DERMATOPATHOLOGY

Objectives:

- To become proficient in the gross examination, description and processing of cutaneous specimens and microscopical terms in dermatopathology.
- To be able to recognize and discuss a wide variety of inflammatory, infective, benign and malignant skin lesions.
- Be able to identify some of the bullous diseases of the skin

Macroscopic Terms

Macule: Flat, circumscribed area of any size distinguished from surrounding skin by coloration

Papule: elevated solid area 5 mm or less in diameter

Nodule: as above but more than 5 mm in diameter

Plaque: elevated flat-topped area, usually more than 5 mm in diameter

Vesicle: fluid-filled raised area 5 mm or less in diameter

Bulla: as above but more than 5 mm in diameter

Blister: common term used for vesicle or bulla

Pustule: discrete, pus-filled raised area

Scale: dry, horny, platelike excrescence; usually the result of imperfect cornification

Lichenification: thickened and rough skin characterized by prominent skin markings; usually the result of repeated rubbing in susceptible persons

Excoriation: a traumatic lesion characterized by breakage of the epidermis, causing a raw linear area usually due to scratching.

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

Acute Inflammatory Dermatoses

In general, acute lesions last from days to weeks and are characterized by inflammation (often marked by mononuclear cells rather than neutrophils) and defined as acute because of the limited course of their natural history.
1. Urticaria (Fig. 13-1)
This is a common disorder mediated by localized mast cell degranulation resulting in dermal microvascular hyperpermeability. This gives rise to erythematous, edematous, and pruritic plaques termed wheals. In most cases, it is a reflection of type I hypersensitivity i.e. IgE-mediated degranulation of mast cells. This follows exposure to a number of antigens including pollens, foods, drugs, and insect venom. IgE-independent urticaria results from substances that directly provoke mast cell degranulation, such as opiates and certain antibiotics. In the vast majority of cases, no cause is discovered. Hereditary angioneurotic edema results from inherited deficiency of C1 esterase inhibitor, leading to uncontrolled activation of the early components of the complement system. The resulting urticaria affects the lips, throat, eyelids, genitals, and distal extremities. Involvement of the larynx can cause suffocation. Microscopically, there is mild perivenular infiltrate of mononuclear cells admixed neutrophils or eosinophils. Superficial dermal edema results in more widely spaced collagen bundles. Individual lesions in urticaria develop and fade within hours (usually <24 hours), but episodes may persist for days or even months.

2. Acute Eczematous Dermatitis (Fig. 13-2)

Eczema is a clinical term that embraces a number of conditions with different etiologies. All are characterized by itchy, red, papulovesicular, oozing, and crusted lesions at an early stage.

Eczematous dermatitis is classified into:
1. Allergic contact dermatitis
2. Atopic dermatitis
3. Drug-related dermatitis
4. Photoeczematous dermatitis
5. Primary irritant dermatitis i.e. the agents are capable of directly damaging the skin this form include occupational dermatitis.

Most of the above forms resolve completely when the offending stimulus is removed.

Contact dermatitis: is the most common form of eczema. Clinical examples of this form include sensitivity to
1. Nickel
2. Constituents of synthetic rubber
3. Topical medicaments

Pathogenesis
• After initial exposure to the sensitizing agent, self-proteins modified by the agent are processed by epidermal Langerhans cells that then migrate to draining lymph nodes and present the antigen to naive T cells. This leads to the development of immunologic memory.
• On re-exposure to the same antigen, the now-educated CD4+ T lymphocytes migrate to the affected skin sites to release cytokines that recruit additional inflammatory cells and also mediate the epidermal damage.
**Pathological features**

- **All forms of eczema are characterized by spongiosis** i.e. the accumulation of edema fluid in-between epidermal cells. This causes stretching of the intercellular bridges. The latter thus become more prominent (spongy appearance).
- There is also superficial dermal perivascular lymphocytic infiltrate, edema, and mast cell degranulation. Eosinophils may be present and are especially prominent in drug-related dermatitis. With persistent antigen stimulation, lesions may become progressively scaly (hyperkeratotic) as the epidermis thickens (acanthosis) and can become chronic. Some of these changes also result from scratching or rubbing of the itchy lesion. **Susceptibility to atopic dermatitis is often inherited.** Atopic individuals often suffer from asthma as well, perhaps another expression of an irritable and overactive immune system.

**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+ Th1 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 (Fig. 13-3)**

- 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 (Fig. 13-4)
- 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 ("sawtothing").
- 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.

INFECTIOUS DERMATOSES
1. Bacterial infection
Numerous bacterial infections occur in skin. These range from superficial infections caused by *Staphylococcus* and *Streptococcus* spp., known as impetigo, to deeper dermal abscesses caused by anaerobes like *Pseudomonas aeruginosa*, associated with puncture wounds. Microscopically, there is spongiosis of the epidermis with a neutrophilic infiltrate. Bacterial cocci can be demonstrated using Gram stain in the superficial epidermis. Bacteriologic culture with assessment of sensitivities to various antibiotics can be useful. One of the most common skin bacterial infections is *impetigo*, which is primarily seen in children. The disease involves direct contact, usually with *Staphylococcus aureus*, or less commonly *Streptococcus pyogenes*. The disease often begins as a single small macule that rapidly evolves into a larger lesion with a "honey-colored crust" (dried serum or scab). The areas most often involved are the extremities, nose, and mouth. (Fig. 13-6)

2. Fungal infection
These range from superficial infections with *Candida* species to life-threatening infections of immunosuppressed individuals with *Aspergillus* species. In general, a fungal infection can be very superficial (stratum corneum, hair, and nails), deep, involving the dermis or subcutis, or systemic involving skin by hematogenous spread (often in an immunocompromised host).

Pathological features
- Superficial infections are often associated with a neutrophilic infiltrate in the epidermis. While dermal fungal infections often elicit a granulomatous response. The deeper infections are usually more destructive; in particular, Aspergillus can be angioinvasive.
- *Superficial Candida infections* often induce a clinical response that can mimic psoriasis, thus, it is essential to perform a fungal stain to exclude infection in a newly diagnosed psoriasis.
• *Deeper fungal infections* produce greater tissue damage, probably induced by both the microbes themselves and the vigorous host immune response to their presence.

3. **Verrucae (warts)**

Verrucae are common lesions of children and adolescents. They are caused by human papillomavirus (HPV). Transmission usually involves direct contact between individuals or autoinoculation. Verrucae are generally self-limited; mostly regress spontaneously within 6 months to 2 years.

**Pathogenesis**

- Verrucae are caused by HPV. However, in contrast to HPV-associated carcinomas, most warts are caused by distinct low-risk HPV types that lack the potential for causing malignant transformation.
- The virus disturbs the cell cycle control to allow increased proliferation of epithelial cells and production of new virus.
- Normal immune response usually limits the growth of these lesions, but immunodeficiency can be associated with increased numbers and size of verrucae.

**Microscopic features** *(Fig. 13-7)*

Common to verrucae are

- *Epidermal hyperplasia* that is often undulant in character and
- *Cytoplasmic vacuolization (koilocytosis)* that preferentially involves the more superficial epidermal layers, producing halos of pallor surrounding infected nuclei.
- Infected cells may also demonstrate *prominent keratohyaline granules & eosinophilic intracytoplasmic inclusions (protein aggregates)* as a result of impaired maturation.

Warts can be classified into several types depending on their morphology and location. In addition, each type of wart is generally caused by a distinct HPV type. *Verruca vulgaris* is the most common type of wart. These lesions are mostly seen on the hands, particularly on the dorsal surfaces and periungual areas, where they appear as gray-white to tan, flat to convex, up to 1.0 cm papules with a rough surface. *(Fig. 13-7)* **Verruca plana,** *(flat wart),* is common on the face or dorsal surfaces of the hands. These warts are flat, smooth, tan macules. *Verruca plantaris and verruca palmaris* occur on the soles and palms, respectively. These rough, scaly lesions may reach up to 2.0 cm in diameter, coalesce, and be confused with ordinary calluses. *Condyloma acuminatum *(venereal wart)* occurs on the penis, female genitalia, urethra, and perianal areas. *(Fig. 10-2)*

**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).

Blister 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. *(Fig. 13-8)*
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. The distribution of these proteins within the epidermis determines the location of the lesions. By direct immunofluorescence, lesional sites show a characteristic netlike pattern of intercellular IgG deposits. (Fig. 13-9) The antibodies seem to function primarily by disrupting the intercellular adhesive function of the desmosomes.

**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). (Fig. 13-10)
- In pemphigus foliaceus, acantholysis selectively involves the superficial epidermis at the level of the stratum granulosum (Fig. 13-11).
- Variable superficial dermal infiltration by lymphocytes, histiocytes, and eosinophils accompanies all forms of pemphigus.

**Pemphigus vulgaris**, by far the most common type, involves mucosa and skin, especially on the scalp, face, axillae, groin, trunk, and points of pressure. The primary lesions are superficial vesicles and bullae that rupture easily, leaving erosions covered with serum crust (Fig. 13-12). **Pemphigus foliaceus**, a rarer, benign form of pemphigus, results in bullae confined to skin, with infrequent involvement of mucous membranes. The blisters are so superficial that only zones of erythema and crusting sites of previous blister rupture are detected (Fig. 13-13).

2. **Bullous Pemphigoid** (Fig. 13-14)

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. IgG autoantibodies fixes complement with subsequent tissue injury by means of locally recruited neutrophils and eosinophils.
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. The bullae do not rupture as readily as in pemphigus and, if uncomplicated by infection, heal without scarring. Sites of occurrence include the inner aspects of the thighs, flexor surfaces of the forearms, axillae, groin, and lower abdomen. Gestational pemphigoid (also known as herpes gestationis, a misnomer, since there is no viral etiology) occurs late in the second or third trimester of pregnancy and resolves after childbirth.

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.

Pathogenesis
- The association of dermatitis herpetiformis with celiac disease provides a clue to its pathogenesis.
- Genetically predisposed individuals develop IgA antibodies to dietary gluten (derived from the wheat protein gliadin). The antibodies cross-react with reticulin, a component of the anchoring fibrils that tether the epidermal basement membrane to the superficial dermis.
- The resultant injury and inflammation produce a subepidermal blister.
- Some people with dermatitis herpetiformis and gluten-sensitive enteropathy respond to a gluten-free diet.

Microscopic features (Fig. 13-15)
- Early, fibrin and neutrophils accumulate selectively at the tips of dermal papillae, forming small microabscesses.
- The basal cells overlying these microabscesses show vacuolization and focal dermoepidermal separation that ultimately coalesce to form a true subepidermal blister.
- By direct immunofluorescence, dermatitis herpetiformis shows discontinuous, granular deposits of IgA selectively localized in the tips of dermal papillae.

The lesions of DH are extremely pruritic. The lesions are bilateral, symmetric, and grouped involving preferentially the extensor surfaces, elbows, knees, upper back, and buttocks.

TUMORS

Benign and Premalignant Epithelial Lesions
The overwhelming majority of these tumors show limited growth and do not undergo malignant transformation.

1. Seborrheic Keratosis is a common epidermal tumor that occurs mostly in middle-aged or older individuals. It arises spontaneously and may become particularly numerous on the trunk, although the extremities, head, and neck may also be involved. These neoplasms are exophytic and composed of sheets of small cells that most resemble monotonous basal cells of the normal epidermis. Variable melanin pigmentation is present within these basaloid cells, accounting for the brown coloration seen clinically. Hyperkeratosis occurs at the surface and the presence of small keratin-filled cysts (horn cysts) and down-growths of keratin into the main tumor mass (pseudo-horn cysts) are characteristic features. (Fig. 13-16)
2. Actinic Keratosis
This refers to dysplastic changes of the epidermis, usually the result of chronic exposure to sunlight and is associated with hyperkeratosis, hence the name. (actinic: sun-related). Mutation of \( p53 \) is often an early event with molecular changes suggestive of ultraviolet light injury.

**Microscopic features** (Fig. 13-17)
- The lower portions of the epidermis show cytologic atypia, often with hyperplasia of basal cells or with early atrophy that results in diffuse epidermal thinning of the epidermis.
- There are thickened, blue-gray dermal elastic fibers (solar elastosis).
- There is hyper- and parakeratosis.
- Lymphocytes are present in superficial dermis.
- Some but not all lesions progress to full-thickness atypia amounting to squamous cell carcinoma in situ.

Lesions of actinic keratosis, very common in fair-skinned individuals, are usually less than 1 cm in diameter; tan-brown, red, or skin colored; and has a rough, sandpaper-like consistency. As would be expected, there is a predilection for sun-exposed areas (face, arms, and dorsum of the hands).

**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 (Fig. 13-18)**
- **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 (Fig. 13-19)**
- 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.
Tumors and Tumor-Like Lesions of Melanocytes

1. Melanocytic Nevi
Melanocytic nevus refers to any benign, congenital or acquired, neoplasm of melanocytes

Common Nevus (Fig. 13-20) 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 RAS or BRAF mutations are encountered in dysplastic as well as in melanocytic nevi; additional complementing mutations occur in melanoma.

Microscopic features (Fig. 13-21)
- 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.

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

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 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 CDKN2A gene can also be silenced by methylation.
- Polymorphisms in the 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.

Clinico-pathologic features (Fig. 13-22)
- 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.

Radial and vertical growth concept: the 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 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.