DERMATOPATHOLOGY

Microscopic Terms

Hyperkeratosis: hyperplasia of the stratum corneum
Parakeratosis: mode(s) of keratinization characterized by retention of the nuclei in the stratum corneum; on mucosal membranes.
Acanthosis: epidermal hyperplasia preferentially involving the stratum spinosum
Dyskeratosis: abnormal keratinization occurring prematurely within individual cells or groups of cells below the stratum granulosum
Acantholysis: loss of intercellular connections resulting in lack of cohesion between keratinocytes
Papillomatosis: hyperplasia of the papillary dermis with elongation and/or widening of the dermal papillae
Spongiosis: intercellular edema of the epidermis

Chronic Inflammatory Dermatoses

1. Psoriasis

This is a common chronic inflammatory skin disease affecting up to 2% of people.

Pathogenesis

- As an immunologic disease, the pathogenesis psoriasis also involves genetic susceptibility and environmental factors.
- It is not known if the inciting antigens are self or environmental.
- Sensitized populations of T cells enter the skin, including dermal CD4+ T_{H1} cells and CD8+ T cells that accumulate in the epidermis. T cells homing to the skin secrete cytokines and growth factors that induce keratinocyte hyper-proliferation.
- Psoriatic lesions can be induced in susceptible individuals by local trauma, a process known as the Koebner phenomenon. The trauma may induce a local inflammatory response that promotes lesion development.

Pathological features

- There is marked epidermal thickening (acanthosis), with regular downward elongation of the rete ridges likened to "test tubes in a rack."
- Increased epidermal cells proliferation and lack of maturation results in loss of the stratum granulosum with extensive overlying parakeratotic scale.
- There is thinning of the epidermal cell layer overlying the tips of dermal papillae and blood vessels within the papillae are dilated and tortuous. These vessels bleed readily when the scale is removed; giving rise to multiple punctate bleeding points (Auspitz sign).
- Neutrophils form small aggregates within both the superficial epidermis and the parakeratotic stratum corneum (microabscesses of Munro).

Similar changes can be seen in superficial fungal infections, and it is important to exclude this possibility with special stains (e.g. PAS) in new diagnoses of psoriasis.

Psoriasis most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal cleft, and glans penis. The most typical lesion is a well-demarcated, pink plaque covered by loosely adherent silver-white scale. Nail changes occur in 30% of cases of psoriasis and consist of yellow-brown discoloration, with pitting, thickening, and crumbling.
2. Lichen planus
Pruritic, purple, polygonal, plane-surfaced papules, and plaques" are the traditional "p's" of this disorder of skin and mucosa. Lichen planus is self-limited and usually resolves spontaneously 1 to 2 years after onset. The pathogenesis is not known. Expression of altered antigens at the level of the basal cell layer and the dermo-epidermal junction may elicit a CD8+ T-cell-mediated cytotoxic immune response. **Pathological features**
- There is characteristically a dense, continuous infiltrate of lymphocytes along the dermoepidermal junction (interface dermatitis).
- The lymphocytes are intimately associated with basal keratinocytes that show degeneration and necrosis.
- This pattern of inflammation causes the dermoepidermal interface to assume an angulated, zigzag contour ("sawtoothing").
- Changes of chronicity include: epidermal hyperplasia, hypergranulosis, and hyperkeratosis.

Cutaneous lesions consist of pruritic, violaceous, flat-topped papules, which may coalesce focally to form plaques. These papules are often highlighted by white dots or lines, called Wickham's striae. Multiple lesions are symmetrically distributed, particularly on the extremities, often about the wrists and elbows, and on the glans penis. In 70% of cases, oral lesions are present as mucosal, white, netlike areas.

3. Lichen Simplex Chronicus (LSC)
LSC presents as roughening of the skin that is reminiscent of lichen on a tree. The pathogenesis is not understood, but it is probable related to the response of the skin to repetitive trauma that induces epithelial hyperplasia with eventual dermal scarring. **Microscopically**, LSC is characterized by acanthosis with hyperkeratosis and hypergranulosis. There is elongation of the rete ridges and fibrosis of the papillary dermis with a chronic inflammatory infiltrate. The lesions are often raised and erythematous and scaly. LSC is often superimposed upon, and masks another (often pruritic) dermatosis.

**BLISTERING (BULLOUS) DISEASES**
These refer to a group of disorders in which blisters are the primary and most distinctive features. These differ from other diseases in which blisters occur as a secondary phenomenon in several unrelated conditions (e.g., herpesvirus infection, spongiotic dermatitis). Blisters refer to “accumulations of fluid within or below epidermis and mucous membranes”. They are divided into
1. Vesicles (< 1.0 cm)
2. Bullae (> 1.0 cm)
Blisters can occur at multiple levels within the skin, and assessment of their location is essential for an accurate histological diagnosis.

1. **Pemphigus** is a rare autoimmune blistering disorder resulting from loss of integrity of normal intercellular bridges (desmosomes) within the epidermis and mucosal epithelium. Most individuals who develop pemphigus are middle-aged and older. The are 5 major variants:
   1. Pemphigus vulgaris
   2. Pemphigus vegetans (a variant of P. vulgaris)
   3. Pemphigus foliaceus
4. Pemphigus erythematosus (a variant of P. foliaceus)
5. Paraneoplastic pemphigus (associated with internal malignancy).

Pathogenesis
Both pemphigus vulgaris and pemphigus foliaceus are caused by a type II hypersensitivity reaction (antibody directed against a fixed tissue antigen) and show linkage to specific HLA types. Patient sera contain pathogenic IgG antibodies to intercellular desmosomal proteins of skin and mucous membranes.

Pathologic features
- The common histologic denominator in all forms of pemphigus is acantholysis (lysis of desmosomes) within a squamous epithelial surface. The detached acantholytic cells become rounded.
- In pemphigus vulgaris, acantholysis selectively involves the layer of cells immediately above the basal cell layer, giving rise to a suprabasal blister; the floor of the cavity is lined by a single layer of intact basal cells (tombstone effect).
- In pemphigus foliaceus, acantholysis selectively involves the superficial epidermis at the level of the stratum granulosum.
- Variable superficial dermal infiltration by lymphocytes, histiocytes, and eosinophils accompanies all forms of pemphigus.

2. Bullous Pemphigoid
Generally affecting elderly individuals that typically presents with generalized cutaneous lesions and involvement of mucosal surfaces. It is an autoimmune disease in which the characteristic finding is linear deposition of IgG antibodies and complement in the basement membrane zone. Microscopically, it is characterized by a subepidermal, nonacantholytic blister. Early lesions show a perivascular infiltrate of lymphocytes and variable numbers of eosinophils. Because the blister roof involves full-thickness epidermis, it is more resistant to rupture than blisters in pemphigus. Clinically, lesions are tense bullae, filled with clear fluid, on normal or erythematous skin.

3. Dermatitis Herpetiformis (DH) is a rare disorder characterized by urticaria and grouped vesicles. The disease affects predominantly males, often in the 20 to 40 years of age. In some cases it occurs in association with intestinal celiac disease and responds to a gluten-free diet.

TUMORS
Benign and Premalignant Epithelial Lesions
The overwhelming majority of these tumors show limited growth and do not undergo malignant transformation, examples are: Seborrheic Keratosis, Actinic Keratosis and Melanocytic nevus

Malignant Epidermal Tumors
1. Squamous Cell Carcinoma (SCC)
This is a common tumor arising on sun-exposed sites in older people. The following are considered predisposing factors
1. Sunlight
2. Industrial carcinogens (tars and oils)
3. Chronic ulcers
4. Old burn scars
5. Ingestion of arsenicals
6. Ionizing radiation
7. Immunosuppression
8. Inherited defects in DNA repair

Pathogenesis

- The most common exogenous cause of cutaneous squamous cell carcinoma is UV light exposure, with subsequent unrepaired DNA damage.
- In addition to inducing mutations, UV light (UVB in particular) may have a transient immunosuppressive effect on skin by impairing antigen presentation by Langerhans cells. This may contribute to carcinogenesis by weakening immunosurveillance.
- $p53$ mutations with associated UV mutation signatures are common, as are activating mutations in RAS.
- Immunosuppressed patients, particularly organ transplant recipients, are at increased risk because they are likely to have high-risk HPV infections.

As with squamous cell carcinomas at other sites, those in the skin may be preceded by in situ lesions.

Microscopic features

- Squamous cell carcinoma in situ is characterized by highly atypical cells at all levels of the epidermis, with nuclear crowding and disorganization.
- When these cells break through the basement membrane, the process has become invasive.
- Invasive squamous cell carcinomas exhibit variable differentiation, ranging from well-differentiated tumors formed by atypical squamous cells arranged in orderly lobules showing large zones of keratinization to poorly-differentiated neoplasms formed by highly anaplastic, rounded cells with foci of necrosis and only abortive, single-cell keratinization (dyskeratosis).
- Squamous cell carcinomas in situ appear as sharply defined, red, scaling plaques; many arise from prior actinic keratoses. More advanced, invasive lesions are nodular, and may ulcerate.

The likelihood of metastasis is related to the thickness of the lesion and degree of invasion into the subcutis. Tumors arising in the context of actinic keratoses may behave in a less aggressive fashion.

2. Basal Cell Carcinoma (BCC)

This is the most common human cancer. It is a slow-growing tumor that rarely metastasizes. BCC tends to occur at sites exposed to chronic sun exposure and in lightly pigmented people. As with squamous cell carcinoma, the incidence of basal cell carcinoma increases with immunosuppression and in individuals with inherited defects in DNA repair.

Pathogenesis

- Inherited defects in the $PTCH$ gene with subsequent loss of heterozygosity in the numerous individual tumor foci cause the familial basal cell carcinoma syndrome, Gorlin syndrome. Thus, $PTCH$ functions as a classic tumor suppressor gene.
- Some component of the $PTCH$ pathway is also mutated in the great majority of sporadic basal cell carcinomas; mutations in $p53$ are also common.

Gross (Clinical) features

- Clinically, these tumors present as pearly papules, often containing prominent, dilated subepidermal blood vessels (telangiectasia).
- Some tumors contain melanin pigment (pigmented BCC) and thus appear similar to melanocytic nevi or melanomas.
- Advanced lesions may ulcerate, and extensive local invasion of bone or facial sinuses may occur after many years of neglect.

Microscopic features
- Because they arise from the epidermis or sometimes follicular epithelium, they are not encountered on mucosal surfaces.
- Tumor cells resemble the normal epidermal basal cell layer from which they are derived.
- Two common patterns are seen: either multifocal growths originating from the epidermis (superficial type), or nodular lesions growing downward into the dermis as cords and islands of basophilic cells with hyperchromatic nuclei, embedded in a fibrotic to mucinous matrix.
- Peripheral tumor cell nuclei align in the outermost layer (palisading) with separation from the stroma, creating a cleft or separation artifact.

3. Malignant melanoma (see below)

Tumors and Tumor-Like Lesions of Melanocytes
1. Melanocytic Nevi
Melanocytic nevus refers to any benign, congenital or acquired, neoplasm of melanocytes

Common Nevus

Pathological features
- Melanocytic nevi are derived from the transformation of highly dendritic melanocytes that are normally scattered among basal cells of the epidermis.
- They are initially composed of round-to-oval cells that grow in "nests" along the dermoepidermal junction. Nuclei are uniform and round, and contain inconspicuous nucleoli with little or no mitotic activity. Such lesions, believed to represent an early developmental stage, are called junctional nevi.
- Eventually, most junctional nevi grow into the underlying dermis as nests or cords of cells (compound nevi).
- In older lesions the epidermal nests may be lost entirely to leave pure dermal nevi.
- It should be noted that progressive growth of nevus cells from the dermoepidermal junction into the underlying dermis is accompanied by maturation. Superficial nevus cells are larger and less mature, tend to produce melanin pigment, and grow in nests; deeper nevus cells are smaller and more mature, produce little or no pigment, and grow in cords. This sequence of maturation of individual nevus cells is of diagnostic importance, since melanomas usually show little or no maturation.

Gross (Clinical) features
- Compound and dermal nevi are often more elevated than are junctional nevi.
- The nevi are tan-to-brown, uniformly pigmented, small (usually ≤5 mm across), papules or macules with well-defined, rounded borders.

2. Dysplastic Nevus
A subset of dysplastic nevi are precursors of melanoma. They form the precursors in familial cases of melanomas (familial melanoma syndrome) with a lifetime risk close to 100%. The number of dysplastic nevi correlates with the risk of developing melanoma. However, most melanomas arise de novo and not from a preexisting
nevus. Activating \textit{RAS} or \textit{BRAF} mutations are encountered in dysplastic as well as in melanocytic nevi; additional complementing mutations occur in melanoma.

\textbf{Microscopic features}

- Dysplastic nevi are mostly compound in type, with both architectural and cytologic evidence of abnormal growth.
- Nevus cell nests within the epidermis may be enlarged and exhibit abnormal bridges with adjacent nests. As part of this process, single nevus cells begin to replace the normal basal cell layer along the dermoepidermal junction, producing so-called lentiginous hyperplasia.
- Cytologic atypia is frequent & consists of irregular nuclear contours and hyperchromasia.
- There is linear fibrosis surrounding epidermal nests of melanocytes.

\textbf{Gross \textit{(clinical) features}}

- Dysplastic nevi are usually larger than most acquired nevi (often >5 mm across) and may occur as hundreds of lesions on the body surface.
- They are usually of variegated color with irregular borders.
- Unlike ordinary nevi, dysplastic nevi tend to occur on both sun unexposed as well exposed body surfaces.

\textbf{3. Melanoma}

Today, as a result of increased public awareness of the earliest signs of skin melanomas, most melanomas are cured surgically.

\textbf{Pathogenesis}

- As with other cutaneous malignancies, sunlight plays an important role in the development of melanoma. The incidence is highest in sun-exposed skin and in localities such as New Zealand and Australia where sun exposure is high and the protective mantle of melanin is sparse.
- The presence of preexisting nevi and hereditary predisposition also play a role.
- Most melanomas occur sporadically, but a few are hereditary (<5\% to 10 \%).
- Germ-line mutations in the \textit{CDKN2A} gene are found in as many as 40\% of those with familial melanoma. This gene encodes p16, an inhibitor that regulates the G1-S transition of the cell cycle. The \textit{CDKN2A} gene can also be silenced by methylation.
- Polymorphisms in the \textit{melanocortin-1-receptor (MC1R)} locus, associated with red hair, fair skin, and easy freckling, are also markers of melanoma susceptibility.
- As with other tumors, malignant transformation of melanocytes is a multistep process with activating mutations in proto-oncogenes and loss of tumor suppressor genes.

\textbf{Clinico-pathologic features}

- Individual melanoma cells are usually considerably larger than nevus cells. They contain large nuclei with irregular contours & chromatin clumping at the periphery of the nuclear membrane. There are prominent cherry red nucleoli.
- Malignant cells grow as poorly formed nests or individual cells at all levels of the epidermis and as dermal expansile, balloon-like nodules; these constitute the radial and vertical growth phases, respectively.

\textit{Radial and vertical growth concept:} the \textit{radial growth} indicates the initial tendency of a melanoma to grow horizontally within the epidermis (in situ) and superficial dermal layers. During this stage of growth, melanoma cells do not have the capacity to metastasize. With time, the pattern of growth assumes a \textit{vertical component}, and the melanoma grows downward into the deeper dermal layers as an expansile mass
lacking cellular maturation. This event is evident clinically by the development of a nodule in the relatively flat radial growth phase and correlates with the emergence of a clone of cells with metastatic potential. The probability of metastasis is predicted by measuring the depth of invasion in millimeters of this vertical growth phase (Breslow thickness).

Metastases involve not only regional lymph nodes but also liver, lungs, brain, etc. Sentinel lymph node biopsy (first draining node(s) of a primary melanoma) at the time of surgery is an assessment of the biological aggressiveness.

**The main clinical warning signs of melanoma are**
1. Enlargement of a preexisting nevus
2. Itching or pain in a preexisting nevus
3. Development of a new pigmented lesion during adult life
4. Irregularity of the borders of a pigmented lesion
5. Variegation of color within a pigmented lesion.

It is vitally important to recognize and intervene in melanoma as rapidly as possible. The vast majority of superficial lesions are cured surgically, while melanomas that become metastatic have a virtually uniformly poor prognosis, with no effective therapy in most cases.