23.14 Tumours of the skin 5732 Edel O’Toole

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ESSENTIALS A variety of tumours, both benign and malignant, are found in skin. Benign skin lesions, such as seborrhoeic keratoses and skin tags, are often just a cosmetic nuisance, but some benign skin lesions can be a component of diseases with serious medical consequences (e.g. neurofibromatosis or LEOPARD syndrome). Exposure to ultraviolet light is a major factor leading to the devel- opment of both benign lesions (e.g. melanocytic naevi) and most skin cancers. Changes in dress style, increased travel abroad, use of sun tanning salons (sunbeds), and the depletion of the ozone layer have all contributed to increased exposure to ultraviolet light. Skin cancer is the most common human cancer and its incidence continues to increase. It most commonly affects older, fair-skinned individuals who have had either acute intermittent exposure to ultra- violet light or chronic ultraviolet light exposure. Organ transplant re- cipients have a 200-fold increased risk of squamous cell carcinoma. About 2% of patients who develop skin cancer have a genetic predis- position, for example, Gorlin’s syndrome in basal cell carcinoma and familial melanoma syndromes in malignant melanoma. Mutations in the PTCH gene cause Gorlin’s syndrome, and loss of heterozygosity at that locus is also present in most sporadic basal cell carcinoma. Nonmelanoma skin cancer is rarely fatal, but can cause a lot of morbidity. Malignant melanoma is a deadly skin cancer which is the second most common cancer (excluding nonmelanoma skin cancer) in young women. Over the last 20 years, its incidence has been increasing faster than any other cancer, with an approximate doubling of rates every 10 years in countries with largely white popu- lations. Early detection and excision of melanoma is the best way to reduce mortality, as there is no curative treatment for metastatic malignant melanoma. Benign skin tumours Benign nonmelanocytic tumours Seborrhoeic keratosis Seborrhoeic keratoses are probably the most common benign skin tumour. These lesions are usually found on the trunk in older individuals. Clinical features The classic seborrhoeic keratosis is a dry, brown, warty plaque with a ‘stuck-on’ appearance (Fig. 23.14.1). There is large variation in colour, including pale and darker lesions which may even simu- late malignant melanoma. The sudden appearance of multiple seborrhoeic keratoses accompanied by the development of a malig- nancy is known as Leser–Trélat sign. Treatment If the lesion is definitely a seborrhoeic wart the patient can be re- assured. As the lesions are a cosmetic nuisance, patients may request treatment which can include cryotherapy or curettage. Sebaceous

hyperplasia Sebaceous hyperplasia is a common benign tumour of the sebaceous glands usually occurring in middle age. The lesions are usually 2– 3 mm, skin-coloured, or yellow papules with central umbilication from which a small amount of sebum can be expressed. Treatment is usually not needed, but if requested for cosmetic reasons, curettage or gentle cautery are appropriate. Extensive sebaceous hyperplasia may be responsive to low-dose isotretinoin or laser therapy. Sebaceous adenoma Sebaceous adenomas are also derived from the sebaceous glands. Tumours present as a yellow, smooth papule, or nodule usually on the face or neck and are associated with Muir–Torre syndrome. This is an autosomal dominant disorder, caused by mutations in the mis- match repair genes, MLH1 or MSH2, with an increased tendency to visceral cancers, particularly colorectal carcinoma. Skin tags Skin tags are extremely common, flesh-coloured, pedunculated skin lesions that usually occur in the flexures, particularly the neck and axillae. There is some correlation with obesity. Treatment can in- clude cryotherapy or snip excision. Epidermoid cyst An epidermoid cyst consists of a sphere of stratified squamous epi- thelium buried within the dermis. These cysts occur mainly on the face, neck, and chest and have a predilection for the genitalia, where they frequently calcify. A common presentation is a dermal nodule 23.14 Tumours of the skin Edel O’Toole

 with a small pore (punctum) on the surface. The cyst wall can rup- ture into the dermis, causing an intense inflammatory response fol- lowed by suppuration which may require antibiotics and/or incision and drainage. If the lesion is bothersome to the patient, it may be surgically excised. Milia Milia present as 1–2 mm white papules, most commonly on the thin skin of the periorbital region in an adult female. Histologically, the lesions are small epidermoid inclusion cysts. A 20 gauge needle can be used to extract milia. Pilar cyst Pilar (trichilemmal) cysts occur on the scalp, where they present as smooth, firm, mobile nodules with overlying hair. A punctum is not usually present and inflammation rarely occurs. Histologically, these cysts differ from epidermoid cysts in having the squamous epithelial lining without the granular layer. Surgical excision can be performed if required. Dermatofibroma The dermatofibroma is a common dermal tumour usually occurring on the limbs. There is sometimes a history of an insect bite or other trauma. The lesions are firm, pink-brown papules that may involute with time. Xanthogranuloma This is a benign tumour of histiocytic cells which occurs predom- inantly in infancy and early childhood and typically regresses spon- taneously. The characteristic clinical appearance is of reddish yellow papule(s) which enlarge up to 1 cm diameter and evolve into yellow- brown plaques and macules. Resolution occurs over months or years to leave small atrophic scars. Visceral involvement might occur in the lung, liver, spleen, testes, pericardium, gastrointestinal tract, and kidney, as well as in the eye. Histologically, the lesions show a mixed dermal infiltrate with histiocytes, lymphocytes, eosinophils, and other cells. A typical feature is the presence of giant cells with a wreath-like arrangement of nuclei, the Touton giant cell. Benign melanocytic tumours Freckles Freckles (ephelides) are brown macules that occur on sun-exposed areas, particularly the nose and the arms, in fair-skinned individ- uals. The lesions often fade in winter. Solar lentigo The solar lentigo is a brown patch occurring on sun-exposed skin that results from UV exposure. Multiple symmetric, hyperpigmented patches on the face, arms, and dorsa of the hands are typical. Lentigines-associated syndromes Extensive lentigines at a young age might indicate underlying gen- etic disorders such as xeroderma pigmentosum (see Chapter 23.9), Carney’s (atrial cutaneous myxomas, lentigines, blue naevi, endo- crine disorders, and testicular tumours) or LEOPARD (lentigines, electrocardiographic conduction defects, ocular hypertelorism, pul- monary stenosis, genital abnormalities, retardation of growth, and deafness)

syndromes. Acquired melanocytic naevi (moles) Melanocytic naevi are benign tumours of melanocytes, and are also known as moles. Aetiology, genetics, and pathogenesis Acquired naevi tend to first appear and increase in number during childhood, reaching their maximum in early adulthood. There is some evidence that the number of acquired naevi might be related to UV exposure. Fair-skinned individuals and white people who live close to the equator have more acquired naevi than nonwhite popu- lations. Naevi commonly darken or enlarge during pregnancy sug- gesting a degree of sex hormone responsiveness. Correlation in sex and age-adjusted naevus density in adolescence is higher in mono- zygotic twins than dizygotic twins suggesting a definite additional genetic effect. About 2% of the UK population have the atypical mole syndrome, which is associated with an increased risk of mel- anoma. Mutations in the BRAF gene, a serine/threonine kinase in- volved in the mitogen-activated kinase pathway, are present in about 80% of melanocytic naevi and might contribute to melanocytic hyperproliferation. Clinical Acquired melanocytic naevi appear and change in the childhood, teenage, and early adult years. As a rule, new melanocytic naevi do not appear after the age of 40 years. Junctional naevi are usu- ally flat, uniformly pigmented macules that appear in childhood. Histologically, nests of naevus cells appear at the dermoepidermal junction. Compound naevi are, usually, slightly elevated pig- mented papules. They may have a smooth or papillomatous (a) (b) Fig. 23.14.1 Seborrhoeic warts are often multiple and may be deeply pigmented (a) or light brown (b).

section 23 Disorders of the skin 5734 surface (Fig. 23.14.2a). Compound naevi usually increase in size during adolescence. Nests of naevus cells are found both at the dermoepidermal junction and in the dermis. Intradermal naevi are seen mainly after adolescence. These are skin-coloured, dome- shaped papules that most frequently occur on the face. A halo naevus is a clinical variant with a ring of depigmentation around an otherwise normal mole (Fig. 23.14.2b). A blue naevus usually occurs on the limbs. It appears blue-grey because the pigmentation is deep in the dermis. A Spitz naevus usually presents as a vascular- looking papule on the face in children. Atypical (dysplastic naevi) are usually more than 5 mm in diameter, have a macular compo- nent, and an indistinct margin, sometimes with background ery- thema. Recognition of atypical naevi is important as individuals with five or more atypical naevi, naevi in unusual locations (scalp, buttocks, dorsum of feet, and iris) and 100 or more naevi more than 2 mm in diameter (atypical mole syndrome) are at increased risk of developing malignant melanoma. Treatment The malignant potential of individual naevi is low, therefore prophy- lactic excision of acquired melanocytic naevi to prevent transform- ation into melanoma is not advised. Excision of naevi is advocated where it is not possible to clinically exclude a diagnosis of melanoma. Complete excision and histological examination is advocated even when moles are removed for purely cosmetic reasons. Although the clinical differentiation of atypical naevi from melanoma is dif- ficult, it can be facilitated by regular surveillance, automated digital imaging systems, and dermoscopy. Removal of an atypical mole is only necessary if melanoma is suspected. Congenital melanocytic naevi Clinical Congenital melanocytic naevi (CMN) are proliferations of nested melanocytes that are present at birth. The term is also used to de- scribe histologically and clinically identical lesions that appear in diameter in infancy. Small CMN (<1.5 cm in diameter) are seen in 1–2% of neonates, intermediate-sized lesions (1.5–20 cm) in 0.6%, and large and giant CMN (>20 cm) in about 0.02%. Giant CMN may also be known as ‘bathing suit naevi’ because of their distribu- tion. The lesions are tan, brown to dark brown patches or plaques at birth. They may have a smooth, nodular, or verrucous surface which might be hair-bearing. Patients with large CMN are at increased risk of developing melanoma within the CMN, in the central nervous system, and elsewhere. Treatment

Most small and intermediate CMN can be managed by routine surveillance. The lifetime risk of malignant melanoma in a patient with a large CMN is about 7%. Parents should be instructed on proper sun avoidance and sun protection techniques including use of sunscreen and use of high-weave, sun-protective clothing. Many specialists recommend partial or complete excision of large CMN. This might require multiple surgical procedures, tissue expansion, and/or grafting. Other surgical options include cur- ettage, dermabrasion, or laser surgery to remove the superficial naevus cells. Premalignant lesions Solar keratosis Solar keratoses (also known as actinic keratoses) are erythematous scaling lesions between 2 and 10 mm in diameter, seen in fair-skinned individuals on areas of maximal sun exposure such as the face, ears, dorsum of the hands, forearms, and lower legs. Histologically, these lesions show dysplasia of the basal keratinocytes. The estimated risk of transformation into squamous cell carcinoma (SCC) is very low, approximately 1% per annum. Some small lesions resolve spontan- eously, particularly with photoprotection. Treatment options include cryotherapy, topical diclofenac, ingenol mebutate, 5-fluorouracil, or imiquimod, a topical immune modifier. Bowen's disease Bowen's disease (squamous cell carcinoma in situ) presents as an asymptomatic, enlarging, erythematous, scaly plaque. Approximately 5% progress to invasive squamous cell carcinoma. Bowen's disease affecting the glans penis is called erythroplasia of Queyrat. Bowen's disease might be misdiagnosed as tinea, psoriasis, or discoid eczema. Biopsy of a typical lesion shows full-thickness dysplasia of the epidermis. Treatment can include cryotherapy, top- ical 5-fluorouracil, topical imiquimod, or photodynamic therapy. (a) (b) Fig. 23.14.2 (a) Benign compound naevus with papillomatous surface. (b) Halo naevus showing an area of depigmention around a benign mole. The mole might eventually regress completely leaving a depigmented patch, which will eventually repigment.

23.14 Tumours of the skin 5735 Malignant skin tumours Nonmelanocytic Basal cell carcinoma Introduction Basal cell carcinoma (BCC) is the most common cancer in humans, which typically occurs in areas of chronic sun exposure. Basal cell carcinomas are usually slow-growing and rarely metastasize. Aetiology The most common factor involved in the pathogenesis of basal cell carcinoma is exposure to ultraviolet light (UV). Fair-skinned individ- uals who burn easily and tan poorly are at greatest risk of developing basal cell carcinoma. Both cumulative lifetime UV exposure and intermittent intense sun exposure are risk factors. Other sources of UV include sunbeds and psoralen ultraviolet A (PUVA) for psoriasis. Other environmental factors leading to the development of basal cell carcinoma include ionizing radiation given for benign conditions (e.g. acne, tinea capitis) and arsenic ingestion. Organ transplant re- cipients have a 10-fold increased risk of basal cell carcinoma. Genetics Several genetic syndromes of increased susceptibility to basal cell carcinoma have been described. The most significant is Gorlin's syndrome (naevoid basal cell carcinoma syndrome) which is char- acterized by the appearance of basal cell carcinomas before the age of 20, an autosomal dominant family history, palmar/plantar pits, odontogenic keratocysts, and bilamellar calcification of the falx cerebri. Mutations are present in the human PTCH gene, the human homologue of the drosophila patched gene Ptch1. Ninety per cent (90%) of sporadic nodular basal cell carcinomas have loss of hetero- zygosity at chromosome 9q21-q31, where the PTCH gene is located and 70% of nodular basal cell carcinomas have detectable PTCH gene mutations. This gene negatively regulates the hedgehog signalling pathway, which is important in epithelial cell growth during hair follicle development, and an inactivating mutation allows uncon- trolled hedgehog signalling. Activating mutations in the SMO gene (smoothened) similarly allow for unregulated hedgehog signalling in basal cell carcinoma. About 40% of basal cell carcinoma have UV-induced transition mutations in TP53. Polymorphisms in genes activated by

exposure to UV, such as reactive oxygen species (GST, CYP450) or DNA repair (xeroderma pigmentosum), are also sig- nificantly associated with risk of basal cell carcinoma development. Pathology The major histological patterns of basal cell carcinoma are nodular, micronodular, superficial, and morphoeic. The nodular type is characterized by well-defined islands of basaloid cells with well- defined peripheral palisading. The superficial type has foci of tu- mour extending from the epidermis into the papillary dermis. The morphoeic subtype has tumour islands of varying size with sur- rounding fibrosis. Epidemiology Basal cell carcinoma most commonly occurs in white, fair-skinned individuals and rarely occurs in darker skin types. Although it more commonly occurs in men, the incidence of basal cell carcinoma con- tinues to rise in women because of increased UV exposure due to changes in dress and lifestyle, including ‘sun holidays’ and use of sunbeds. Prevention The most important risk factor is cumulative lifetime UV exposure. Avoidance of exposure to UV radiation is encouraged. Helpful preventive measures include avoidance of midday/afternoon sun, wearing a broad-brimmed hat during outdoor activities, and using sunscreens with sun protection factor (SPF) of 15 or greater (see Chapter 23.9). Patient education about the appearance of new le- sions to maximize early detection should be encouraged. Clinical features Approximately 50% of basal cell carcinomas occur on the head and neck, 30% on the upper trunk, and the remainder elsewhere. The clinical variants include nodular/nodulocystic, morphoeic, superfi- cial, and pigmented basal cell carcinomas. The nodular subtype rep- resents about 60% of basal cell carcinomas and presents as a small, pink nodule, with a translucent, pearly appearance with telangi- ectasia (Fig. 23.14.3a). As the lesion enlarges, central ulceration can occur (‘rodent ulcer’). Although slow-growing, if neglected, these tumours can enlarge and extend deeply, causing significant damage to eyelids, nose, or ears. Superficial basal cell carcinoma accounts for about 20% of such carcinomas and is more commonly found on the trunk and extremities. Typically, the lesion is a slightly scaly, pink plaque with a threadlike, translucent, raised border. Multiple lesions might be present. Melanin pigmentation can occur in both superficial and nodular basal cell carcinomas, giving a pigmented variant which is more common in individuals with dark skin (a) (b) Fig. 23.14.3 (a) Basal cell carcinoma in a common location, nasal aspect of the nasolabial fold. Note the surface crusting and telangiectasia. (b) Pigmented basal cell carcinoma.

 (Fig. 23.14.3b). Morphoeic (infiltrative) basal cell carcinomas pre- sent as an indurated, ivory plaque, often resembling a scar. The name is derived from its resemblance to a plaque of localized scleroderma (morphoea). This variant is notable for its tendency to extend be- yond the apparent clinical borders and a high local recurrence rate after treatment. Differential diagnoses of nodulocystic basal cell carcinoma to consider include intradermal naevi and rarer tumours derived from appendageal structures. Clinical investigation Dermoscopy (a magnifying device with or without polarizing light) can be used to refine the clinical diagnosis of basal cell carcinoma. Features include arborizing telangiectasias, leaf-like areas, foci of ul- ceration, blue/grey globules, and large blue/grey ovoid nests. A small shave or punch biopsy is usually sufficient to confirm the diagnosis and histological subtype of basal cell carcinoma. Treatment Treatments are influenced both by tumour factors (the size, site, margin, and subtype of the basal cell carcinoma) and patient fac- tors (such as age, coexisting illnesses, e.g. bleeding diathesis, anti- coagulant therapy, or susceptibility to bacterial endocarditis), access to specific treatments locally, and patient preference. Options for superficial basal cell carcinoma include topical imiquimod, which has largely replaced 5-fluorouracil, and cryotherapy. Nodular basal cell carcinoma can be treated by curettage and cautery or simple excision. Morphoeic or nodular basal

cell carcinomas in high-risk sites ideally should be treated with Mohs' micrographic surgery, which is performed in stages with examination of the histological margins, but wide excision can be performed if this is not available. Photodynamic therapy may be useful for thin basal cell carcinomas at cosmetically difficult sites. Radiotherapy can be useful in older patients where surgery is not feasible. With appropriate patient selection, the treatments just described will give cure rates exceeding 95%. Patients who have had one basal cell carcinoma have a 20% risk of developing a further basal cell car- cinoma over the following five years. It is likely that over the next 5–10 years, further basal cell car- cinoma tumour suppressor genes will be identified. Clinical trials of oral vismodegib, a small molecule inhibitor of smoothened, showed antitumour activity in inoperable basal cell carcinoma and Gorlin's syndrome. Other small molecule inhibitors of the hedgehog pathway might be used routinely in the future, either systemically or topically. Squamous cell carcinoma (SCC) Squamous cell carcinoma is the second most common form of skin cancer and usually occurs on sun-exposed areas in older individuals. Aetiology, genetics, pathogenesis, and pathology Squamous cell carcinoma is a malignant tumour of epidermal kera- tinocytes. Its development is multifactorial, involving both gen- etic predisposition and environmental factors. Most squamous cell carcinomas occur on sun-exposed areas (head and neck, dorsum of hands). Individuals with type I and II skin types (who burn easily) are at greatest risk. Africans with oculocutaneous albinism, who have lost their protective melanin, also have an increased risk of squamous cell carcinoma. The amount of chronic cumulative sun exposure is a major risk factor for squamous cell carcinoma. The highest incidence of squa- mous cell carcinoma worldwide is in Australia, a country with a large white population and year-round sunshine. Absorption of UVB by DNA in skin keratinocytes induces unique mutations at the site of pyrimidine dimers. Ultraviolet B (UVB) irradiation also leads to the activation of cell cycle checkpoint controls and apoptotic pathways. The repair and/or elimination of such apoptotic and mutated cells from the epidermis by 'gatekeeper genes' such as TP53 is important, as clonal proliferation of mutated cells may eventually lead to cancer development. Mutations in TP53 are found in up to 90% of squamous cell carcinomas. Mutations in HRAS, KRAS, p16INK4a and p14ARF, as well as hypermethylation without mutation, have also been docu- mented in squamous cell carcinoma. Exome sequencing has recently identified inactivating mutations in NOTCH1/2 in cutaneous squa- mous cell carcinoma. The Notch pathway is an important regulator of differentiation, epidermal barrier formation and inflammation. Finally, mutations in HRAS, KRAS, and KNSTRN, which encodes a kinetochore protein, have also been demonstrated in squamous cell carcinoma. UVA also plays a role in squamous cell carcinoma car- cinogenesis through DNA damage, modulation of protein kinase C, and immunosuppression. There is evidence that human papillomavirus (HPV) might play a causal role in the condition (Chapter 8.5.19). Epidermodysplasia verruciformis (EV), a rare inherited disorder with a high risk of squa- mous cell carcinoma is associated with susceptibility to infection with specific HPV types, called 'EV types', including the oncogenic HPV-5. Organ transplant recipients are highly susceptible to HPV infection, particularly warts, and have a c.200-fold risk of squamous cell carcinoma compared to the immunocompetent population. Up to 80% of transplant squamous cell carcinomas have detectable EV- type HPV DNA. HPV E6 and E7 proteins functionally inactivate TP53. Azathioprine and UVA radiation have recently been shown to generate oxidative DNA damage which may be a further risk factor in organ transplant recipients. Other documented risk factors include arsenic ingestion and exposure to chemical carcinogens such as polycyclic aromatic hy- drocarbons found in soot and tar (a historical example of this is squamous cell carcinoma of the scrotum in chimney sweeps). Other conditions predisposing to squamous cell carcinoma include chronic ulcers (known as Marjolin's ulcer), recessive dystrophic epi- dermolysis

bullosa (an inherited blistering disease which heals with extensive scarring), skin damage from ionizing radiation, thermal injury, and lymphoedema. Chronic infection and chronic inflam- mation, such as discoid lupus erythematosus, erosive lichen planus, and lichen sclerosus et atrophicus, also increase the predisposition to squamous cell carcinoma. Mutations in nucleotide excision re- pair genes in xeroderma pigmentosum causing defective DNA repair result in a 1000-fold increased risk of skin cancers (both non- melanoma and melanoma). Epidemiology The incidence of squamous cell carcinoma has doubled over the last 40 years. The British Association of Dermatology estimates that there are 25 000 new cases of squamous cell carcinoma in the United Kingdom annually, representing about one-quarter of non- melanoma skin cancers. Men are affected 2 to 3 times more than women probably because of outdoor occupations, less protective

 clothing, and a greater lifetime cumulative UV radiation exposure. The success of organ transplantation and immunosuppression has also contributed to the increased incidence of squamous cell carcinoma. Prevention Recommendations include photoprotection against UVA and UVB, patient education about warning signs, regular skin examination, and treatment of actinic keratoses. Systemic chemoprevention with oral retinoids may be an option for high-risk patients (e.g. organ transplant recipients with multiple squamous cell carcinomas). Clinical features The classical squamous cell carcinoma is a pink, keratotic papule or nodule (Fig. 23.14.4) appearing on the head and neck regions on sun-damaged skin. Surface changes may include ulceration, crusting, scaling, or the presence of a cutaneous horn. As the lesion progresses, it will become nodular and/or ulcerated. These lesions are frequently tender to compression. Squamous cell carcinoma of the lip generally occurs on the vermilion border of the lip in men with a background of actinic cheilitis (the lower lips are scaly, ir- regularly pigmented, and atrophic). Squamous cell carcinoma of the anogenital region can present with pruritus, a palpable lump, or ero- sion. A full skin examination and palpation of regional lymph nodes is important. The common differential diagnoses of squamous cell carcinoma include keratoacanthoma, hypertrophic actinic keratosis, verruca vulgaris, and basal cell carcinoma. Clinical investigation In most patients, the clinical diagnosis of squamous cell carcinoma is confirmed by excision and histopathology. Where there is diag- nostic doubt, a small biopsy will confirm the diagnosis. Treatment Simple excision with a 4 mm margin of normal surrounding skin is adequate treatment for most low-risk squamous cell carcinoma. High-risk tumours (>2 cm in diameter, depth more than 4 mm, lo- cated on ears, lip, nose, or scalp, poorly differentiated, desmoplastic histology, perineural invasion, or subcutaneous invasion and recurrent tumours) should be removed with a margin of 6 mm or ideally using Mohs’ micrographic surgery. Selected small, low-risk squamous cell carcinomas can be treated with curettage and cau- tery or cryotherapy after a confirmatory biopsy. Radiotherapy can be used for nonresectable tumours. Prognosis The 5-year cure rate after simple excision of squamous cell carcinoma is 92%. The overall risk of metastasis from squamous cell carcinoma is in the range of 2–5%. High-risk squamous cell carcinomas have the greatest risk of metastasis. Chronically immunosuppressed pa- tients also have an increased rate of metastasis. The overall five-year survival after regional metastasis is just 25%. In addition, patients are at risk of developing a second primary skin cancer. Within five years, 12% cent of patients will have developed a new squamous cell carcinoma, 43% a new basal cell carcinoma, and 2% a malignant melanoma. It is likely that over the next 5–10 years, the use of genomic and proteomic technology will identify new therapeutic targets in cuta- neous and metastatic squamous cell carcinoma. Cyclo-oxygenase-2 inhibitors and antioxidants (e.g. green and black tea compounds), might be potentially useful as chemopreventative agents in pa- tients with multiple actinic keratoses. There

will be more aggressive management of patients with high-risk squamous cell carcinoma, including sentinel lymph node mapping. If a role for HPV in squa- mous cell carcinoma development is validated, there may be ran- domized clinic trials of vaccination against EV-type HPV in high-risk groups such as organ transplant recipients. The use of sirolimus, an mTOR inhibitor, instead of calcineurin inhibitors or azathioprine in transplant immunosuppression regimes may reduce the incidence of post-transplantation cancer. Keratoacanthoma Keratoacanthoma is a clinically and genetically distinct subtype of squamous cell carcinoma. A nodule with a central keratin crater develops rapidly over several weeks, stabilizes in size, and then spontaneously resolves over several months. Histologically and clin- ically (apart from the history), it is difficult to distinguish from a well-differentiated squamous cell carcinoma. There are minimal mi- toses or cellular atypia. Ferguson Smith syndrome is an autosomal dominant disorder presenting with multiple keratoacanthomas at a young age, recently found to be caused by mutations in the trans- forming growth factor receptor β 1 gene (TGFBR1). Hundreds of eruptive keratoacanthomas occur in the Grzybowski variant. Keratoacanthomas are also found in Muir–Torre syndrome. Melanocytic tumours Malignant melanoma Malignant melanoma (MM) is a melanocyte-derived tumour located predominantly in the skin, but also found in the eyes, leptomen- inges, and oral, genital, and rectal mucous membranes. Melanoma accounts for only 4% of all skin cancers, but causes about 80% of skin cancer-related deaths worldwide. Aetiology, genetics, pathogenesis, and pathology The development of malignant melanoma is multifactorial. Risk factors include fair skin phenotype (blonde/red hair, freckles easily, blue eyes), blistering sunburn in childhood or adolescence, history Fig. 23.14.4 Squamous cell carcinoma presenting as a nodule with central keratinization on the forehead.

 of excessive UV exposure, greater than 100 melanocytic naevi, greater than five atypical/dysplastic naevi, personal or family his- tory of malignant melanoma, and changing moles. The presence of the atypical mole syndrome (also known as familial atypical mole melanoma syndrome) or xeroderma pigmentosum increases the risk by 500–1000-fold. More than 60% of melanomas arise de novo (no pre-existing lesion). The genetics of inherited cancers are further discussed in Chapter 5.3. BRAF mutations occur in 70% of melanomas arising in intermit- tently sun-exposed sites. The receptor tyrosine kinase gene, KIT, is mutated in 20% of acral and mucosal melanomas. Melanocortin 1 receptor variants that cause red hair and freckling are associ- ated with a small increase in melanoma risk (two–threefold) and an increased risk of melanoma with BRAF mutations. There are probably at least three other genes which underlie predisposition to familial melanoma. The most common is a gene on chromo- some 9, CDKN2A, which codes for p16INK4a, an inhibitor of the cyclin-dependent kinases 4 and 6. In the United Kingdom, 50% of families with three or more melanoma cases have CDKN2A muta- tions, but only 12% of families with two or fewer cases. The second is the CDK4 gene. A rare, dominant activating mutation in this gene renders it insensitive to p16 inhibition. The third is p14ARF, a second product of the CDKN2A locus. Very rare deletions of this gene have been shown to underlie susceptibility to melanoma and neural tumours. Recent exome sequencing of 14 metastatic melanoma tumours has revealed a novel melanoma oncogene, TRRAP, which is part of a complex regulating the transcriptional activity of TP53 and c-Myc, and a new tumour suppressor gene, GRIN2A, encoding a glutamate receptor. Melanoma might also occur as a second tumour in familial retinoblastoma and in the Li–Fraumeni syndrome (associated with sarcomas, brain, and breast tumours). Histologically, a malignant melanoma is an asymmetric le- sion consisting of single or nested melanocytes in the epidermis (pagetoid spread), appendageal structures, and dermis. The

tumour melanocytes do not mature as they descend into the dermis. The dis- tribution of melanin is irregular and the melanocytes display atypia and mitoses. An initial radial growth phase (melanocytes prolifer- ating in the epidermis and papillary dermis) is followed by a more aggressive vertical growth phase with more extensive spread deep into the dermis. Epidemiology Malignant melanoma is the most serious type of skin cancer and is primarily a disease of white individuals. It rarely occurs in black and Asian individuals. There were 15 906 new cases of malignant mel- anoma in the United Kingdom in 2015 and about 2459 melanoma related deaths (Cancer Research UK statistics). In the age group 20– 39, melanoma is the second most common cancer (excluding basal cell carcinoma and squamous cell carcinoma). The incidence of mel- anoma increases with age with a peak in the fifth decade. Prevention The general public should be encouraged to avoid sunburn and other excessive UV exposure. At risk individuals should use sun- block and wear protective clothing and take vitamin D supple- mentation if levels are suboptimal (see Chapter 23.9). Healthcare professionals and patients should be educated about the features of early malignant melanoma as early detection of thin melanoma is the best method of reducing mortality. Clinical features The major clinical characteristic of melanoma is a changing mole. The seven-point checklist is useful. Major features (2 points each) are change in size, irregular colour, and irregular shape, while minor features (1 point each) are inflammation, oozing, change in sensa- tion, and diameter 7 mm or less. Suspicion of melanoma is greater for lesions scoring 3 points or more. The mnemonic ABCDE is also used which stands for asymmetry, border irregularity, colour varie- gation, diameter more than 6 mm, and evolving (changing). Four major clinicopathological variants of malignant melanoma have been identified. Superficial spreading melanoma represents about 70% of melanomas and occurs most commonly on the legs in women and on the trunk in men (Fig. 23.14.5a). It presents as a flat, pigmented lesion with variegation in colour and an irregular border. Nodular melanoma accounts for about 15–20% of melan- omas and presents as a papule or nodule on the trunk (usually in men) or limbs. There is frequently a history of rapid growth. This variant is more likely to be amelanotic (no pigmentation) and there might be a delay in diagnosis (Fig. 23.14.5b). Lentigo maligna, also known as Hutchinson’s melanotic freckle, occurs on the head and neck of older people who have been heavily exposed to sunlight. These are slow- growing in situ melanomas (Fig. 23.14.5c) with the potential to progress to invasive melanoma (lentigo maligna mel- anoma) and metastasize. Acral lentiginous melanoma occurs on palmoplantar skin (Fig. 23.14.5d) or the nail bed. It occurs in all races and therefore does not appear to be caused by exposure to the sun. A tendency to delayed diagnosis gives this variant a poor prognosis. At presentation, 10% of cutaneous melanomas will have metasta- sized. The primary lesion might regress, leaving a hypopigmented patch, or the primary can be noncutaneous. Although systemic me- tastasis is predominantly to the lung, liver, brain, and bone, lesions can arise anywhere including bowel, kidney, and muscle. Localized skin metastasis is also common. Differential diagnosis Atypical naevi, deeply pigmented seborrhoeic warts, and pigmented basal cell carcinoma might all simulate melanoma. Dermoscopy can be helpful in discriminating between melanocytic and non- melanocytic lesions. Features of malignant melanoma include a broadened pigment network, multiple colours, a blue-white veil, pseudopods, and peripheral black dots and globules. Clinical investigation The diagnosis should always be based on a full-thickness excisional biopsy down to fat with a margin of 2 mm of normal skin around the lesion. Sentinel lymph node (initial draining lymph node) bi- opsy (SLNB) with selective complete clearance of regional nodes is now performed in many centres for lesions of AJCC Stage IB or above. Patients with AJCC Stage IIB melanoma or higher will require a CT scan of brain/chest/abdomen/pelvis or a PET scan depending on local preference. Molecular profiling for

BRAF muta- tions on the primary tumour is also offered in many centres in the United Kingdom for patients with stage IIB melanoma or more at initial diagnosis.

23.14 Tumours of the skin 5739 Treatment The definitive treatment of localized disease is wide excision of the tu- mour with a normal skin margin of 0.5 cm for in situ melanoma (con- fined to the epidermis), 1 cm minimum and up to 2 cm for tumours with a Breslow's thickness of 1–2 mm and 2–3 cm for thicker lesions. Completion lymphadenopathy can be considered for people whose SLNB shows micro-metastases. Lymph node dissection is offered to individuals with palpable lymph nodes or nodal disease detected on imaging. NICE guidelines currently suggest offering dabrefinib or vemurafenib, potent inhibitors of BRAF, for treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. Complications of treatment include the development of keratoacanthomas, caused by paradoxical activation of the MAP Kinase pathway. Ipilimumab (an antibody against cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) is currently offered as a second-line treatment in patients with unresectable or metastatic melanoma. Limited metastatic disease can also be managed with excision or carbon dioxide laser ablation. Extensive recurrent disease in a limb can be treated with isolated limb perfusion with melphalan or electrochemotherapy. Prognosis Breslow's thickness is the distance from the granular layer to the deepest level of the tumour and is the most important prognostic factor in malignant melanoma. Patients with lesions confined to the epidermis (melanoma in situ) have an approximate five-year survival rate of 100%; those less than 1 mm, 95–100%; between 1 and 2 mm, 80– 96%; between 2.1 and 4 mm, 60–75%; and lesions of more than 4 mm in depth, 50%. If a single lymph node is involved the five-year survival is 45%, if two lymph nodes are involved, the survival rate is 28%, but this rate drops to 9% if more than four lymph nodes are involved. The me- dian survival time following metastasis is between 5 and 16 months. It is likely that over the next 5–10 years, immunotherapy might provide hope for those patients with metastatic disease. In patients with advanced melanoma, combined treatment with ipilimumab and nivolumab (an antibody against the programmed death 1 [PD- 1] receptor) produced an objective response in 53% of patients. Clinical trials combining BRAF and MEK inhibitors also show promise. Tyrosine kinase inhibitors targeting KIT mutations are in clinical trials for acral and mucosal melanoma. Advances in gen- omic technology should provide new targets for investigation. Other cutaneous malignancies Cutaneous lymphoma Cutaneous lymphomas are rare lymphoproliferative disorders of the skin, mainly of T- or B-cell origin. The most common cutaneous lymphoma is mycosis fungoides (MF), a T-cell lymphoma. (a) (c) (b) (d) Fig. 23.14.5 Malignant melanoma: (a) superficial spreading melanoma with variegation in colour and irregular margin, (b) amelanotic (no pigment) nodular melanoma, (c) invasive nodular melanoma arising in a lentigo maligna; and (d) acral lentiginous melanoma on the sole.

section 23 Disorders of the skin 5740 Aetiology, genetics, pathogenesis, and pathology Clonal lymphocyte proliferation has been ascribed to viral infection, chromosomal alterations, overexpression of oncogenes, or environ- mental toxins. Chromosomal aberrations associated with cutaneous T-cell lymphoma include losses on chromosomes 1p (38%) and 17p (21%) and gains on chromosomes 4/4p, 18, and 17q/17. These loci contain two well-known tumour suppressor genes, TP53(17p) and PTEN(10q). A recent study identified recurrent alterations in the TNFR2 pathway in addition to other genes regulating T-cell survival and proliferation affecting more than a third of patients with my- cosis fungoides and Sézary syndrome. Biopsy of a patch or plaque lesion in MF shows prominent atypical lymphocyte invasion of the epidermis (epidermotropism), forma- tion of

intraepidermal collections called Pautrier's microabscesses, and a band-like infiltrate in the papillary dermis. The clonal nature of the lymphocyte infiltration can be confirmed by demonstration of rearrangement of the TCRB gene by polymerase chain reaction. However, clonal T-cell populations are also found in inflammatory dermatoses. Immunohistochemistry shows that the lymphocytic in- filtrate expresses T-cell antigens (CD2, CD3, CD4, CD5) with loss of CD7 and CD26. Mycosis fungoides most commonly occurs in the fourth to fifth decade and is approximately twice as common in black individuals as it is in white individuals. Clinical features Mycosis fungoides—the typical clinical presentation of MF is with brownish-red patches and plaques. Some lesions may have an an- nular or serpiginous configuration and poikiloderma (telangi- ectasia, pigmentation, and atrophy), particularly on the breasts and buttocks. Some patients will progress to develop thicker plaques and tumours. Widespread erythroderma with ulcerated tumours is the final stage of the disease. Other clinical variants that may have the immunophenotypic features of MF include granulomatous slack skin disease, follicular mucinosis, and large plaque parapsoriasis. Sézary's syndrome—this is part of the spectrum of MF and is characterized by generalized erythroderma ('red man') with scaling and pruritus, lymphadenopathy, and circulating atypical lymphoid cells (Sézary cells) which have cerebriform nuclei (usually >1000 atypical lymphocytes/mm3). Adult T-cell leukaemia/lymphoma—this is a high-grade CD4- positive lymphoproliferative disorder associated with infection with human T-lymphotropic virus 1 (HTLV-1). It is most common in Japan and in the Caribbean and in immigrants from these regions. The cutaneous manifestations include patches, plaques, and tu- mours. Atypical lymphocytes (clover leaf cells) are commonly seen in the peripheral blood. Extracutaneous manifestations include lymphadenopathy, hypercalcaemia, splenomegaly, pulmonary infil- trates, and opportunistic infections. B-cell lymphoma—cutaneous B-cell lymphoma usually presents as grouped dermal nodules, sometimes in an annular configuration. These generally progress slowly and remain confined to the skin. Other inflammatory skin disorders may simulate MF including psoriasis, eczema, and parapsoriasis. Clinical investigation A clinical diagnosis of MF is confirmed by a skin biopsy. Initial histology can be subtle and several biopsies might be required to see the histological features of MF. Initial clinical investigation of a newly diagnosed patient with MF should include a thorough his- tory (looking for systemic symptoms such as fever, weight loss, night sweats) and examination (looking for lymphadenopathy or hepatosplenomegaly). Routine investigations should include full blood count/blood film, liver function tests, lactate dehydrogenase (an indicator of tumour load), and HTLV-1 antibodies. If lymph node enlargement is present, a lymph node aspirate/biopsy should be performed. Patients with an elevated lactate dehydrogenase (LDH), abnormal full blood count, or rapidly progressive disease should have a staging CT of chest, abdomen, and pelvis and bone marrow biopsy. Treatment Potent topical corticosteroids are usually the initial treatment for limited patch or plaque stage cutaneous T-cell lymphoma (CTCL). Topical nitrogen mustard is also effective in adults with patch or plaque stage disease but application is time-consuming. Superficial (patch stage) disease also responds well to narrowband UVB, but psoralen ultraviolet A (PUVA) is better for plaque stage disease. Combined treatment with α-interferon improves the duration of response. Total skin electron beam therapy is a further option. Bexarotene, a synthetic retinoid-X receptor agonist, is a promising new therapy for cutaneous T-cell lymphoma with response rates of up to 70%, even in tumour stage disease. Bexarotene-related tox- icity includes marked hypertriglyceridaemia and hypercholesterol- aemia. Photopheresis and denileukin diftitox are other options for more advanced disease. Patients with resistant early stage disease or advanced disease should be offered entry into clinical trials where available. Prognosis Patients with early stage disease have a similar life expectancy to their peers. Patients presenting

with tumours or erythroderma have a 10-year survival of approximately 40% (tumour-node-metastasis (TMN) Stage III or higher). Poor prognostic factors include presen- tation with extensive thick plaques, tumours, or erythroderma, a late age of onset, or folliculotropic histology. There are many newer agents in development/trials directed at receptors, tumour-specific genes, or signalling pathways. These in- clude alemtuzumab, a humanized anti-CD52 antibody that targets a cell surface antigen expressed on normal and malignant T cells, individualized dendritic cell-based vaccines, depsipeptide, a histone deacetylase inhibitor molecule (in Phase I-II clinical trials), topical tazarotene, and allogenic haematopoietic stem cell transplant. Other targets include PI3K isoforms, CTLA4 and NF-κB processing. Leukaemic infiltrates Leukaemic infiltrates of skin are known as leukaemia cutis. Leukaemia cutis is most commonly associated with myeloid subtypes of leu- kaemia, particularly acute monocytic or myelomonocytic leukae- mias, but might also herald the transformation of myelodysplastic syndrome to leukaemia. It is less commonly associated with lymph- atic leukaemia. The most characteristic lesions of leukaemia cutis are red-brown to violaceous papules, nodules, and plaques which may be purpuric from thrombocytopenia. The lesions might localize to sites of skin trauma or surgical scars. A granulocytic sarcoma (or chloroma) presents as a rapidly growing, firm nodule that at times

 has a green hue. This tumour is usually associated with acute myeloid leukaemia, and the greenish colour is related to myeloperoxidase in the granulocytes. Leukaemia cutis is usually an indicator of ad- vanced disease. If there is diagnostic doubt, immunophenotyping of a skin biopsy may be helpful. Cutaneous metastases Skin metastases usually occur at a late stage of disease and indicate a poor prognosis. The most common skin tumour to metastasize to the skin is malignant melanoma. Frequent visceral primary sites that metastasize to skin include breast, stomach, lung, uterus, colon, kidney, prostate gland, and ovary. Metastases from other organs are transferred via lymphatic or haematogenous spread and this occurs in about 3% of cancer cases. The presenting lesions are often rather inflammatory in appearance (Fig. 23.14.6). The most common pres- entation is isolated or multiple nodules. Intra-abdominal metastasis may produce an umbilical nodule, known as Sister Mary Joseph’s nodule. The primary cancer is often ovarian or gastric and this may be the presenting sign. Metastases from renal cell carcinoma are often very vascular. In breast carcinoma, metastases can pre- sent as inflammatory plaques resembling erysipelas (carcinoma erysipeloides). Breast cancer can also cause dermal oedema which resembles orange peel (peau d’orange). Rarely, infiltrative breast cancer metastases can cause scarring alopecia. The presenting lesion is usually excised to confirm the diagnosis. Immunohistochemistry can be performed with tumour-specific markers to confirm the pri- mary source. Paget’s disease Paget’s disease of the nipple is the presenting feature of about 2% of breast cancers, usually intraductal carcinoma. It occurs most fre- quently in the fifth or sixth decade. Early changes might be very minimal (e.g. only a very small amount of nipple discharge). An erythematous plaque subsequently develops over the nipple and areola which may simulate eczema. The main differential diagnosis is nipple eczema, which is almost always bilateral. A biopsy will con- firm the diagnosis. Langerhans cell histiocytosis Langerhans cell histiocytosis is a rare disease of unknown aetiology, but characterized histologically by a proliferation of Langerhans cells expressing CD1a and CD207, and with the presence of Birbeck granules on electron microscopy. The clinical presentation varies with the nature of organ involvement and whether it is single system or multisystem disease. Skin, bone, and lymph node are the most common sites of involvement, but other systems include liver, lung, gastrointestinal, endocrine, nervous system, and haematological. The characteristic skin presentation is the

presence of greasy scales on the scalp, reminiscent of seborrhoeic dermatitis. On the trunk, the lesions are discrete, yellow-brown, scaly papules, often with areas of purpura. Ulceration in the flexures and groin is a common presen- tation in adults. The disease is discussed in detail in Chapter 22.3.9. FURTHER READING Agar NS, et al. (2004). The basal layer in human squamous tumors har- bors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis. Proc Natl Acad Sci U S A, 101, 4954–9. Ananthaswamy HN, et al. (1997). Sunlight and skin cancer: inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens. Nat Med, 3, 510–14. Chapman PB, et al. (2011). Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med, 364, 2507–16. Dajee M, et al. (2003). NF-κB blockade and oncogenic Ras trigger in- vasive human epidermal neoplasia. Nature, 421, 639–43. Euvrard S, et al. (2012). Sirolimus and secondary skin-cancer preven- tion in kidney transplantation. N Engl J Med, 367, 329–39. Fan H, et al. (1997). Induction of basal cell carcinoma features in transgenic human skin expressing Sonic Hedgehog. Nature Med, 3, 788–92. Goudie DR, et al. (2011). Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. Nat Genet, 43, 365–9. Gudbjartsson DF, et al. (2008). ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet, 40, 886–91. Hussussian CJ, et al. (1994). Germline p16 mutations in familial mel- anoma. Nat Genet, 8, 15–21. Landi MT, et al. (2006). MC1R germline variants confer risk for BRAF mutant melanoma. Science, 313, 521–2. Marsden JR, et al. (2010). Revised UK guidelines for the management of cutaneous melanoma 2010. Br J Dermatol, 163, 238–56. Morton DL, et al. (2006). Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med, 355, 1307–17. Motley R, et al. (2002). Multiprofessional guidelines for the manage- ment of the patient with primary cutaneous squamous cell car- cinoma. Br J Dermatol, 146, 18–25. National Institute for Health and Care Excellence (NICE) (2015). Melanoma: assessment and management. NICE guideline [NG14]. http://www.nice.org.uk/Guidance/NG14 O'Donovan P, et al. (2005). Azathioprine and UVA light generate mu- tagenic oxidative DNA damage. Science, 309, 1871–4. Pho L, Grossman D, Leachman SA (2006). Melanoma genetics: a re- view of genetic factors and clinical phenotypes in familial mel- anoma. Curr Opin Oncol, 18, 173–9. Prickett TD, et al. (2009). Analysis of the tyrosine kinome in melanoma reveals recurrent mutations in ERBB4. Nat Genet, 41, 1127–32. Fig. 23.14.6 Erythematous nodule on abdomen. This was a cutaneous metastasis from breast carcinoma.

 Stacey SN, et al. (2009). New common variants affecting susceptibility to basal cell carcinoma. Nat Genet, 41, 909–14. Stern RS, et al. (1984). Cutaneous squamous-cell carcinoma in pa- tients treated with PUVA. N Engl J Med, 310, 1156–61. Su F, et al. (2012). RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med, 366, 207–15. Teh MT, et al. (2005). Genomewide single nucleotide poly- morphism microarray mapping in basal cell carcinomas un- veils uniparental disomy as a key somatic event. Cancer Res, 65, 8597–603. Telfer NR, Colver GB, Morton CA (2008). British Association of Dermatologists: guidelines for the management of basal cell car- cinoma. Br J Dermatology, 159, 35–48. Thompson JF, Scolyer RA, Kefford RF (2009). Cutaneous melanoma in the era of molecular profiling. Lancet, 374, 362–65. Ungewickell A et al. (2015). Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2. Nat Genet, 47, 1056–60. Von Hoff DD, et al. (2009). Inhibition of the hedgehog pathway in ad- vanced basal-cell carcinoma. N Engl J Med, 361, 1164–72. Wang NJ, et al. (2011). Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc Natl Acad Sci USA, 108, 17761–6. Wei X, et al. (2011). Exome sequencing identifies GRIN2A as fre- quently mutated in melanoma. Nat Genet, 43, 442–6. Wolchok JD, et al. (2017). Overall Survival with Combined Nivolumab and

Ipilimumab in Advanced Melanoma. N Engl J Med, 377, 1345–56.

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