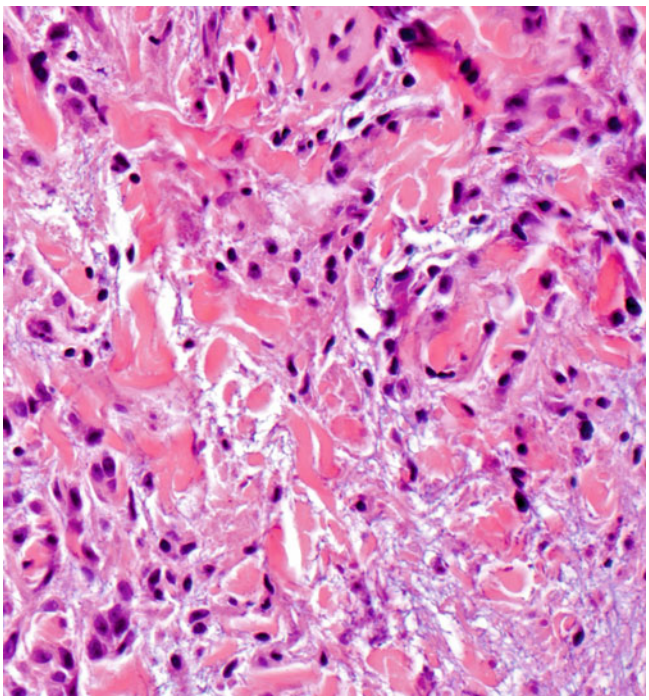

Fig. 18.1 Granuloma annulare. Lymphocytes and histiocytes palisade around a hypocellular dermis with abundant basophilic mucin

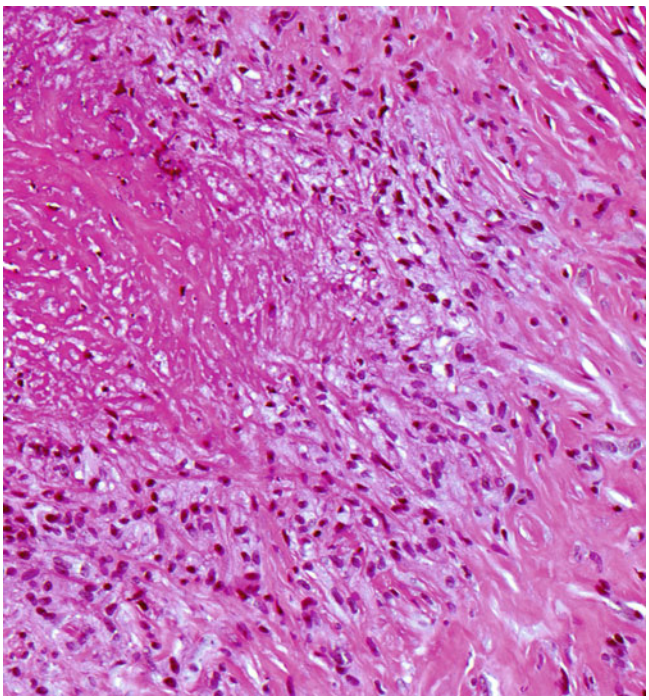

Fig. 18.3 Rheumatoid nodule. There is fibrinoid dermal necrosis with palisading zones of fibroblasts and inflammatory cells

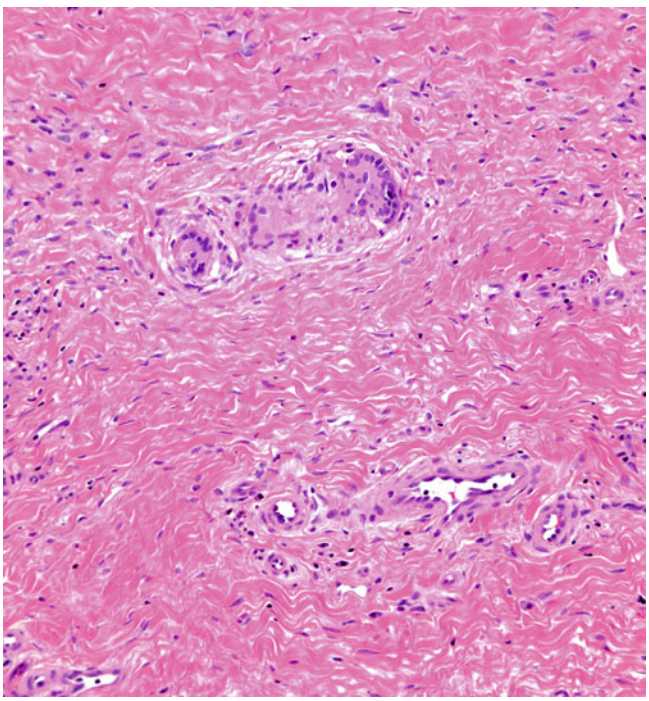

Fig. 18.2 Necrobiosis lipoidica. Zones of eosinophilic sclerotic collagen are observed with multinucleate giant cells

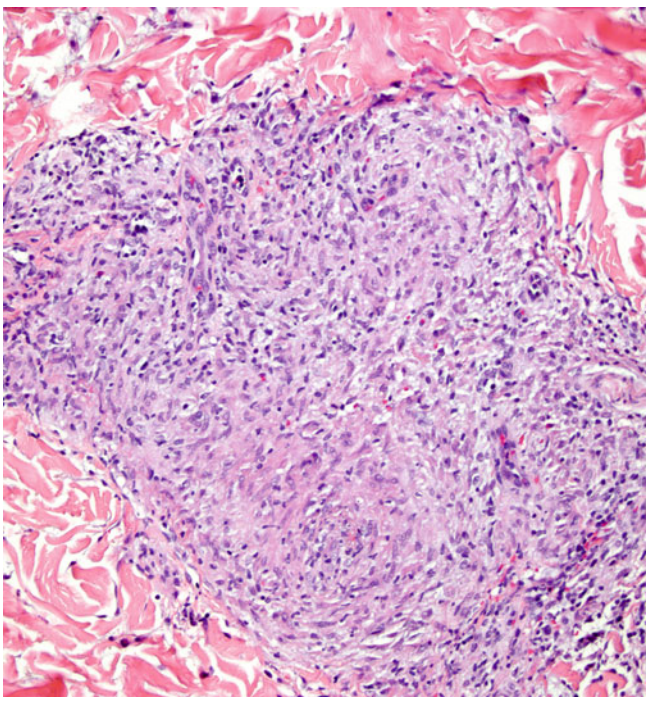

Fig. 18.4 Sarcoidosis. Compact aggregates of epithelioid histiocytes may have a few lymphocytes at the periphery

19 The Seven L's of Superficial and Deep Perivascular Mononuclear/Lymphoid Infiltrates

The mnemonic 7 L's has been used to prompt the histological differential diagnosis of a superficial and deep perivascular mononuclear and lymphoid infiltrate. The presence of prominent superficial dermal edema is seen in polymorphous light eruption; whereas an infiltrate that involves the adnexal structures, particularly the eccrine units supports a diagnosis of lupus. The presence of eosinophils and reactive lymphoid follicles may be seen in cutaneous lymphoid hyperplasia, particularly if the etiology is a persistent reaction to arthropod bite.

Table 19.1 The differential diagnosis of superficial and deep perivascular lymphoid infiltrates, epidermal and dermal changes

	Epidermal changes	Dermis	Periadnexal inflammation	Lymphoid follicles	Eosinophils
Lupus	Atrophy, interface	Mucin	+	–	–
Lymphocytic infiltrate of Jessner	Atrophy, interface	Mucin	+	–	–
Polymorphous **l**ight eruption (PMLE)	Acanthosis, dyskeratosis	Edema	–	–	–
Lyme- Gyrate Borrelia	None or puncture site	–	–	–	–/+
Lues (syphillis)	Hyperplasia	Plasma cells	–/+	–	–
Leukemia (rare) (CLL)	–	–	–	–	–
Lymphocytoma (CLH)	–	–	–	–/+	–/+

CLL chronic lymphocytic leukemia, *CLH* cutaneous lymphoid hyperplasia

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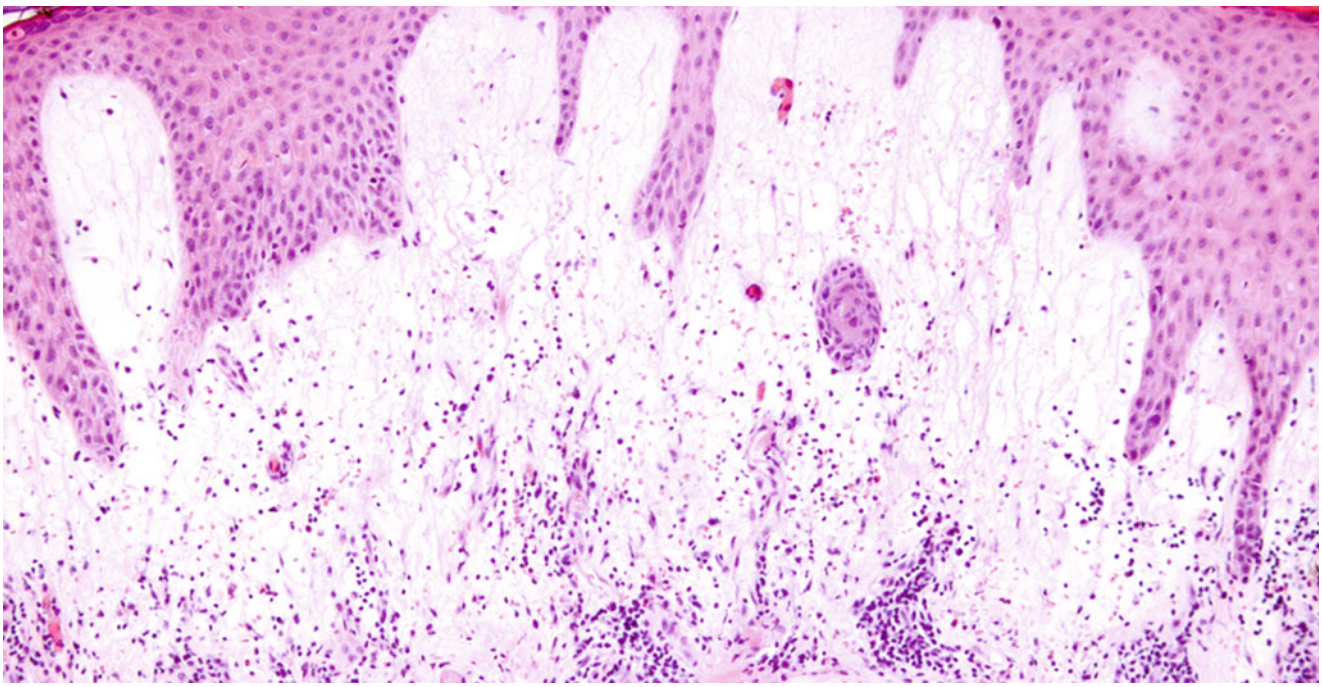

Fig. 19.1 Polymorphous light eruption. There is prominent papillary dermal edema and epidermal acanthosis

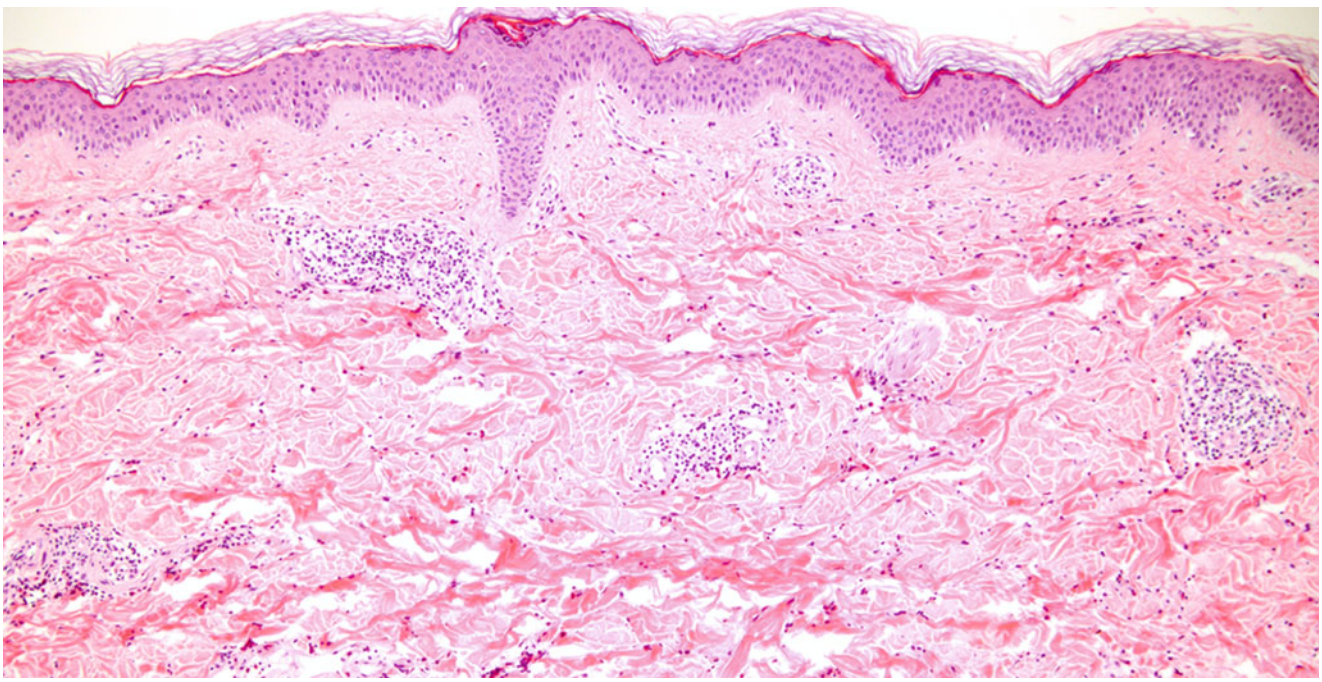

Fig. 19.2 Erythema chronicum migrans (Lyme disease, gyrate erythema). There are minimal epidermal changes. A perivascular mononuclear infiltrate with scattered eosinophils is present

20 Vasculitis and Vasculopathy

Vasculitis is characterized by damage to the vascular endothelium and necrosis of the vessel wall; vasculopathy demonstrates intravascular thrombosis often without significant inflammation. Leukocytoclastic vasculitis is characterized by the presence of neutrophils, nuclear dust (leukocytoclasia) and fibrinoid necrosis of vessel walls.

Table 20.1 Characteristics of vasculitis and vasculopathy

	Mixed cryoglobulinemia, Protein C deficiency, DIC, Sepsis, Lupus anticoagulant	Purpura fulminans, Monoclonal cryoglobulinemia, Coumadin (Warfarin) necrosis	Lymphocytic vasculitis, Drug-induced	Bechet's disease, Perniosis
Intraluminal vascular thrombi	–/+	+	+/–	–/+
Vascular wall necrosis	+	–/+	+/–	+/–
Neutrophils, leukocytoclasia	+	–	–	–/+
Eosinophils	–	–	+/–	–/+
Lymphocytes	–	–	+	+

DIC disseminated intravascular coagulopathy

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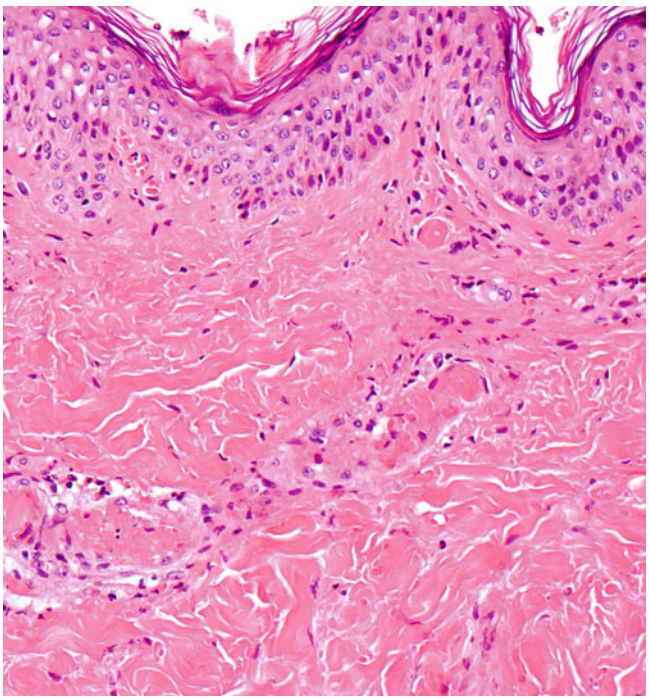

Fig. 20.1 Purpura fulminans. The superficial dermal vessels are occluded by microthrombi, there is minimal inflammation

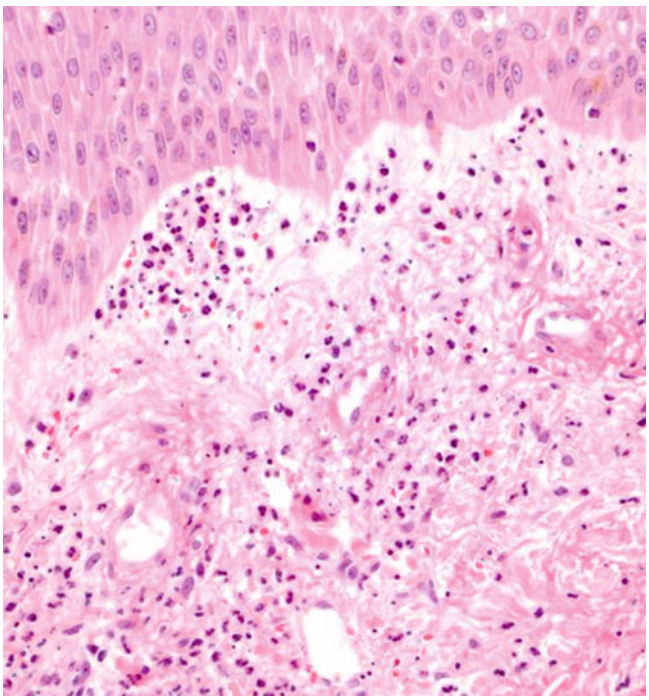

Fig. 20.3 Henoch - Schoenlein purpura (HSP). There is a leukocytoclastic vasculitis, characterized by the presence of nuclear debris and fibrinoid necrosis of the vessel wall

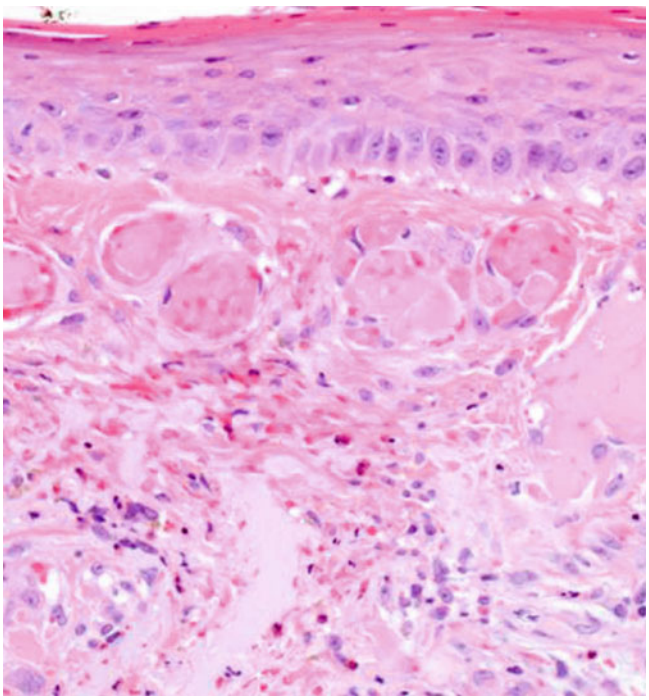

Fig. 20.2 Monoclonal cryoglobulinemia. The superficial dermal vessels are occluded by homogeneous thrombi that may be clefted, there is minimal inflammatory infiltrate

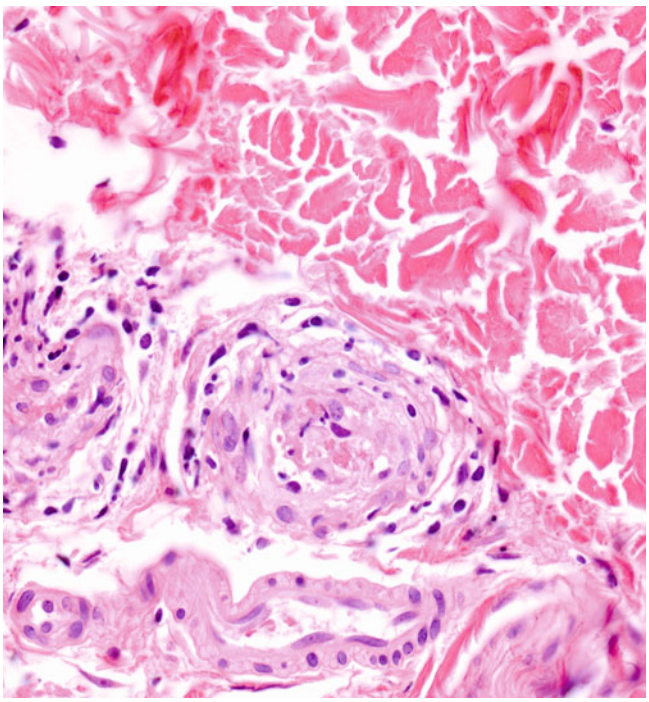

Fig. 20.4 Perniosis. There is a lymphocytic vasculitis without significant neutrophilic infiltrate or intraluminal thrombi

Part IV

Nodular Lymphoid Proliferations

21 Lymphoid Antigens

Immunohistochemistry is a valuable tool in the analysis of lymphocytic infiltrates. Specific antibody reagents have been developed to detect cellular proteins that characterize cells as to lineage and differentiation state.

Table 21.1 Lymphoid antigens commonly detected in the immunohistochemical analysis of cutaneous lymphoid infiltrates

	Normal cells	Tumors	Uses
CD2	Most T cells	CTCL	May be lost in some CTCL
CD3	T cells	CTCL	Best Pan-T cell marker
CD4	T Helper cells	Most MF	Normal CD4:CD8 ≈ 2:1
CD5	T cells, some B cells	CLL, some pcMZL	Occasional loss in CTCL, co-expression with CD43 and CD20 = CLL or pcMZL
CD8	T Suppressor cells	Aggressive epidermotropic $CD8^+$ CTCL; Indolent CD8+ lymphoid proliferation of the ear	Normal CD4:CD8 ≈ 2:1
CD10	Follicle center cells	FCL, some MZL	Positive in FCL
CD20	B cells	B cell lymphomas	Best Pan-B cell marker
CD21	Follicular dendritic cells	Dendritic cell sarcoma	Defines lymphoid follicles in $CD21^+$ FDC meshworks
CD23	Follicular dendritic cells, some B cells	CLL	
CD25	T cells, Mast cells	CTCL	IL2R (CD25) may be drug target in CTCL
CD30	Activated T cells	$CD30^+$ large cells in LPD	Confirms $CD30^+$ LPD
BCL2	All lymphocytes EXCEPT follicle center B cells	Strongly positive in DLBCL; Absent in most pcFCL	pcFCL and reactive lymphoid follicles negative
BCL6	Follicle center B cells	pcFCL, DLBCL (dim)	Evaluation of B cell lymphomas; strongly positive in FCL
βF1	Alpha/Beta T cells	Alpha/Beta tumors usually positive; Gamma/Delta tumors negative	Confirms Alpha/Beta tumors if positive

pcDLBCL primary cutaneous diffuse large B-cell lymphoma, *pcMZL* extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, primary cutaneous marginal zone lymphoma, *pcFCL* primary cutaneous follicle center lymphoma, *CTCL* cutaneous T-cell lymphoma, *CLL* chronic lymphocytic leukemia/lymphoma, *LPD* lymphoproliferative disease, *MF* mycosis fungoides, *FDC* follicular dendritic cell

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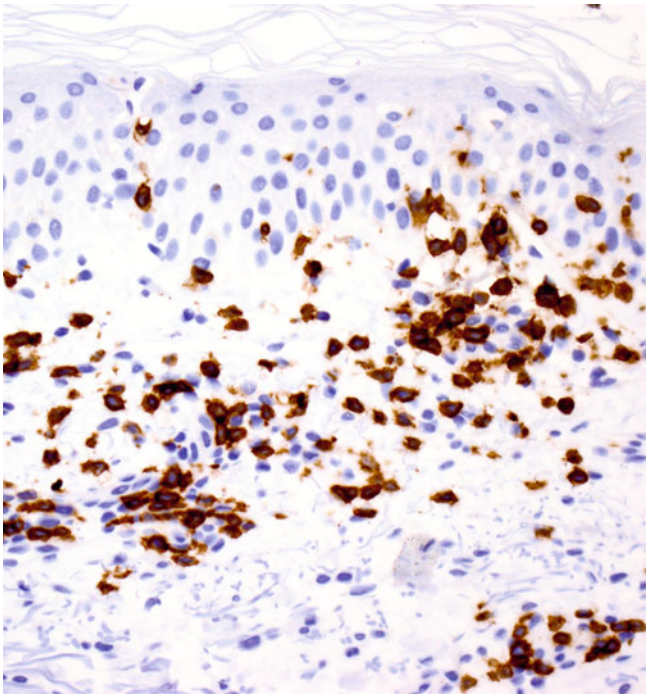

Fig. 21.1 CD8+ T cells in cutaneous hypersensitivity reaction

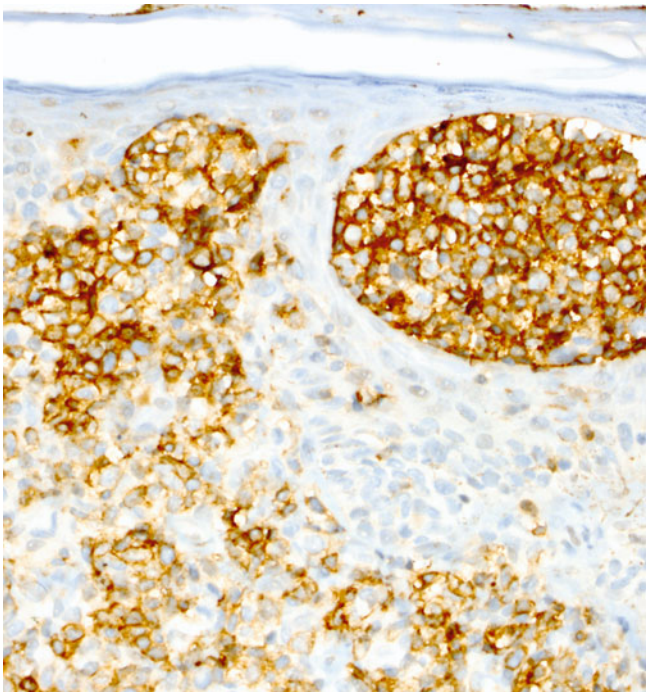

Fig. 21.3 CD25+ T lymphocytes in mycosis fungoides

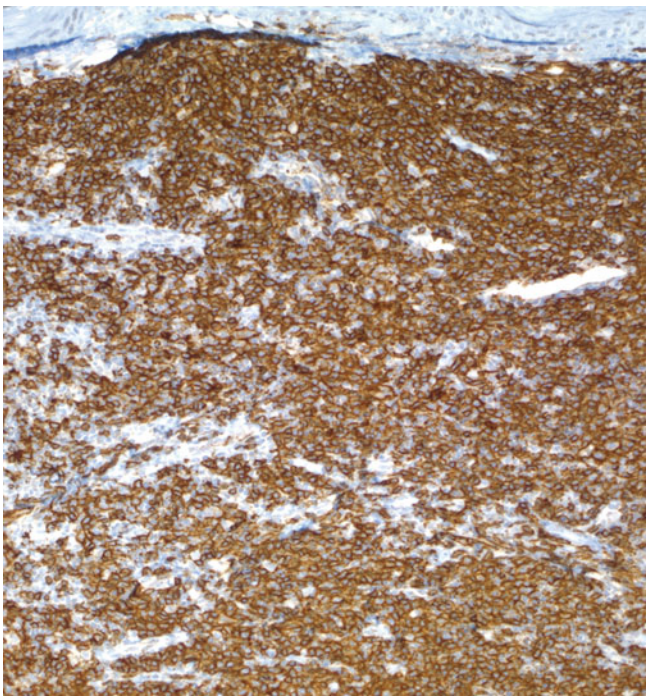

Fig. 21.2 CD20+ B cells in primary cutaneous follicle center lymphoma

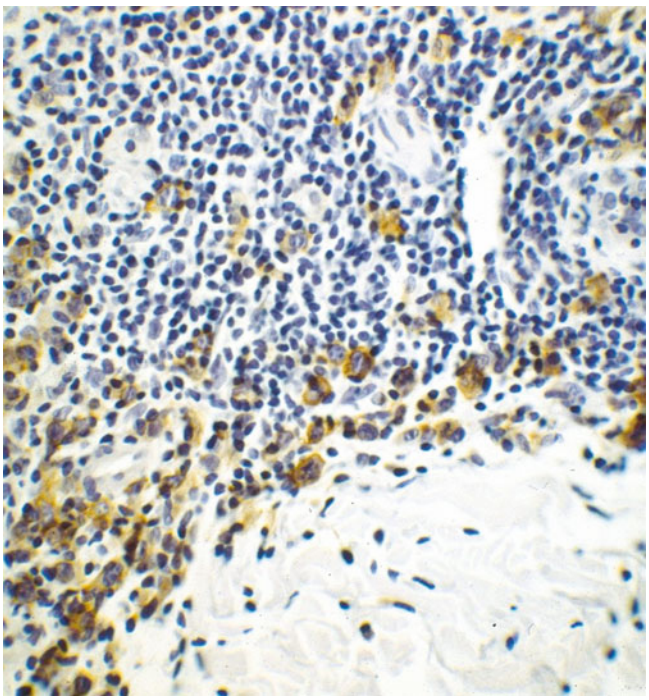

Fig. 21.4 CD30+ large cells in lymphomatoid papulosis

22 Lymphoid Follicles in Hyperplasia and Neoplasia

Cutaneous lymphoid follicles may be observed in cutaneous lymphoid hyperplasia and are characteristically present in the low grade B cell lymphomas (extranodal B-cell lymphoma of mucosa associated lymphoid tissue type/marginal zone lymphoma and follicle center lymphoma).

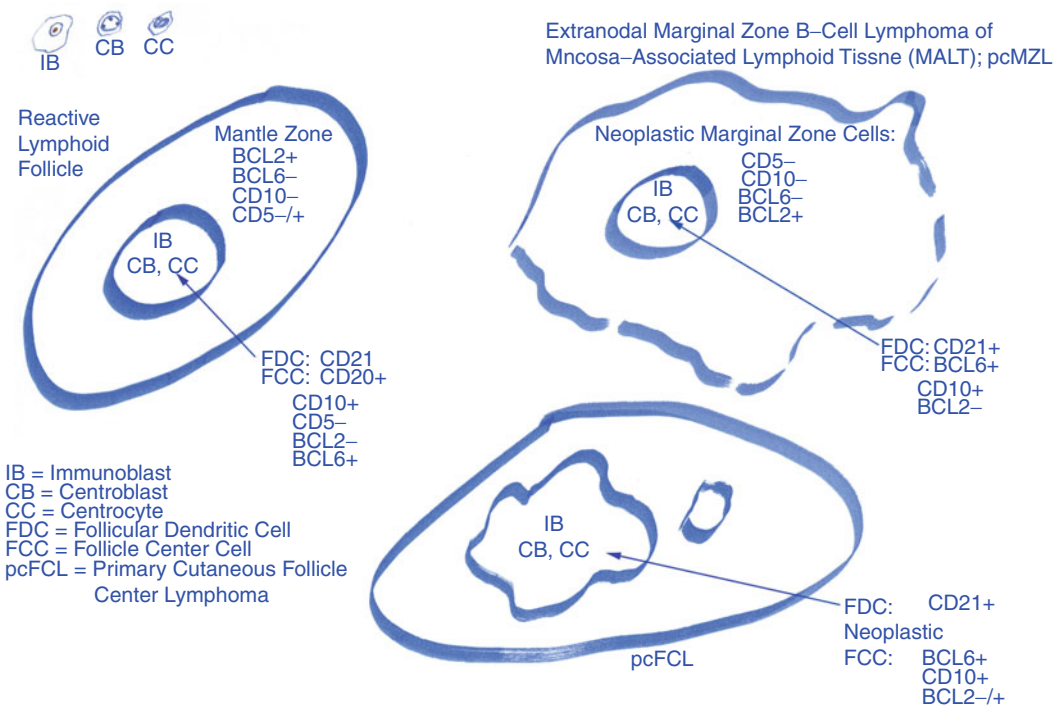

Fig. 22.1 Lymphoid follicle structure in lymphoid hyperplasia and B cell lymphoma. Reactive lymphoid follicles usually have round or oval follicle centers with compact central collections of BCL6+, BCL2– B cells. The lymphoid follicles of marginal zone lymphoma are surrounded by zones of plasma cells and or sheets of marginal zone B cells. Occasionally the neoplastic BCL6–, BCL2+ marginal zone B cells will infiltrate or colonize the lymphoid follicle, splaying the BCL6+, BCL2– follicle center cells. The lymphoid follicles in follicle center lymphoma may be irregularly shaped as the neoplastic BCL6+ B cells out grow the normal follicular architecture

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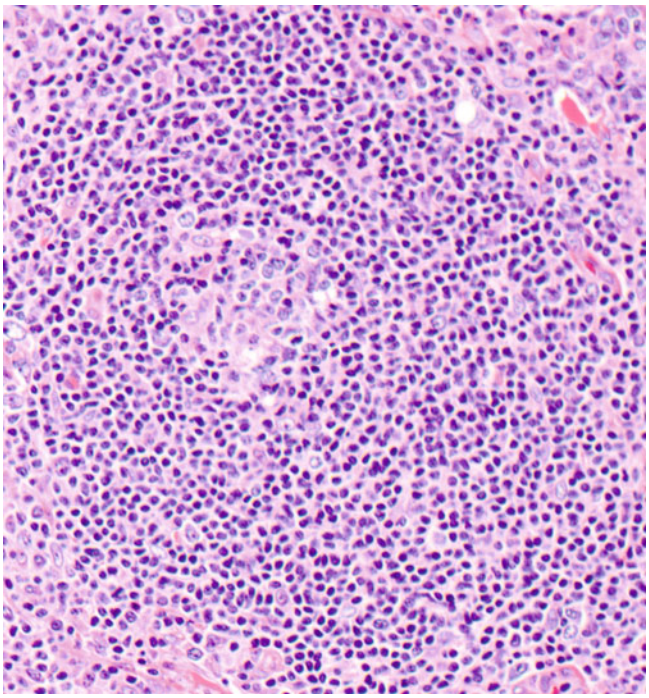

Fig. 22.2 Reactive lymphoid follicle, hematoxylin and eosin (H&E) stain

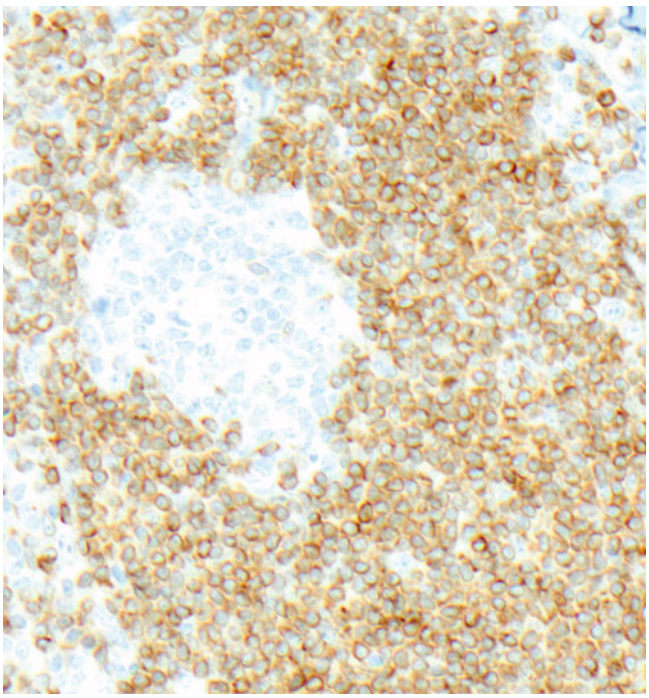

Fig. 22.3 Reactive lymphoid follicle, BCL2 stain highlights all lymphocytes except the follicle center B cells

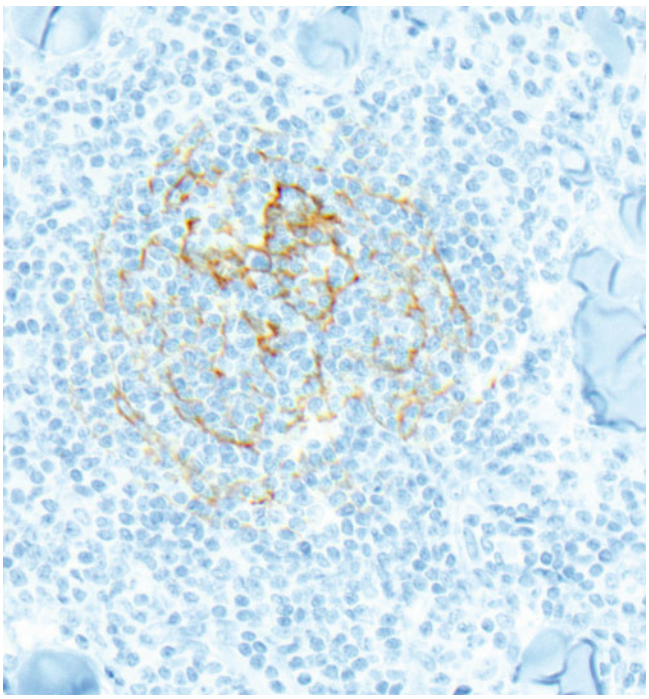

Fig. 22.4 Reactive lymphoid follicle, CD21 stain highlights the follicular dendritic cell meshwork

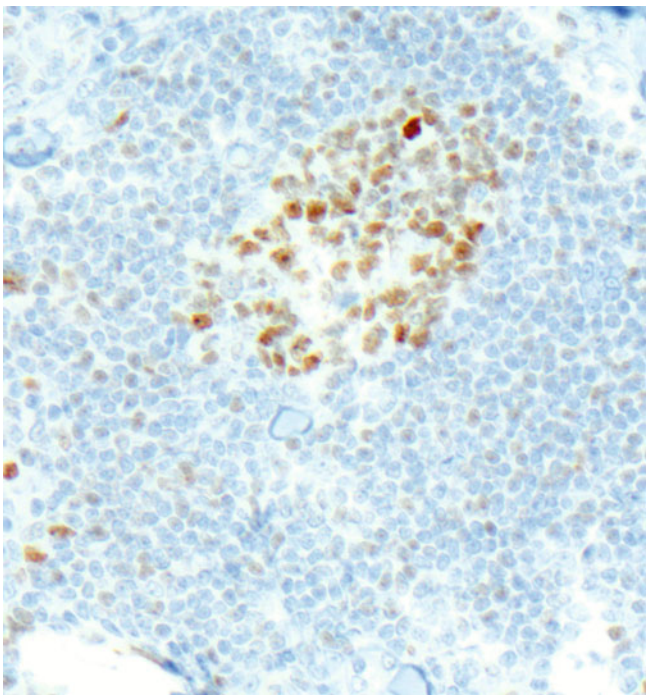

Fig. 22.5 Reactive lymphoid follicle, BCL6 stain highlights the follicle center B cells

Part V

Epithelial Proliferations

23 Immunohistochemistry of Epithelial Proliferations

Epithelial tumors that derive from the epidermis and adnexal structures may share keratinocytic cytology and epithelial growth patterns. Immunohistochemical stains using antibodies to detect specific proteins that are associated with the tumor cell origin are helpful in diagnosis.

Table 23.1 Immunohistochemical stains in the differential diagnosis of tumors with pilar, squamous, and adnexal origins

	Tricho epithelioma	Basal cell carcinoma	Squamous cell carcinoma	Sebaceous carcinoma	Eccrine carcinoma	Microcystic adnexal carcinoma
BCL-2	+ (Peripheral cells only)	+ (Diffuse)	– (25 % focally +)			+ (Focal)
BerEP4	+ (60 %)	+ (Diffuse)	– (+ in metastases)			–
CK5/6	+	+	+	+	+	
CK7	–	– (60 %)	–	+	+	–
CK15	+ (Focal)	–	–	+		+
CK17		+ (Diffuse)	– (Patchy or Rim +)		+ (Central)	
CK20	+ (Focal)	–	–	–	–	
CK903	+	+	+		+	+
CAM 5.2		+ (Rim)	–	+	–	
CD10	+ (Stromal cells)	+ (60 %)	–			
CEA	–		–	– (+ in normal glands)	+	+ (Inner cuticle)
EMA	±	–	+	+	+	±
Ki-67	<1 %	20–40 %	25–35 %	40–50 %		5 %
P53	–	+		–	+	–
SMA		±	–		+	

Blank spaces indicate the marker distribution is not well documented in this tumor

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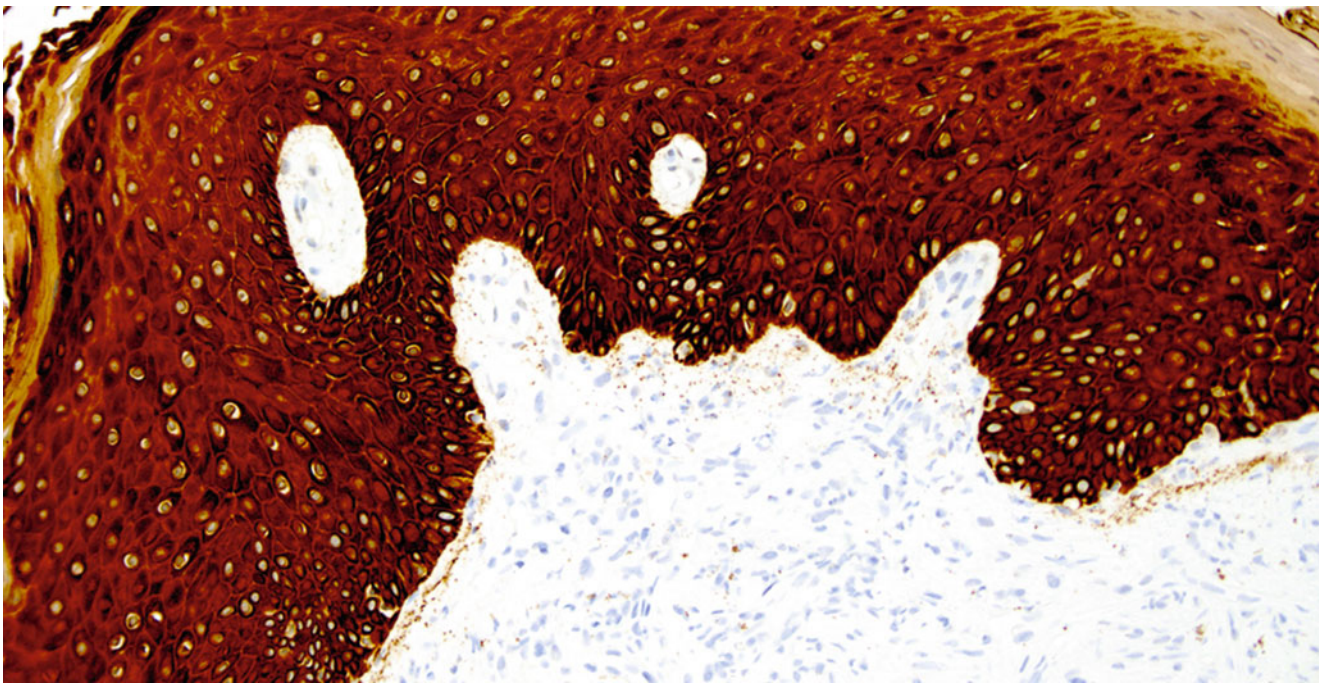

Fig. 23.1 Cytokeratins 5/6 (CK5/6) in the epidermis. There is diffuse staining of the epidermal keratinocytes

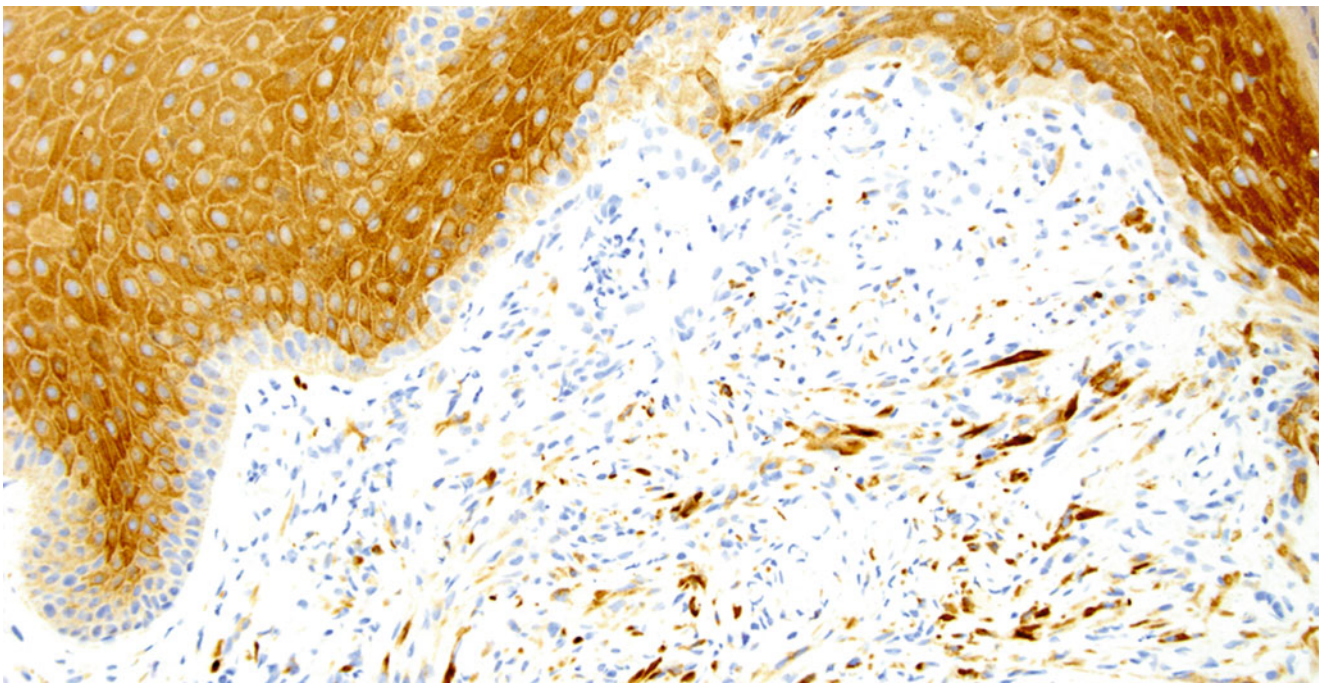

Fig. 23.2 Cytokeratins AE1.3/CAM5.2 in epidermis and spindled squamous cell carcinoma. CK AE1.3/CAM5.2 stains the epidermis less uniformly than CK5/6. CK AE1.3/CAM5.2 is positive in the underlying invasive spindled cells of squamous cell carcinoma

24 Actinic Keratosis

The acronym "SPAIN" corresponds to the histological criteria:

Solar elastosis
Parakeratosis
Atypical basal layer keratinocytes
Inflammatory infiltrate
No full thickness keratinocyte atypia (if there is full thickness keratinocytic atypia consider squamous cell carcinoma in situ)

SPAK (Spreading pigmented AK):

- Also uses SPAIN mnemonic
- However, there is no parakeratosis
  - Instead "P" in SPAK = pigmentation of basal layer keratinocytes
- The clinical differential diagnosis includes lentigo or lentigo maligna

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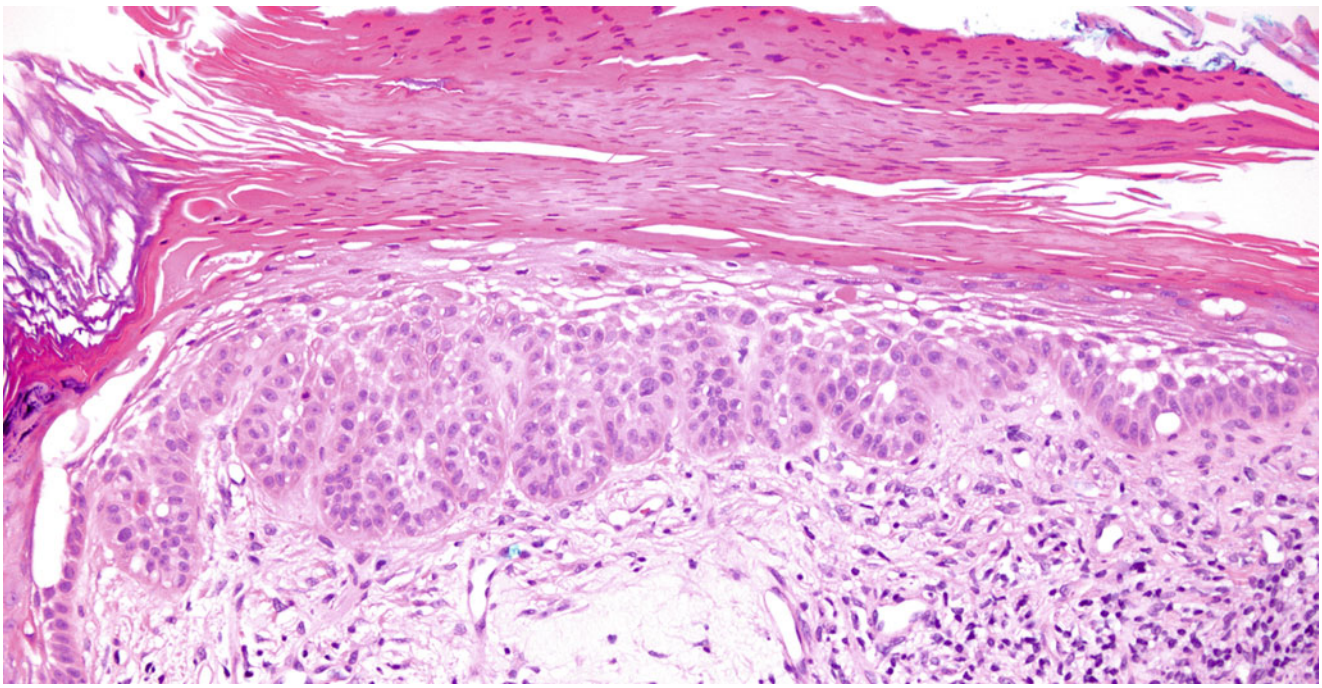

Fig. 24.1 Actinic keratosis. There is marked parakeratosis, keratinocytic atypia, inflammation and solar elastosis

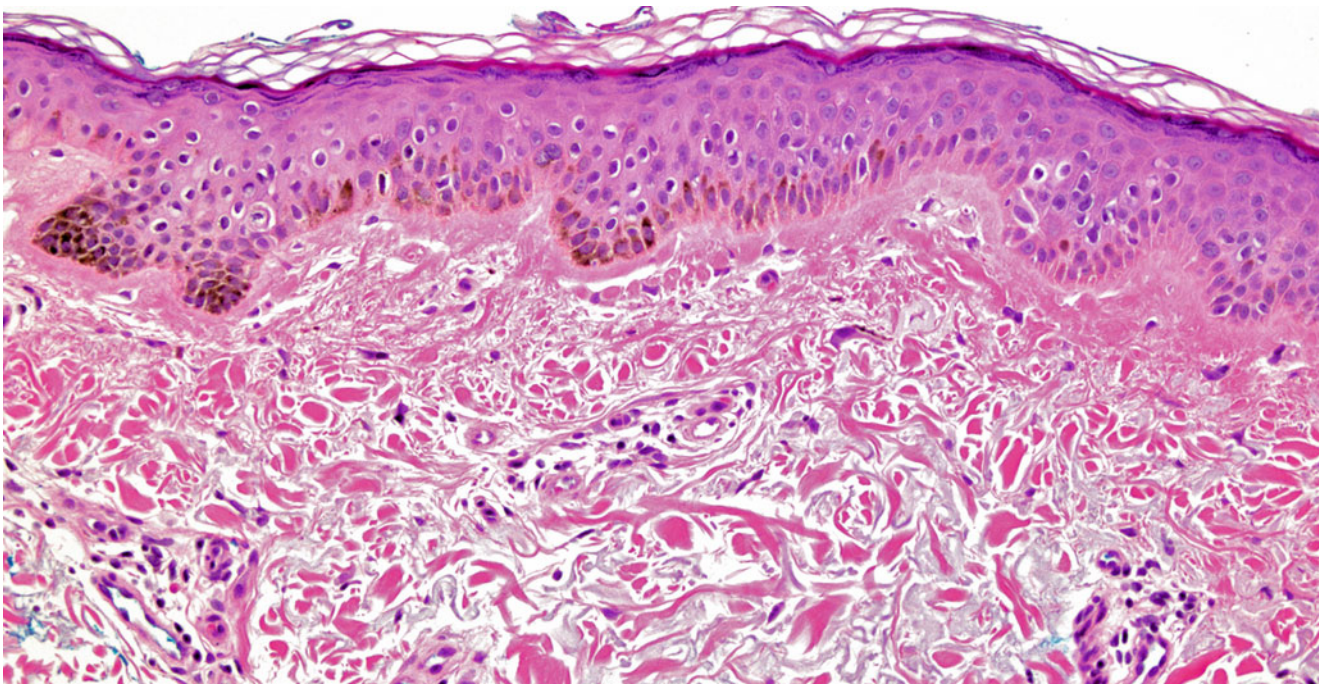

Fig. 24.2 Spreading pigmented actinic keratosis. Basal layer keratinocytic hyperpigmentation is present with keratinocytic atypia and solar elastosis

25 Progression of Actinic Keratosis to Squamous Cell Carcinoma

The evolution of sun-damaged skin to invasive squamous cell carcinoma may occur along two main pathways. In both cases, the basal layer keratinocytes are transformed, appear cytologically atypical and proliferate at a higher rate than normal.

1. Most common path: When transformed basal keratinocytes have the capacity to breach the basement membrane zone, they invade the dermis, usually as well-differentiated squamous cell carcinoma.
2. Less common path: When transformed basal keratinocytes do not have the capacity to breach the basement membrane zone, they fill all layers of the epidermis and replace the hair follicle epithelium, progressing to squamous cell carcinoma in situ. After the development of carcinoma in situ, if these tumor cells develop the capacity to breach the basement membrane zone, they invade the dermis as moderately-differentiated squamous cell carcinoma.

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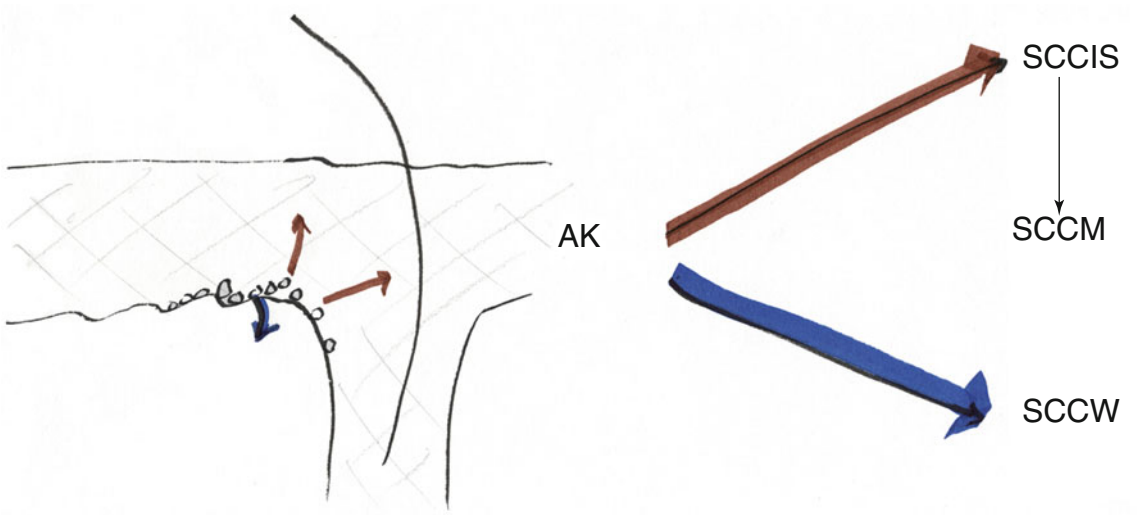

Fig. 25.1 Schematic of squamous cell neoplasia and progression to invasion. Actinic keratosis (*AK*) is the most common direct precursor to well differentiated invasive squamous cell carcinoma (*SCCW*). Squamous cell carcinoma in situ is a more common precursor to moderately differentiated invasive squamous cell carcinoma (*SCCM*)

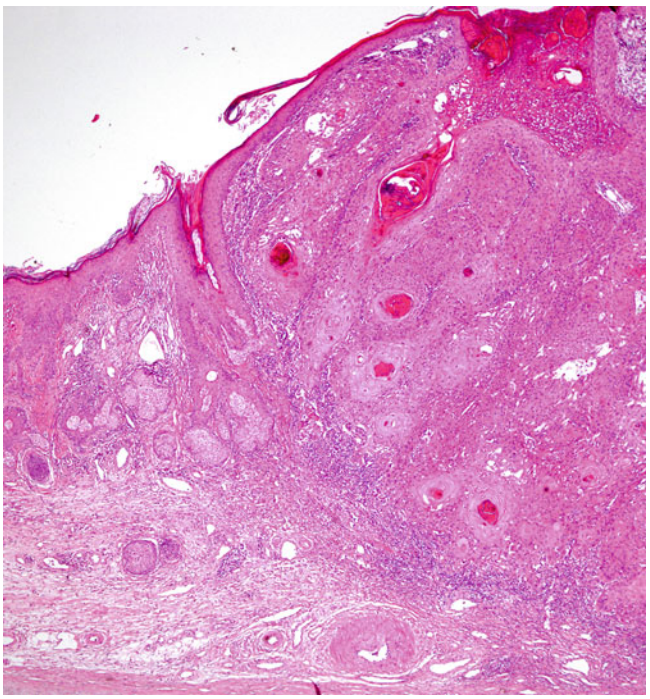

Fig. 25.2 Well differentiated, invasive squamous cell carcinoma (*right*) adjacent to and actinic keratosis (*left*)

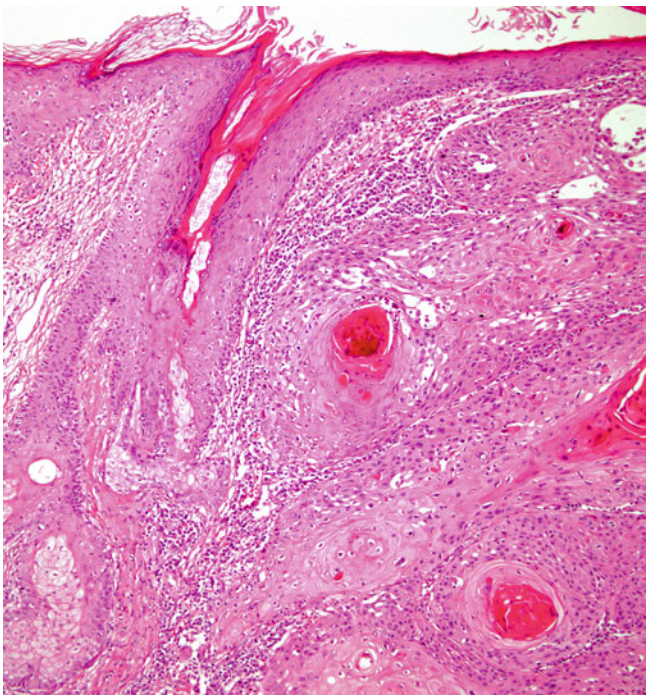

Fig. 25.3 Well differentiated invasive squamous cell carcinoma. There is no in situ precursor, the precursor is actinic keratosis

26 Vulvar Dysplasia and Neoplasia

The differential diagnosis of abnormalities of the vulvar epithelium includes inflammatory diseases and changes caused by infection with human papilloma virus (HPV). Condyloma is the most common discrete lesion caused by HPV. The changes may be subtle and resemble seborrheic keratosis or there may be extensive koilocytosis. There is significant histological overlap between dysplasia associated with inflammatory processes such as lichen planus or lichen sclerosus and HPV associated dysplasia. The separation of these processes into classic/bowenoid and simplex/differentiated vulvar intraepidermal neoplasia (VIN) provides a framework for differential diagnosis.

Condyloma

- Parakeratosis, hyperkeratosis, hypergranulosis, papillomatous acanthosis
- Koilocytosis with coarse keratohyaline granules
- Associated with HPV types 6 and 11
- Mitoses restricted to the lower 1/3 of the epithelium (VIN I)

Classic (Bowenoid) VIN – often HPV-positive

- Parakeratosis, hyperkeratosis
- Epidermal hyperplasia with maturation disarray, dyskeratosis, cell crowding, scant cytoplasm and high N:C ratio (**BLUE**), irregular nuclear membranes
  - Superficial cells may display koilocytic atypia
- Abnormal mitoses at all levels of the epithelium
- May involve follicular epithelium and Bartholin's ducts
- Occasionally progresses to HPV-associated SCC
- p16-positive

Simplex (Differentiated) VIN – usually HPV-negative

- Parakeratosis, hyperkeratosis
- Epidermal hyperplasia with slight to moderate basilar cell atypia
  - Enlarged squamous cells with prominent intercellular bridges, abundant brightly eosinophilic (**PINK**) cytoplasm, vesicular nuclei, and macronucleoli (e.g., well differentiated)
  - Absence of maturation disarray, minimal nuclear pleomorphism
- Large whorls of abnormally differentiated keratinocytes, occasionally with keratin pearls
- Scattered mitotic figures at base of epithelium
- Often associated with a lichenoid inflammatory infiltrate (lichen planus, lichen sclerosus, lichen simplex chronicus)
- Often progresses to HPV-negative SCC
  - Greater potential for progression to invasive SCC than classic VIN
  - Look for small foci of stromal microinvasion into papillary dermis
- p53-positive

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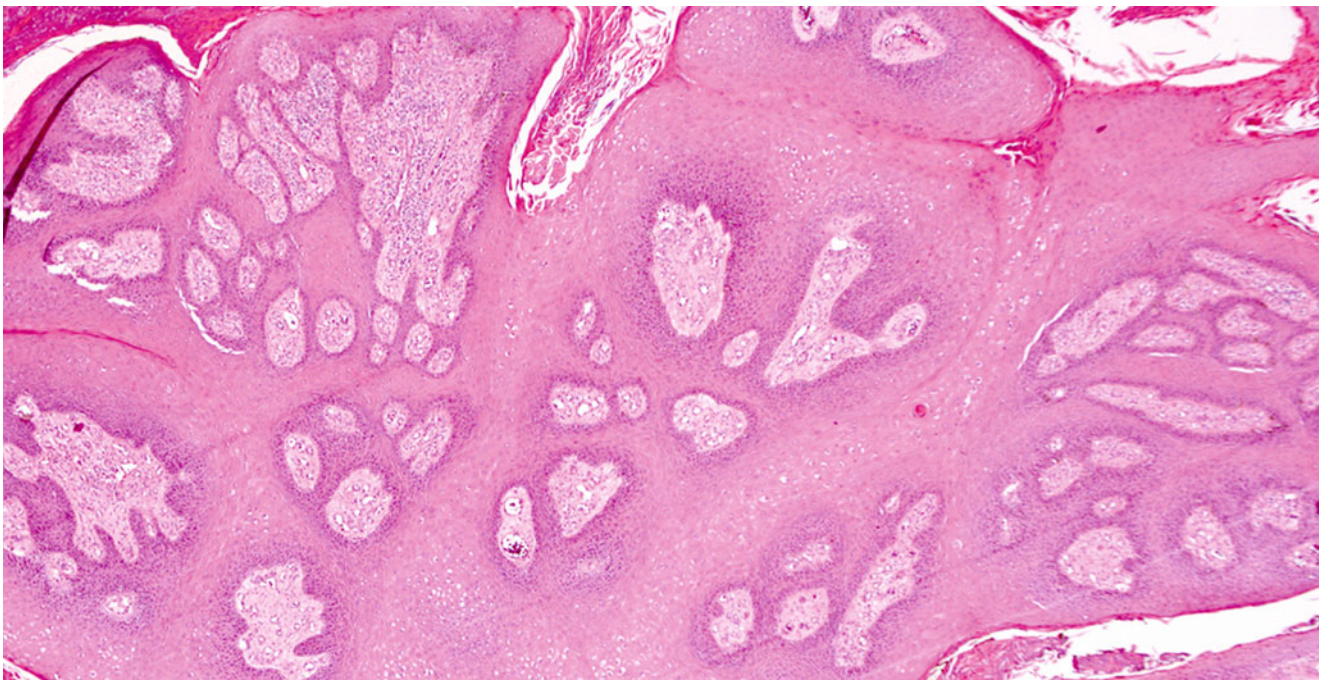

Fig. 26.1 Condyloma Accuminatum. There is a papillomatous acanthosis of the epidermis and hyperkeratosis

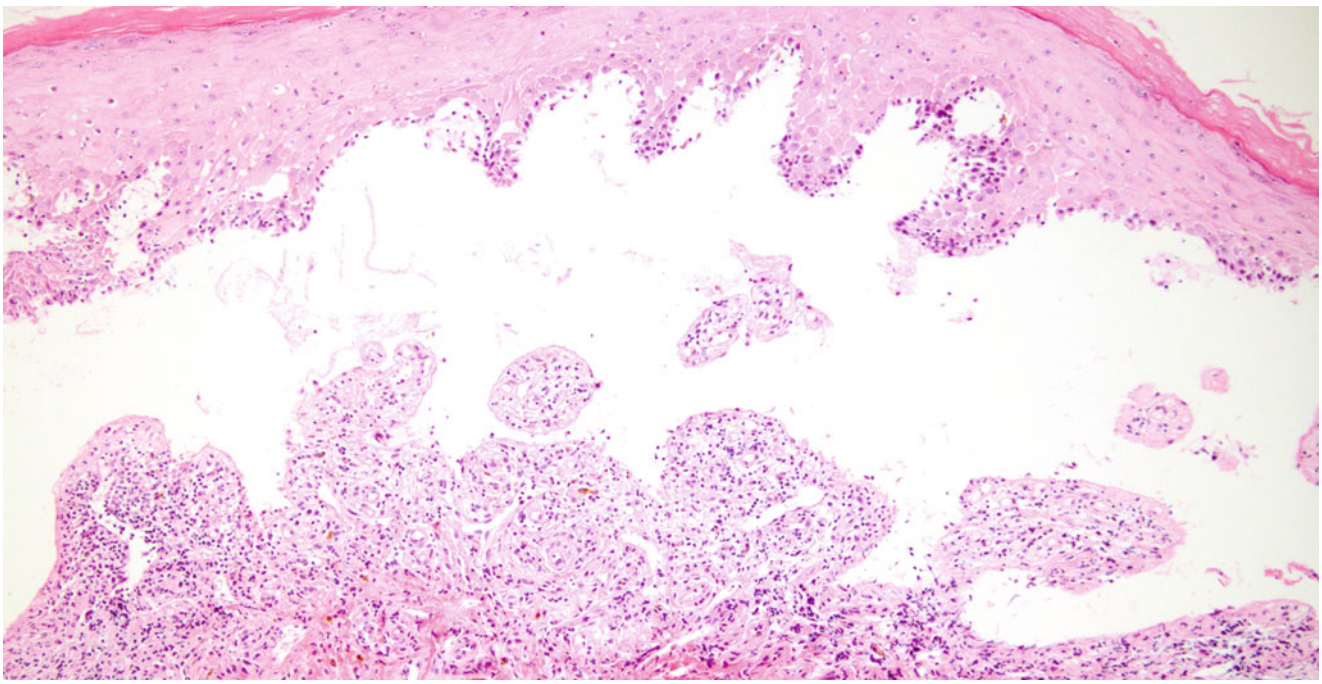

Fig. 26.2 Vulvar Lichen Planus. There is a lichenoid inflammatory infiltrate, squamatization of basal layer keratinocytes and formation of a large subepidermal cleft, the so-called Max-Joseph space

27 Nested Intraepidermal Proliferations

A nested intraepidermal pattern of growth may be observed in several distinctive neoplasms derived from normal epidermal elements: melanocytic tumors from melanocytes, squamous tumors from keratinocytes and adnexal tumors from intraepidermal adnexal elements.

Table 27.1 Differential diagnosis of nested intraepidermal proliferations

	Melanocytic	Keratinocytic	Pagetoid	Atypical mitoses	Dyskeratosis	Other features
Malignant melanoma in situ	+ (Atypical)	–	+	+	–	
Nevus	+	–	–/+	–	–	
Squamous cell carcinoma in situ	–	+ (Atypical)	+/–	+	+	Multinucleated cells; Full thickness atypia
Extra mammary Paget's disease	–	+ (Intra-cytoplasmic Mucin)	+	–	–	Intact basal layer keratinocytes; Melanin pigment may be present
Eccrine poroma	–	+ (Monomorphous)	–	–	–	Pores with lining cuticle; Round nuclei
Seborrheic keratosis	–	+ (Monomorphous)	–	–	–	Pseudohorncysts; Flat base

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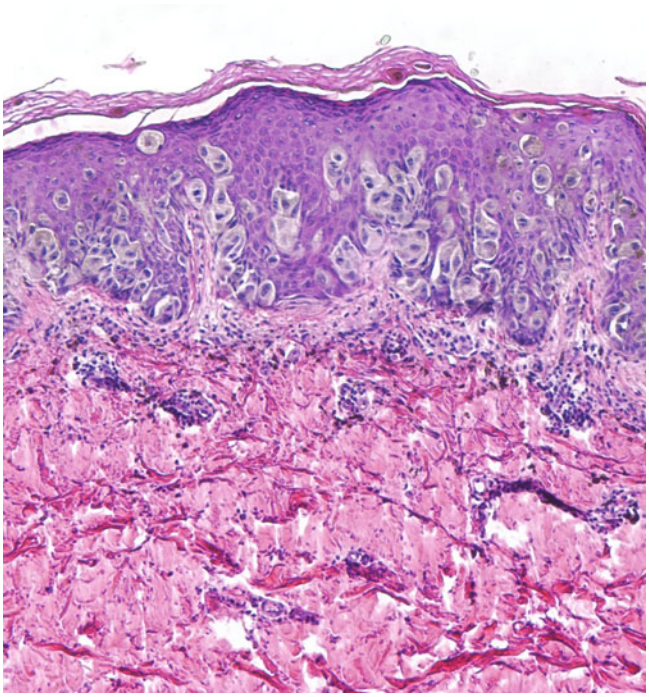

Fig. 27.1 Malignant melanoma in situ

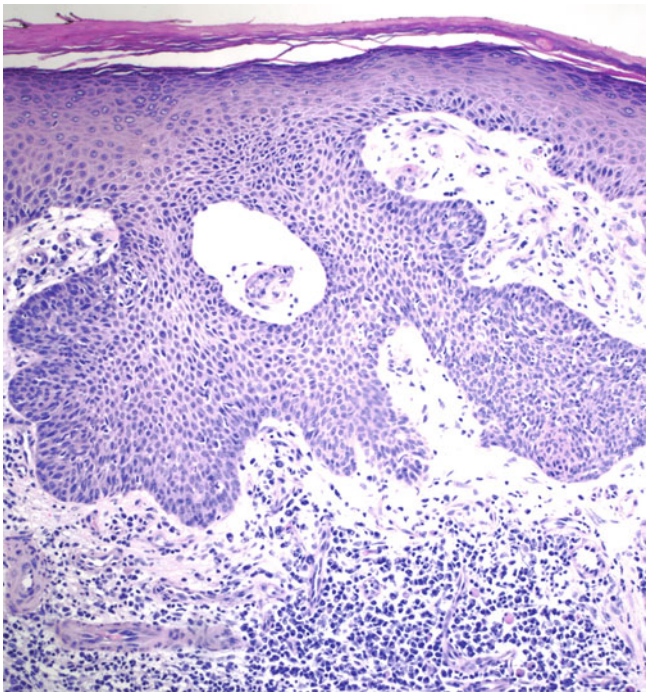

Fig. 27.3 Eccrine poroma

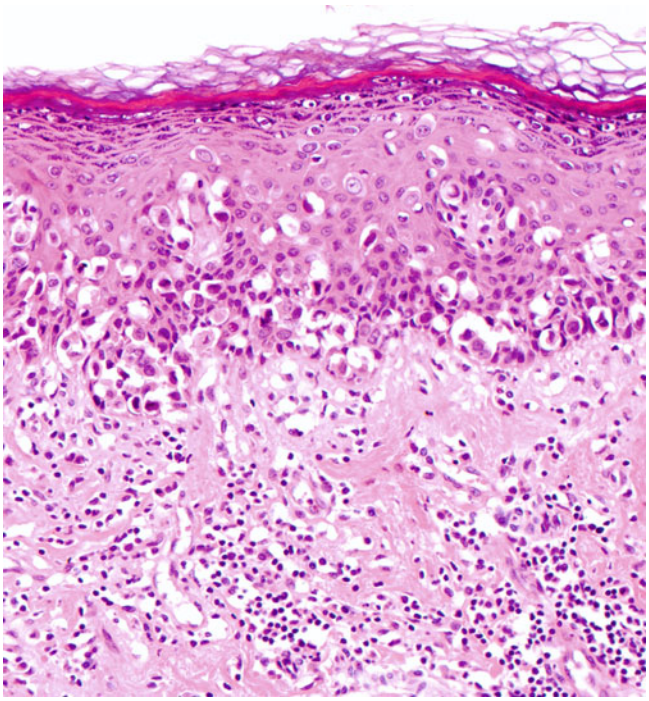

Fig. 27.2 Extramammary Paget's disease

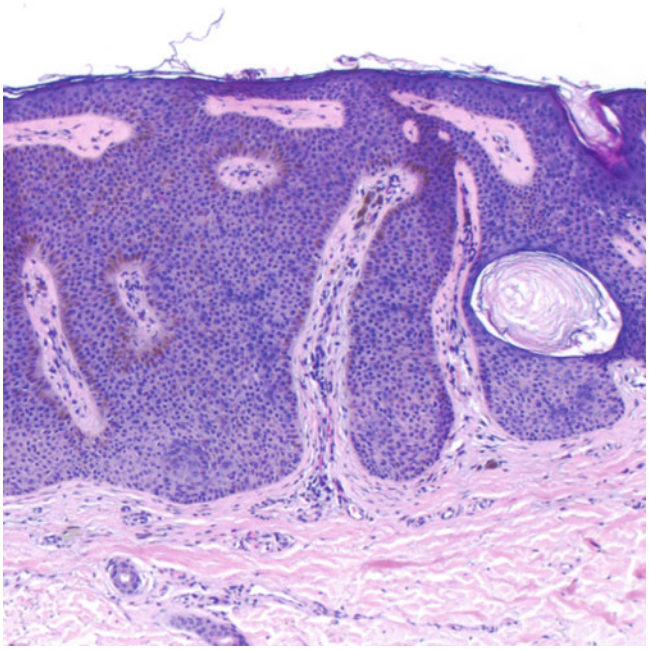

Fig. 27.4 Seborrheic keratosis

28 Clinical Differential Diagnosis of Histological Squamous Cell Carcinoma In-Situ

The major histological criterion for the diagnosis of squamous cell carcinoma in-situ (SCCIS) is the presence of full thickness epidermal keratinocytic maturation disarray (in marked cases the epidermis appears similar viewed from the top or upside down). Other histological findings that help to secure the diagnosis are atypical mitoses and mitoses in the upper levels of the epidermis and keratinocyte apoptosis. Several clinically distinct entities share the histopathological appearance of squamous cell carcinoma in-situ as noted below.

Bowen's Disease

- Non sun-exposed skin (often mucosal)

SCCIS

- Sun-exposed
- Viral infection

Epidermodysplasia Verruciformis

- HIV population
- HPV associated

Bowenoid Papulosis

- Clinically resembles warts, on genitalia
- Histologically identical to SCCIS

Pedophyllin treatment of warts (non-neoplastic)

- Mitoses all arrested at the same stage

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DOI 10.1007/978-1-4471-4471-7_28, © Springer-Verlag London 2013

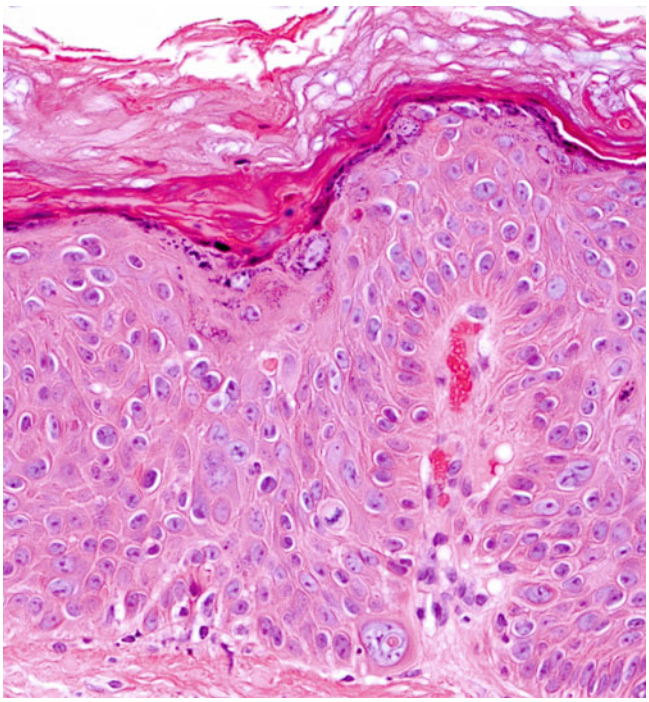

Fig. 28.1 Squamous cell carcinoma in situ

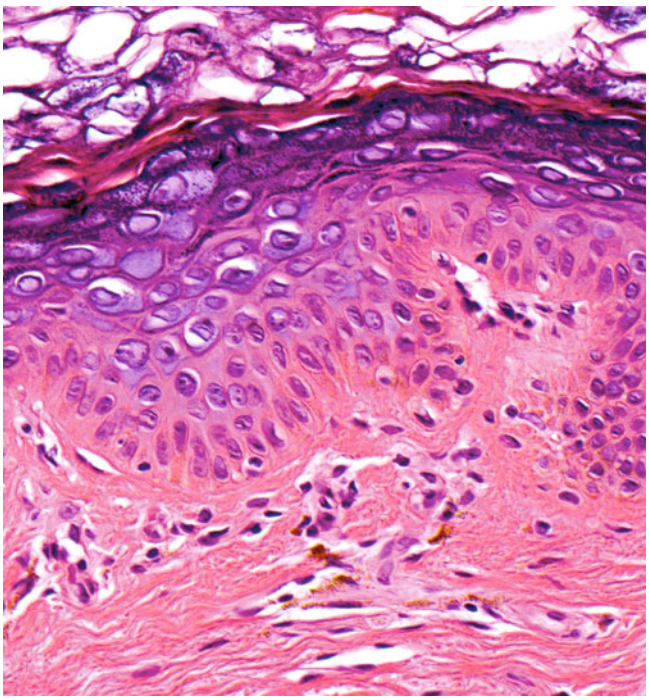

Fig. 28.3 Epidermodysplasia verruciformis with viral cytopathic changes in the superficial epidermis

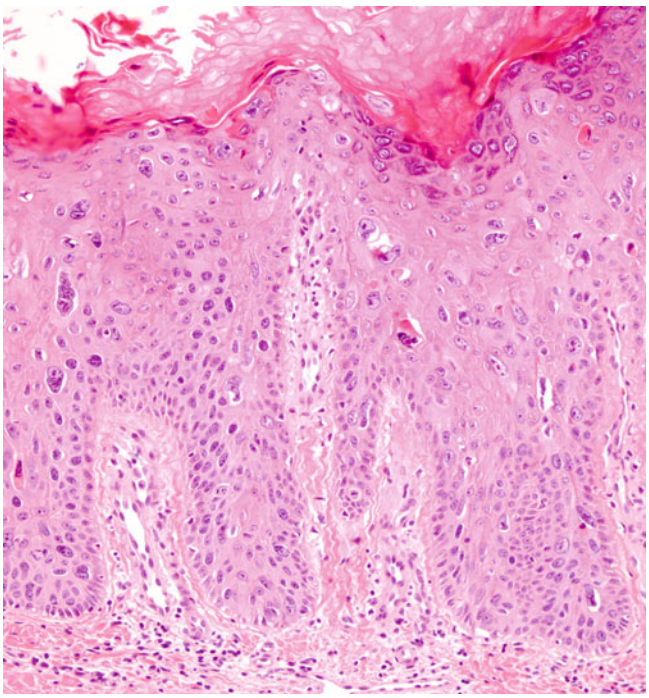

Fig. 28.2 Bowen's disease

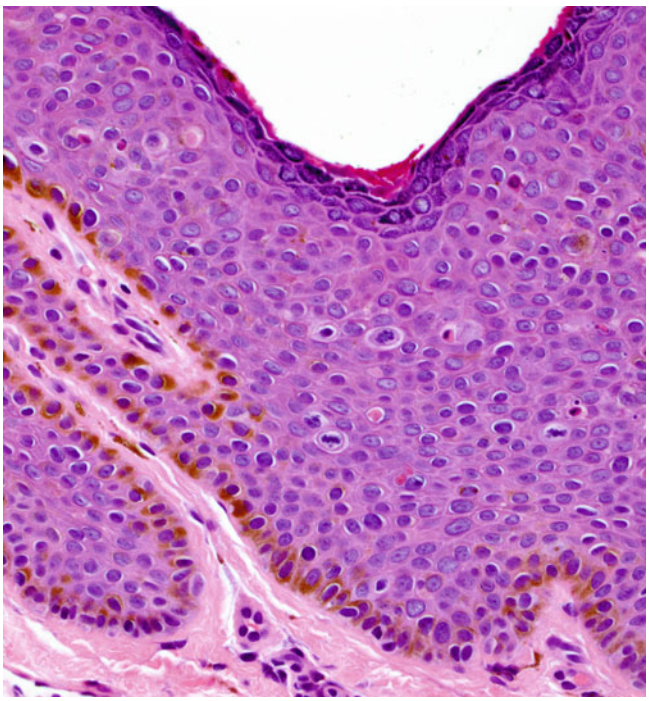

Fig. 28.4 Bowenoid papulosis

29 Basal Cell Carcinoma (BCC) Types

Basal cell carcinoma (BCC) types can be summarized as follows:

- Superficial
- Nodular
- Squamotized: focal keratinization
- Metatypical: foci of atypical squamous cells consistent with squamous cell carcinoma (SCC)
- Micronodular: multiple small dermal nodules
- Morphea: hyalinized eosinophilic stroma with BCC cords of one to two cells
- Infiltrative: like morphea but no eosinophilic collagen, instead there is a hyaluronic acid-rich fibrotic stroma
- Basosquamous: collision tumor between BCC and SCC

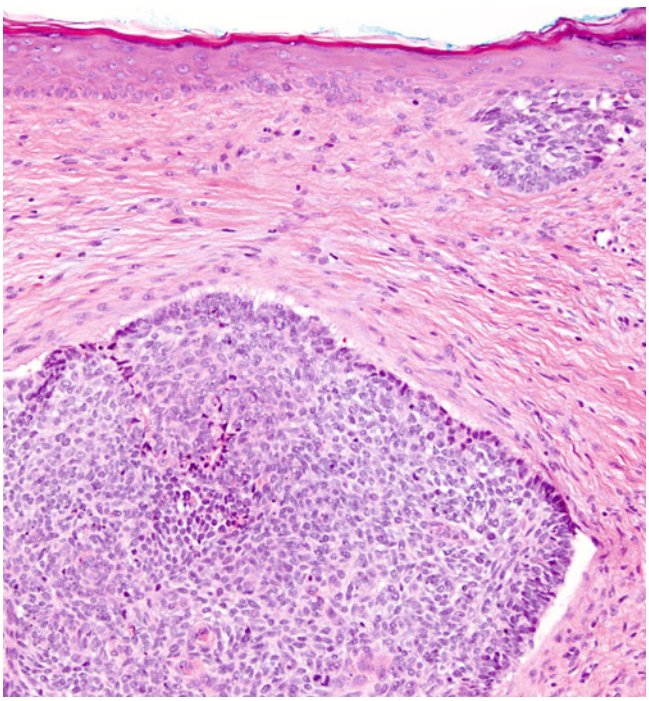

Fig. 29.1 Basal cell carcinoma, superficial and nodular types.

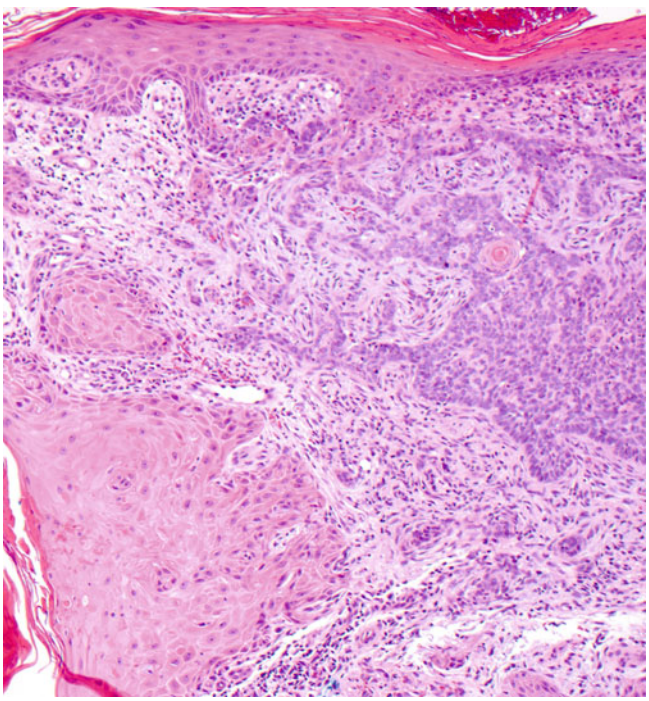

Fig. 29.2 Basosquamous carcinoma, a collision between basal cell carcinoma and squamous cell carcinoma

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DOI 10.1007/978-1-4471-4471-7_29, © Springer-Verlag London 2013

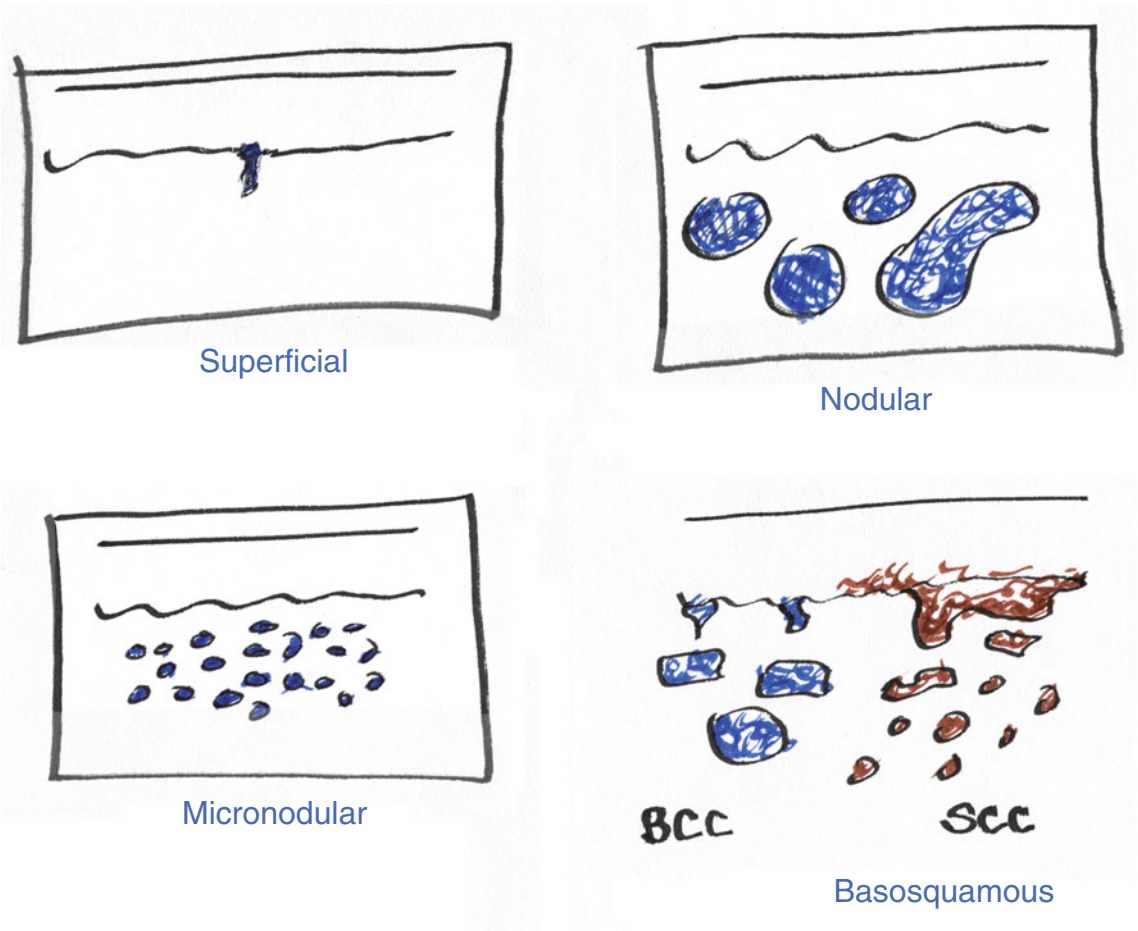

Fig. 29.3 Types of basal cell carcinoma (BCC). Superficial BCC is attached to the epidermis, nodular BCC forms basaloid nodules in the dermis, micronodular BCC is composed of multiple small nodules, and basosquamous cell carcinoma is a collision tumor. BCC characteristically is associated with a separation cleft between the palisaded basaloid tumor cells and a basophilic mucin-rich dermis

Part VI

Adnexal Tumors

30 Sebaceous Neoplasms

Tumors with sebaceous differentiation range from hyperplasias that resemble normal sebaceous glands to carcinoma that are anaplastic or basaloid. Mature sebaceous elements have multivacuolated cytoplasm; the basaloid cells surround the mature elements in the normal sebaceus gland. The percentage of vacuolated cells as compared to the percentage of basaloid cells is often helpful in distinguishing the benign sebaceous neoplasms. Cytological atypia, maturation disarray and mitotic activity are features of sebaceous carcinoma.

Table 30.1 Differential diagnosis of sebaceous neoplasms

	Histologic features
Sebaceous hyperplasia	Rim of basaloid cells
Sebaceous adenoma	<50 % basaloid component
	>50 % mature sebaceous elements
Sebaceous epithelioma (Sebaceoma)	>50 % basaloid component
	<50 % mature sebaceous elements
BCC with sebaceous differentiation	Diagnostic BCC at margins of sebaceous proliferation
Sebaceous carcinoma	Atypical mitoses, SCCIS-like changes with sebaceous differentiation
Muir-Torre syndrome	Multiple keratoacanthomas and difficult to classify sebaceous tumors Absence of nuclear staining for MSH2, MSH6, MLH1, and/or PMS2 Protein is observed

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DOI 10.1007/978-1-4471-4471-7_30, © Springer-Verlag London 2013

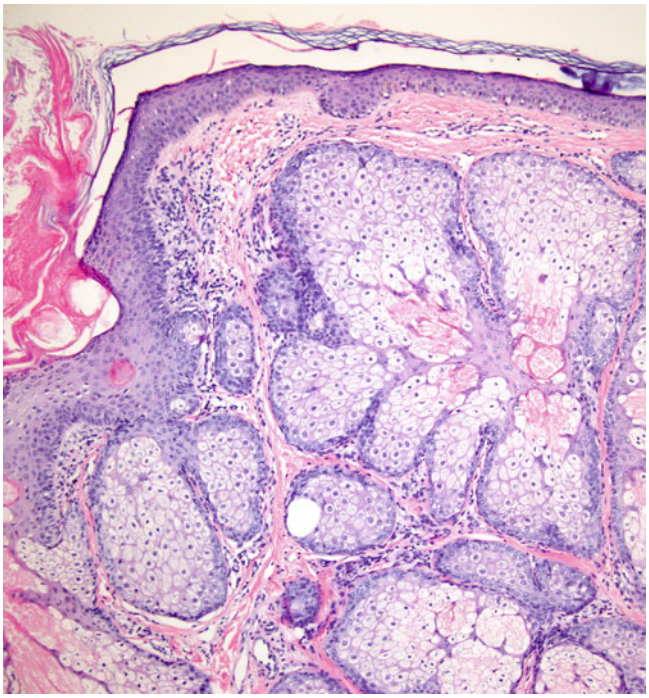

Fig. 30.1 Sebaceous hyperplasia

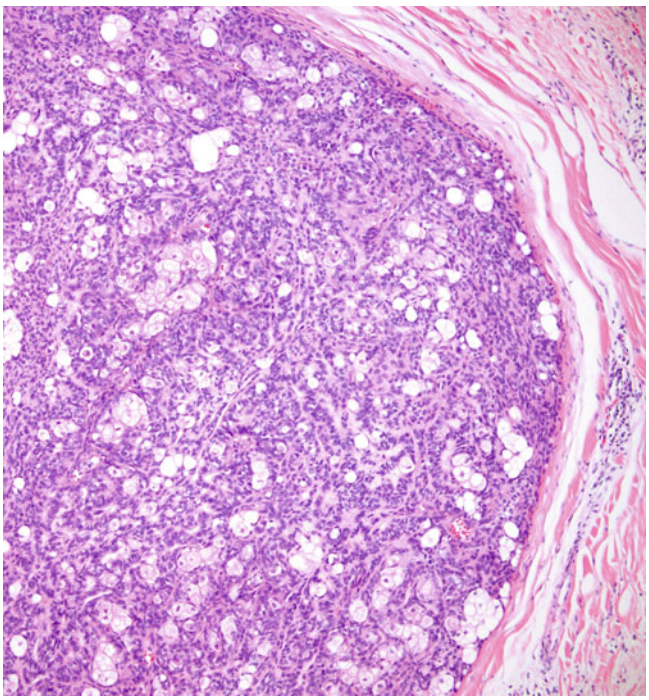

Fig. 30.3 Sebaceous epithelioma

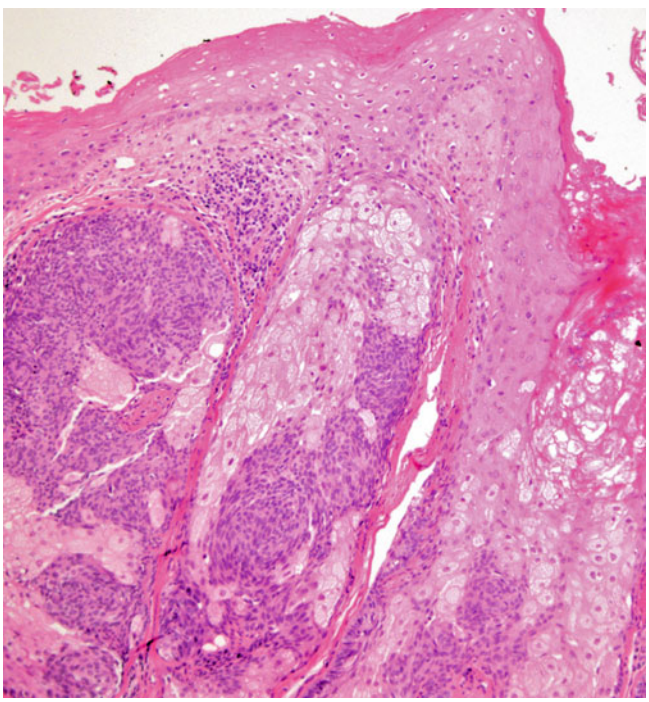

Fig. 30.2 Sebaceous adenoma

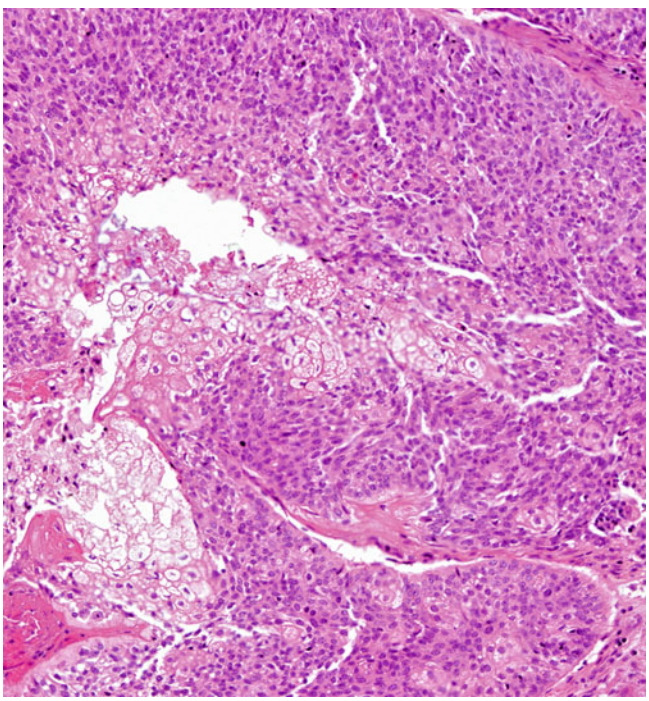

Fig. 30.4 Sebaceous carcinoma

31 Nevus Sebaceus

Nevus sebaceus is a hamartoma of the pilosebaceous apocrine apparatus that usually occurs on the scalp.

Histological Features of Nevus Sebaceus:

- Seborrheic keratosis-like epidermal hyperplasia
- Sebaceous glands enter directly into epidermis
- Small and immature pilar-sebaceous apparati
- Apocrine glands

Neoplasms Commonly Associated with Nevus Sebaceus

- BCC
- Syringocystadenoma Papilliferum

Table 31.1 The histological differential diagnosis of syringocystadenoma papilliferum and hidradenoma papilliferum

	Syringocystadenoma papilliferum	Hidradenoma papilliferum
Connection with the epidermis	+	–
Plasma cells	+	–
Site	Scalp	Vulva
Scale crust	–	+
Benign epithelial proliferation with apocrine Differentiation	+	+

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DOI 10.1007/978-1-4471-4471-7_31, © Springer-Verlag London 2013

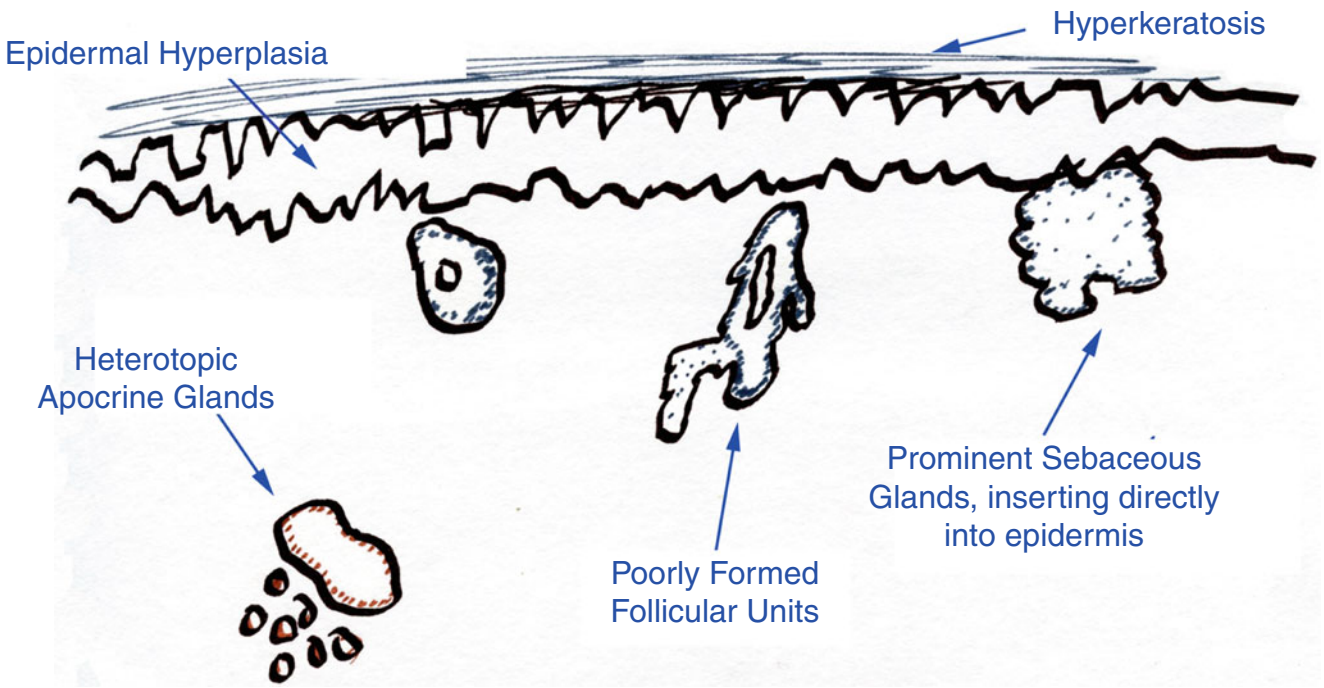

Fig. 31.1 Schematic of nevus sebaceus

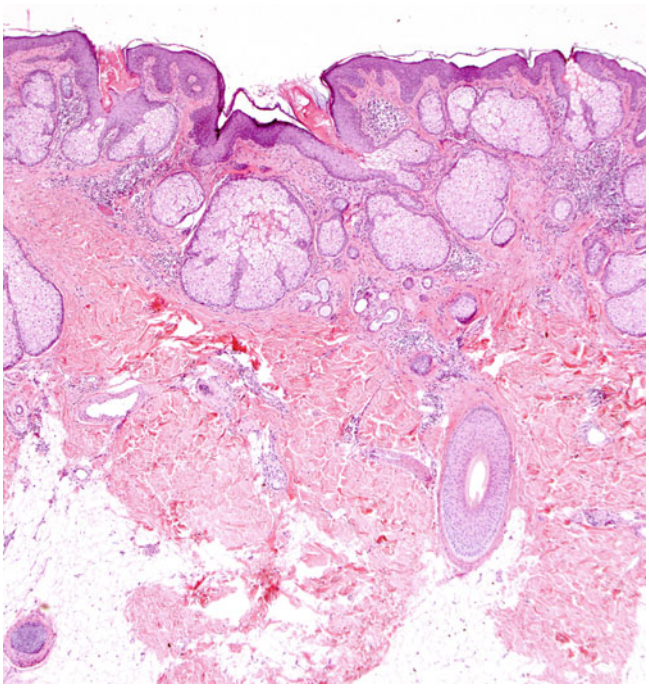

Fig. 31.2 Nevus sebaceus. This is a hamartoma (nevus) of the pilosebaceous apocrine unit

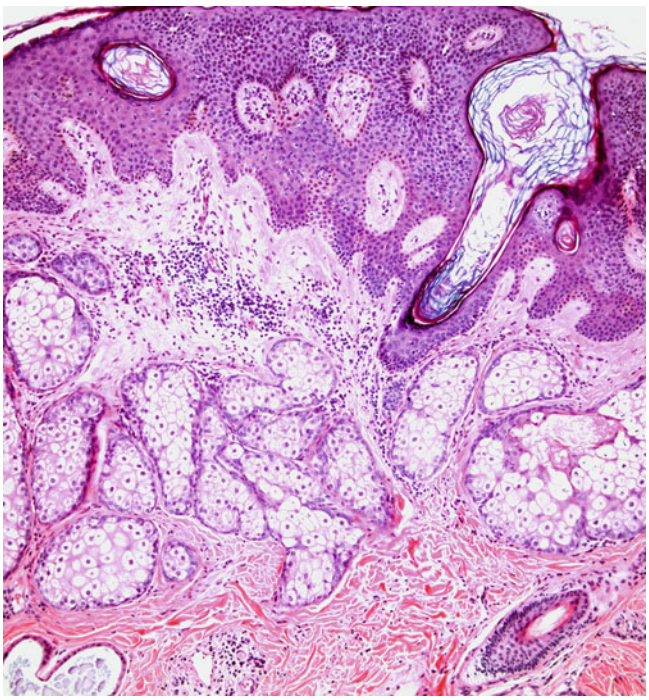

Fig. 31.3 Nevus sebaceus. The epidermal hyperplasia may resemble seborrheic keratosis

32 Eccrine and Apocrine Neoplasms

Eccrine Tumors

Eccrine tumors are characterized by eosinophilic basement membrane material:

- Ductal origin
  - Poroma: cuticle-lined lumens, pavement-like monomorphous proliferation of round cells
  - Porocarcioma: poroma-like, but with infiltrative growth pattern, atypical mitoses, and tumor cell necrosis.
- Secretory origin
  - Acrospiroma/Clear Cell Hidradenoma: clear cytoplasm, solid and cystic
  - Clear Cell Hidradenocarcinoma: acrospiroma-like, but with infiltration, atypical mitoses, and tumor cell necrosis.
- Other
  - Spiradenoma: basaloid, "blue balls" in the dermis
    - 2 cell populations
    - Granular, eosinophilic material in lumens

Apocrine Tumors

Apocrine tumors are characterized by decapitation secretion ("snouts"):

- Ductal origin
  - Rare tumors because apocrine duct is very short
- Secretory origin
  - Tubular Apocrine Adenoma
  - Syringocystadenoma Papilliferum (associated with Nevus Sebaceus)
    - Connects to surface, plasma cells present
  - Hidradenoma Papilliferum (genital)
    - No connection to surface
  - Apocrine Carcinoma
    - Variable atypia, infiltrative, papillary

Mixed Tumors

- Syringoma: "Tadpole" tubules, organoid stroma
- Cylindroma: Basaloid "puzzle pieces" with eosinophilic droplets and mortar
- Microcystic Adnexal Carcinoma: Deeply infiltrative benign appearing ducts

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DOI 10.1007/978-1-4471-4471-7_32, © Springer-Verlag London 2013

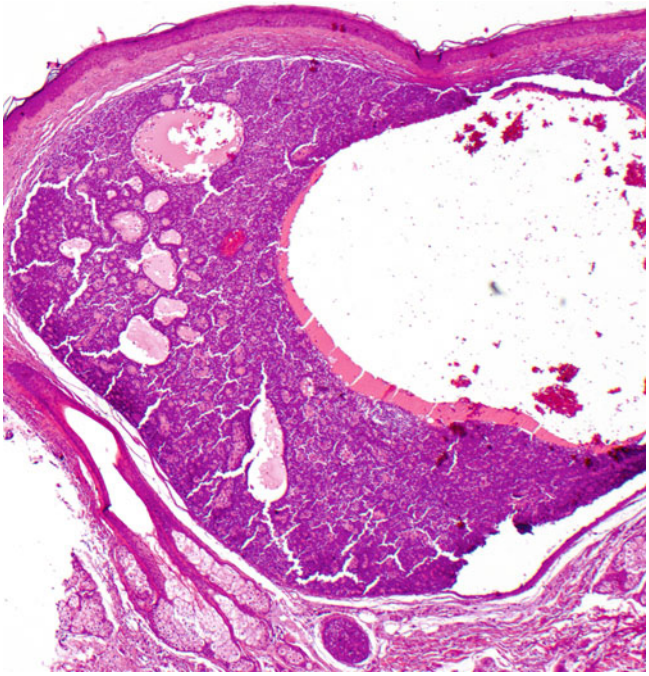

Fig. 32.1 Eccrine Spiradenoma

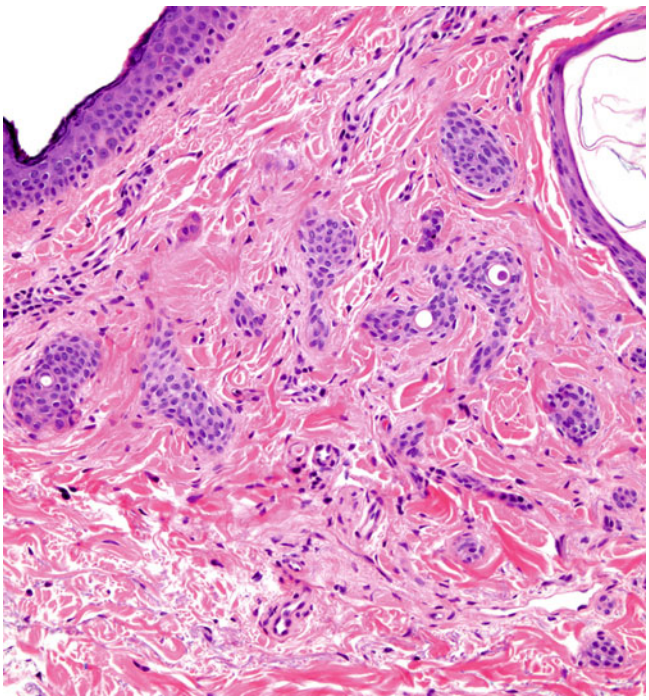

Fig. 32.3 Syringoma

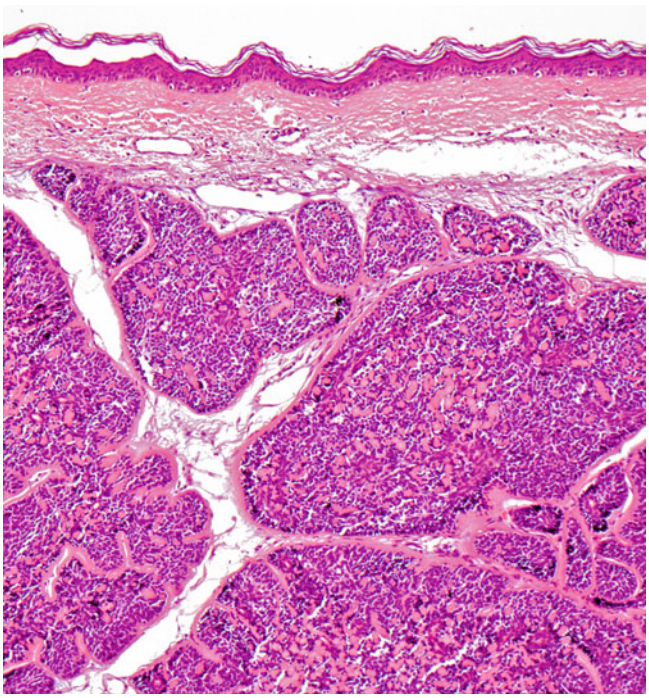

Fig. 32.2 Cylindroma

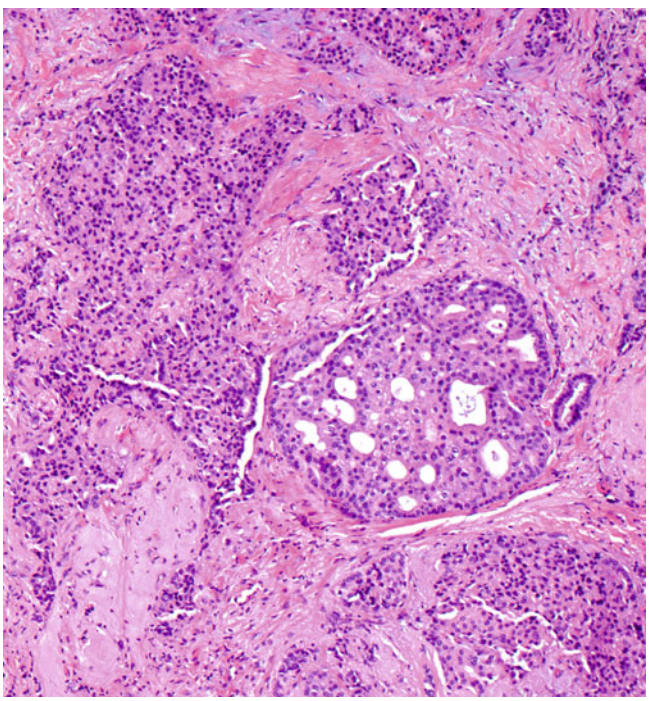

Fig. 32.4 Apocrine carcinoma

Part VII

Mesenchymal Tumors

33 Immunophenotype of Dermal Spindled Cell Tumors

Spindled cell neoplasms of the dermis may have overlapping histological features. Immunohistochemical stains allow the detection of proteins that characteristically are expressed by specific tumors.

Table 33.1 Differential diagnosis of dermal spindled cell tumors

	CD34	Factor XIIIa	CD31	CD10	S100	Vimentin	MART-1
Melanoma	–	–	–	–	+	+	+
Dermatofibroma	–	+	–	–	–	+	–
DFSP	+	–/+	–	–	–	+	–
AFX	–	–	–	+	–/+	+	–
Leiomyoma	–	–	–	–	–	+	–

DFSP dermatofibrosarcoma protuberans, *AFX* atypical fibroxanthoma (superficial malignant fibrous histiocytoma). All stains display internal positive controls with normal cell types; e.g. CD31+ vasculature, S100+ melanocytes and dermal dendritic cells, MART-1 + melanocytes

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
DOI 10.1007/978-1-4471-4471-7_33, © Springer-Verlag London 2013

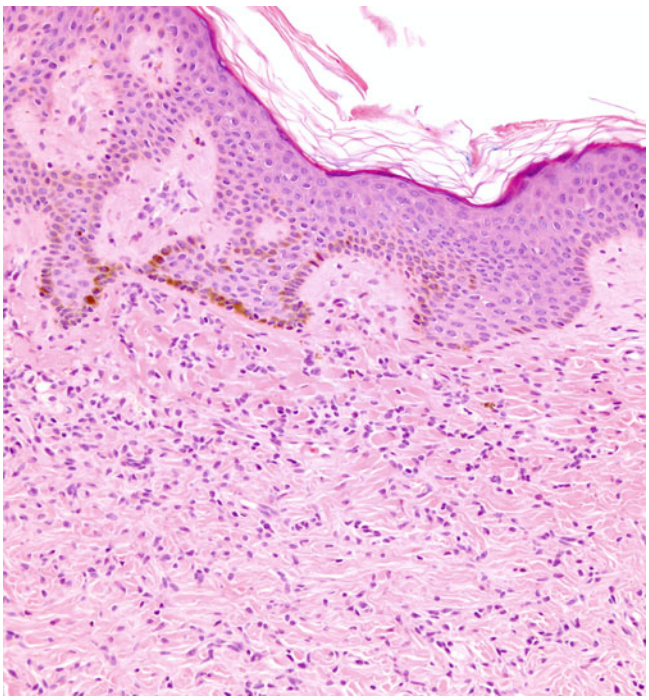

Fig. 33.1 Dermatofibroma with characteristic dermal spindle cell proliferation in a storiform growth pattern with epidermal hyperplasia and basilar hyperpigmentation

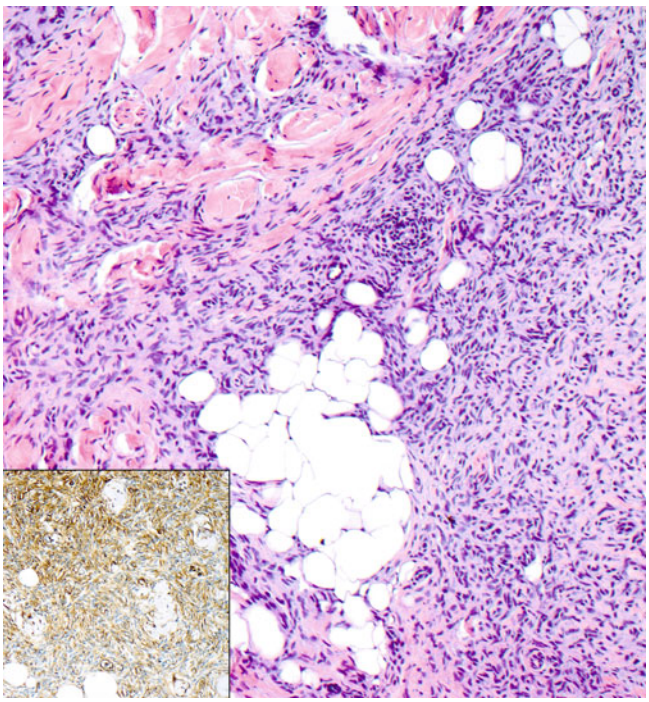

Fig. 33.3 Dermatofibroscarcoma protuberans with dermal spindle cells in a storiform growth pattern and infiltrating subcutaneous fat. The tumor cells are CD34-positive

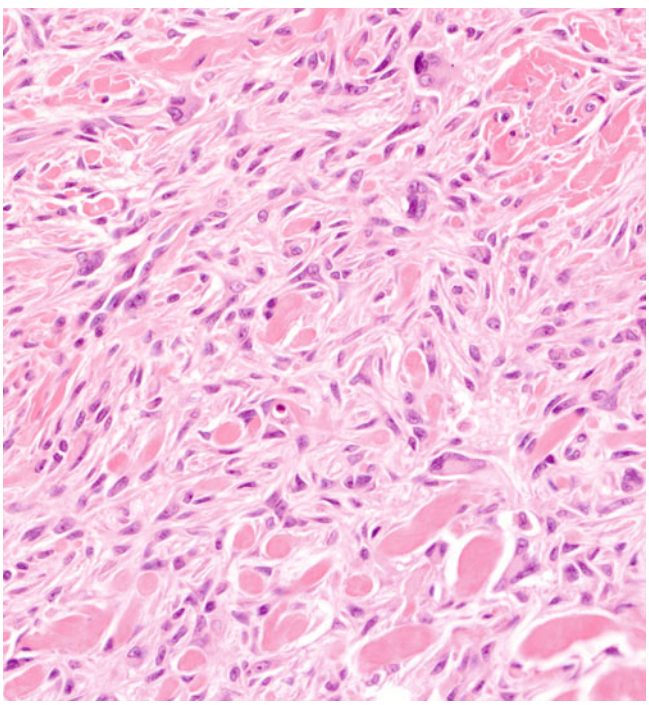

Fig. 33.2 Dermatofibroma with multinucleate histiocytes and characteristic wrapping around the reticular dermal collagen fibers

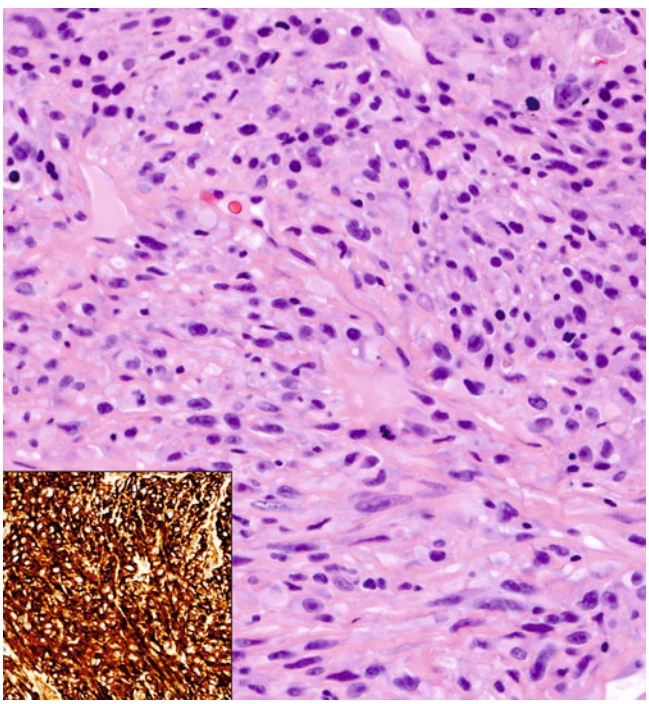

Fig. 33.4 Atypical fibroxanthoma with pleomorphic dermal spindled and epithelioid cells in a fascicular growth pattern. The tumor cells are CD10-positive

34 Fibrous Papule (Angiofibroma)

An angiofibroma is a common benign firm papule on the central face, often the nose.

Histology

- Dermal spindled, stellate, and/or multinucleated fibroblasts
- Collagenous stroma with perifollicular fibrosis
- Prominent blood vessels
- Absent or rare mitotic figures

Immunohistochemistry

- Factor XIIIa: +
- CD34: +/–
- S100: –

Also,

- Angiofibroma of face in Tuberous Sclerosis (developmental delay, epilepsy, angiofibromas, ash-leaf macules)
- Pearly Penile Papule
- Acral angiofibroma (rare)

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
DOI 10.1007/978-1-4471-4471-7_34, © Springer-Verlag London 2013

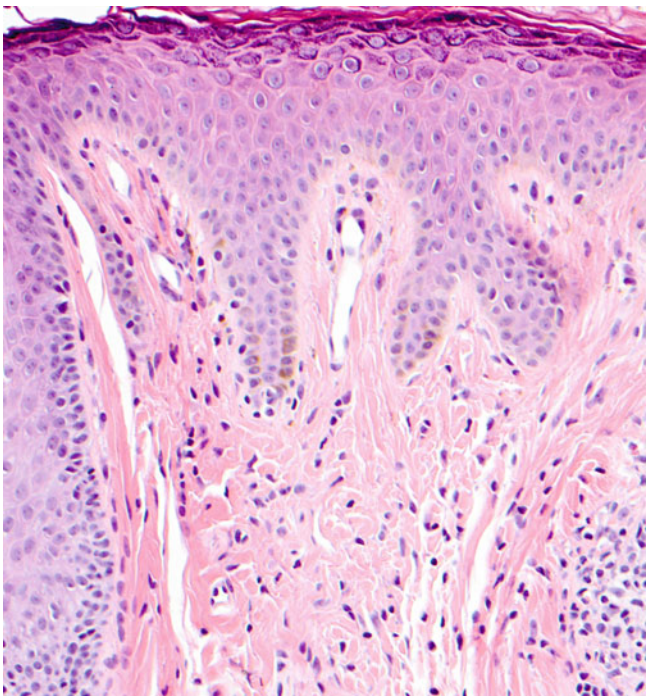

Fig. 34.1 Angiofibroma (fibrous papule) of the nose

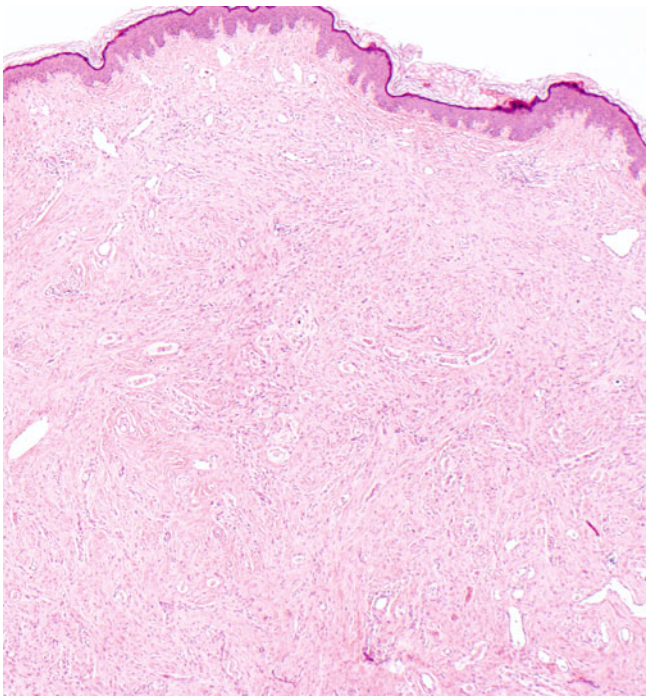

Fig. 34.3 Angiofibroma of the flank

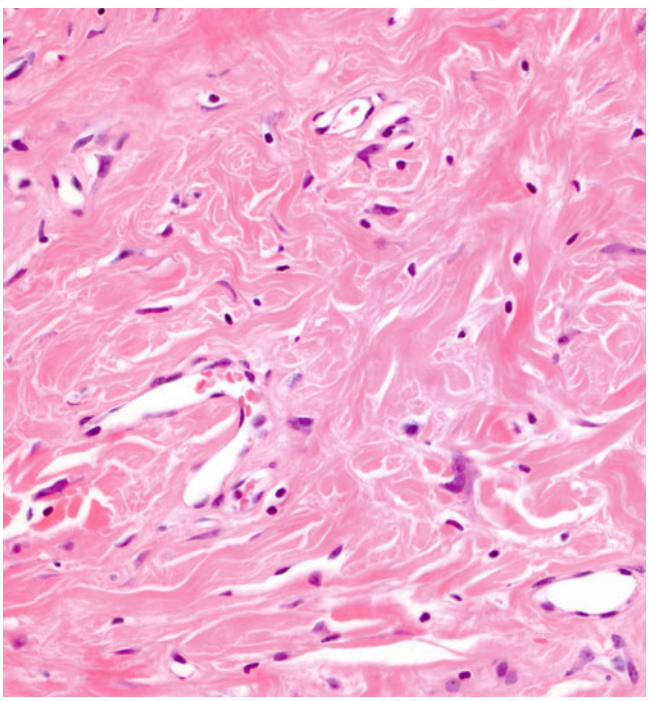

Fig. 34.2 Angiofibroma (fibrous papule) of the nose. The multinucleate dermal fibroblasts may have a stellate morphology

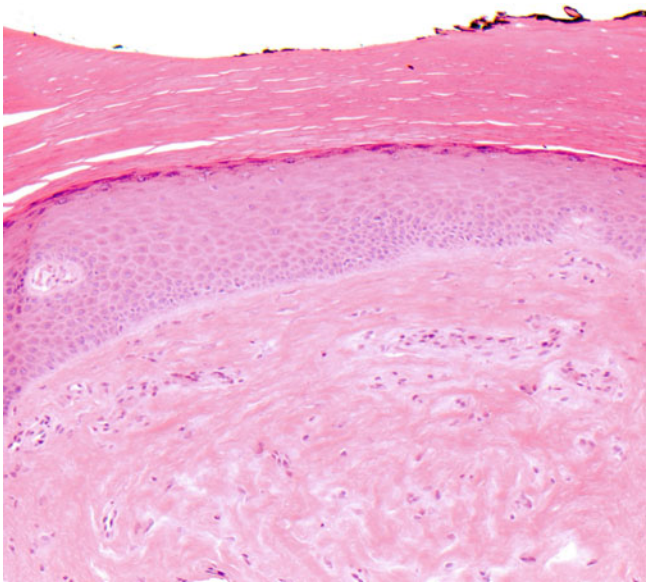

Fig. 34.4 Acral angiofibroma

35 Angiokeratoma

Angiokeratoma is represented by superficial dermal vascular ectasia with surrounding epidermal hyperplasia and hyperkeratosis.

Types:

- Angiokeratoma Circumscriptum - papules coalesce to plaques on extremities
  - COBB syndrome = Angiokeratoma Circumscriptum, Nevus Flammeus, Spinal Cord Angioma
- Angiokeratoma Corporis Diffusum – generalized papules
  - Fabry's Disease (lysosomal storage disease, alpha-galactosidase A deficiency)
- Angiokeratoma of Mibelli –dorsum of fingers and toes, warty-like
- Angiokeratoma of Fordyce –scrotum (less often on penis and vulva), associated with varicocele and hernia
- Solitary and Multiple Angiokeratomas –typically on lower extremities

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
DOI 10.1007/978-1-4471-4471-7_35, © Springer-Verlag London 2013

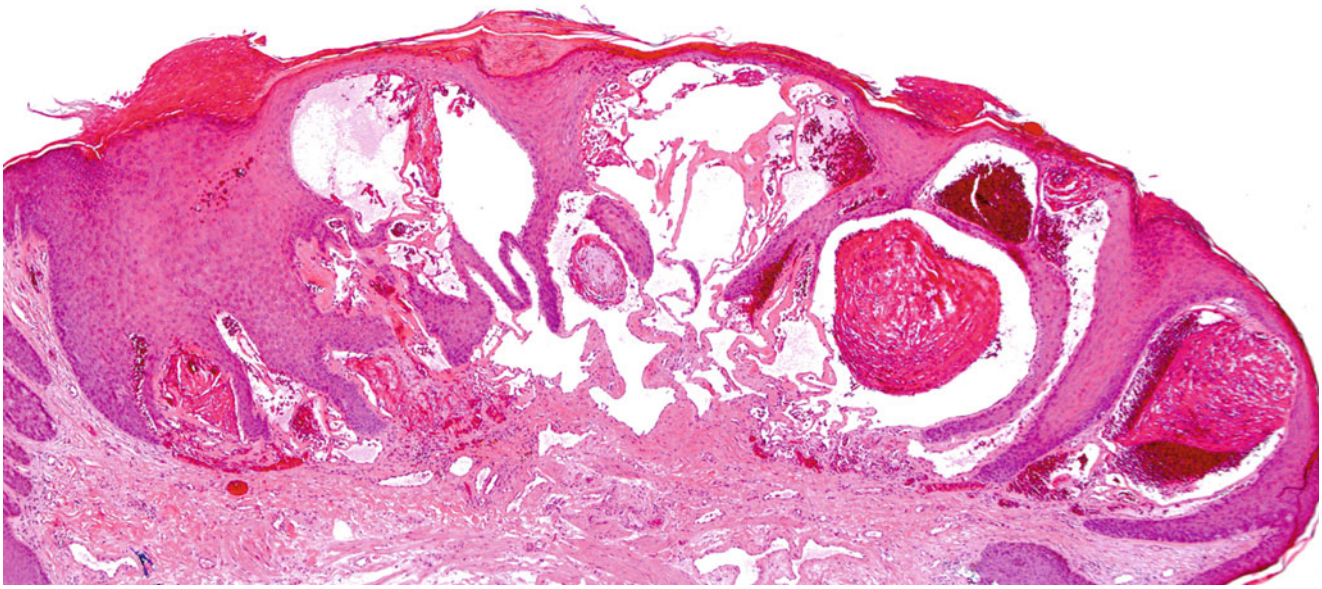

Fig. 35.1 Angiokeratoma

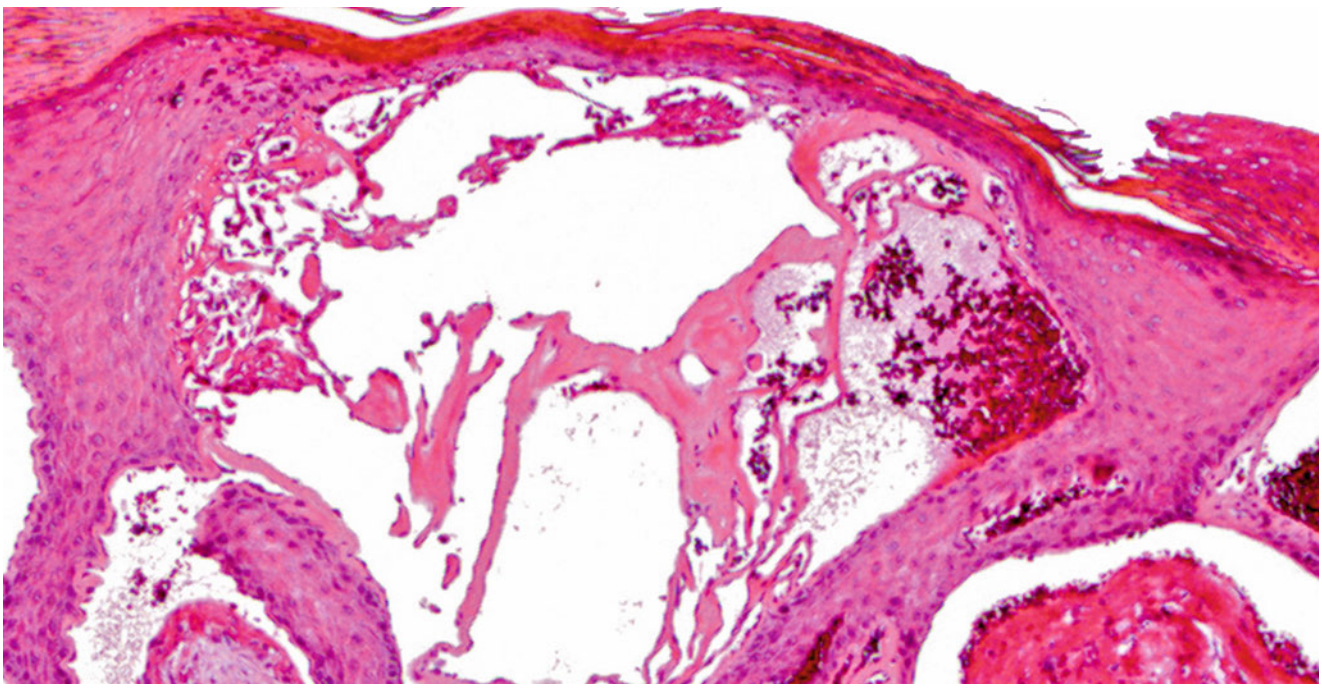

Fig. 35.2 Angiokeratoma. The ectatic vessels appear to be within epidermis but are separated by a rim of papillary dermis

Part VIII

Melanocytic Proliferations

36 Lentigo Versus Lentiginous

Lentigo is a term that describes a clinically distinct lesion that may be sub-classified as solar lentigo and lentigo simplex. Lentiginous is a descriptive term of a pattern of melanocytic growth as individual cells along the dermal epidermal junction. Lentiginous melanocytic proliferation may be observed in lentigo, however it is also observed in other processes including dysplastic nevus, lentigo maligna, acral lentiginous melanoma and mucosal melanoma.

Lentigo

- Increased basal layer keratonocyte pigmentation (as in ephelis)
- +/− hyperplasia of basal keratinocytes → budding (not in ephelis)
- +/− lentiginous melanocytic hyperplasia (not in ephelis)

Lentiginous

- Increased density of melanocytes at base of epidermis
- No nesting (nest = three or more melanocytes)

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DOI 10.1007/978-1-4471-4471-7_36, © Springer-Verlag London 2013

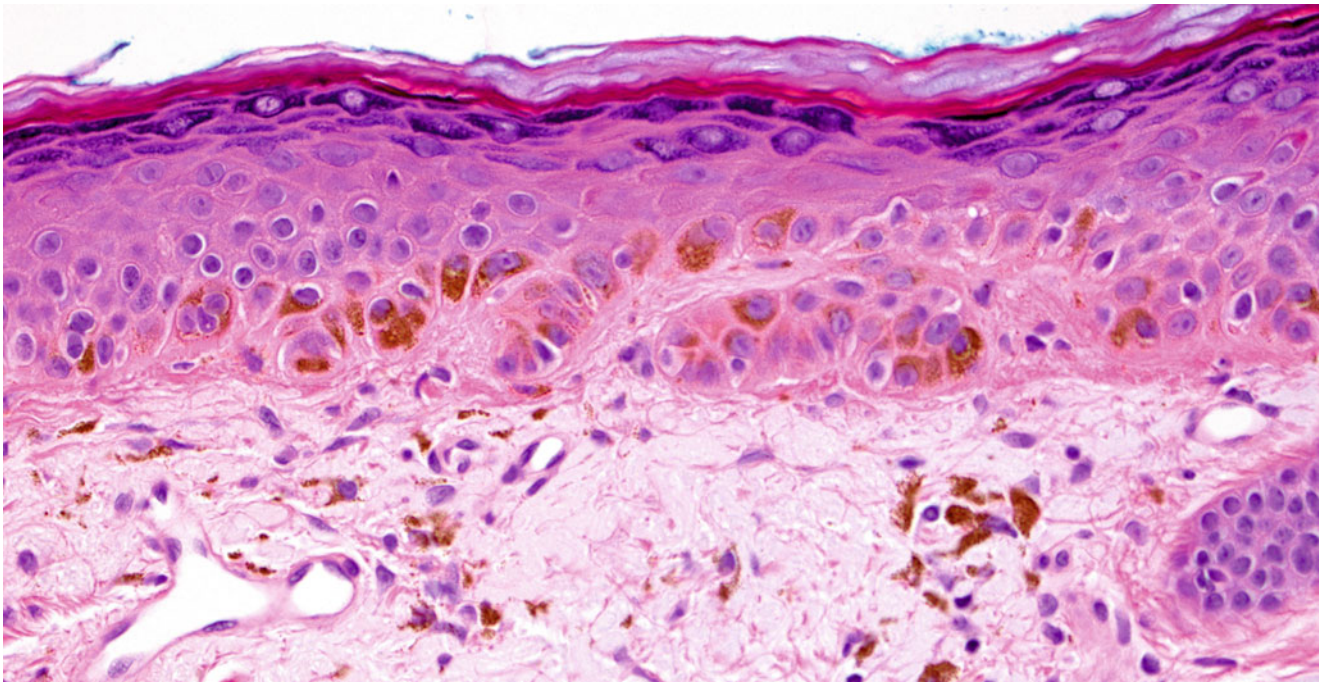

Fig. 36.1 Lentigo. There is keratinocytic hyperplasia and increased pigmentation of basal layer keratinocytes

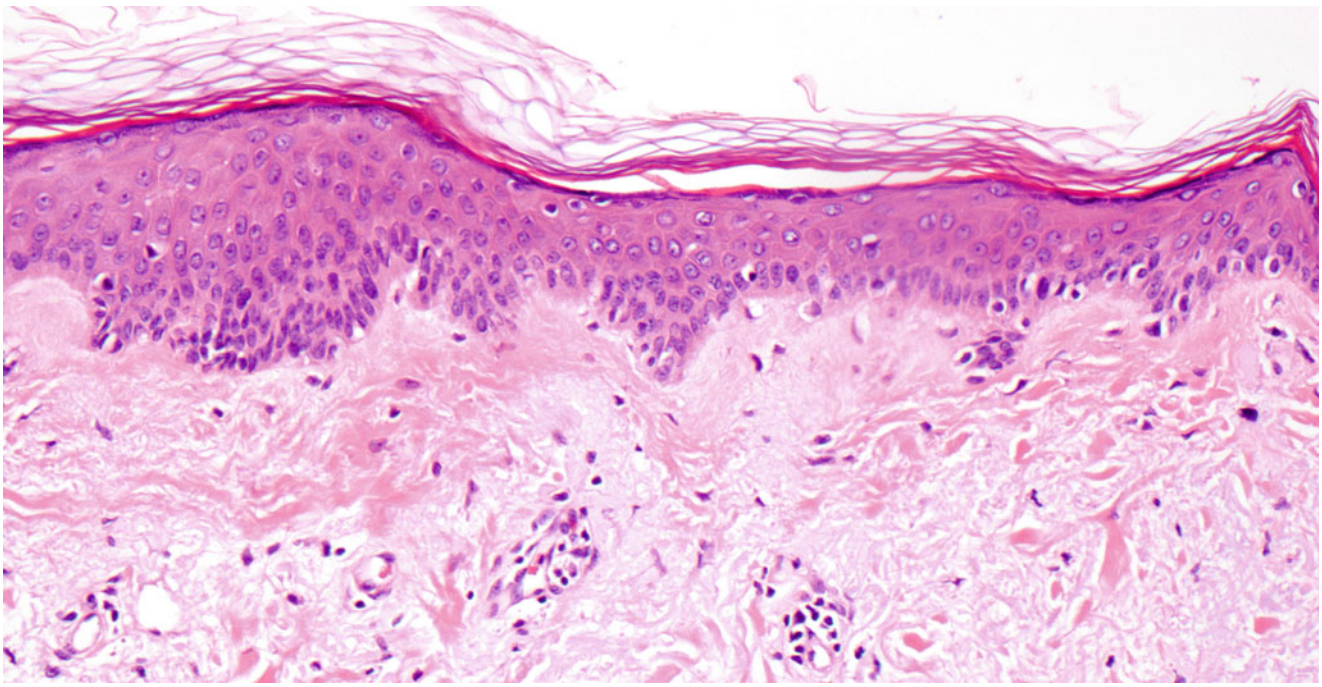

Fig. 36.2 Lentiginous melanocytic proliferation. There are increased numbers of melanocytes at the base of the epidermis without nesting

37 Dermal Dendritic Melanocytic Proliferations

There are several distinct forms of dermal dendritic melanocytic proliferations; the most commonly observed is the blue nevus. The melanocytes have delicately pigmented dendritic processes and oval or round nuclei with delicately dispersed chromatin.

Blue nevus

- In addition to the common blue nevus there are several types of combined nevi that have a blue nevus component

Nevus of Ito

- Typically occurs on shoulder or upper arm

Nevus of Ota

- Typically occurs on skin innervated by the ophthalmic and maxillary branches of the trigeminal nerve

Mongolian spot

- Typically occurs in lumbosacral region

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DOI 10.1007/978-1-4471-4471-7_37, © Springer-Verlag London 2013

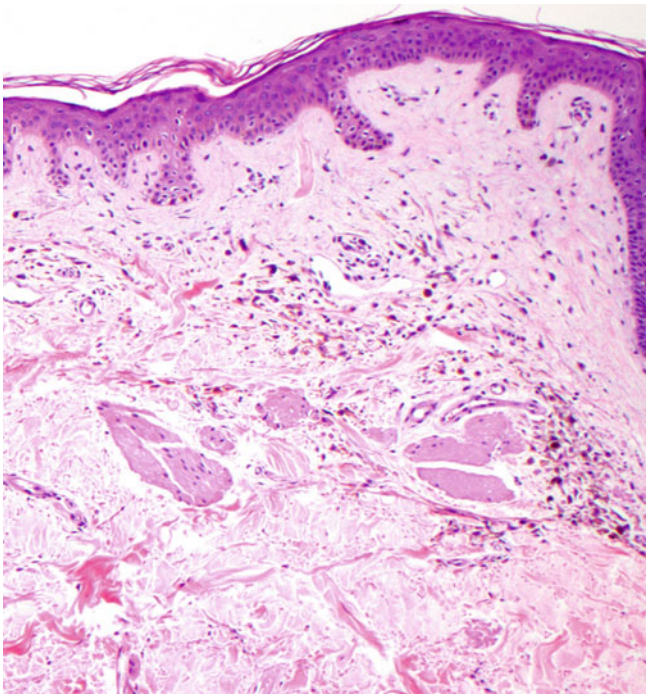

Fig. 37.1 Blue nevus. This proliferation of pigmented dendritic melanocytes is present in the interstitial reticular dermis and about adnexal structures

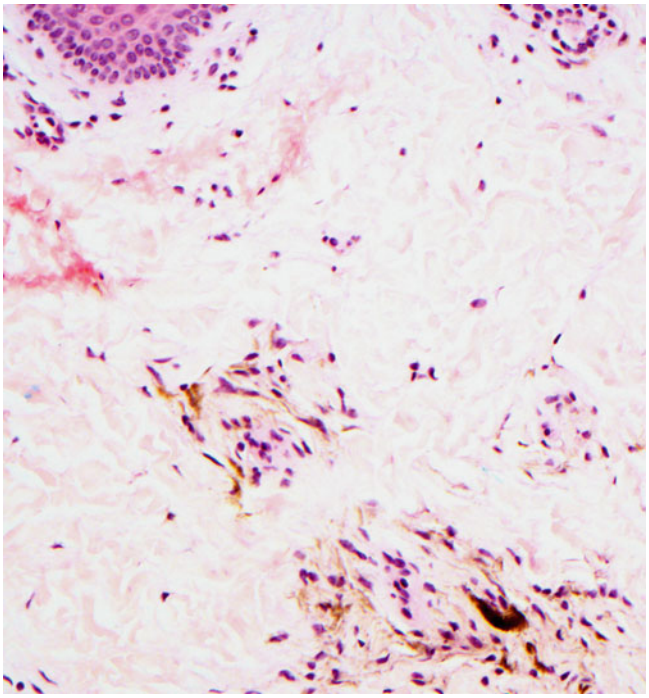

Fig. 37.3 Mongolian spot. There is a patchy distribution of pigmented dendritic melanocytes in the dermis

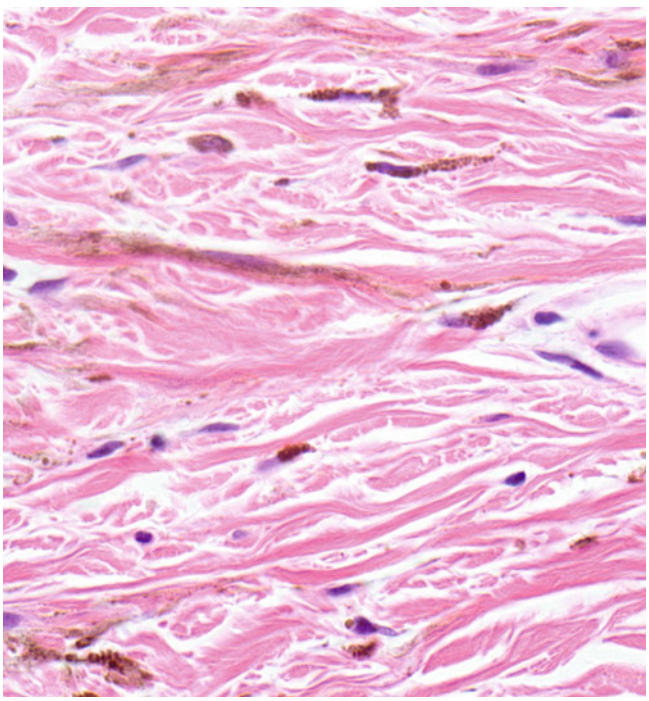

Fig. 37.2 Blue nevus. The elongated pigmented cytoplasm is characteristic of blue nevus cells

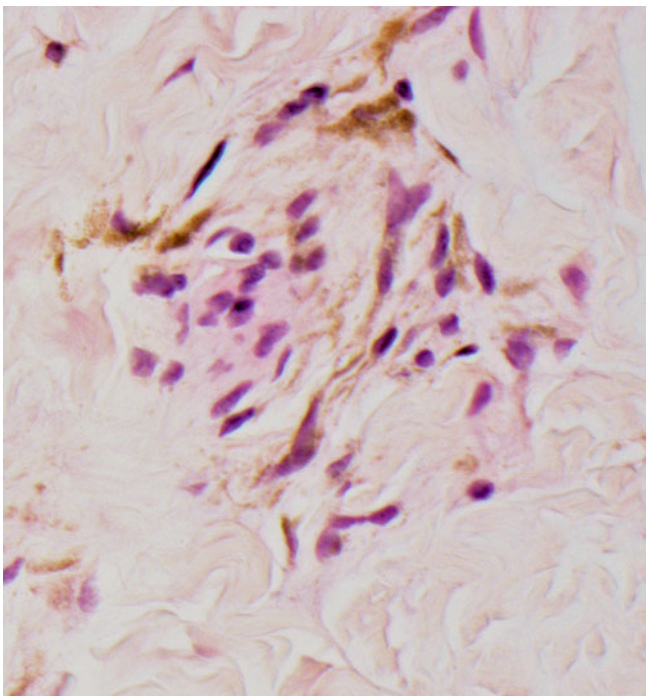

Fig. 37.4 Mongolian spot. The pigmented dendritic cells are histologically similar to the cells of blue nevus

38 Dysplastic Nevi Criteria

The histological diagnosis of dysplastic nevus is based upon several histological features including the pattern of growth and the host response to the tumor. The following criteria allow for consistent diagnosis of dysplastic nevi. Both major criteria are required (except in the case of a junctional nevus there will be no shoulder), and at least two of the minor criteria are required. After these criteria are met, the cytologic appearance of the melanocytes is evaluated to determine the grade of atypia.

Major Criteria, Need 2/2

- Lentiginous and nested cytologically atypical intraepidermal melanocytic proliferation
- Shoulder (intraepidermal component >3 rete beyond dermal component)

Minor Criteria, Need ≥2/4

- **V**ascularity (prominent superficial vascular plexus)
- **F**ibrosis (eosinophilic concentric or lamellar)
- **I**nflammation (mononuclear cell inflammatory infiltrate about superficial vascular plexus)
- **B**ridging (nest expansion and fusion at dermal-epidermal junction)

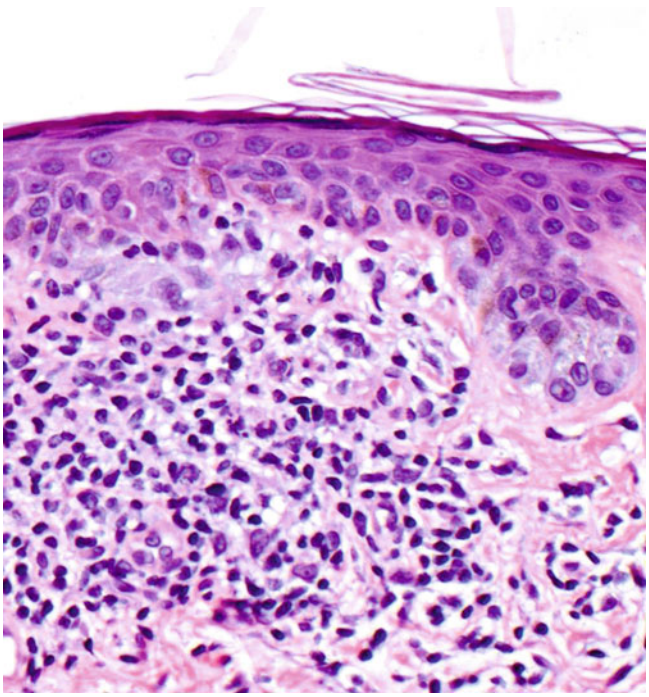

Fig. 38.1 Dysplastic nevus major criteria: lentiginous and nested atypical melanocyte proliferation

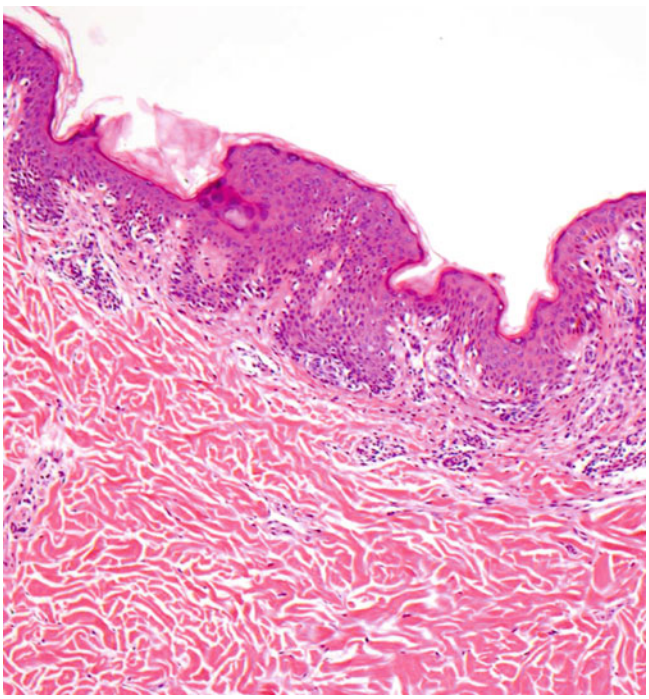

Fig. 38.2 Dysplastic nevus major criteria: basilar proliferation of atypical melanocytes extending three rete beyond the dermal component ("shoulder")

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DOI 10.1007/978-1-4471-4471-7_38, © Springer-Verlag London 2013

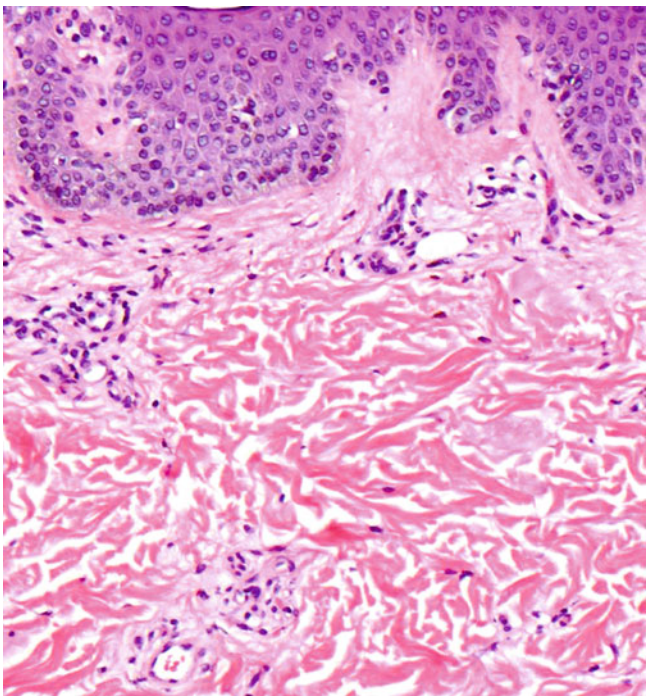

Fig. 38.3 Dysplastic nevus minor criteria: increased vascularity with endothelial cell hypertrophy

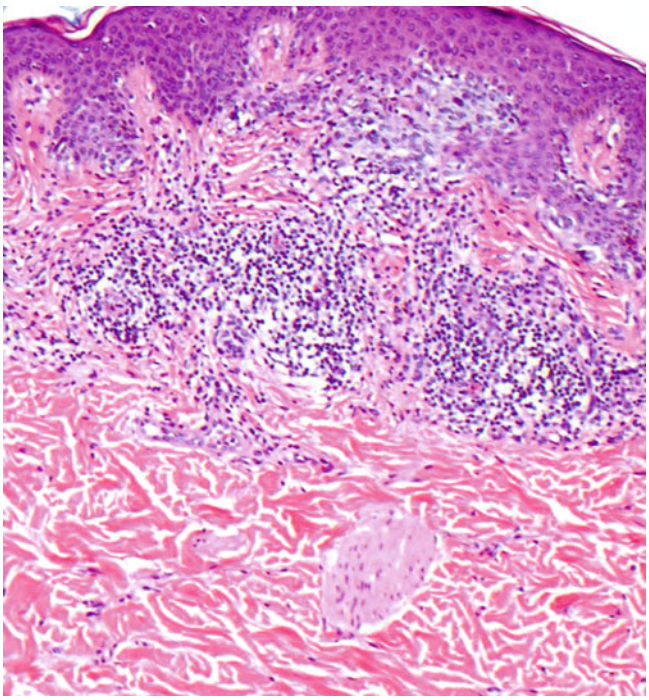

Fig. 38.5 Dysplastic nevus minor criteria: superficial perivascular lymphoid infiltrate

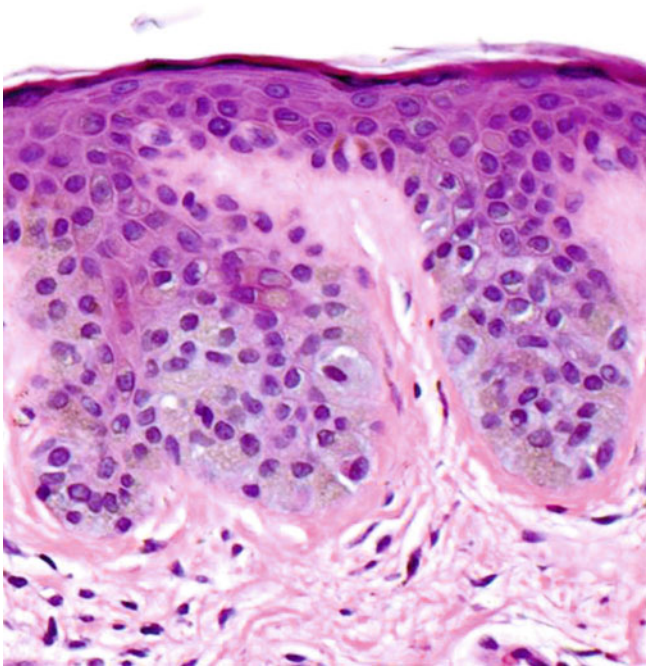

Fig. 38.4 Dysplastic nevus minor criteria: eosinophilic concentric fibrosis

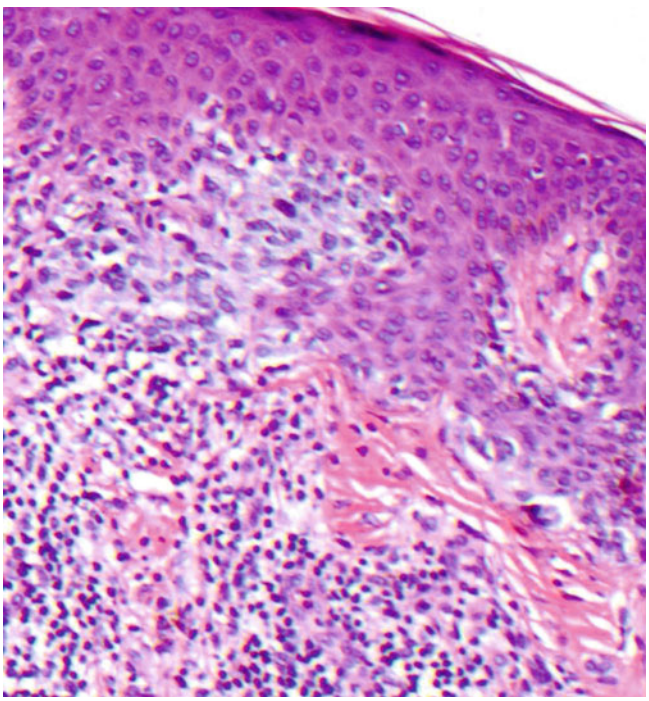

Fig. 38.6 Dysplastic nevus minor criteria: bridging of rete by nests of atypical melanocytes

39 Dysplastic Nevi Melanocytic Grading Criteria

The criteria for diagnosis of dysplastic melanocytic nevi are defined as architectural and cytological. Cytological atypia is required for the diagnosis of dysplastic nevus, however, there is a range of degree of cytological atypia. When criteria for dysplastic nevi are met the tumors are graded based on the degree of melanocytic atypia.

With increasing degree of atypia the size of the nuclei increase; a good reference for size is the nucleus of the mid-layer keratinocyte. The nuclear shape becomes more irregular and the chromatin may be densely chromatic or clumped, nucleoli may be prominent.

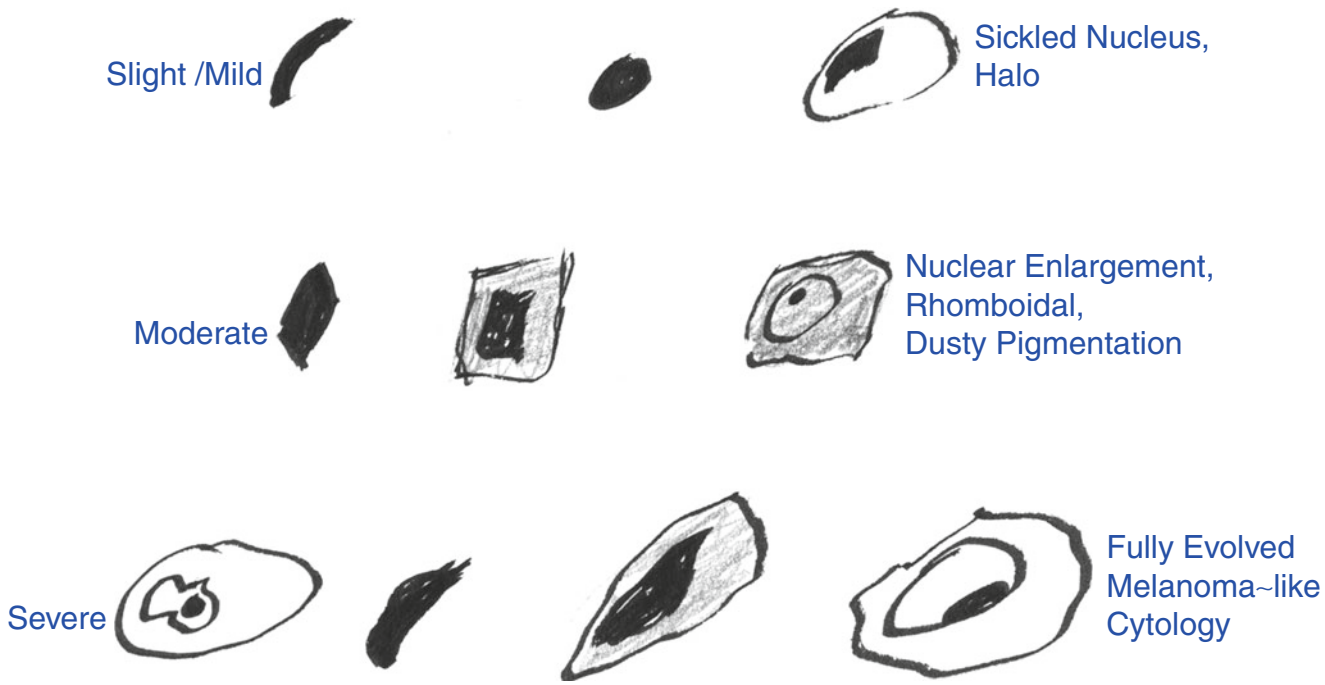

Fig. 39.1 Grades of melanocytic atypia in dysplastic nevus

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DOI 10.1007/978-1-4471-4471-7_39, © Springer-Verlag London 2013

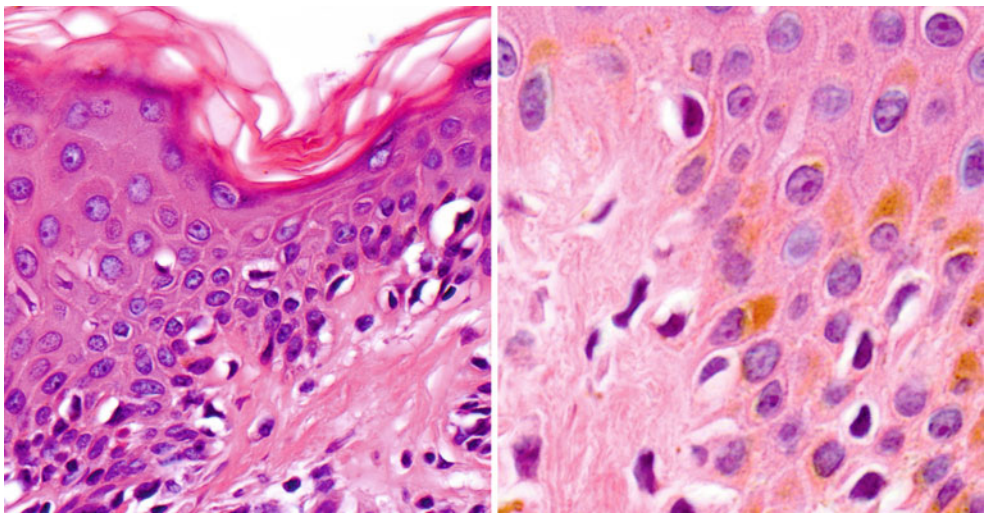

Fig. 39.2 Slight (mild) cytological atypia in the junctional tumor cells in dysplastic nevus

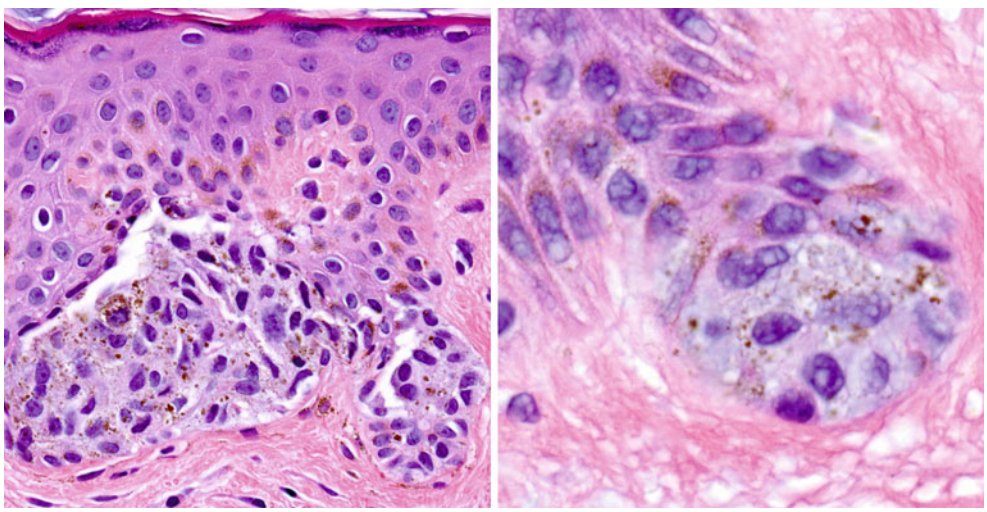

Fig. 39.3 Moderate cytological atypia in the junctional tumor cells in dysplastic nevus

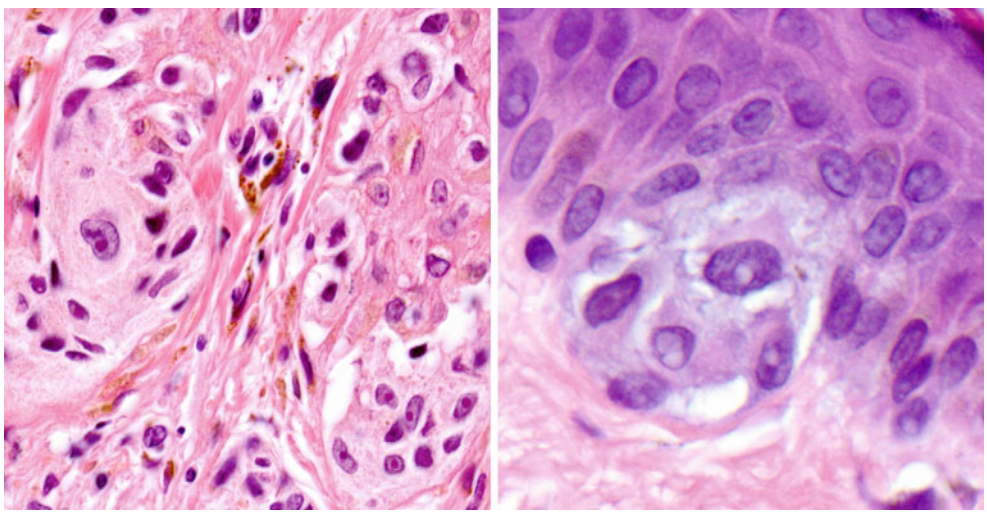

Fig. 39.4 Severe cytological atypia in the junctional tumor cells in dysplastic nevus

40 Congenital Melanocytic Nevi

Melanocytic nevi with features of congenital onset may display several distinct patterns of growth. Congenital nevi are usually compound or dermal and characteristically involve the reticular dermis.

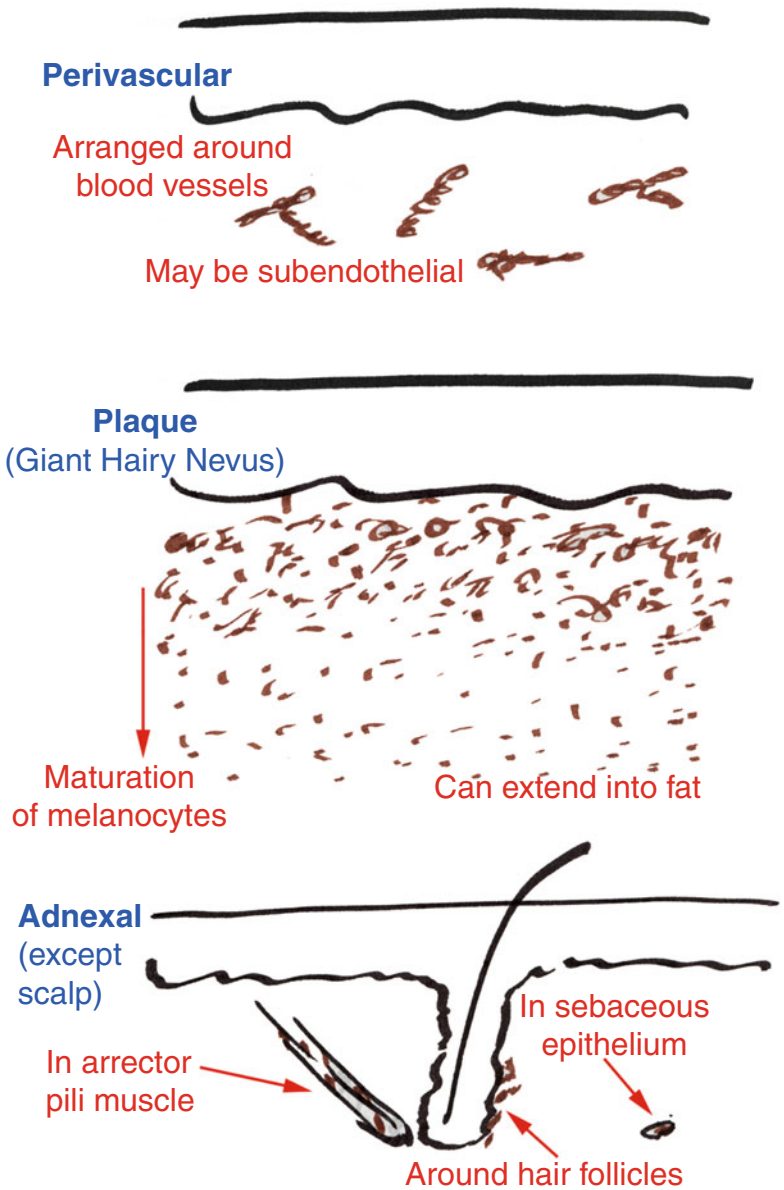

Fig. 40.1 Congenital nevi. This schematic depicts the variations of dermal growth patterns that may be observed in congenital melanocytic nevi

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
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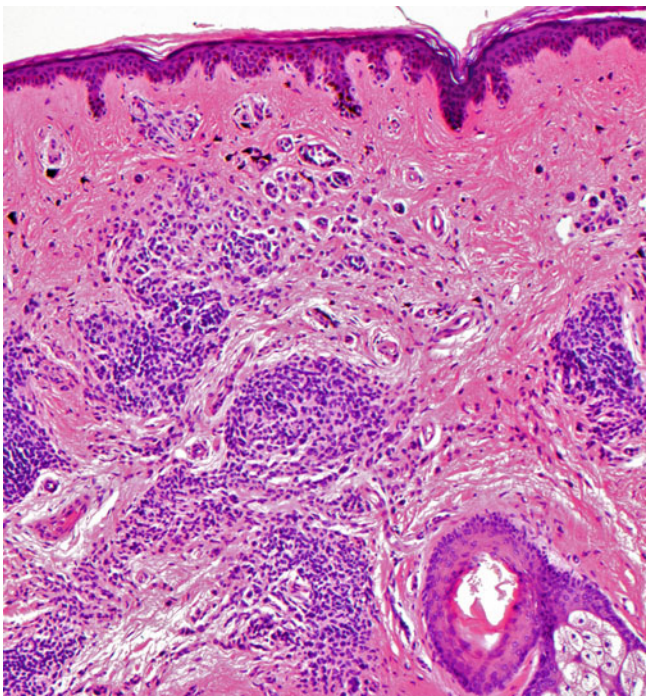

Fig. 40.2 Congenital nevus with a perivascular dermal growth pattern

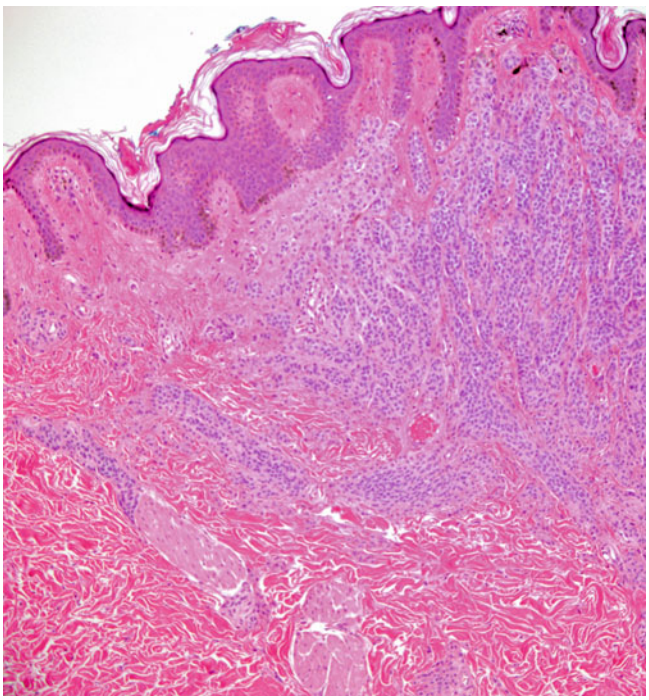

Fig. 40.4 Congenital nevus with extension around adnexal structures and infiltration of the arrector pili smooth muscle

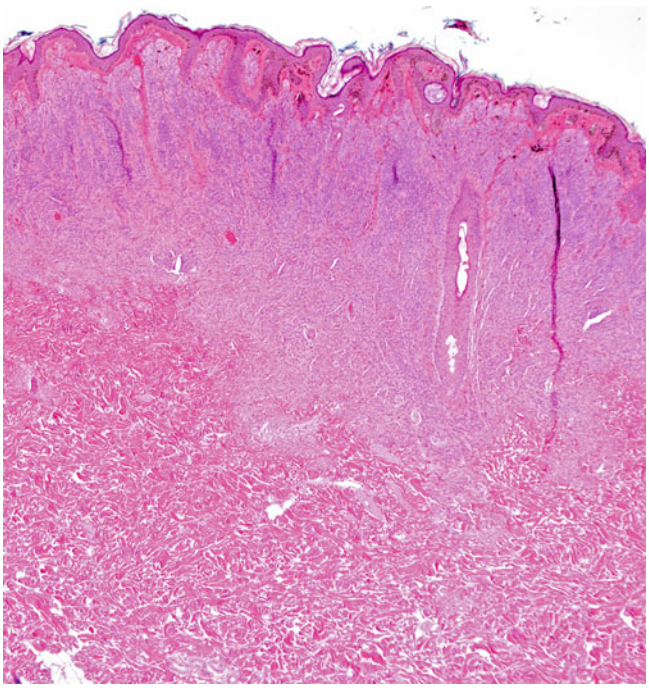

Fig. 40.3 Congenital nevus with a dermal component that diffusely infiltrates to form a plaque

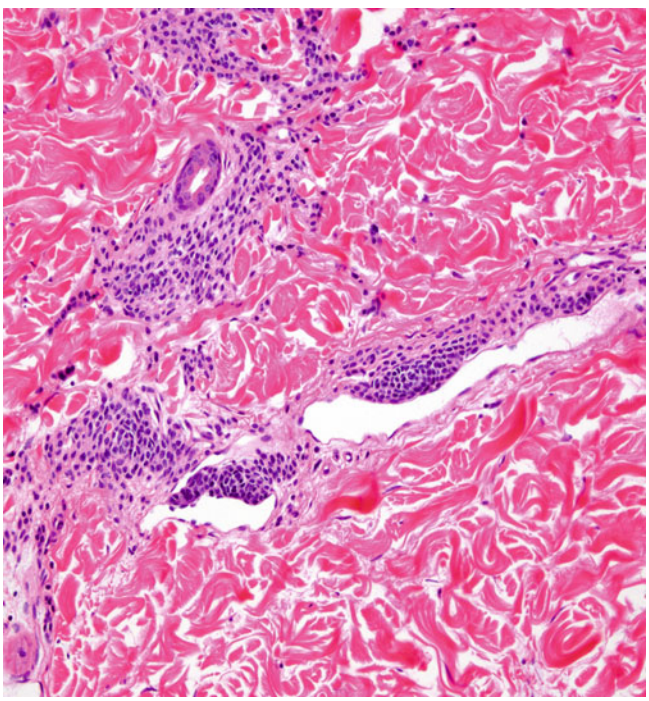

Fig. 40.5 Congenital nevus with a subendothelial growth pattern

41 Types of Combined Nevi

Following are the various types of combined nevi:

- Junctional, dermal, compound common or dysplastic nevus combined with one of the following:
  - Blue nevus (the most common)
  - Spindled and epithelioid cell nevus (Spitz or pigmented spindled cell nevus [PSCN])
  - Deep pigmented nevus (plexiform/deep penetrating or inverted type A/clonal)
- Other combinations with or without a common nevus component

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DOI 10.1007/978-1-4471-4471-7_41, © Springer-Verlag London 2013

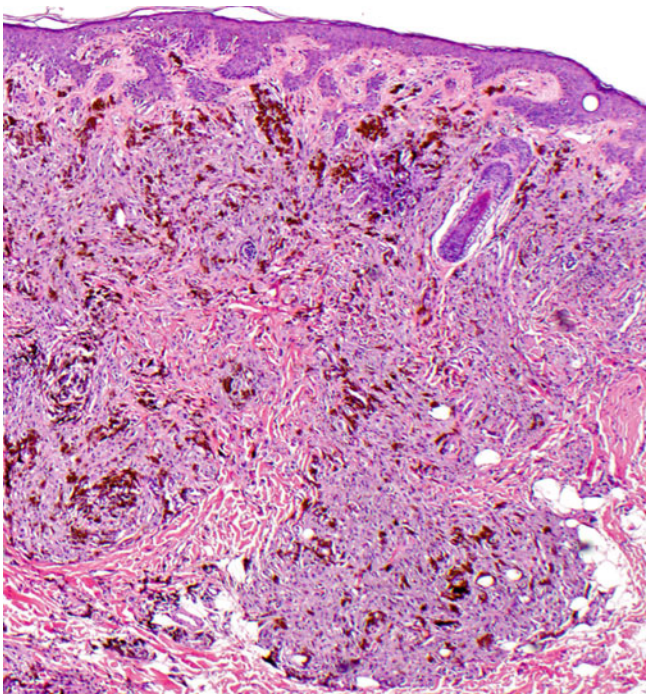

Fig. 41.1 Compound deep penetrating/plexiform nevus. This is a combined nevus with deep pigmented elements

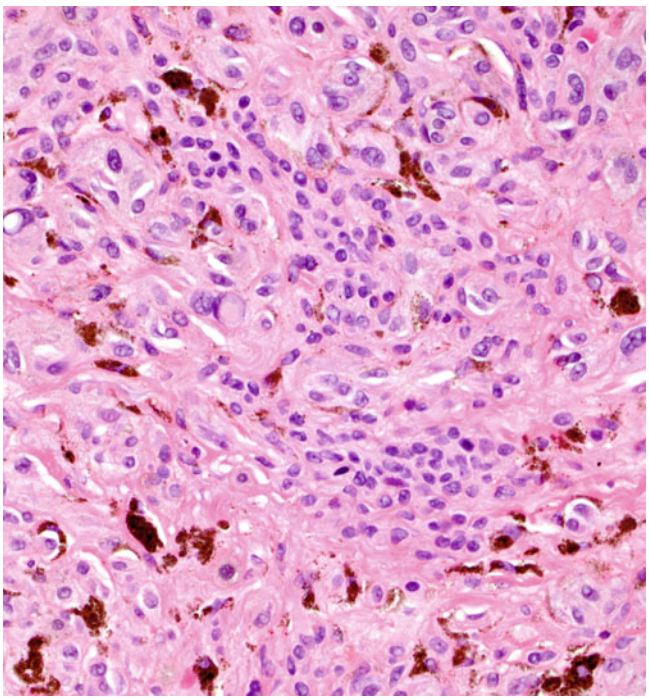

Fig. 41.3 Inverted type A nevus

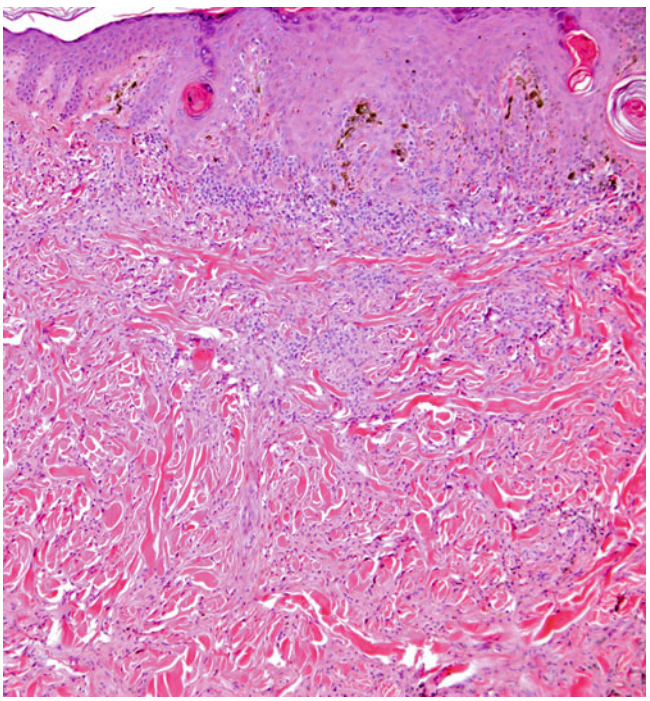

Fig. 41.2 Compound combined congenital and blue nevus

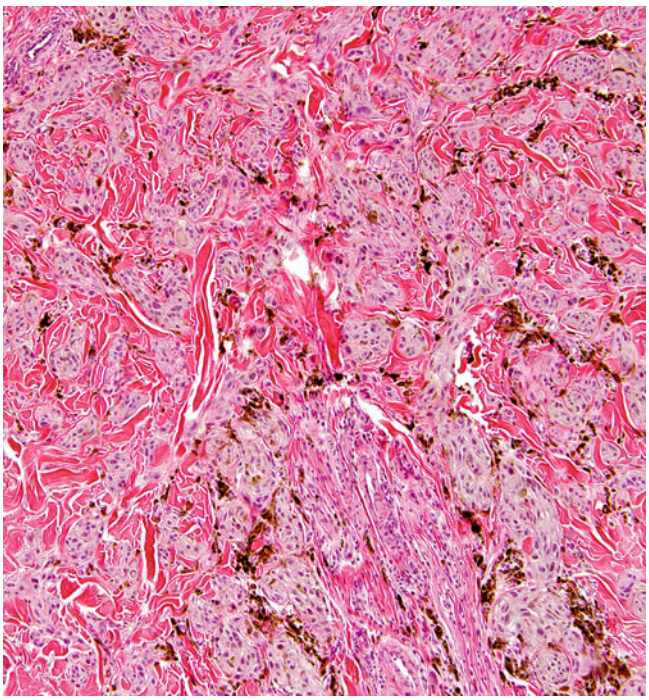

Fig. 41.4 Deep penetrating/plexiform nevus

42 Benign Melanocytic Proliferations with Pagetoid Spread

Pagetoid spread is defined as an individual cell proliferation in the upper levels of the epidermis, similar to the pattern of epidermal involvement by Paget's disease of the breast. When the melanocytes have marked cytological atypia, pagetoid spread is considered a major criterion for the diagnosis of melanoma-in-situ. There are several types of benign melanocytic proliferations that also display pagetoid spread and can be distinguished from melanoma.

The acronym PSPREAD highlights the types of tumors that may display pagetoid spread

Pediatric (nevus in infant, <5 years old; congenital nevus)
Spitz nevus
Pigmented spindled cell nevus
Recurrent nevus
Excoriated nevus
Acral nevus (MANIAC = melanocytic acral nevus with intraepidermal ascent of cells)
Dysplastic nevus

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DOI 10.1007/978-1-4471-4471-7_42, © Springer-Verlag London 2013

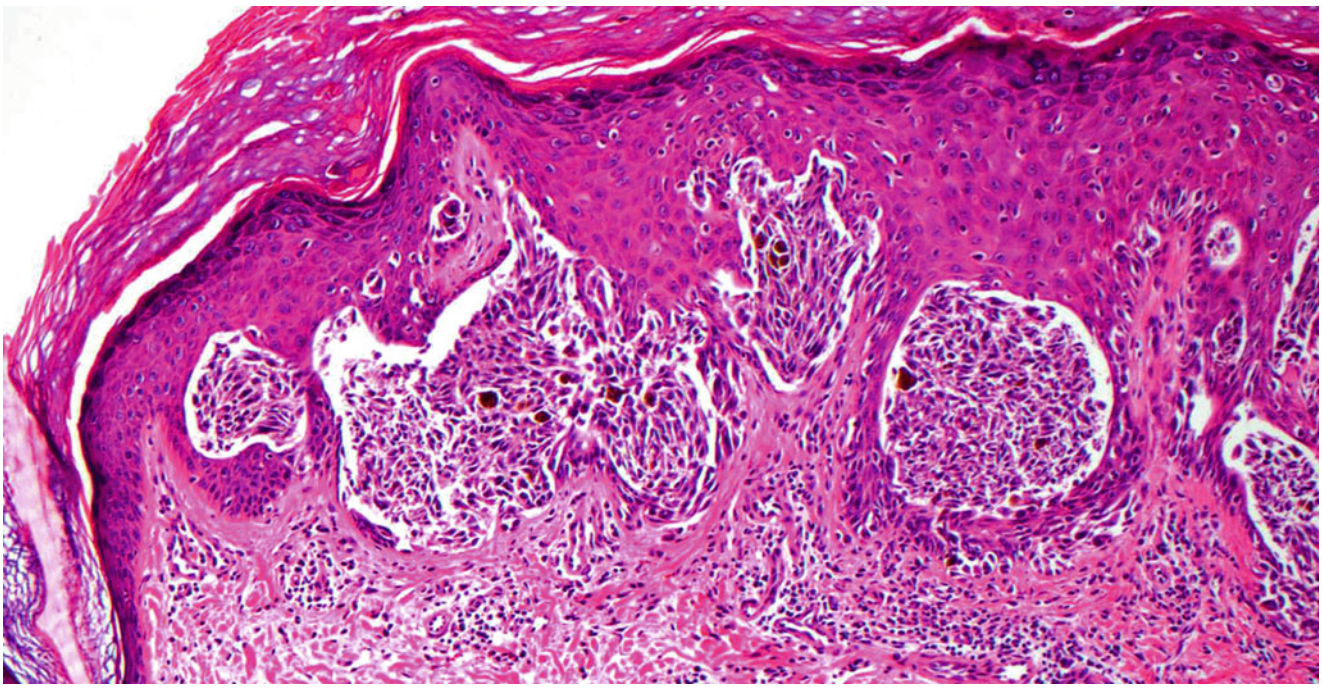

Fig. 42.1 Pigmented spindled cell nevus with pagetoid spread of individual melanocytes in the epidermis

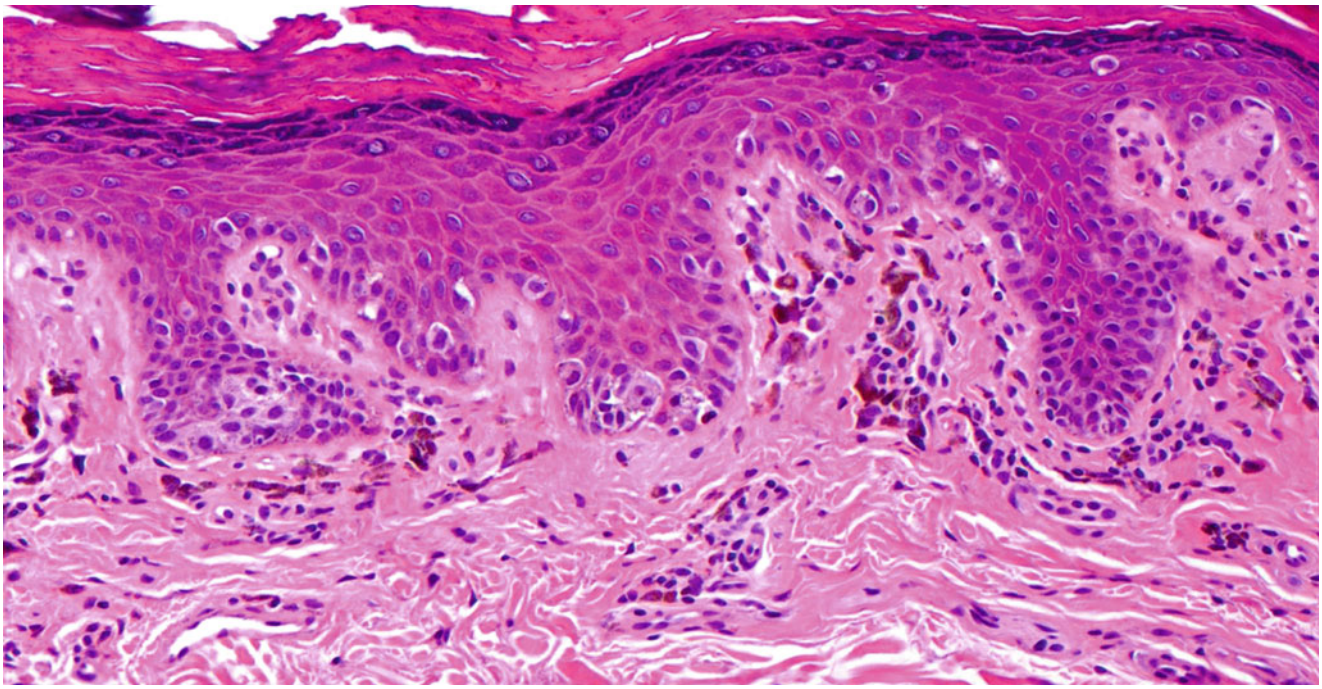

Fig. 42.2 Melanocytic acral nevus with intraepidermal ascent of cells (MANIAC)

Part IX

Reporting Melanoma

43 Invasive Primary Cutaneous Melanoma

Radial Growth Phase (RGP)
- Single cell dermal invasion
- Small invasive nests (dermal nests smaller than intraepidermal nests)
- No dermal tumor cell mitoses
- Inflammatory infiltrate
- Papillary dermis (Clark level II)

Vertical Growth Phase (VGP)
- Expansile nodule
- Nests in dermis larger than epidermis
- Dermal mitoses
- Stromal changes (desmoplastic)
- Papillary/reticular dermis, fat (Clark level III, IV, V)

Table 43.1 Primary cutaneous melanoma Types

	% of cases	RGP	VGP
SSM	70 %	+	–/+
LMM	3 %	+	–/+
ALM	2 %	+	–/+
NM	25 %	–	+ (pure VGP melanoma)

SSM superficial spreading melanoma, *LMM* lentigo maligna melanoma, *ALM* acral lentiginous melanoma, *NM* nodular melanoma

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
DOI 10.1007/978-1-4471-4471-7_43, © Springer-Verlag London 2013

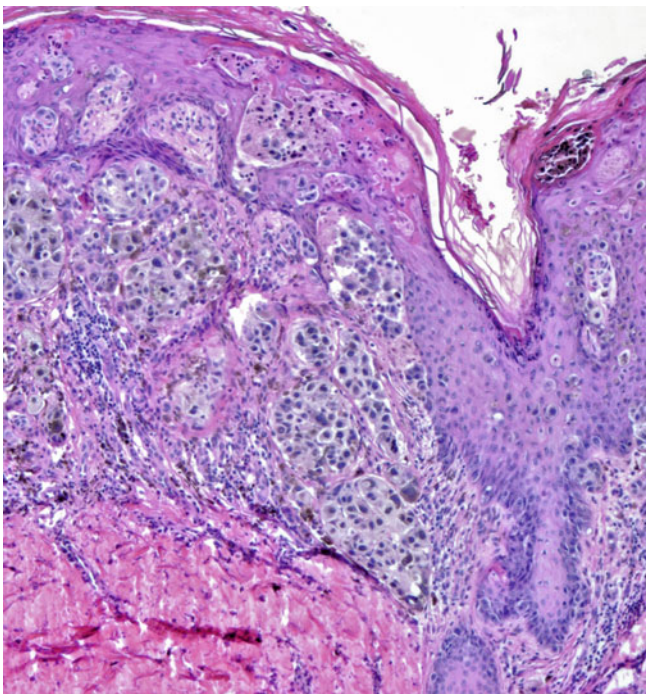

Fig. 43.1 Superficial spreading melanoma with radial growth phase and vertical growth phase

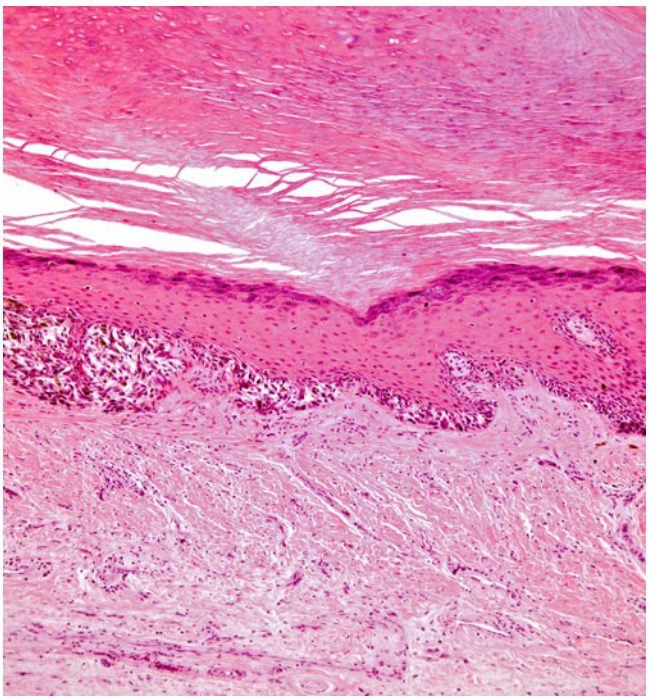

Fig. 43.3 Acral lentiginous melanoma in situ

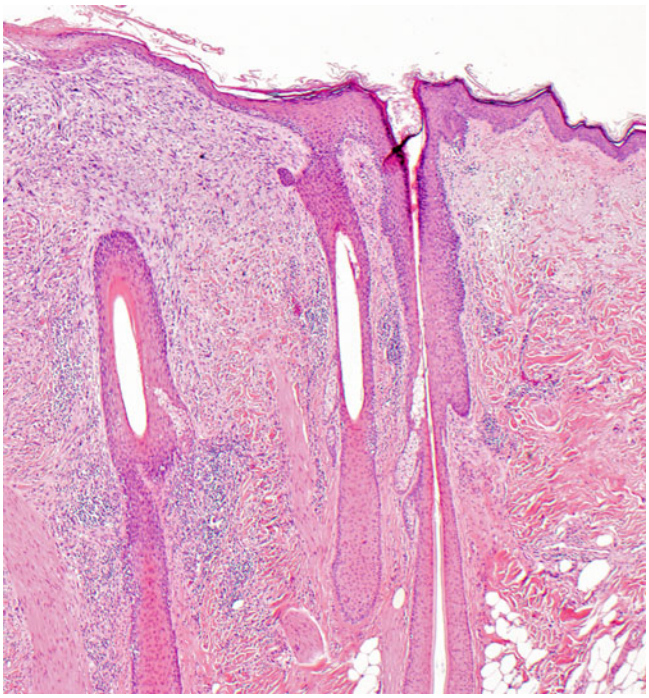

Fig. 43.2 Desmoplastic lentigo maligna melanoma with radial growth phase and vertical growth phase

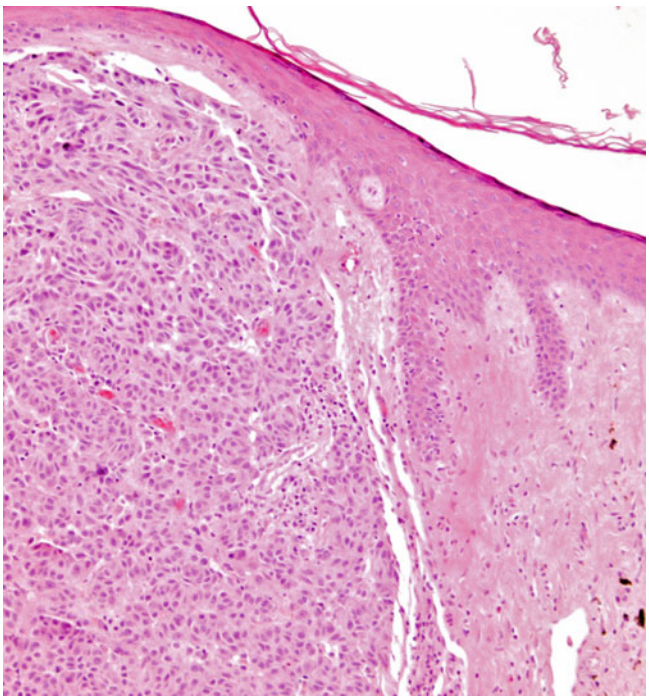

Fig. 43.4 Nodular melanoma is always a purely vertical growth phase tumor

44 Measuring Melanoma Thickness

Primary tumor thickness is the most powerful prognostic indicator in patients with cutaneous melanoma. Adhering to consistent methods for measuring and reporting primary tumor thickness is critical for patient care. The measurement of tumor thickness is done at the microscope using an intraocular micrometer. The microscope has a calibration table that allows for conversion of the measurement in the micrometer to the actual measurement in millimeters. The primary tumor thickness is measured from the top of the epidermal granular cell layer to the deepest invasive melanoma cell in the dermis. If the thickest region of tumor is associated with overlying ulceration, the measurement is taken from the base of the ulcer to the deepest melanoma cell. Melanoma cells that extend along adnexal structures, nerves or vessels are not used for this evaluation. In the case of a tumor with polypoidal architecture, the tumor thickness measured perpendicular to the skin surface across the largest diameter of the polypoidal projection.

Guidelines for measuring primary melanoma tumor thickness:

- Use a microscope with an intraocular micrometer and calibration table
- Measure perpendicular to the epidermal surface from the top of the stratum granulosum to the deepest dermal melanoma cell
- Do NOT include tumor cells within the adventitial dermis, within perineural spaces, or within vessels in this measurement
- If there is an ulcer over the thickest part of the tumor, measure from the most superficial viable tumor cell to the deepest dermal melanoma cell

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DOI 10.1007/978-1-4471-4471-7_44, © Springer-Verlag London 2013

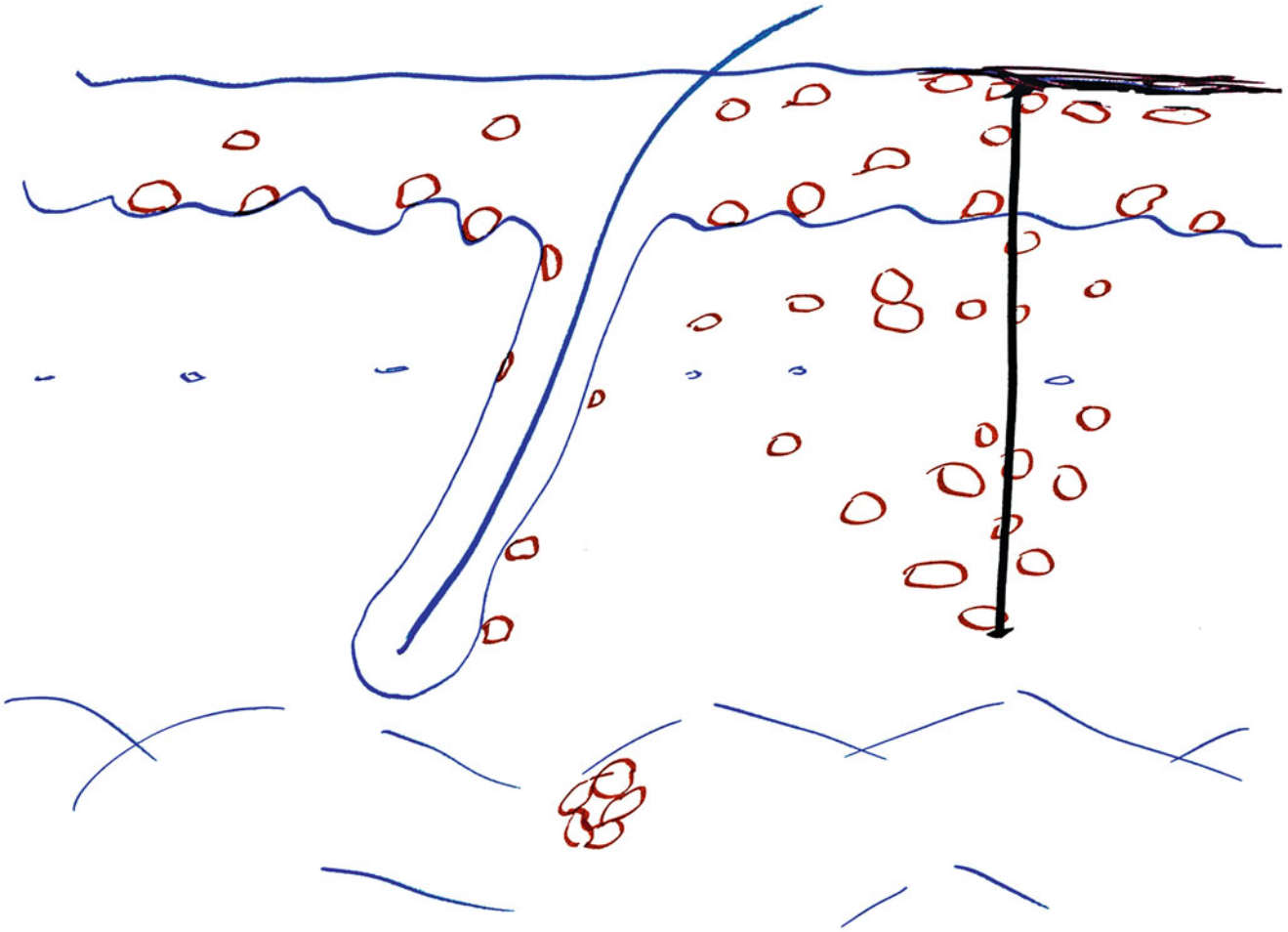

Fig. 44.1 Measuring primary cutaneous melanoma thickness. The melanoma cells in this schematic (*brown circles*) are present in the epidermis, in the dermis beneath a focus of ulceration, along the edge of a hair follicle and as a microscopic satellite in the subcutaneous fat. The *black line* indicates the appropriate location for measuring the tumor thickness. In this case, the tumor thickness, also known as the Breslow measurement, is taken from the top most viable cell beneath the ulcer to the deepest melanoma cell that is not associated with adnexal structures. Microscopic satellites are not included in the Breslow measurement

45 Melanoma Regression

The presence of regression in primary melanoma is associated with an increased risk of metastasis, particularly in thin melanoma. The most consistent correlations with prognosis occur when strict definitions in evaluating regression are adhered to. Regression is characterized by complete absence of melanoma cells in the epidermis and dermis, flanked by melanoma in the epidermis or dermis. The criteria for reporting regression are as follows:

- Focal complete absence of melanoma cells in the epidermis AND dermis within or adjacent to an invasive melanoma
- Often associated with a thin epidermis and underlying fibrosis, increased vascularity, chronic inflammation, and melanophages

K.S. Masterpol et al., *Atlas of Essential Dermatopathology*,
DOI 10.1007/978-1-4471-4471-7_45, © Springer-Verlag London 2013

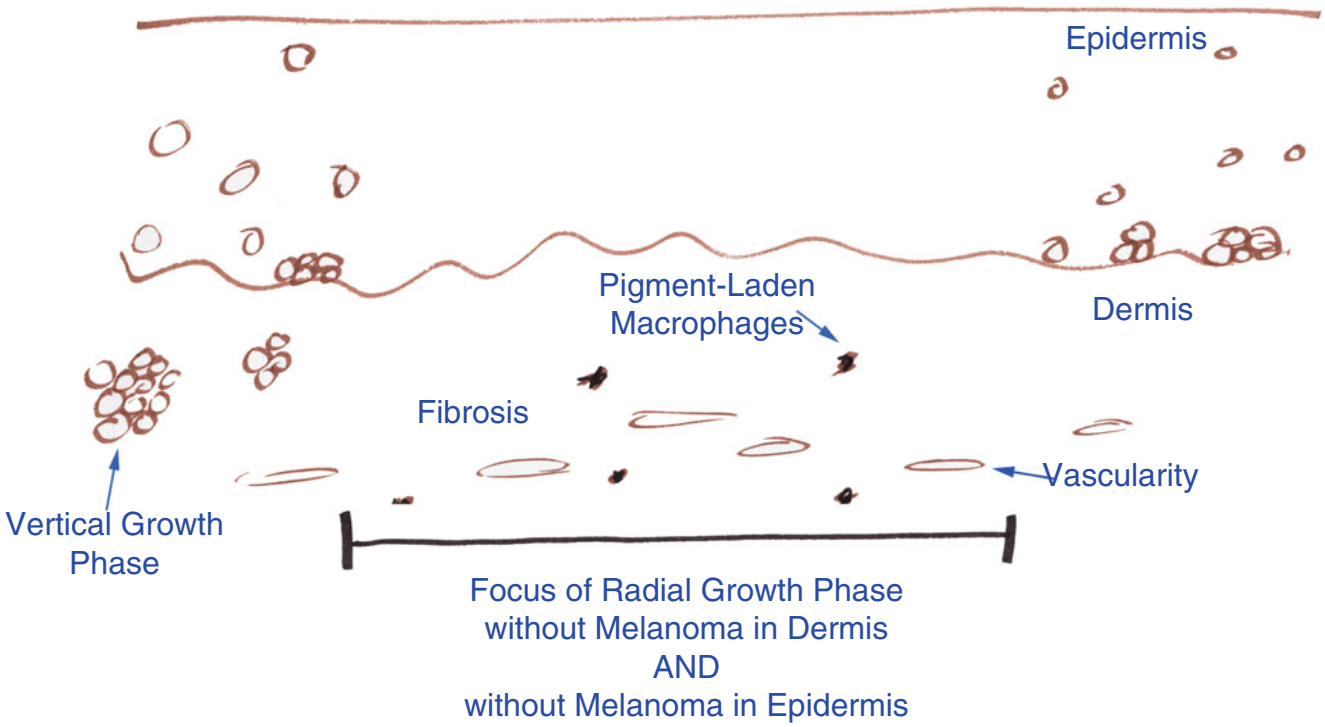

Fig. 45.1 Regression in primary cutaneous melanoma. The melanoma cells (*brown circles*) are present in the epidermis and dermis. There is a region in the center that lacks tumor in the epidermis and dermis, and is flanked by melanoma. This is the regressed focus. The presence of regression is associated with an increased risk of metastasis

46 Counting Melanoma Mitoses

Mitogenicity is an important prognostic factor in patients with thin primary cutaneous melanoma. In the American Joint Commission on Cancer (AJCC) seventh edition melanoma staging system, mitoses, ulceration and tumor thickness form the foundation for staging thin primary cutaneous melanoma. Studies demonstrating the prognostic value of mitogenicity used the "hot spot" technique for quantitation. The AJCC Melanoma Staging Committee recommends the use of the hot spot method with reports containing the number of mitoses counted in a square millimeter. This is accomplished by examination of routine hematoxylin and eosin (H&E) stained tissue sections; exhaustive tissue sectioning is not necessary.

- Use the "hot spot" method:
  - Scan the H&E stained tissue section for the region of the dermal tumor with the greatest number of mitotic figures → this is the starting point of the count. Count the next consecutive high power fields till one square millimeter has been evaluated. (Each microscope is different; 1 mm squared is four fields at 40× in some microscopes.)
- Report the number of mitotic figures counted per mm^2
- If only one mitosis is found in any field, report this as 1 mitosis/mm^2
  - Do NOT report as <1 mitosis/mm^2
- If no mitoses are identified in the vertical growth phase, report this as 0 mitoses/mm^2
  - Do NOT report as <1 mitosis/mm^2

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DOI 10.1007/978-1-4471-4471-7_46, © Springer-Verlag London 2013

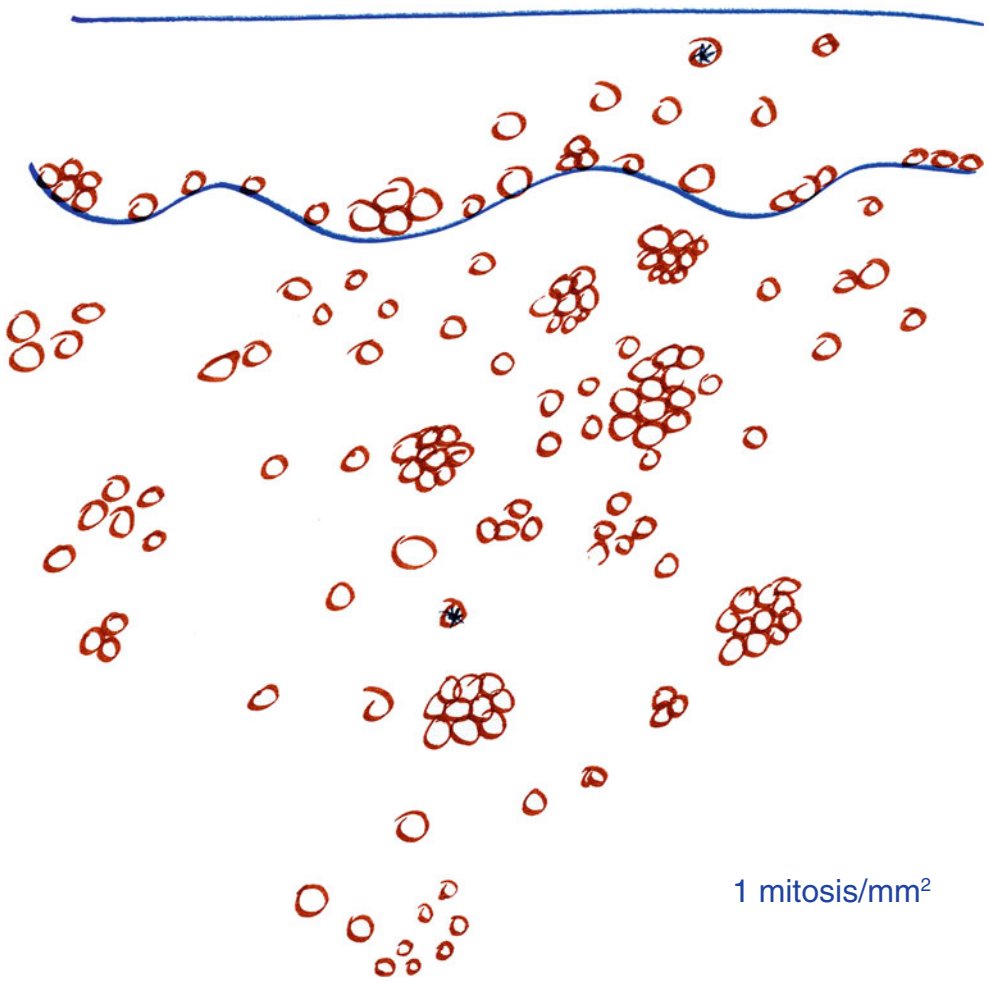

Fig. 46.1 Schematic of a melanoma that is reported as 1 mitosis/mm^2. The melanoma cells (*brown circles*) are observed in the epidermis and the dermis. Two tumor cells in mitosis (*brown circle with black asterisk*) are present. Intraepidermal tumor cells are not included in the evaluation. While this tumor is larger than 1 mm^2 total volume, there is one mitosis in the "hot spot" region of 1 mm^2. This case is reported as 1 mitosis/mm^2 (not <1 mitosis/mm^2)

47 Reporting Tumor Infiltrating Lymphocytes

The presence of many tumor infiltrating lymphocytes (TILs) in primary cutaneous melanoma is associated with a better prognosis. The degree of lymphocytic interaction with the tumor cells is graded as "brisk", "non-brisk" or "absent" as defined below:

Brisk

- TILs present throughout the substance of the vertical growth phase or infiltrating across the entire base of the vertical growth phase (VGP). Lymphocytes must be directly apposed to melanoma cells.

Non-Brisk

- TILs present in one or more foci of vertical growth phase

Absent

- Lymphocytes may be present but DO NOT infiltrate the melanoma. For example they may be around vessels, in a fibrotic zone, or surrounding but not infiltrating the melanoma
- There are no lymphocytes in association with any part of the VGP
- There is a dermal nodule of melanoma without inflammation

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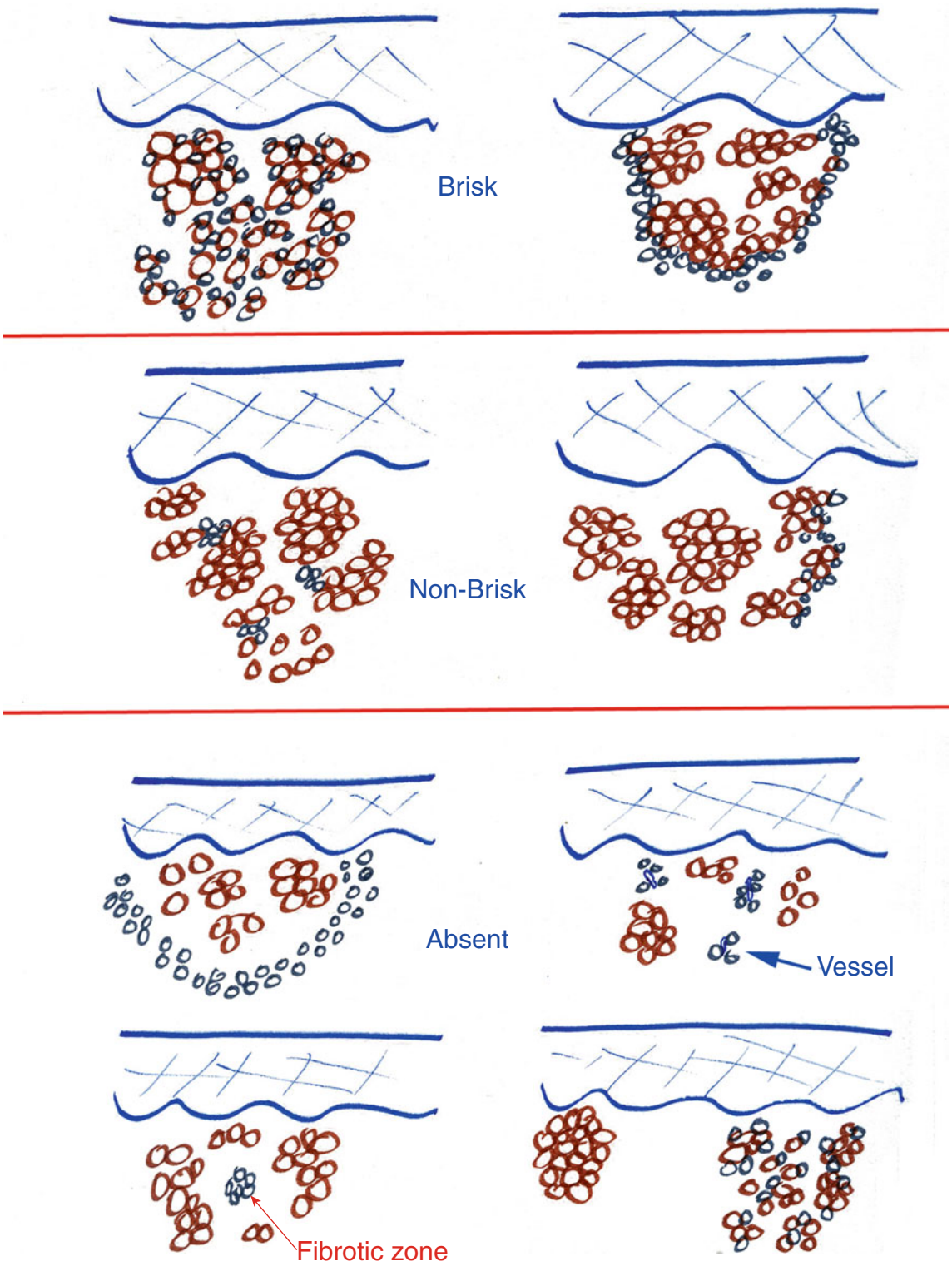

Fig. 47.1 Schematic of tumor infiltrating lymphocytes (TILs) in primary cutaneous melanoma. In a brisk pattern the TILs (*black small circles*) infiltrate throughout the vertical growth phase (VGP) or all along the peripheral margin, touching the melanoma cells (*brown circles*). In non-brisk infiltrates the interaction between the TILs and melanoma cells is more patchy or focal. In infiltrates termed absent, lymphocytes may be present but do not interact with the melanoma cells

48 Lentigo Maligna, Lentigo Maligna Melanoma In Situ and Lentigo Maligna Melanoma

The spectrum of severely atypical melanocytic proliferations in sun-damaged skin of the elderly ranges from a proliferation of scattered individual cells along the dermal epidermal junction (lentigo maligna), to a dense intraepidermal proliferation of cytologically atypical tumor cells with nesting, confluence and pagetoid spread (lentigo maligna melanoma in situ). When the tumor cells invade the dermis, this is invasive melanoma. Below are the criteria for distinguishing these three steps in melanocytic neoplasia.

Lentigo Maligna (LM)

- Atypical lentiginous melanocytic hyperplasia with focal confluence
- Epidermal atrophy
- Solar elastosis

Lentigo Maligna Melanoma In Situ (LMMIS)

LM and at least 2 of the 3 following criteria:

- Pagetoid spread of atypical melanocytes
- Intraepidermal melanocytic nests
- Confluence of cytologically atypical melanocytes along the dermal-epidermal junction

Lentigo Maligna Melanoma

- LMMIS and dermal invasion by atypical cells

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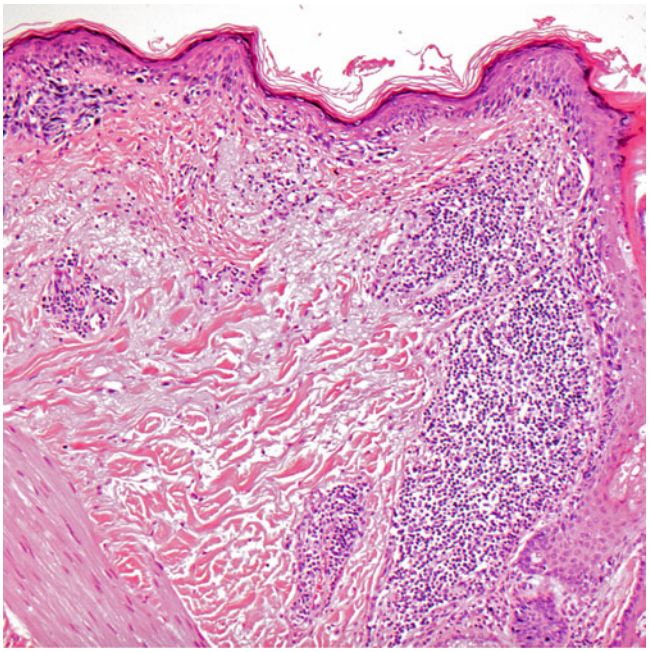

Fig. 48.1 Lentigo maligna melanoma in situ (LMMIS) with melanocytic nesting and confluence

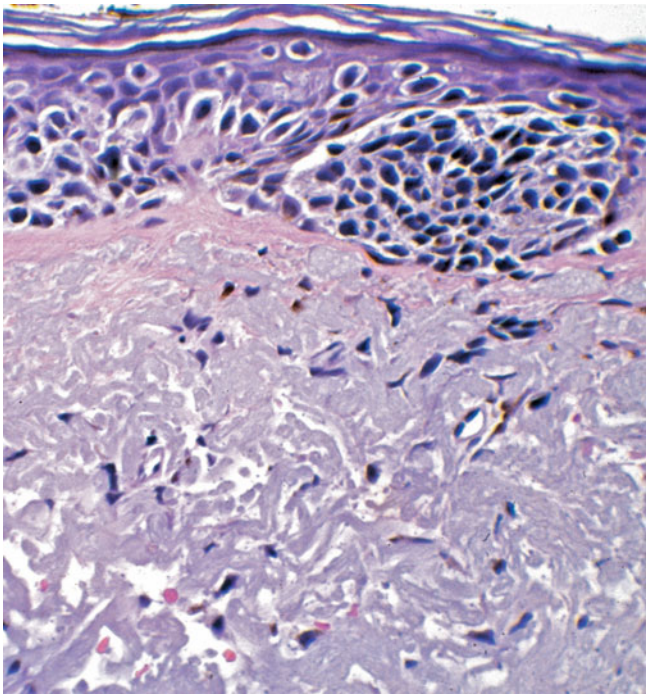

Fig. 48.2 Lentigo maligna melanoma in situ (LMMIS) with melanocytic nesting and pagetoid spread

Table 48.1 Characteristics of LM, LMMIS, LMM

	Lentigo maligna (LM)	LM melanoma in-situ (LMMIS)	LM melanoma (LMM)
Macular pigmented lesion on sun-exposed skin	+	+	+
Focal papule	–	–	+
Epidermal atrophy	+	+	+
Solar elastosis	+	+	+
Atypical lentiginous melanocytic hyperplasia	+	+	+
Intraepidermal nesting	–	+/–[a]	+/–
Pagetoid growth	–	+/–[a]	+/–
Confluence	–	+/–	+/–
Dermal component	–	–	+

[a]At least two of these three features are present in LMMIS

Part X

Special Stains

49 Histochemical Stains

In contrast to immunohistochemical stains which rely upon antibodies to detect specific antigens, histochemical stains use chemical reactions to detect tissue specific elements.

Table 49.1 Commonly used histochemical stains in the evaluation of cutaneous disease

Stain	Components stained	Examples of common uses
Alcian Blue	Acid dermal mucins	Lupus, dermatomyositis, myxedema
Brown Hopps (tissue gram stain)	Gram-positive: blue gram-negative: red	Necrotizing fasciitis
Colloidal Iron	Acid mucins	Lupus, dermatomyositis, myxedema
Chloracetate Esterase (Leder)	Mature myeloid cells/granulocytes	Acute myelogenous leukemia, granulocytic sarcoma
Elastic	Elastic fibers	Perforating disorders, pseudoxanthoma elasticum, anetoderma
Fontana-Masson	Melanin, neuroendocrine secretory granules	Post-inflammatory hyperpigmentation, vitiligo
Giemsa	Mast cells, protozoa	Urticaria pigmentosa, leishmaniasis
GMS (Grocott's Methenamine Silver)	Fungi	Deep fungal infections
Mucicarmine	Epithelial, Mucin, and acid Mucin	Adenocarcinoma, wall of Cryptococcus
PAS (Periodic Acid-Schiff)	Glycogen, basement membrane zone glycoproteins, sialomucins	Onychomycosis
PAS-D (PAS-Diastase)	Same as above but diastase breaks down glycogen	Lupus, deep fungal infections
Toluidine Blue	Acid mucins, mast cells	Lupus, dermatomyositis
Trichrome	Collagen	Perforating disorders
Von Kossa	Calcium	Calciphylaxis

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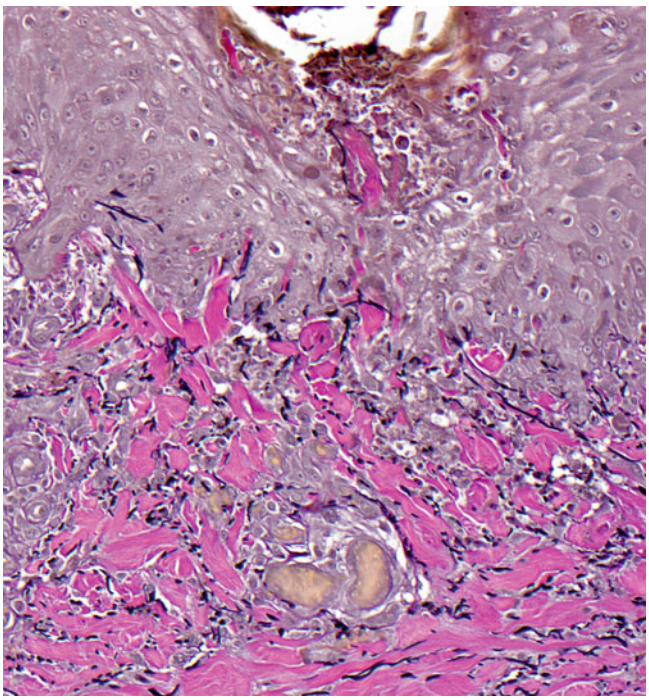

Fig. 49.1 Elastic tissue stain in elastosis perforans serpiginosa

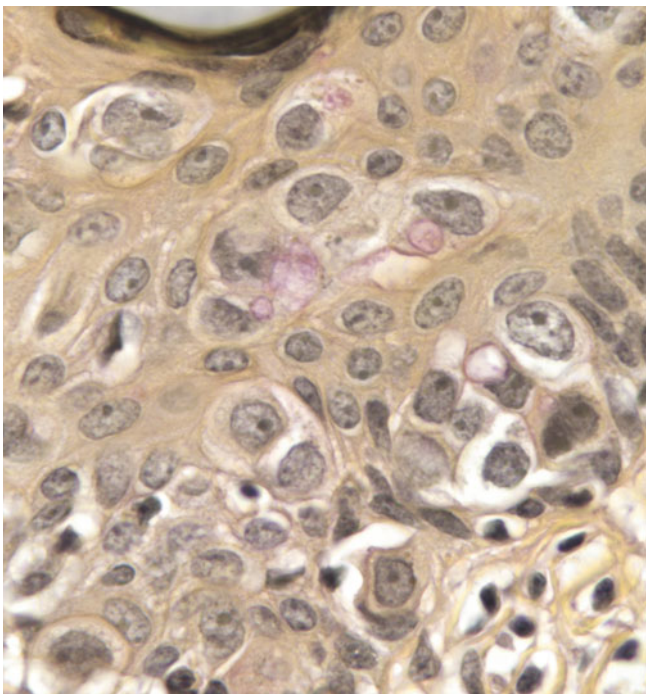

Fig. 49.3 Mucicarmine stain marks intracytoplasmic mucin (*pink*) in extramammary Paget's disease

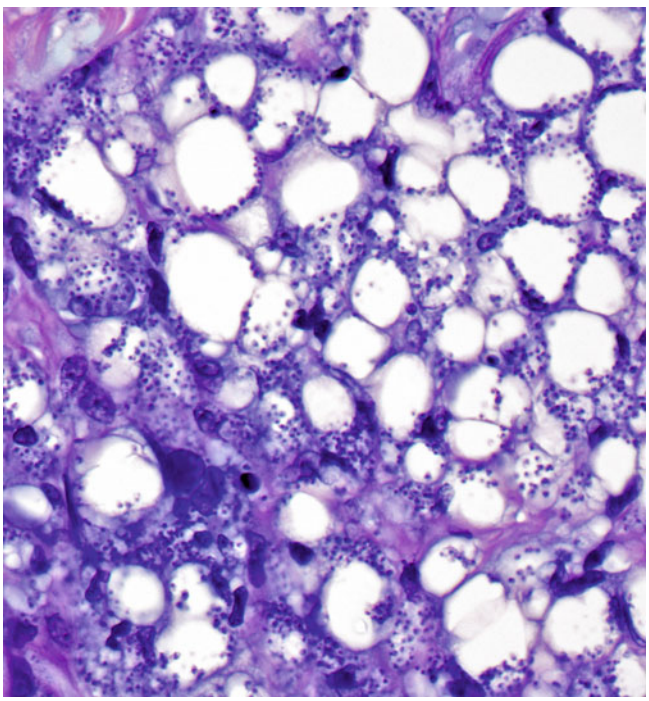

Fig. 49.2 Giemsa stains intracytoplasmic organisms in leishmaniasis

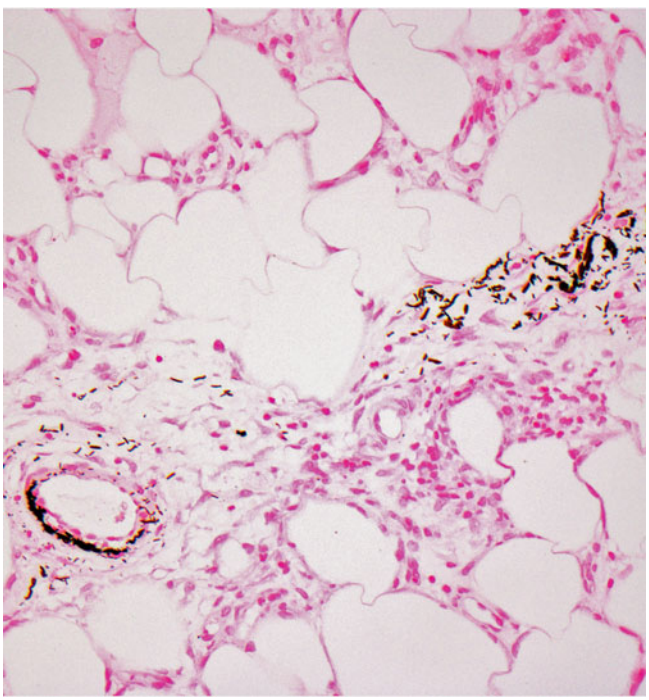

Fig. 49.4 von Kossa stain highlights perivascular and interstitial calcification (*brown-black*) in calciphylaxis

50 Immunohistochemical Stains

Immunohistochemistry is a valuable supplement to hematoxylin and eosin staining that uses tagged antibodies to detect tissue specific proteins.

Table 50.1 Immunohistochemical stains in dermatopathology

Stain	Components stained	Uses
CD1a	Intraepidermal Langerhans cell and some dermal dendritic cells	Langerhans cell histiocytosis
CD34	Endothelial cells, hematopoietic progenitor cells, dermal dendritic cells	Vessels and stromal elements
CD68	Histiocytes	General marker of histiocytes, not specific
CD163	Histiocytes	More specific for histiocytes than CD68
CEA	Adnexal ducts	Stains ductal differentiation in adnexal neoplasms
Cytokeratin	Intermediate filaments of epithelial cells	CK5/6: squamous cells
		CK7: adnexa, breast
		CK20: Merkel cells (punctate)
		AE1.3: most carcinomas
		CAM5.2: most carcinomas
		CK903: high molecular weight keratin (HMWK), basal and myoepithelial cells
D240	Lymphatic endothelium	Lymphovascular invasion
Desmin	Intermediate filaments of myocytes	Tumors with muscle differentiation
EMA	Sebaceous cells and other adnexal cells	Tumors with sebaceous differentiation
Factor XIIIa	Fibroblasts	Tumors with fibroblastic differentiation
Fli-1	Endothelial cells	Vascular tumors
GFAP (Glial filament sssociated protein)	Intermediate filaments of CNS cells	Tumors with neural differentiation
HMB-45	Melanocytes	Identification of melanoma and intraepidermal nevi
Ki-67	Cycling cells	Proliferative index
LCA (Leukocyte common antigen)	All lymphoid cells	Positive in almost all non-Hodgkin lymphomas
MART-1	Melanocytes	Melanoma and nevi
Melan-A	Melanocytes	Melanoma and nevi
MITF	Melanocytes and some histiocytes	Melanoma and melanocytes (nuclear)
NKIC3	Selected neural crest dermal cells	Some melanomas and neurothekoma
S100	Neural tissue, secretory components of adnexa, melanocytes	Melanoma, nevi, and clear cell adnexal carcinoma
SMA (Smooth muscle actin)	Smooth muscle, myoepithelial cells, myofibroblasts	Smooth muscle tumors, glomus cell tumors, eccrine carcinoma
Vimentin	Mesenchymal tissues and melanocytes	Soft tissue tumor and melanoma

This table is not comprehensive, but includes many of the most commonly used immunohistochemical stains in dermatopathology

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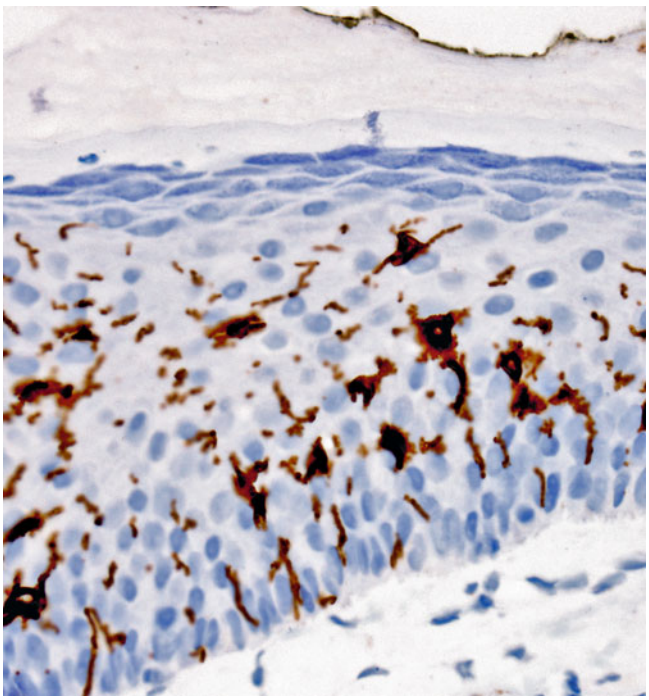

Fig. 50.1 CD1a stain highlights intraepidermal Langerhans cells

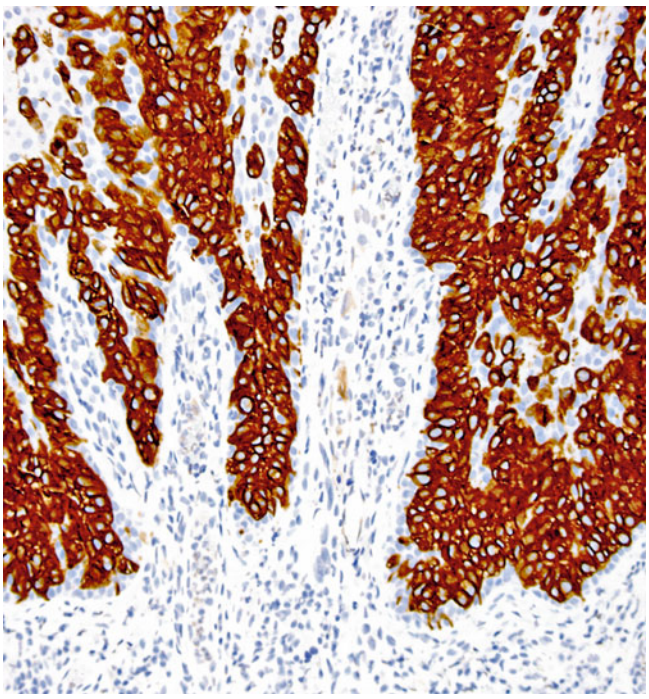

Fig. 50.3 Cytokeratin 7 (CK7) in extramammary Paget's disease. There is staining of intraepidermal tumor cells. Note the rim of CK7 negative keratinocytes at the dermal epidermal junction

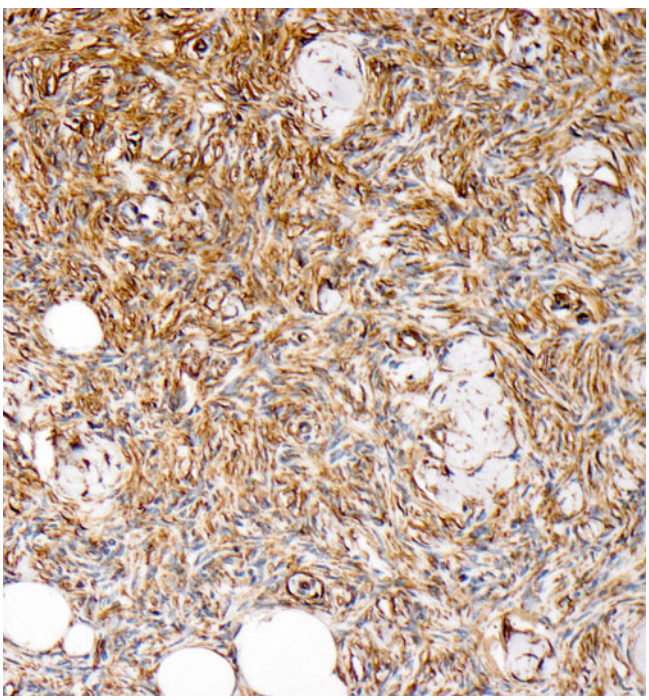

Fig.50.2 CD34 stain marked the neoplastic cells in dermatofibrosarcoma protruberans

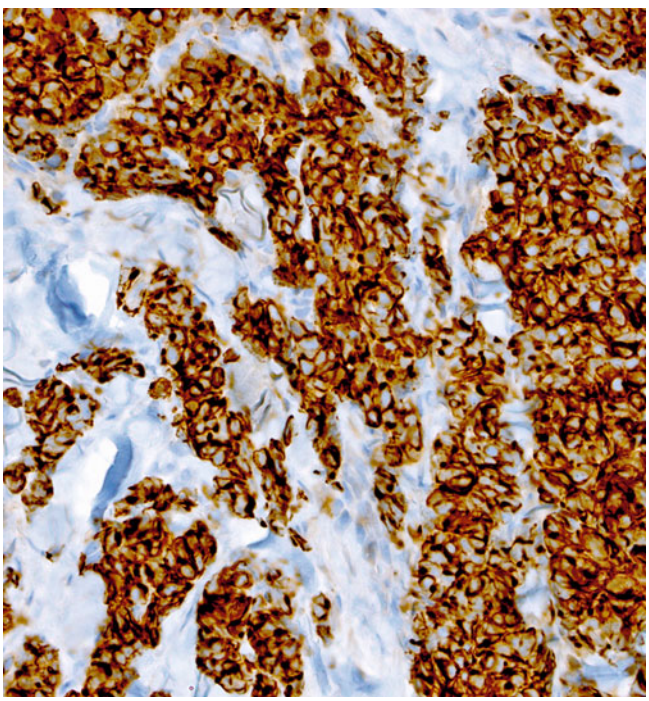

Fig. 50.4 Cytokeratin 20 (CK20) in merkel cell carcinoma. There is punctate dot-like perinuclear staining

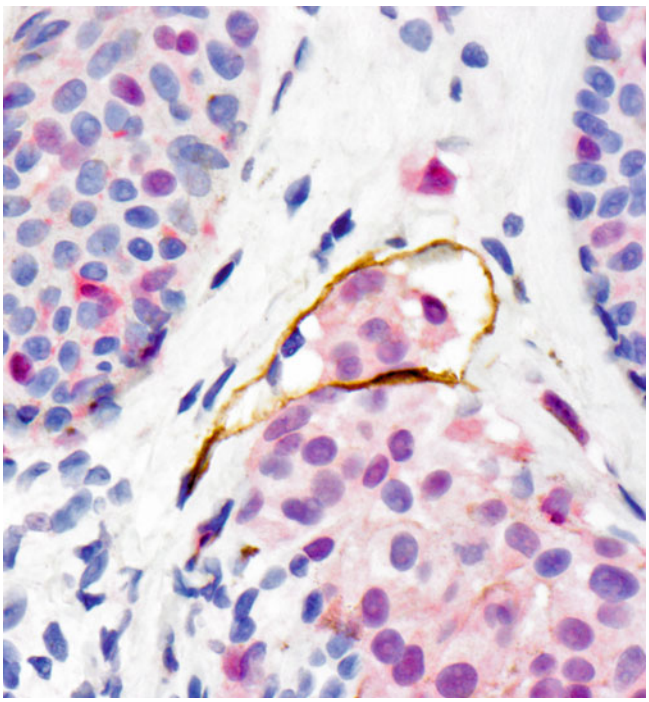

Fig. 50.5 D240 and S100 combined stain allows for the identification of S100+ melanoma cells (pink) within D240+ lymphatics (*brown*)

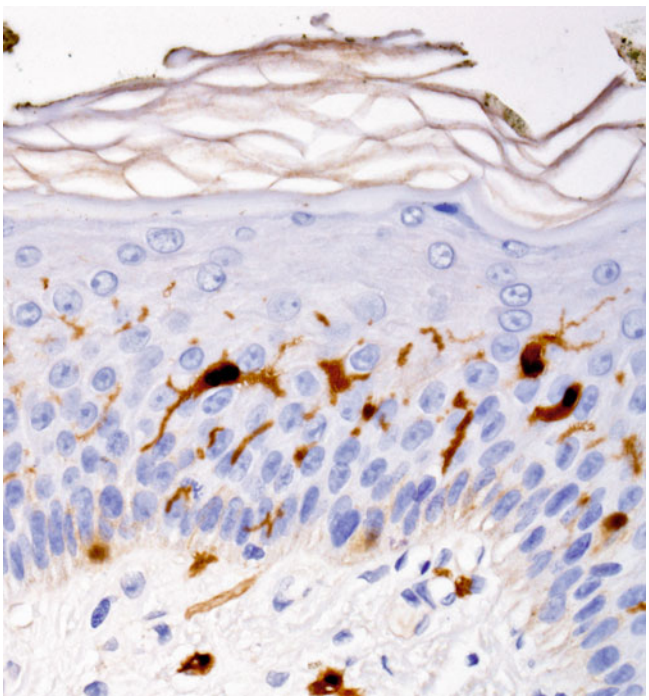

Fig. 50.7 S100 stains intraepidermal melanocytes and Langerhans cells

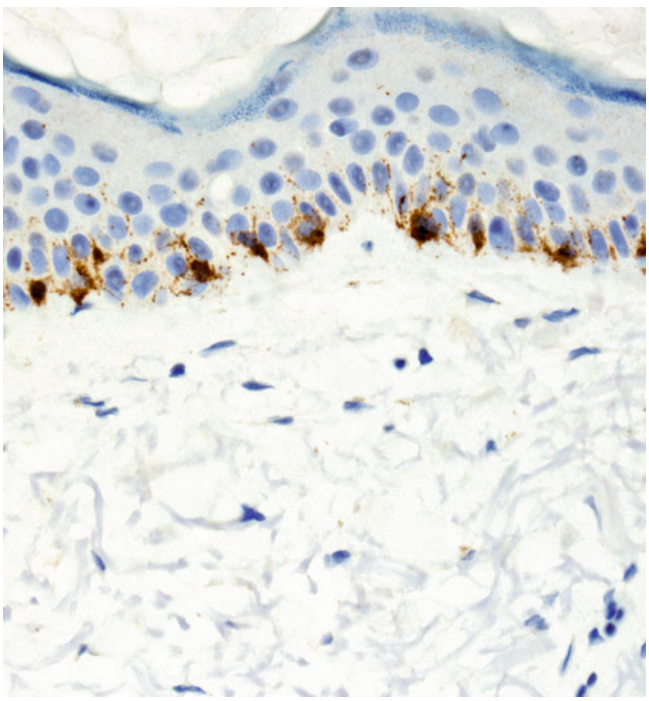

Fig. 50.6 HMB-45 stains intraepidermal melanocytes

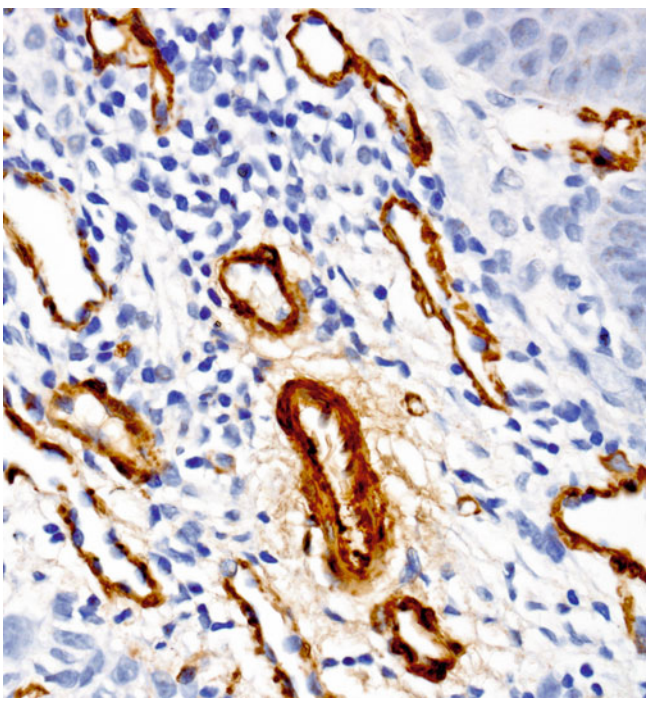

Fig. 50.8 SMA stains perivascular smooth muscle

Glossary

Acantholysis Loss of intercellular coherence between keratinocytes

Acanthosis Epidermal hyperplasia with increased thickness of stratum spinosum

Apoptosis Programmed cell death characterized by shrinkage of the cell, condensation of chromatin, and nuclear fragmentation

Bulla Intraepidermal or sub-epidermal cavity greater than 5 mm in diameter containing serous fluid and/or inflammatory debris

Civatte/Colloid Bodies Intraepidermal or superficial papillary dermal eosinophilic, round bodies, common in lichenoid processes

Corps Ronds Keratinocytes in stratum spinosum with eosinophilic cytoplasm and perinuclear halos of basophilic keratohyaline granules in acantholytic dyskeratosis

Dyskeratosis Abnormal, premature keratinization of individual keratinocytes below the stratum corneum

Epidermotropism The presence of cytologically atypical T-lymphocytes within the epidermis usually without associated spongiosis, characteristic of mycosis fungoides

Erosion Incomplete loss of epidermis without epidermal basement membrane zone damage

Exocytosis The presence of mononuclear cells within the epidermis usually with associated spongiosis

Giant Cell Foreign body giant cell: multinucleate giant cell with haphazard arrangement of nuclei. Touton giant cell: multinucleate giant cell with a ring of nuclei surrounding a central area of non-foamy eosinophilic cytoplasm with a peripheral wreath-like area of foamy cytoplasm

Grains Remnant tiny pyknotic nuclei of keratinocytes in superficial epidermis in acantholytic dyskeratosis

Granulation Tissue Newly formed loose collagenous tissue in healing wounds composed of fibroblasts, new capillaries, and an infiltrate of lymphocytes, plasma cells, and macrophages

Grenz Zone A narrow area of uninvolved papillary dermis separating the epidermis from an underlying dermal cellular infiltrate or neoplasm

Hyperkeratosis Thickening of the stratum corneum

Kamino Body Eosinophilic hyaline globules composed of basement membrane material typically found in Spitz nevi at the dermal-epidermal junction or dermal papillae

Karyorrhexis Fragmentation of the nucleus of a dying cell resulting in nuclear dust (apoptosis)

Leukocytoclasis The destruction of leukocytes, particularly neutrophils, resulting in nuclear dust

Mucin Dermal mucin: acid mucopolysaccharides (mostly hyaluronic acid); stains with alcian blue, colloidal iron, or toluidine blue; PAS negative; occurs in connective tissue diseases. Epithelial mucin (sialomucin): consists of neutral and acid mucopolysaccharides; PAS positive and diastase resistant, mucicarmine positive

Munro's Microabscess Small accumulation of degenerated neutrophils within the stratum corneum in psoriasis

Orthokeratosis Hyperkeratosis without retention of keratinocyte nuclei

Parakeratosis Hyperkeratosis in which stratum corneum contains retained keratinocyte nuclei

Pautrier Microabscess Intraepidermal accumulation of three or more cytologically atypical T-lymphocytes within the stratum spinosum

Plexiform Following existing neurovascular structures forming a plexus or network, web-like

Pseudo-Pautrier Microabscess Intraepidermal accumulation of three or more Langerhans cells and lymphocytes within the stratum spinosum

Pustule Intraepidermal or sub-epidermal space containing fluid and inflammatory cells, usually neutrophils

Reticular Degeneration Severe intracellular edema resulting in bursting of keratinocytes and formation of a

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multilocular vesicle with septa composed of remaining cell walls, characteristic of viral exanthem

Spongiform Pustule of Kogoj Multilocular neutrophilic pustule in upper stratum spinosum in psoriasis

Spongiosis Intercellular epidermal edema causing increased space between keratinocytes

Ulcer Complete loss of epidermis often with basement membrane zone destruction

Vesicle A small bulla, less than 5 mm in diameter

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