

CHAPTER 22 Skin Tumors

GENERAL CONSIDERATIONS

Histology

The skin consists of epidermis, dermis and the subcutaneous fat. The epidermis contains different types of cells each representing a specific lineage. These include keratinocytes, melanocytes, Langerhans and Merkel cells (Elder et al, 2005). The epidermis is divided into 4 layers; stratum basale (basal cell layer), stratum spinosum (spinous cell layer), stratum granulosum (granular cell layer), and stratum corneum (Fig 22-1). The dermis has 2 layers; a superficial (papillary dermis) and deep (reticular dermis) layers. The dermis contains supporting stroma, blood vessels and hemato-lymphoid cells. The basal layer of the epidermis is attached to the superficial dermis by the basement membrane. There are five appendages in normal skin; hair, nail, apocrine, eccrine, and sebaceous glands. The hair follicle, sebaceous glands and erector pili muscle form the hair apparatus (Fig 22 -1) .

Incidence

Cutaneous malignancies account for nearly half of all cancers in the Unites States. In Australia and New Zealand, where the incidence of skin cancer is the highest in the world, the total number of skin cancer exceeds that of all other cancers combined by several folds (Ch'ng et al, 2006). Non melanoma skin cancer is not registered in USA and UK national registries because it is almost curable by simple surgical excision. The variations of incidence in distinct geographic areas are probably related to the degree of skin pigmentation of the population. The median age at diagnosis of skin cancer (excluding basal and squamous cell carcinoma) was 61 years (Howlader et al, 2011). In Egypt, skin cancer constituted 4% of total malignancies, affects mainly adults with male predominance (1.5:1) (Mokhtar et al, 2007).

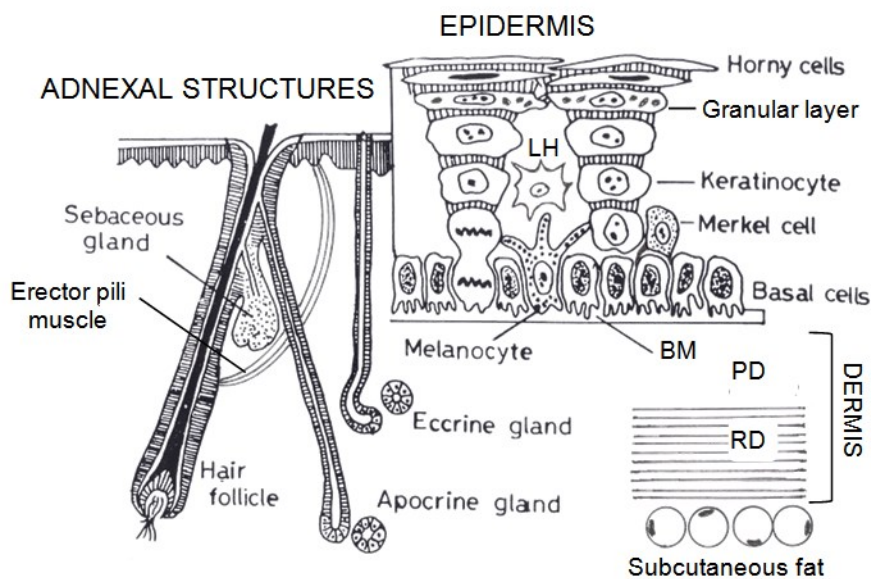


Figure 22-1 Normal histology of skin. The epidermis contains 4 different types of cells namely; keratinocytes, Merkle cells, melanocytes, and Langerhans cells. Adnexal structures are formed of eccrine, apocrine, sebaceous glands and hair. The pilar apparatus is formed of hair follicle, erector pili muscle and sebaceous glands. The dermis is formed of papillary and reticular dermis. Abbreviations: BM basement membrane, LH Langerhans cell, PD papillary dermis and RD reticular dermis.

Pathogenesis

The most effective wavelengths in carcinogenesis of skin cancers are the ultraviolet B (UV-B) region of the solar spectrum. UV-B wavelength (290-320nm) plays a key role in all types. Two mechanisms were proposed to explain UV tumorigenesis.

1. Mutagenic effect of UV: The first molecular step is the induction of DNA photoproducts by UVB photons, which mainly leads to abnormal DNA structure. On replication, the originally damaged cytosine is replaced by a normal thymine resulting in a disturbed base sequence. This C-T mutation is almost pathognomonic for ultraviolet radiation. In patients with xeroderma pigmentosum, these mutations accumulate due to the defect in DNA excision repair genes. Another important outcome of UV radiation is inactivation of the onco-suppressor gene TP53 resulting in genomic instability and cellular proliferation. Activation of RAS gene may also occur.

Sunlight-induced carcinogenesis is a long process, starting at young age (20 years), with the tumors developing 30 to 40 years later (Fig 22-2). Basal cell carcinoma (BCC) is related to intense ultraviolet radiation, whereas, squamous cell carcinoma (SCC) is related to prolonged cumulative

irradiation and malignant melanoma to intermittent irradiation particularly in childhood.

2. Mast cell activation by UV leads to histamine secretion with subsequent immunosuppression, angiogenic, mitogenic effects, as well as, extracellular matrix degradation (Ch'ng et al, 2006).

In addition, the hypothesis that UVA is important in the etiology of melanoma is also supported by epidemiological studies, in which exposure to UVA emitting sun beds was related to an increased melanoma risk.

According to the above mentioned models, ultraviolet radiation acts both as an initiating and a promoting agent in skin carcinogenesis. *Other initiators* of skin cancer are: polycyclic aromatic hydrocarbons PAH (e.g. tar), nitrogen mustard, and psoralen used in (PUVA) photochemotherapy. *Promoting agents* include: phenol, anthralin, phorbol esters and benzoyl peroxide.

Classification

The WHO classified malignant skin tumors based on its differentiation into keratinocytic, melanocytic, appendageal, hematolymphoid and soft tissue (LeBoit et al, 2006). A modified scheme of the WHO classification is presented in (Table 22-1) taking into consideration that all tumors arise from cancer stem cells that exhibit different lines

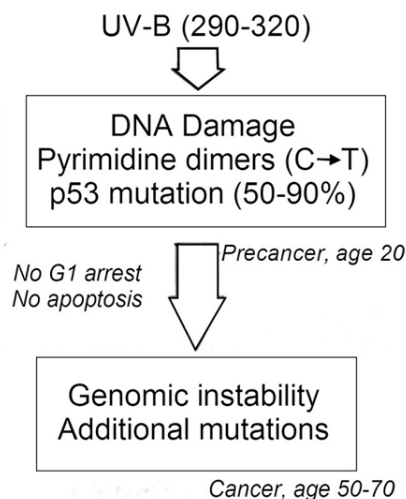


Figure 22-2 Role of ultraviolet (UV) radiation in skin carcinogenesis. UV causes genomic instability due to pyrimidine base dimers and TP53 gene mutation. Subsequent accumulation of mutations takes several years.

Table 22-1 Modified WHO Classification and Frequency of Skin Cancer

Type	Frequency (%)
Epithelial	81.2
<i>Keratinocytic</i>	79
Basal cell carcinoma	43
Squamous cell carcinoma	35.5
<i>Adnexal</i>	2
<i>Merkel cell carcinoma</i>	0.2
<i>Others</i>	0.5
Tumors of neural crest	4.8
<i>Melanoma</i>	4.8
Mesenchymal tumors	7
<i>Dermatofibrosarcoma</i>	4.1
<i>Kaposi sarcoma</i>	2
<i>Others</i>	0.9
Hematolymphoid tumors	6.4
Histiocytic tumors	0.6

(NCI registry, Cairo, 2000-2011)

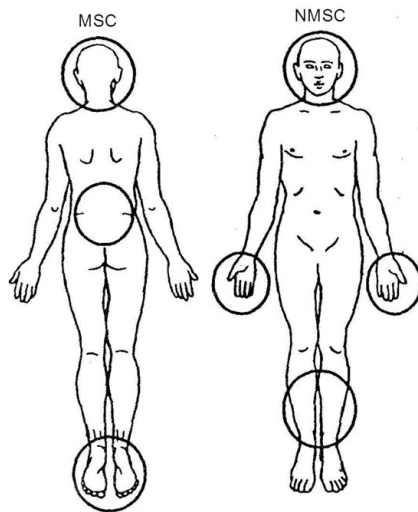


Figure 22-3 Site distribution of skin cancer. Melanoma affects exposed as well as non-exposed skin, but non-melanoma skin cancer (NMSC) is restricted to exposed areas of skin

of differentiation (epithelial, melanocytic, mesenchymal, lymphoid and histiocytic). *Epithelial tumors* include keratinocytic, adnexal and Merkel cell carcinoma. Moreover, *histiocytic tumors* are categorized as separate entity from *hematolymphoid tumors*. In addition the approximate frequency of each type is demonstrated as obtained from the NCI registry data of years 2000 to 2011.

Clinically, it is customary to divide skin cancer into non-melanoma skin cancer (NMSC) and melanoma skin cancer (MSC). NMSC is a heterogeneous group where basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) form the majority of cases. There are basic biological differences between the two classes of skin cancer. In contrast to NMSC which occurs only on sun-exposed skin, MSC affects exposed as well as, covered skin (Fig 22-3). Moreover, NMSC is a most favorable cancer, with case fatality rate of <0.1%. Conversely, melanoma is an aggressive malignant tumor with case-fatality rate of 15% (Rees, 2011).

More recently, the AJCC has separated Merkel cell carcinoma (MCC) from the NMSC and put it as a single entity due to its worse prognosis as compared to other tumors in this group (Edge et al, 2010).

KERATINOCYTIC TUMORS

About 1 million cases of keratinocytic carcino-

mas occur annually in the United States, a figure that approaches the total incidence of all non-cutaneous cancers combined. They are represented by Basal cell carcinoma and squamous cell carcinoma. Conventional cancer registries such as the SEER program exclude it. The case fatality rate for basal cell carcinoma and squamous cell carcinoma is 0.05% and 0.7% respectively.

The major environmental risk factor for keratinocytic tumors is solar radiation, particularly ultraviolet B (UVB, 290-320 nm). Persons with increased susceptibility include: fair skinned, blue eyed and red-haired individuals (e.g. Scandinavians). Ionizing radiation is also a risk factor. Certain inherited diseases of the skin (genodermatoses) increase the risk of developing keratinocytic cancer through an increased sensitivity to the damaging effects of solar radiation. Albinism, due to the lack of protective melanin pigment, and xeroderma pigmentosum, due to faulty DNA repair mechanism, are examples.

Additional etiologic factors predispose to keratinocytic carcinomas. These include: (1) polycyclic aromatic hydrocarbons (coal tar and soot), (2) inorganic arsenic used as pesticide and natural contamination of water in wells, (3) nitrogen mustard, (4) psoralen (PUVA) photochemotherapy. Additional etiological factors mainly related to squamous cell carcinoma include: (1) immunosuppressed patients (AIDS), HPV 16 and 18-related, (2) epidermodysplasia verruciformis, a HPV-related familial disease, and (3) chronic ulcers, sinuses and burn scars (Marjolin ulcers).

BASAL CELL CARCINOMA (BCC)

Incidence

It is the most common skin cancer. Australia has the highest incidence of BCC in the world with 1383 new cases diagnosed for every 100,000 population in 2008 (Samarasinghe et al, 2011). Basal cell carcinoma is commonly diagnosed after the age of 40 with a median age of 64 years, but those seen in patients who are younger than 35 tend to be more aggressive. It is seen in children in the setting of genodermatoses. The head and neck region is most commonly affected (70%) and more specifically the nose (Crowson, 2006).

Precursor lesions

Actinic keratosis is associated with 10% progression to BCC (Foote et al, 2001). Three syndromes are known to be associated with BCC e.g. xeroderma pigmentosum (P 22-1), albinism (P 22-2) and Gorlin syndrome.

Histogenesis

In the past, BCC was thought to arise from the basal cells within the hair follicle and this explains its synonym trichoblastic carcinoma. However, the origin of basal cell carcinoma from a pluripotent epidermal stem cell capable of diverse differentiation has been widely accepted. But, whether it arises from a pluripotent stem cell within the interfollicular epidermis or from the hair follicle is still debatable and even it may not be the same in all circumstances (Gu and Xie, 2011).

Molecular Oncogenesis

Almost, all basal cell carcinomas (sporadic and syndromic) exhibit activation of the sonic Hedgehog (SHH) signaling pathway (which is the critical regulator of cell proliferation and tissue differentiation). In normal skin, Hedgehog signaling is temporally controlled to regulate hair follicle growth and morphogenesis. However, it is dysregulated in BCC due to loss of function mutations in tumor suppressor gene PTCH1 or gain of function mutations in SMO (Busam, 2010) (Fig 22-4).

Pathology

Grossly, most basal cell carcinomas are ulcerative lesions with rolled-in, beaded edges (P 22-3A). The basic histopathologic features include: (1) undifferentiated basal cell structure, (2) peripheral palisading (Fig 22-5), (3) focal apoptotic keratinocytes, (4) mitotic figures, (5) spindle cell myxomatous stroma, and (6) cleft formation between tumor cell groups and the stroma (P 22-3).

The growth pattern of BCC (nodular, superficial, and infiltrating) is an important indicator for the risk of local recurrence (Fig 22-6). BCC may show prominent squamous, follicular, sebaceous, or sweat duct differentiation. Except for basosquamous carcinoma which has aggressive behavior, the differentiation pattern has little impact on behavior. Melanin pigmentation may also be marked, especially in the superficial type.

Histologic variants of BCC include nodular, superficial multicentric, infiltrating, keratotic, basosquamous, fibroepithelial, adenoid and BCC with adnexal differentiation (P 22-4 to P 22-10).

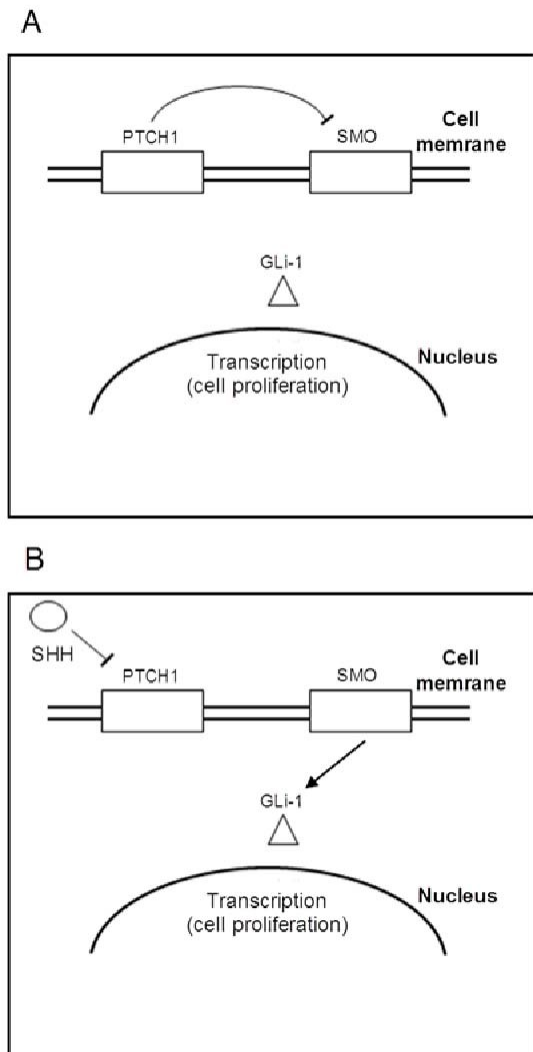


Figure 22-4 Molecular oncogenesis of basal cell carcinoma. This involves dysregulation of the Sonic Hedgehog (SHH) mitogenic signaling pathway. A) Normally, PTCH1 (patched homologue 1) gene product represses the transmembrane protein smo (smoothened protein). B) In Basal cell carcinoma, binding of the ligand SHH to PTCH1 relieves its inhibition of SMO resulting in transcriptional activation through the GLI (glioma transcription factor) family of proteins. The latter induces cellular proliferation

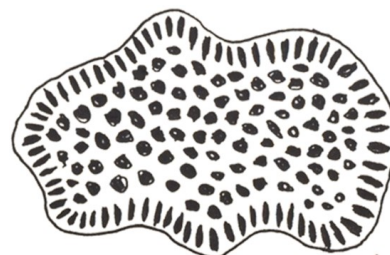


Figure 22-5 Basal cell carcinoma showing peripheral palisading.

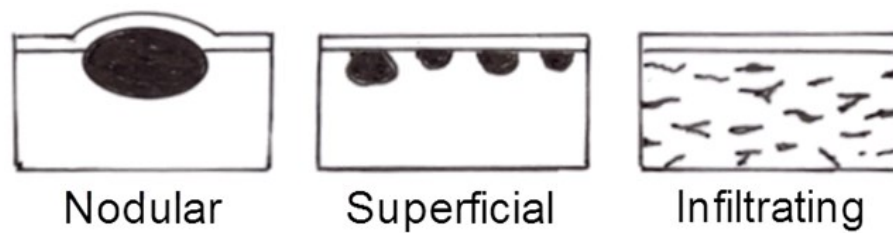


Figure 22-6 Growth patterns of basal cell carcinoma. This classification has prognostic significance in regard to local recurrence. The infiltrating pattern is associated with the highest rate of recurrence. This is attributed to ill-defined edge of the tumor which allows for inadequate resection with proper safety margins. Superficial type has the lowest risk of recurrence.

Differential Diagnosis

1. *Seborrheic keratosis* (P 22-11): It is composed of epidermal proliferation of monomorphic keratinocytes. Laminated hyperkeratosis and pseudohorn cysts are characteristic features.

2. *Trichoblastoma (trichopithelioma)* (P 22-12): A benign neoplasm of follicular epithelium origin. In contradistinction to BCC, trichoepithelioma lacks retraction stromal artifacts, minimal mitosis, lack of apoptosis and shows stromal cell positivity to CD34. However, it is not always possible to differentiate between them especially in the setting of prominent solar change.

3. *Squamous cell carcinoma (SCC)*: Sometimes, especially on the superficial biopsy, it is impossible to distinguish metatypical BCC and SCC. In those cases, additional sampling or even complete excision can help in establishing the diagnosis.

4. *Microcystic adnexal carcinoma*: This is a low grade malignancy derived from sweat (eccrine) ducts, with high recurrence and increased incidence of metastases. It should be differentiated from morpheaform BCC. In microcystic adnexal carcinoma, there are more ductal structures. In addition, it stains for CK7 and CEA which are usually negative in BCC.

Prognosis

The prognosis for patients with BCC is excellent, with a cure rate of about 95% and survival rate of 100% for cases that have not spread to other sites. Nevertheless, if BCC is allowed to progress, it can result in significant morbidity and cosmetic disfigurement. BCC rarely metastasizes (<0.1%) mainly to the lymph nodes (Akinci et al, 2008).

Patients who are diagnosed with BCC have a 35% chance of developing another tumor within 3 years and a 50% chance of developing another new primary BCC within 5 years. Therefore, regular skin screening is recommended (Mc Loone et

al, 2006).

The postoperative recurrence rate is about 10%. It depends on several factors: (1) positive resection margin, (2) growth pattern, being highest (27%) in the infiltrating type, intermediate (6.4%) in the nodular type and lowest (3.6%) in the superficial type, (3) type of treatment, being lowest with Mohs micrographic surgery (1%) (4) size of the tumor and (5) anatomic site of the tumor with the worst prognosis associated with large BCC at the center of the face (Crowson, 2006).

SQUAMOUS CELL CARCINOMA (SCC)

Incidence

Squamous cell carcinoma is the second most common cutaneous malignancy. The median age for squamous cell carcinoma is 70 years. The common sites are the lower lip, ear, upper face and dorsum of the hands. The SCC: BCC incidence ratio is about 1:2 in Australia (Staples et al, 2006). In Egypt, the ratio is 1:1.2. This is probably attributed to genetic factors.

Precursor lesions

Precursor lesions of squamous cell carcinoma are presented in (Table 22-2). *Actinic (solar) keratosis* does not involve the stratum corneum and the keratinocytes are enlarged with loss of polarity (P 22-13). *Bowen's disease* represents squamous carcinoma in situ that involves the entire thickness of the epidermis as well as the adnexal epithelium (P 22-14, P 22-15).

Histopathology

Grossly, the tumor presents as an ulcer with raised everted edge (P 22-16 and P 22-17). Histologically, microinvasive squamous cell carcinoma

Table 22-2 Precursor Lesions for Cutaneous Squamous Cell Carcinoma

Lesion	Malignancy risk (%)
1. Actinic keratosis	5-10%
2. Bowen's disease	3-5%
3. Porokeratosis	----
4. Radiodermatitis	----
5. Lichen sclerosus et atrophicus	4%
6. Epidermodysplasia verruciformis, HPV types 5 and 8-mediated	30%

(Alam and Ranter, 2001/ Salasche, 2000)

is diagnosed when isolated cells or small tumor nests invading the basement membrane (2-3 cell thickness) are observed invading the basement membrane (P 22-18). Conventional squamous cell carcinoma is composed of neoplastic keratinocytes with loss of polarity, cell nest formation, features of anaplasia and mitosis (Fig. 22-7) (P 22-19). *Verrucous squamous carcinoma* is a low-grade non-metastasizing tumor with characteristic filamentous pattern (P 22-20). *Keratoacanthoma* is a distinct subtype of squamous cell carcinoma that usually regresses spontaneously. This categorizes it in the unpredictable biologic behavior (P 22-21 and P 22-22). The *acantholytic* (P 22-23), *adenosquamous* and *spindle cell types* (P 22-24) are aggressive variants of squamous cell carcinoma (Smoller, 2006). The ultrastructural features of squamous cell carcinoma are the presence of desmosomes and tonofilaments (P 22-25).

Differential Diagnosis

1. *Pseudoepitheliomatous hyperplasia (PEH)* (P 22-26): is a benign condition, characterized by hyperplasia of the epidermis and adnexal epithelium. PEH may be present in a number of conditions characterized by prolonged inflammation and/or chronic infection, as well as, in association with some neoplasms e.g. granular cell tumor.
2. *Condyloma accuminatum* (P 22-27).
3. *Verruca vulgaris* (P 22-28).
4. *Proliferating pilar cyst* (P 22-29).



Figure 22-7 Histology of squamous cell carcinoma showing a cell nest and intercellular bridges (desmosomes).

Staging

This stage grouping is applicable in squamous cell and basal cell carcinoma (Table 22-3). Merkel cell carcinoma follows a separate staging scheme.

Prognosis

Lymph node metastases are unusual (3%), but more common than for basal cell carcinoma. SCC is associated with a much higher recurrence rate of about 23%. The presence of two or more of the features listed in (Table 22-4) is associated with poor prognosis. The 5-year survival for all stages is 87%.

Prevention

Primary prevention includes avoidance of sun exposure between 11 am and 4 pm, or the use of protective clothes, sunglasses or application of sunscreen formulas. The development of one skin cancer is a warning that others will develop. About 52% of patients with NMSC will develop a new primary within 5 years of the diagnosis. Most of the recurrences develop within the first year. A minimal recommendation is monthly *self-examination* and periodic follow up of physician. Patients with additional risk factors, such as immunosuppression, a genodermatoses or a known chemical or radiation exposure, may require more intensive surveillance.

ADNEXAL SKIN TUMORS

Adnexal tumors (Table 22-5) are characterized by their location in the dermis and covered by intact skin. *Benign tumors* predominate and appear well circumscribed unattached to epidermis (except poroma, papillary syringadenoma and tricholemmoma) and composed of multiple cell types. *Malignant tumors* show invasion of dermis ulceration through epidermis, anaplasia and mitotic activity. The pathologist should never depend on a scanty biopsy material in diagnosing adnexal skin tumor.

Table 22-3 Descriptive Staging of Cutaneous Carcinomas

Stage	Features
0	Carcinoma in situ (Tis), N0, M0
I	Tumor <2 cm with less than 2 high risk features (T1, N0, M0)
II	Tumor >2 cm in greatest dimension or any tumor size with 2 or more high risk features (T2, N0, M0)
III	Tumor with invasion of maxilla, mandible, orbit, or temporal bone (T3), or metastasis in a single ipsilateral lymph node \leq 3 cm in greatest dimension (N1), M0
IV	Tumor with invasion of skeleton or perineural invasion of skull base (T4), or lymph node (s) metastases >3 cm (N2-3), or distant metastases (M1)

(Edge et al, 2010). N.B. Invasion of bones of paranasal sinus is (T3), but invasion of basal skull or any other bones is (T4).

Table 22-4 High Risk Factors of Recurrence and Metastases in Cutaneous Squamous Cell Carcinoma**Clinical factors**

Tumor size: >2 cm
 Location: ear, lip, genitalia
 Ill-defined borders
 Prior irradiation
 History of immunosuppression
 Recurrent tumor
 Arising on top of scar

Histologic factors

Poor differentiation
 Perineural invasion
 Depth of invasion
 \geq 4 mm or Clark level IV/V
 Histologic subtype
 acantholytic,
 adenosquamous and spindle cell
 Incomplete excision

(Feig and Ching, 2011)

Table 22- 5 WHO Classification of Adnexal (Appendageal) Skin Tumors

Differentiation	Benign	Malignant
Eccrine	Poroma (P 22-30) Syringoma (P 22-31) Hidradenoma (P 22-32).	Microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) (P 22-39) Tubular carcinoma Adenoid cystic carcinoma (P 22-40) Mucinous carcinoma (P22-41)
Apocrine	Tubulopapillary adenoma Hidradenoma papillaferum (P 22-33) Cylindroma (P 22-34)	Extramammary Paget disease (P 22-42) Apocrine carcinoma
Sebaceous	Adenoma (P22-35)	Sebaceous carcinoma (P 22-43)
Hair follicle	Tricholemmoma (P 22-36) Trichoblastoma (trichoepithelioma) (P 22-37) Trichofolliculoma Pilomatricoma (P 22-38)	Pilomatrical carcinoma Proliferating tricholemmal tumor (P 22-44)

(Le Boit et al, 2006)

Complete excision is mandatory to avoid over- or under diagnosis of malignancy. A modified WHO classification (Table 22-5) presents the most frequent adnexal tumors and their histopathologic features (discussed with pictures).

MERKEL CELL CARCINOMA (MCC)

Incidence

Merkel cell carcinoma is a relatively rare primary cutaneous neuroendocrine carcinoma. The highest incidence is observed in western Australia. It occurs most commonly on sun-exposed skin in fair skinned individuals older than 50 years with a slight male predominance.

Histogenesis

Merkel cell carcinoma was first described in 1972 by Toker. The histological features suggesting a neuroendocrine origin was confirmed by the discovery of electron-dense neurosecretory granules. It was named after the postulated cell of origin, the Merkel cell, as it is the only cutaneous cell that form neurosecretory granules. However, epithelial, sarcomatous morphology can also be identified in MCCs suggesting that MCC may arise from primitive totipotent epidermal stem cells.

Recently, both hypotheses have been linked when Van Keymeulen et al, 2009 demonstrated that mammalian Merkel cell does not develop from neural crest progenitors but rather from epidermal stem cells (ectoderm) (Schrama et al, 2012).

Pathogenesis

Although the molecular pathogenesis is unknown, ultraviolet radiation and immune suppression (e.g. HIV, organ transplantation) are likely significant predisposing factors. The identification of a novel polyomavirus termed Merkel cell polyoma virus in the majority of MCC tumors suggests a viral etiologic component in many cases.

Macroscopy

Grossly, it appears as a rapidly growing reddish grey firm non-tender papule or nodule confined to the dermis and subcutaneous fat. Average size is 2-3 cm.

Histopathology

Merkel cell carcinoma appears as a densely cellular dermal mass with rare epidermal involvement. It may show the following histologic patterns: solid, trabecular, compact nests, rosette formation and pseudoglandular (P 22-45). Angiolymphatic invasion and necrosis are common.

Diagnosis is made invariably with the aid of immunohistochemistry; CK20 (a characteristic paranuclear dot pattern) and other neuroendocrine markers.

Differential Diagnosis

1. *NHL*: The presence of cell nests and organoid pattern of arrangement, as well as, LCA negativity are important for exclusion of lymphoma.

2. *Metastatic neuroendocrine carcinoma*: Thorough clinical examination to detect any primary neuroendocrine tumor, as well as, CK20 paranuclear positivity may help in establishing the diagnosis.

Staging

A separate staging system, apart from that used for other NMSCs, was adopted by the AJCC, 2010. Table 22-6 shows the descriptive staging of MCC and the 5-year survival.

Prognosis

Merkel cell carcinoma is an aggressive tumor with 30% developing local recurrences, 60% regional lymph node metastases and 30 % distant metastases. The mortality rate (30%) is twice that observed in melanoma. Large tumor size (>2 cm), lymph node metastases, angioinvasion, immunosuppression are bad prognostic indicators.

Table 22-6 Descriptive Staging of Merkel Cell Carcinoma and Corresponding 5-Year Survival

Stage	Feature	5-year Survival (%)
0	Carcinoma in situ (Tis), N0, M0	60
I	Tumor ≤2 cm (T1), N0, M0	
II	Tumor >2 cm (T2-4), N0, M0	
III	Regional lymph node metastases (N1-2), M0	40
IV	Distant metastases (M1)	20

(Edge et al, 2010)

MALIGNANT MELANOMA

Incidence

In the United States, melanoma is the fifth most prevalent cancer among men and the sixth most common in women. The median age at diagnosis for melanoma is 59 years. The high rate of melanoma in USA is surpassed only in Australia, New Zealand, Norway and Israel (Kantarjian et al, 2012). In Egypt, it constitutes 4.8% of all cutaneous malignancy. It is exceedingly rare in children, and when it occurs, it always develops on top of a large congenital nevus. Melanoma affects exposed skin (head), as well as, covered skin (trunk and foot).

Risk Factors

Certain risk factors predispose to increased susceptibility to develop melanoma. These include intermittent *solar exposure to UVB light* especially in white colored fair-skinned individuals. Also, *genodermatoses* e.g. xeroderma pigmentosum, dysplastic nevus syndrome are associated with increased risk of developing melanoma.

A list of *precancerous nevi* is presented in (Table 22-7). In the *dysplastic nevus syndrome* (first described by Clark, 1978), multiple nevi tend to occur on the trunk, have an irregular border, are usually greater than 5 mm and have a variable color (P 22-46 and P 22-47). In the familial type of the disease, the nevi invariably turn malignant. *Lentigo maligna* (Hutchinson melanotic freckle) occurs in sun-damaged skin (face and dorsum of hands) of elderly patients. It presents as large, flat,

Table 22-7 Precursor Lesions of Malignant Melanoma

Lesion	Malignancy risk (%)
Congenital giant nevus	15%
Multiple acquired nevi	1-2%
Dysplastic nevus	
Sporadic	6%
Familial	100%
Melanoma in situ	5-10%
Cellular blue nevus	Rare

(Anderson, 2012, Taylor, 2004, Gaunt et al, 2008, Bernier, 2011, Dummer et al, 2011)

pigmented lesion which gradually enlarges over the years and ultimately terminates into lentigo maligna melanoma. *Giant congenital nevi* (>20 cm) are at increased risk of developing malignant melanoma (P 22-48).

Pathogenesis

Malignant melanoma is a tumor derived from melanocytes which are of neural crest (neuroectodermal) origin. The natural history of malignant melanoma involves two phases of growth (Fig 22-8): a slow *radial growth phase* (RGP) and a rapid *vertical growth phase* (VGP). In the RGP the spread is superficial and horizontal, involving the epidermis and superficial dermis only. In this phase the tumor is almost 100% curable by surgical excision. Conversely, with the VGP, invasion occurs in depth in an expansile manner to infiltrate reticular dermis, as well as, fat and the tumor acquire metastatic potential. Superficial spreading, acral lentiginous, lentigo maligna melanomas acquire a vertical growth phase on top of pre-existing radial growth phase. Nodular melanomas acquire de novo vertical growth phase. The differences between the two phases are presented in (Table 22-8).

Molecular Oncogenesis

A number of genetic events have been identified in melanoma, including both *germline changes* that predispose individuals to melanoma and *somatic changes* that contribute to the development and progression of tumors (Kantarjian et al, 2012). The molecular mechanism involved include: signal transduction (page 95) and cell cycle control (page 125).

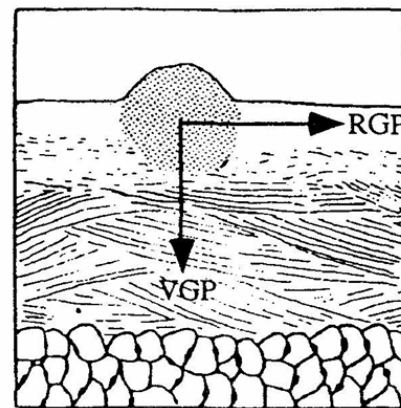


Figure 22-8 Growth phases of malignant melanoma. The radial growth phase (RGP) is an early favorable pattern, whereas, vertical growth phase (VGP) is most unfavourable.

Table 22-8 Comparison between Growth Phases of Malignant Melanoma

Feature	Radial growth phase (RGP)	Vertical growth phase (VGP)
Chronology	Early phase	Late phase
Clark stage	I-II	III-IV-V
Size	< 1 mm	> 1 mm
Gross	Plaque	Nodule
Growth rate	Slow	Rapid
Mitosis	Predominantly epidermal, may involve papillary dermis	Dermal and Epidermal
Cell clusters	Small	Large, expansible
Lymphocytic reaction at base	Marked	Absent
Metastatic potential	None	Significant
Surgical clearance	1 cm	2.5 cm
Prognosis	Excellent	Unfavorable

Germline mutations

Approximately 10% of melanomas are familial. The most common genetic alterations in these melanomas are: (1) Loss of the *CDKN2A* locus on chromosome 9. This locus encodes p16 which regulates cell cycle progression through inhibiting CDK4/CDK6 and cyclin D. (2) In addition to cell cycle regulation, polymorphisms in *MC1R* (*melanocortin-1 receptor*) gene involved in melanin synthesis have been associated with an increased risk of melanoma.

Somatic mutations

(1) *BRAF* and *NRAS*: The overwhelming majority of melanomas have acquired somatic point mutations in the *BRAF* and *NRAS* genes, resulting in hyperactivation of RAS-RAF-MAPK protein kinase signaling pathways. This pathway has been implicated in promoting cancer cell growth and survival. (2) *PI3K-AKT* pathway has an important role in promotion of tumor proliferation, survival and invasion. The most common *PI3K-AKT* mutation detected in melanoma are deletions of *PTEN* that inhibits this pathway.

Somatic amplifications

c-Kit, *MITF* and *CCND1* are amplified in 20% of melanoma patients. C-KIT is a transmembrane receptor tyrosine kinase that is mutated in gastrointestinal stromal tumors. The *MITF* (Microphthalmia transcription factor) gene is a downstream of *MC1R* gene. *CCND1* encodes cyclin D1 which interacts with CDK4 and CDK6 to phosphorylate RB and promote S-phase cell cycle entry.

Macroscopy

A rapid increase in size of a mole, ulceration, bleeding, irregularity of outline, marked variation in color or itching, all should arouse suspicion. Five major diagnostic characteristics have been described as the (ABCDE) criteria for melanoma diagnosis. A stands for asymmetry, B for border irregularity, C for color variation, D stands for diameter exceeding 6 mm and E for elevation of lesion above skin surface (P 22-49).

Histopathology

Melanoma is characterized by: (1) a pleomorphic cell structure, including: epithelioid, spindle and giant cells, (2) dissociated or non-cohesive cells; (3) prominent nucleoli; (4) mitotic activity even in the deeper part of the tumor (5) fine me-

lanin pigment may be present in the cytoplasm of tumor cells; and (6) solid or nodular pattern (P 22-50).

Additional diagnostic tools include: (1) *immunohistochemical* positivity to S-100 protein, Melan-A [MART-1 (Melanoma Antigen Recognized by T-cells)] and HMB-45, and (2) characteristic laminated structure of melanosomes by *electron microscopy* (P 22-51, P 22-52) (Smoller BR, 2006).

Variants

Five basic clinicopathologic variants are recognized based on their site of origin, duration of radial growth phase, presence or absence of invasion and type of associated intraepidermal component (Fig. 22-9). These variants are: mela-

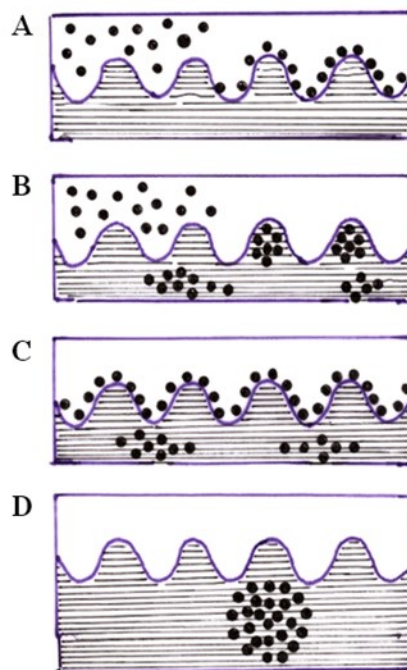


Figure 22-9 Histologic patterns of malignant melanoma. Four patterns are recognized. A) Melanoma in situ, pagetoid and lentiginous subtypes. The latter is seen in lentigo maligna. B) Superficial spreading melanoma, shows junctional nests with invasion of both epidermis and dermis. C) Acral lentiginous melanoma and lentigo maligna melanoma are characterized by lentiginous pattern in basal layer as well as dermal invasion. D) Nodular melanoma showing a nodular growth in dermis without any junctional or epidermal component. The common patterns are the superficial spreading (70%) and nodular (20%).

noma in situ, superficial spreading melanoma, lentigo malignant melanoma, acral lentiginous melanoma and nodular melanoma.

1. *Melanoma in situ*: typically occurs in the sun exposed areas of elderly white persons, most commonly on the cheek. It is characterized by pagetoid and lentiginous spread (P 22-53).

2. *Superficial spreading melanoma*: This is the most common type of melanoma (70%), affects middle age (mean 47 years) and its incidence is increasing worldwide. It occurs in both covered and uncovered areas of skin, often on back in men and legs in women. The associated radial growth phase is long (mean 4 years). The intraepidermal component is both pagetoid invasion of epidermis, as well as, junctional activity with nesting of melanocytes at the dermoepidermal junction (P 22-54, P 22-55).

3. *Nodular melanoma*: This constitutes 10% of melanomas in the West, but is the most common type in developing countries. It commonly affects the trunk of middle aged patients (mean 50 years) and appears as an ulcerated nodule. The radial growth phase is very short (few months) and it shows a prominent vertical growth phase. Histologically, there is no associated intraepidermal component. This type has a significantly worse prognosis than other variants (P 22-56).

4. *Lentigo maligna melanoma*: It contributes about 10% of cases and arises on a background of lentigo maligna, and therefore almost always on sun-damaged skin of the face (P 22-57A) or the dorsum of the hands in elderly people (mean age 70 years). The associated radial growth phase is long (over 5 years). The associated intraepidermal component is lentiginous, with continuous proliferation of atypical melanocytes along the basal layer. Additionally, there are islands of malignant melanocytes in the upper dermis, actinic degeneration of collagen and atrophy of epidermis (P 22-57).

5. *Acral lentiginous melanoma*: This type of melanoma is the least common in the West (5%) affecting middle aged patients. It occurs in hairless skin, particularly on the subungual regions, soles of the feet and palms of the hands. This is the most common type in south East Asia and in black races. The associated radial growth phase is rather short (1.5 years). The intraepidermal component is of the lentiginous type, however, in contrast to lentigo maligna, the epidermis is hyperplastic and hyperkeratotic (P 22-58)

Unusual histologic variants of melanoma include: amelanotic melanoma (P 22-59), desmoplastic melanoma, minimal deviation melanoma, melanoma arising in blue nevus (P 22-60), balloon cell melanoma (P 22-61), signet-ring melanoma, and small-cell malignant melanoma.

Differential Diagnosis

1. *Benign Nevi* have architectural and cytologic features distinct from those of melanoma and include: small size, symmetry, circumscription and evenly spaced junctional nests. Maturation of deep melanocytes is a helpful diagnostic feature in nevi. In pigmented spindle cell nevus, depigmentation is needed to visualize cytological features. Illustrative examples of cellular spitz nevus, blue nevus and compound nevus are presented in (P 22-62 to P 22-65).

2. *Amelanotic melanoma* is difficult to differentiate from undifferentiated carcinoma. Immunohistochemical studies (melan-A and CK) are helpful.

3. *Small-cell melanoma* is difficult to differentiate from small NHL. Melan-A and LCA are important differentiating markers.

Spread

1. *Local spread*: Initially, melanoma invades the upper dermis in a radial direction. Subsequently, vertical invasion of dermis occurs reaching subcutaneous fat. Adequate surgical excision requires a safe clearance of normal tissue around the tumor. This varies (5-30 mm) according to melanoma size (chapter 5, page 90).

2. *Lymphatic spread*: This is relatively common but largely determined by the size of tumor. Melanomas 4 mm or more have a risk of node metastases of about 50% (Poston et al, 2008), but, melanomas larger than 1 cm are invariably associated with metastases. Pathologic study of sentinel nodes is a valuable approach to select patients with small melanomas (1-2 mm) for lymphadenectomy. Satellite nodules and in-transit metastases represent a form of lymphatic spread.

3. *Distant spread: Hematogenous*, occurs in about one third of patients and is characterized by multisystem affection (lung, liver, brain, bone and skin). However, metastases with unknown primary are not uncommon (5 to 10% of metastatic cases).

Staging

A detailed TNM description of each of the 4 stages, as well as, the 5-year survival for each are shown in (Table 22-9).

Table 22-9 Descriptive TNM Staging of Malignant Melanoma And The Corresponding 5-Year Survival

Stage	Features	5-year survival
0	Melanoma in situ (Tis), N0, M0	100%
IA	Melanoma \leq 1 mm in thickness with no ulceration and mitosis $<1/mm^2$ (T1a), N0, M0	97%
IB	Melanoma \leq 1 mm in thickness with ulceration and mitosis $\geq 1/mm^2$ (T1b) or melanoma 1-2 mm in thickness with no ulceration (T2a), N0, M0	92%
IIA	Melanoma 1-2 mm in thickness with ulceration (T2b) or Melanoma 2.01-4 mm with no ulceration (T3a), N0, M0	80%
IIB	Melanoma 2-4 mm with ulceration (T3b) or melanoma >4 mm with no ulceration (T4a), N0, M0	70%
IIC	Melanoma >4 mm with ulceration (T4b), N0, M0	53%
III	T1-4, regional lymph node metastases (N1-3), M0	40-78%*
IV	Distant metastases	0.0%**

(Edge et al, 2010) *according to N category, ** Median survival of stage IV melanoma is 6-9 months (Klimek et al, 2000)

Prognosis

A number of clinical and histologic factors are associated with favorable prognosis in cutaneous malignant melanoma (Table 22-10). The most important factors involved in determining the overall prognosis in *early node negative* melanoma are: the depth of invasion of the primary tumor, ulceration, and mitotic activity (Feig and Chang, 2011).

1. *Depth of invasion* is determined by level of invasion or by thickness of the tumor. Levels of invasion can be determined histologically by the Clark technique (1969) and the thickness of tumor can be determined micrometrically by Breslow technique (1975) as demonstrated in (Fig 22-10). Breslow method is more practical because it is not dependent on histologic interpretation, besides, although Clark level of invasion is an independent prognostic indicator, yet, it is the least of the other prognostic factors related to survival. The 10-year survival is 100% for tumors <1 mm, but, 45% for tumors >4 mm (SEER data, Ries et al, 2007)

2. *Primary mitotic* rate was the second most powerful predictor of survival outcome, after tumor thickness, in Stage I and II melanomas (Gimotty et al, 2007).

3. *Presence of ulceration* is the third important prognostic indicator

Table 22-10 Favorable Prognostic Factors in Cutaneous Malignant Melanoma

Factor	Better prognosis
Clinical factors	
Age	< 60
Sex	Women
Location	Extremities
Number of lymph nodes involved	None
Distant metastases	Absent
Lactate dehydrogenase serum level	Normal
Histologic factors	
Thickness	<1 mm
Ulceration	Absent
Clark level	Level I
Tumor vascularity	Absent
Vascular invasion	Absent
Microsatellites	Absent
Mitotic rate	$<1/mm^2$
Regression	Absent
Inflammation at tumor base	Present

(Homsy et al, 2005 and Crowsan, 2006)

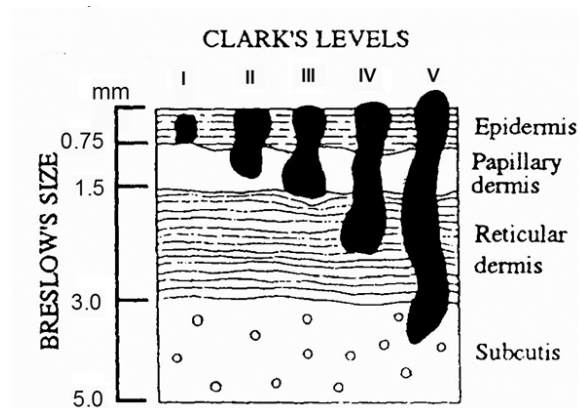


Figure 22-10 Microstaging system for malignant melanoma. Melanoma is classified according to its size into 3 groups: thin melanoma (<1 mm), intermediate thickness melanoma (1-4 mm) and thick melanoma (>4 mm).

MESENCHYMAL TUMORS

A variety of mesenchymal neoplasms may involve the skin. Because of the similarity with their soft tissue counterparts, they are discussed in chapter 21. Only those that show specific distinctive features in the skin are discussed here.

Dermatofibrosarcoma

It is a dermal/subcutaneous mesenchymal neoplasm which shows fibroblastic, myofibroblastic and histiocytic differentiation. The WHO (2006) included it in the tumors of intermediate malignancy. CD34 helps to differentiate it from its benign cellular dermatofibroma (P 22-66, P 22-67).

Kaposi sarcoma

This tumor is etiologically related to human herpes virus HHV-8. It often begins in the skin but can involve lymph nodes and many internal organs. It is manifested by multiple purple macules or nodules of soft consistency. Histologically, early lesions show only dilated vascular spaces, but established lesions show perivascular proliferation of atypical spindle cells (probably of endothelial origin) with extravasated red blood cells and hemosiderin in the stroma (P 22-68 and P 22-69)

Four variants of Kaposi's sarcoma are described (Schwartz, 1996): (1) *classic type*: is an indolent disease affecting elderly patients (common in Jews) with predominant localization in the legs (P 22-70), (2) *endemic or African type*: is an aggressive variant of young patients with

more widespread lesions (legs, lymph nodes and viscera), (3) *epidemic or HIV-associated* is an aggressive type affecting AIDS patients, involving mainly head and trunk. CD4 counts below 200 cells per cubic mm are diagnostic and (4) *immunosuppressed patients*: is also an aggressive variant of KS encountered in organ-transplant patients and affects mainly lymph nodes (P 22-71).

HEMATOLYMPHOID MALIGNANCIES

Cutaneous lymphoma may arise *primary* in the skin or *secondary* from lymphoma elsewhere. Primary lymphoma may be T or B phenotype.

Cutaneous T-cell lymphomas

1. *Mycosis Fungoides* presents only in the skin but never primarily in lymph nodes or other extranodal sites. It is the most common form of primary cutaneous T-cell lymphoma (CTCL), an indolent disease of elderly males. It causes multiple lesions in lower trunk, buttocks and thigh (P 22-72). The disease passes through three stages characterized by: macules, plaques and then tumors. Histologically, the atypical lymphocytes infiltrate the epidermis (epidermotropism) with focal collections (Darier-Pautrier microabscesses). The dermal infiltrate is superficial and contains scattered giant lymphocytes with hyperlobated nuclei. The neoplastic lymphocytes have a T-helper phenotype (CD4) (P 22-72).

2. *Sezary syndrome* is a variant of CTCL characterized by skin manifestations (erythroderma and hyperkeratosis) and virus-unrelated T-cell leukemia.

3. *Anaplastic large T-cell lymphoma* differs from mycosis fungoides in being localized and composed of giant T-lymphoid cells which are positive for CD30.

4. *Peripheral large T-cell lymphoma* account for 5-10% of all primary cutaneous T-cell lymphomas. Adults are most commonly affected. Skin infiltrates are usually diffuse and rapidly growing.

Cutaneous B-cell lymphomas

1. *Follicular lymphoma* is characterized by the formation of large nodules of atypical lymphoid cells that occupy the dermis and infiltrate deep into the subcutaneous fat. Areas where the tumor nodules are replaced by diffuse sheets are found.

The tumor cells express B-cell associated antigens such as CD20 and Bcl-2.

2. *Marginal zone lymphoma* is a low grade lymphoma. It presents as plaques, nodules or papules on the head, trunk or extremities. The tumors are associated with indolent growth and excellent prognosis. It is characterized by a diffuse lymphoid infiltrate in the dermis and subcutaneous fat. It is composed of small to medium sized lymphoid cells (monocytoid B-cells). Reactive lymphoid follicles are often found. The tumor cells express B-cell antigens (P 22-73).

3. *Large B-cell lymphoma* is characterized by diffuse dermal infiltrate of large atypical lymphoid infiltrate in the dermis and subcutis. It shows marked predilection for the lower extremities of elderly patients. The tumor cells express CD20 and Bcl-2.

Differential Diagnosis

The main differentiating points between *reactive follicular hyperplasia* and lymphoma are the presence of mixed cell types and biphenotypic nature of these cells in reactive hyperplasia. In contrast to predominance (80%) of a single phenotype in lymphomas (P 22-74). The presence of stromal fibrosis and vascularity favors reactive lymphoid hyperplasia.

HISTIOCYTIC TUMORS

Cutaneous histiocytic infiltrates occur mostly in children. They can broadly be classified into Langerhans and non-Langerhans types. Juvenile xanthogranuloma, xanthoma, reticulohistiocytoma, Langerhans cell histiocytosis and Rosai Dorfman disease are the most common types. Histiocytic tumors are discussed in details in chapter 26.

CUTANEOUS MANIFESTATIONS OF INTERNAL MALIGNANCY

Some malignant tumors may present with cutaneous lesions which arise through various mechanisms. Recognition of this association is of utmost importance for detection of the underlying malignancy. These cutaneous manifestations are classified into 4 main groups according to the pathogenetic mechanism (Thiers et al, 2009).

Malignant Dermatoses (Direct Dermatoses)

In this group, the lesions in the skin are malignant, representing either a primary cutaneous tumor or metastases from a primary elsewhere. Malignant dermatoses can be divided into:

A. *Tumors that arise primarily in the skin* and subsequently affect the viscera such as:

1. Cutaneous T-cell lymphoma: Mycosis fungoides, Sezary syndrome, human T-cell leukemia/lymphoma (HTLV-1).

2. Langerhans cell histiocytosis including Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma.

3. Mastocytosis (urticarial pigmentosa)

4. Kaposi sarcoma

B. *Tumors that primarily arise from skin adnexa* and ultimately invade the epidermis. Examples are mammary and extramammary Paget disease. The latter arises from apocrine glands in axillary and anogenital regions.

C. *Visceral tumors metastatic to the skin* include: (1) metastatic carcinoma, especially of breast, lung and stomach. (2) Non-Hodgkin lymphoma and leukemia. (3) visceral melanoma. (4) Angiosarcoma. (5) Neuroblastoma.

Inherited Syndromic Dermatoses (Genodermatoses)

A syndrome is an aggregate of symptoms and signs associated with a disease or neoplastic process and that serves as a marker helping in its diagnosis. The syndromic association is explained on genetic grounds. Thus, in view of proximity of genes involved, the mutation that causes the tumor also affects neighboring genes responsible for the associated manifestations. Many inherited cancer syndromes have prominent dermatologic features. The gene involved, its locus, as well as, the associated skin changes and cancer are summarized in (Table 22-11).

1. *Gardner syndrome* (P 22-75) is an autosomal dominant condition involving 5q21. It is characterized by the presence of skin tumors such as epidermoid cysts, fibromas, lipomas, leiomyomas, trichoepitheliomas and neurofibromas. Osteomas are present in 50 % of cases. Patients with this syndrome typically have multiple polyps of the colon and rectum which have a high potential for malignant change.

2. *Peutz-Jeghers syndrome* (P 22-76) is also an autosomal dominant condition involving 19p13.3. It is characterized by hyperpigmented freckle-like

Table 22-11 Inherited Cancer Syndromes, Their Genetic Basis, and Associated Skin Changes and Tumors

Syndrome	Locus	Gene	Skin change	Associated tumor
Gardner	5q21	APC	Epidermoid cysts	GIT polyps, fibromas, lipomas, leiomyomas, trichepithelioma
Peutz-Jeghers	19p13.3	LKPI/ STK11	Hyperpigmented freckle-like macules	GIT polyps
Muir-torre	2p22	MSH2	Sebaceous gland neoplasms	Colonic, breast, urogenital malignancy
Multiple endocrine neoplasia II b	10q11.2	RET	Mucosal neuromas	Thyroid medullary carcinoma, pheochromocytoma, parathyroid tumors
Neurofibromatosis I	17q11.2	NF1	Café' au lait patches	MPNST, pheochromocytoma
Cowden	10q23	PTEN	Tricholemmomas	GIT hamartomatous polyps, breast and thyroid malignancy
Tuberous sclerosis	16p13.3	TSC	Cutaneous angiofibroma	Angiomyolipoma, subependymal giant cell astrocytoma, renal and pulmonary cysts
Gorlin	9q22.3	PTCH	Palmar and plantar pits	BCCs, Medulloblastoma, ovarian fibroma
Ataxia-telangiectasia	11q22	ATM	Conjunctival telangiectasia	Lymphoma and leukemia

(Thiers et al., 2009)

macules on the lips, the nose and buccal mucosa, associated with gastrointestinal polyps. The disease is less extensive and less likely to undergo malignant change. The evolving malignancy is most common in small intestine.

3. *Muir-Torre syndrome* describes the association of sebaceous gland neoplasms of the skin with visceral malignant disease. It is inherited as an autosomal dominant trait and involves 2p22. About 50% of these patients develop internal malignancy which affect the colon in 50% of cases. Other malignant tumors include: the breast, the stomach, lymphomas, and urogenital sites.

4. *Multiple endocrine neoplasia II b (MEN II b)* An autosomal dominant disorder involving 10q11.2, is a syndrome of multiple mucosal neuromas of lip associated with endocrine tumors such as medullary carcinoma of thyroid, parathyroid tumors and pheochromocytoma.

5. *Neurofibromatosis I (von Recklinghausen disease)* (P 22-77) is inherited as autosomal dominant trait and involves 17q11.2. It is characterized by mul-

tiple neurofibromas, cafe' au lait patches of skin and increased risk of neurosarcomas and pheochromocytoma.

6. *Cowden syndrome (multiple hamartoma syndrome)* (P 22-78) An autosomal dominant condition involving 10q23. It is characterized by trichilemmomas affecting mainly head and neck (P 22), fibrocystic breast disease and multiple GIT hamartomatous polyps. There is associated increased risk of breast and thyroid cancer.

7. *Tuberous sclerosis* (P 22-79) is an autosomal dominant disorder which involves 16p13.3. It is characterized by giant cell subependymal astrocytoma, cutaneous angiofibromas (adenoma sebaceum), renal and pulmonary cysts, renal angiomyolipomas, adenomatous polyps of the duodenum and the small intestine.

8. *Nevoid basal cell syndrome (Gorlin syndrome)* (P 22-80) is inherited as autosomal dominant trait and involves 9q22.3. It is characterized by medulloblastoma, multiple basal cell carcinomas, Jaw cysts, ovarian fibroma, skeletal abnormalities, palmar and

plantar pits.

9. *Ataxia telangiectasia (Louis-Bar)*, Bloom and Wiskott-Aldrich syndromes are inherited immunodeficiency disorders with autosomal recessive pattern of inheritance. They show increased risk of lymphomas and leukemias. Ataxia telangiectasia patients show a defect in 11q22. They show conjunctival (P 22-81) and cheek telangiectasia. Bloom syndrome patients have facial telangiectatic erythema, photosensitivity and dwarfism. Wiskott-Aldrich syndrome shows hemorrhagic eczema with secondary cutaneous and systemic infectious complications.

Paraneoplastic Dermatoses

It is a clinical or biochemical manifestation associated with a malignant tumor, not directly related to invasion of the primary tumor or its metastases. Non-endocrine cancer may secrete ectopic hormones or growth factors which causes these clinical manifestations. This association must fulfill Curth's criteria (1976), namely: concurrent onset and parallel course, specificity and significant statistical and genetic association. This group can be classified according to the associated tumors whether neuroendocrine or non-endocrine.

A. *Paraneoplastic manifestation associated with neuroendocrine tumors:*

1. Functioning carcinoid tumors produce serotonin as well as the enzyme kallikrein with subsequent conversion to bradykinin. These are responsible for the carcinoid syndrome manifested by *episodes of skin flushing*.

2. Glucagonoma, a pancreatic islet cell tumor may be associated with necrotizing migratory erythema.

B. *Paraneoplastic manifestations associated with non-endocrine tumors* include many non-specific cutaneous changes that have been reported both in association and in the absence of underlying malignant disease. Finding of any of these changes mandates complete physical examination and in no way guarantee the presence of a tumor. These include:

1. *Skin hyperpigmentation* which may be related to ectopic ACTH- producing small cell lung cancer.

2. *Acanthosis nigricans* is characterized by papillomatous dark plaques of the skin mostly associated with gastric carcinoma. EGF has been proposed as a pathogenetic factor. The dermatoses usually regress after surgical excision of the tumor (P 22-82).

3. *Seborrheic keratosis* may be associated with

gastrointestinal cancer, female genital cancer and lymphomas. It appears as superficial well-demarcated brown plaques, acutely developing on the upper trunk (P 22-83).

4. *Hypertrichosis* is a paraneoplastic condition that is thought to be related to pulmonary or gastrointestinal cancer. The sudden appearance of long hair in a previously hairless area of the body usually signals the presence of internal cancer. No specific hormonal or biochemical abnormalities have been identified.

5. *Sweet syndrome* (acute febrile neutrophilic dermatoses) is characterized by fever, neutrophilia and painful erythematous cutaneous plaques with dense dermal neutrophilic inflammation. An association with malignant disease has been described in about 15% of cases, most commonly acute myelogenous leukemia although solid tumors and lymphomas may also occur.

6. *Amyloidosis* of the skin may occur with multiple myeloma as a result of cutaneous deposition of the light chain proteins of the tumor (P 22-84).

7. *Pruritis* develops in 10 to 25% of patients with Hodgkin lymphoma. A less intense, but more generalized pruritis may be observed with non-Hodgkin lymphoma and leukemia.

8. *Dermatomyositis* appears as thick erythematous patches of the skin. The commonly associated cancers are those of lung, gastrointestinal tract and breast.

9. *Migratory thrombophlebitis* may be associated with carcinoma of pancreas, lung, stomach and prostate.

10. *Paraneoplastic pemphigus* appears as vesicles with red eroded skin. It is commonly associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia.

Toxic Dermatoses

This is related to some carcinogenic chemicals which also produce cutaneous lesions. The exposure to these chemical carcinogens may be occupational or environmental or during receiving medications. Pesticides containing arsenic, chromium (used as oxidizing agent) and aflatoxins cause skin changes, as well as, skin, lung and liver cancer respectively. Certain drugs used in the treatment of myeloid leukemia and radiation therapy can cause dermatitis.

In case of chronic arsenic exposure, a characteristic raindrop hypopigmentation on a background of bronze hyperpigmentation is seen.

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