

CHAPTER

29

Epidermal Nevi, Neoplasms, and Cysts

EPIDERMAL NEVI

Keratinizing epidermal nevi are described by a great variety of terms, such as *hard nevus of Unna*, *soft epidermal nevus*, *nevus verrucosus (verrucous nevus)*, *nevus unius lateris*, *linear epidermal nevus*, and *ichthyosis hystrix*. Hyperkeratosis without cellular atypia characterizes them all: melanocytic nevus cells do not occur. In some cases the primary constituent is hyperplasia of an adnexal component (nevus comedonicus, nevus sebaceous). These lesions are all considered to represent somatic mosaicism in the affected region. The histologic features are apparently a consequence of the genetic mutation affecting that region. These lesions follow the lines of Blaschko rather than dermatomes, suggesting they represent mutations that occurred at some post-zygotic time during fetal development. Epidermal nevi are relatively common, with a prevalence of about 1 in 1000.

Linear Verrucous Epidermal Nevus

The individual lesions are verrucous skin-colored, dirty-gray or brown papules, which coalesce to form a serpiginous plaque (Figs 29-1 and 29-2). Interspersed in the localized patch may be horny excrescences and, rarely, comedones. The age of onset of epidermal nevi is generally at birth, but they may also develop within the first 10 years of life. They



Fig. 29-1 Verrucous linear epidermal nevus, note the superficial resemblance to seborrheic keratosis.

follow the lines of Blaschko. The term *ichthyosis hystrix* had been used to describe cases with extensive bilateral involvement.

The histologic changes in the epidermis are hyperplastic and affect chiefly the stratum corneum and stratum malpighii. There is variable hyperkeratosis, acanthosis, and papillomatosis. Up to 62% of biopsies of epidermal nevi have this pattern. About 16% show epidermolytic hyperkeratosis. At times, other histologic patterns may be found, including a psoriatic type, an acrokeratosis verruciformis-like type, and a Darier disease-like type.

Rarely keratinocytic and adnexal malignancies occur in epidermal nevi. Any newly appearing lesion within a stable epidermal nevus should be biopsied to exclude this possibility. Management of epidermal nevi is difficult, since unless the treatment also affects the dermis (and hence may cause scarring), the lesion recurs. The combination of 5% 5-fluorouracil (5-FU) plus 0.1% tretinoin creams once a day may



Fig. 29-2 Linear epidermal nevus, histologically this lesion showed epidermolytic hyperkeratosis.

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be beneficial and the response may be enhanced by occlusion. CO₂ and Er:YAG laser treatment may also be effective.

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Nevus Comedonicus

Nevus comedonicus is characterized by closely arranged, grouped, often linear, slightly elevated papules that have at their center keratinous plugs resembling comedones (Fig. 29-3). Cysts, abscesses, fistulas, and scars develop in about half the cases, which have been described as “inflammatory” nevus comedonicus. As with other epidermal nevi, lesions may be localized to a small area or have an extensive nevoid type of distribution. They are most commonly unilateral; however, bilateral cases are also seen. Lesions occur mostly on the trunk and follow the lines of Blascko. The lesions may develop any time from birth to age 15, but are usually present by the age of 10. Associated abnormalities of bone, the central nervous system (CNS), skin, and eyes, which may accompany epidermal nevi, may also be seen in extensive nevus comedonicus.



Fig. 29-3 Nevus comedonicus.

The pilosebaceous follicles are dilated and filled with keratinous plugs. On the palms, pseudocomedones are present. Histologic examination reveals large dilated follicles filled with orthokeratotic horny material and lined by atrophic squamous epithelium. The interfollicular epidermis is papillomatous, as is seen in typical epidermal nevi. Hair follicle differentiation, well-formed follicular structures, and normal sebaceous glands are not common in well-formed lesions. Occasionally, epidermolytic hyperkeratosis may be present, supporting the contention that nevus comedonicus is a form of “epidermal” nevus.

Treatment of lesions not complicated by inflammatory cysts and nodules is primarily cosmetic. Pore-removing cosmetic strips and comedone expression may improve the cosmetic appearance. Topical tretinoin may be beneficial. Patients with inflammatory lesions are much more difficult to manage. If the area affected is limited, surgical excision may be considered. Oral isotretinoin, chronically at the minimum effective dose (0.5 mg/kg/day or less if possible) may partially suppress the formation of cysts and inflammatory nodules; however, as in hidradenitis suppurativa, many cases of nevus comedonicus fail to respond. The comedonal lesions are not improved by the oral isotretinoin.

Ioue Y, et al: Two cases of nevus comedonicus: successful treatment of keratin plugs with a pore strip. *J Am Acad Dermatol* 2000;43:927.

Kargi E, et al: Nevus comedonicus. *Plast Reconstr Surg* 2003; 112:1183.

Kirtak N, et al: Extensive inflammatory nevus comedonicus involving half of the body. *Int J Dermatol* 2004;43:434.

Milburn S, et al: The treatment of naevus comedonicus. *Br J Plast Surg* 2004;57:805.

Schechter AK, et al: Linear nevus comedonicus with epidermolytic hyperkeratosis. *J Cutan Pathol* 2004;31:502.

Wakahara M, et al: Bilateral nevus comedonicus: efficacy of topical tacalcitol ointment. *Acta Dermatol Venereol* 2003; 83:51.

Woods KA, et al: Extensive naevus comedonicus in a child with Alagille syndrome. *Clin Exp Dermatol* 1994;19:163.

Epidermal Nevus Syndrome

In 1968, Solomon et al described the epidermal nevus syndrome (ENS), consisting of extensive epidermal nevi with abnormalities of the CNS, skeleton, skin, cardiovascular system, genitourinary system, and eyes. About 8% of patients with epidermal nevi have systemic involvement, and 10% to 18% have systemic developmental disorders (as compared to 1.7% of children without epidermal nevi). The more extensive the epidermal nevus, the more likely there is to be systemic disease. Bladder cancer at an early age (<21 years) has been reported in patients with epidermal nevi and pigmentary abnormalities.

Cutaneous lesions other than epidermal nevi in ENS that may occur are café-au-lait spots, speckled lentiginous nevi, multiple melanocytic nevi, and vascular malformations (phakomatosis pigmentovascularis). The combination of an organoid sebaceous nevus and a speckled lentiginous nevus is termed *phakomatosis pigmentokeratolica*. In virtually all cases, the cutaneous lesions and abnormalities are congenital. Since the original description of systemic involvement with keratotic epidermal nevi, similar cases have been

reported in association with sebaceous nevi and nevus comedonicus. This has led Happle to suggest a broader concept for the “epidermal nevus” syndrome. At least six types exist:

1. *Schimmelpenning syndrome* (sebaceous nevus associated with cerebral anomalies, coloboma, and lipodermoid of the conjunctiva) (Fig. 29-4)
2. *Nevus comedonicus syndrome* (associated with cataracts, scoliosis, and neurologic abnormalities)
3. *Pigmented hairy epidermal nevus syndrome* (Becker nevus, ipsilateral hypoplasia of the breast, and skeletal defects such as scoliosis)
4. *Proteus syndrome* (the epidermal nevus is of the verrucous/keratinocytic type)
5. *CHILD syndrome*
6. *Phakomatosis pigmentokeratolica* (hypophosphatemic rickets)

Many cases, especially those reported from pediatric dermatology referral centers, do not fit one of these categories. Final classification will await the finding of the genetic basis for each of these syndromes.

de Jalón AG, et al: Epidermal naevus syndrome (Solomon's syndrome) associated with bladder cancer in a 20-year-old female. *Scand J Urol Nephrol* 2004;38:85.

Davies D, Rogers M: Review of neurological manifestations in 196 patients with sebaceous naevi. *Australas J Dermatol* 2002;45:20.

Happle R: Epidermal nevus syndrome. *Semin Dermatol* 1995;14:111.

Rogers M, et al: Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. *Pediatr Dermatol* 1992;9:233.

Seo YJ, et al: A case of nevus comedonicus syndrome associated with neurologic and skeletal abnormalities. *Int J Dermatol* 2001;40:648.

Vidaurri-de la Cruz H, et al: Epidermal nevus syndromes: clinical findings in 35 patients. *Pediatr Dermatol* 2004;21:432.

Vujevich JJ, Mancini AJ: The epidermal nevus syndromes: Multi-system disorders. *J Am Acad Dermatol* 2004;50:957.



Fig. 29-4 Nevus sebaceous syndrome with lipodermoid of the conjunctiva.

Zakrzewski JL, et al: Epidermal naevus and segmental hypermelanosis associated with an intraspinal mass: overlap between different mosaic neuroectodermal syndromes. *Eur J Pediatr* 2001;160:603.

Inflammatory Linear Verrucous Epidermal Nevus

The term ILVEN may encompass as many as four separate conditions. The most common form is the classic ILVEN or “dermatitic” epidermal nevus. At least three-quarters of these cases appear before age 5 years, most before age 6 months. Later onset in adulthood has been reported. ILVEN is characteristically pruritic and pursues a chronic course. Lesions follow the lines of Blascko. The individual lesions comprising the affected region are erythematous papules and plaques with fine scale (Fig. 29-5). The lesions are morphologically nondescript and, if the distribution is not recognized, could be easily overlooked as an area of dermatitis. Multiple widely separated areas may be affected, usually on only one side of the body; it may be bilateral, analogous to other epidermal nevi. Familial cases have been reported. Rarely, systemic involvement with musculoskeletal and neurologic sequelae (developmental delay, epilepsy) have been reported.

Histologically, classic ILVEN demonstrates abruptly alternating areas of hypergranulosis with orthokeratosis, and parakeratosis with agranulosis. The epidermis is acanthotic and the stratum corneum is hyperkeratotic throughout the lesion. An inflammatory infiltrate of lymphocytes is present in the upper dermis. At times the histology may simply be that of a subacute dermatitis. While the histologic diagnosis of psoriasis can be considered, the correct diagnosis can be established if the dermatopathologist is made aware of ILVEN as a consideration. If there is a question, the presence of involucrin expression in the parakeratotic areas can distinguish ILVEN from psoriasis.



Fig. 29-5 Inflammatory linear verrucous epidermal nevus.

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Three other types of inflammatory nevi have been included in this group. Some cases of "linear" lichen planus have been considered as "epidermal nevi," as they commonly follow lines of Blascko. CHILD syndrome, also considered a type of "inflammatory" epidermal nevus, is usually clinically distinct, demonstrating its characteristic hemidysplasia. The most confusing entity has been the so-called "nevoid" or "linear" psoriasis. These cases are of two types. The first type is a child with a family history of psoriasis who has a nevoid lesion at or near birth. The child later develops psoriasis which "koebnerizes" into the ILVEN lesion, suggesting it is a "locus minoris resistensiae" for psoriasis. Treatment of the psoriasis clears the psoriasis overlying the ILVEN, but not the ILVEN. Arthritis developed in one such case. The second type is one in which psoriasis initially presents in one band or area. Histologically, it resembles psoriasis. Most of these cases later develop typical psoriasis later in life, suggesting a mosaicism which allowed expression of the psoriasis earlier in the initially affected area.

ILVEN is differentiated from other epidermal nevus by the presence of erythema and pruritus clinically and by histologic features. Lichen striatus can be distinguished by its histology and natural history. Topical steroids and topical retinoids appear to have limited benefit in ILVEN. Topical Vitamin D (calcipotriol and calcitriol) and topical anthralin have been beneficial, however. Surgical modalities include excision, cryotherapy, and pulsed dye laser. In cases of "nevoid" psoriasis, eximer laser could be considered if topical treatments fail.

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- Ulkur E, et al: Carbon dioxide laser therapy for an inflammatory linear verrucous epidermal nevus: a case report. *Aesthetic Plast Surg* 2004;28:428.

HYPERKERATOSIS OF THE NIPPLE AND AREOLA

Hyperkeratosis of the nipple and areola (HNA) is an uncommon benign, asymptomatic, acquired condition of

unknown pathogenesis. Women represent 80% of cases and it presents in their second or third decade. In men the time of presentation is variable. Most cases are bilateral, although unilateral cases can occur. In about half the cases, both the areola and nipple are involved. Isolated involvement of the areola is more common than isolated involvement of the nipple. Breastfeeding is usually not affected. Clinically, there is verrucous thickening and brownish discoloration of the nipple and/or areola. Histologically, there is orthokeratotic hyperkeratosis with occasional keratinous cysts in the filiform acanthotic epidermis. The course is chronic. Treatment with calcipotriol has benefited some patients. It must be distinguished from epidermal nevi, ichthyosis, acanthosis nigricans, Darier disease, and lichen simplex chronicus. Isolated papules or small plaques in this location probably represent seborrheic keratoses affecting the nipple or areola.

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- Krishnan RZ, et al: Nevoid hyperkeratosis of the nipple and/or areola: a report of two cases and a review of the literature. *Int J Dermatol* 2002;41:775.
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- Xifra M, et al: Nevoid keratosis of the nipple. *J Am Acad Dermatol* 1999;41:325.

CLEAR CELL ACANTHOMA (PALE CELL ACANTHOMA)

Clear cell acanthoma is also known as *Degos acanthoma* and *acanthome cellulées claires of Degos and Civatte*. The typical lesion is a circumscribed, reddish, moist nodule with some crusting and peripheral scales; it is usually about 1 to 2 cm in diameter. A collarette is commonly observed and there may be pigmented variants. The favorite site is on the shin, calf, or occasionally the thigh, although other sites have been reported, such as the abdomen and scrotum. The lesion is asymptomatic, slow-growing, and can occur in either sex, usually after the age of 40. Solitary lesions are most common, but multiple ones have been described. Rarely, an eruptive form of the disease occurs, producing up to 400 lesions. Squamous cell carcinoma (SCC) arising from clear cell acanthoma has also been reported. Lesions occurring in plaques of psoriasis on the buttocks have been described.

The acanthotic epidermis consists of pale, edematous cells and is sharply demarcated. The basal cell layer is normal. Neutrophils are scattered within the acanthoma and in groups below and within the stratum corneum, a finding similar to the micropustules of psoriasis. The dermal blood vessels are dilated and tortuous, as seen in psoriasis. The clear keratinocytes abound in glycogen, staining positive with periodic acid-Schiff (PAS).

Clear cell acanthoma must be differentiated from eccrine poroma, which appears most frequently on the hair-free part of the foot, and from clear cell hidradenoma, which occurs most frequently on the head, especially on the face and eyelids. Treatment is surgical, either with cryotherapy or excision.

Betti R, et al: Successful cryotherapy treatment and overview of multiple clear cell acanthomas. *Dermatol Surg* 1995;21:342.

Burg G, et al: Eruptive hamartomatous clear-cell acanthomas. *Dermatology (Switzerland)* 1994;189:437.

Finch TM, Tan CY: Clear cell acanthoma developing on a psoriatic plaque: further evidence of an inflammatory aetiology? *Br J Dermatol* 2000;142:842.

Innocenzi D, et al: Disseminated eruptive clear cell acanthoma: a case report with review of the literature. *Clin Exp Dermatol* 1994;19:249.

Kavanagh GM, et al: Multiple clear cell acanthomas treated by cryotherapy. *Australas J Dermatol* 1995;36:33.

Langer K, et al: Pigmented clear cell acanthoma. *Am J Dermatol* 1994;16:134.

Murphy R, et al: Giant clear cell acanthoma. *Br J Dermatol* 2000;143:1114.

Parsons ME, et al: Squamous cell carcinoma in situ arising within clear cell acanthoma. *Dermatol Surg* 1997;23:487.

WAXY KERATOSES OF CHILDHOOD (KERINOKERATOSIS PAPULOSA)

Waxy keratosis of childhood is a genodermatosis that is either sporadic or familial. It may be generalized or segmental. Clinically, the lesions are keratotic, flesh-colored papules which affect the trunk and extremities. They appear before the age of 3 years. Histologically, there is papillomatosis with focal “church-spire” tenting of the epidermis and marked hyperkeratosis. The natural history of this rare disorder is unknown. Clinically and histologically the lesions must be distinguished from warts.

Happle R, et al: Kerinokeratosis papulosa with a type 2 segmental manifestation. *J Am Acad Dermatol* 2004;50:S84.

Mehrabi D, et al: Waxy keratoses of childhood in a segmental distribution. *Pediatr Dermatol* 2001;18:415.

MULTIPLE MINUTE DIGITATE HYPERKERATOSIS

Multiple minute digitate hyperkeratosis (MMDH) is a rare disorder. About half of cases are familial, inherited in an autosomal-dominant fashion, and the other half are sporadic. This condition has also been called *digitate keratoses*, *disseminated spiked hyperkeratosis*, *minute aggregate keratosis*, and *familial disseminated piliform hyperkeratosis*. Clinically, hundreds of asymptomatic tiny digitate keratotic papules appear on the trunk and proximal extremities. Histologically, each lesion represents a spiked, digitate or tented area of acanthotic epidermis with overlying orthohyperkeratosis. Similar lesions can be seen after inflammation and radiation therapy. The relationship of the familial/sporadic cases and the postinflammatory condition is unclear.

Takagawa S, et al: Multiple minute digitate hyperkeratoses. *Br J Dermatol* 2000;142:1044.

SEBORRHEIC KERATOSIS

Seborrheic keratoses are incredibly common and usually multiple. They present as oval, slightly raised, tan/light brown to black, sharply demarcated papules or plaques, rarely more than 3 cm in diameter. They appear “stuck-on” the skin, as if they could be removed with the flick of a



Fig. 29-6
Seborrheic keratosis.

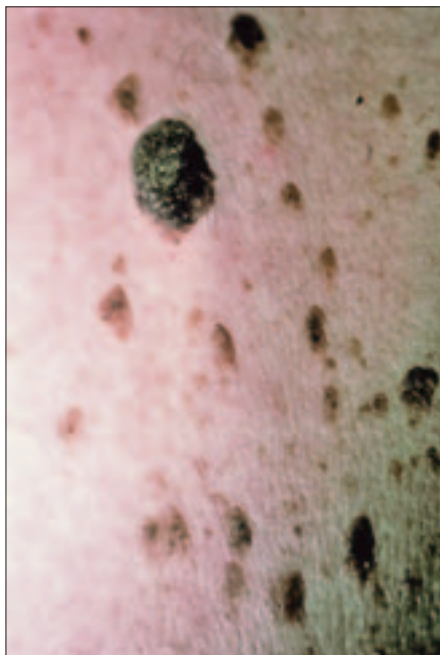


Fig. 29-7
Seborrheic keratosis.

finger nail (Fig. 29-6). They are located mostly on the chest and back, but also commonly involve the scalp, face, neck, and extremities (Fig. 29-7). An inframammary accumulation is common. Occasionally, genital lesions are seen. The palms and soles are spared; “seborrheic keratoses” in these areas are usually eccrine poromas. The surface of the warty lesions often becomes crumbly, like a crust that is loosely attached. When this is removed, a raw, moist base is revealed. Seborrheic keratoses may be associated with itching. Some patients have hundreds of these lesions on the trunk. While it had been thought that the age of onset is generally in the fourth to fifth decade, in Australia the prevalence of seborrheic keratoses was 20% in males and 25% in females aged 15 to 25 years. Typical lesions of the trunk are much more common in white persons; however, the “dermatosis papulosa nigra” variant of the central face is common in African Americans and Asians.

The pathogenesis of seborrheic keratoses is unknown. Clinically they usually originate *de novo* or appear initially as a lentigo. A sudden eruption of many seborrheic keratoses may follow an exfoliative erythroderma, erythrodermic

psoriasis, or an erythrodermic drug eruption. These lesions may be transient.

Histologically, most seborrheic keratoses demonstrate acanthosis, varying degrees of papillomatosis, hyperkeratosis, and at times keratin accumulations within the acanthotic epidermis (pseudo-horn cysts). The epidermal cells lack cytologic atypia, except at times in the irritated variant where typical normal mitoses may occur. Six histologic types—hyperkeratotic, acanthotic, adenoid or reticulated, clonal, irritated, and melanoacanthoma—are distinguished. There is a poor correlation between the clinical appearance and the observed histology, unlike for inverted follicular keratosis, dermatosis papulosa nigra, and stucco keratosis, where the histologic features are characteristic and match the clinical lesion. Melanoacanthoma differs from regular seborrheic keratosis by the presence of numerous dendritic melanocytes within the acanthotic epidermis. Oral melanoacanthoma, which has also been called *melanoacanthosis*, is clinically a reactive pigmented lesion seen primarily in young black patients (see Chapter 34). Many cases of inverted follicular keratosis represent irritated seborrheic keratoses.

The differential diagnosis usually poses no problems in most cases, but clinically atypical lesions can be a challenge. The most difficult, especially for the nondermatologist, is to differentiate the solitary black seborrheic keratosis from melanoma. The regularly shaped verrucous lesion is often different from the smooth-surfaced and slightly infiltrating pattern of melanoma. Dermoscopy can at times be of great value; however, at times seborrheic keratoses may demonstrate dermoscopic features typical of melanocytic lesions, and the presence of horn cysts does not exclude a melanocytic lesion. Actinic keratoses are usually erythematous, more sharply rough, and slightly scaly. The edges are not sharply demarcated, and they occur most often on sun-exposed surfaces, especially the face, bald scalp, and backs of the hands. Nevi may be closely simulated. Clonal seborrheic keratoses demonstrate intraepidermal nests suggestive of intraepidermal epithelioma of Jadassohn. Rarely, Bowen disease, SCC, basal cell carcinoma (BCC), or melanoma arise within typical-appearing seborrheic keratosis. It is prudent to biopsy any lesion that appears atypical, since even the most seasoned dermatologist has been humbled by the occasional diagnosis of melanoma in low-suspect lesions.

Seborrheic keratoses are easily removed with liquid nitrogen, curettage, or the combination of the two to avoid the need for local anesthesia to perform the curettage. The spray freezes the lesion to make it brittle enough for easy removal with the curette. Scarring is not produced by this method. Light freezing with liquid nitrogen alone is also effective, as is simple curettage with local anesthesia. Light fulguration, shave removal, and CO₂ laser vaporization are other acceptable methods.

Sign of Leser-Trélat

The sudden appearance of numerous seborrheic keratoses in an adult may be the cutaneous finding of internal malignancy. Sixty percent of the neoplasms have been adenocarcinomas, primarily of the stomach. Other common malignancies are lymphoma, breast cancer, and SCC of the lung, but many other types have been reported. To be considered a case of Leser-Trélat, the keratoses should begin at approximately the same time as the development of the cancer and run a

parallel course in regard to growth and remission. The lesions are often pruritis and acanthosis nigricans, and tripe palms may accompany the appearance of the seborrheic keratoses of Leser-Trélat.

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DERMATOSIS PAPULOSA NIGRA

Dermatosis papulosa nigra occurs in about 35% of black persons and is also relatively common in Asians. It usually begins in adolescence, appearing first as minute, round, skin-colored or hyperpigmented macules or papules that develop singly or in sparse numbers on the malar regions or on the cheeks below the eyes. It has been described as early as the age of 3. The lesions increase in number and size over time, so that in the course of years the patient may have hundreds of lesions. They are distributed over the periorbital regions initially, but may occur on the rest of the face, neck, and upper chest. Lesions do not spontaneously resolve. These lesions closely simulate seborrheic keratoses. They are asymptomatic and do not develop scaling, crusting, or ulceration.

Microscopically, the chief alterations are in the epidermis. Irregular acanthosis, papillomatosis, and deposits of uncommonly large amounts of pigment throughout the rete,

and particularly in the basal layer, are characteristic. Many believe it to be a form of seborrheic keratosis.

Treatment is made difficult by the tendency for the development of dyspigmentation. Light curettage with or without anesthesia; light, superficial liquid nitrogen application; and light electrodesiccation are effective, but may result in hyper- or hypo-pigmentation. Aggressive treatment should be avoided to minimize dyspigmentation and scarring.

Babapour R, et al: Dermatitis papulosa nigra in a young child. *Pediatr Dermatol* 1993;10:356.

STUCCO KERATOSIS

Stucco keratoses or keratoelastoidosis verrucosa of the extremities have been described as “stuck-on” lesions occurring on the lower legs, especially in the vicinity of the Achilles tendon. They are also seen on the instep, dorsa of the feet, forearms, and dorsal hands. The palms, soles, trunk, and head are never affected. Varying in diameter from 1 to 5 mm, they are loosely attached, so that they can easily be scratched off. They vary in number from a few to more than 50. Stucco keratoses are common in the US and Australia. They occur mostly in men over 40 years old. Histologically, the picture is that of a hyperkeratotic type of seborrheic keratosis, with no hypergranulosis and no wart particles seen by electron microscopy. The treatment, if any is required, consists of emollients, which soften the skin and cause the scaly lesions to fall off. Ammonium lactate lotion, 12%, may be effective in improving the appearance of the lesions. Imiquimod improved one widespread case, which may have represented widespread human papillomavirus infection. Stucco keratoses must be distinguished from Flegel disease.

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HYPERKERATOSIS LENTICULARIS PERSTANS (FLEGEL DISEASE)

Rough, yellow-brown keratotic, flat-topped papules, 2 to 5 mm in diameter, and primarily on the calves are characteristic. The palms, soles, and oral mucosa may rarely be involved. Familial cases have been reported.

The histologic findings are distinctive, with hyperkeratosis and parakeratosis overlying a thinned epidermis, and irregular acanthosis at the periphery. A bandlike inflammatory infiltrate occurs in the papillary dermis. Topical emollients, topical 5-FU, and PUVA have been reported as useful. Oral retinoids may cause improvement, but are hard to justify in this chronic asymptomatic condition. The lesions do not recur after shallow shave excision.

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WARTY DYSKERATOMA

Warty dyskeratomas are most commonly solitary and found on the head and neck (70%), trunk (20%), or extremities. Rare oral lesions occur. The lesion is a brownish-red papule or nodule with a soft, yellowish, central keratotic plug. Histologically, a cup-like depression filled with a keratotic plug is most common. The epithelium lining the invagination shows the features of Darier disease with intraepidermal clefts, acantholytic cells, and pseudovilli. Keratin pearls, corps ronds, and grains may be seen. Cystic lesions with prominent keratinous cysts can occur. Cutaneous lesions appear to originate from a hair follicle. Warty dyskeratoma must be distinguished histologically from keratoacanthoma and acantholytic SCC. Treatment is surgical.

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BENIGN LICHENOID KERATOSES (LICHEN PLANUS-LIKE KERATOSIS)

Benign lichenoid keratoses are usually solitary dusky-red to violaceous papular lesions up to 1 cm in diameter, but are at times larger (Fig. 29-8). They occur most often on the distal forearms, hands, or chests of middle-aged white women. The lesions are commonly biopsied since the clinical features are identical to a superficial BCC. A slight violaceous hue or the presence of an adjacent solar lentigo can raise the suspicion of lichen planus-like keratosis. Multiple lesions may simulate a photodermatitis, such as lupus erythematosus. Evolution from preexisting solar lentigines is often noted histologically or by history.

Histologically, the lesion may be indistinguishable from idiopathic lichen planus. While idiopathic lichen planus rarely demonstrates parakeratosis, plasma cells or eosinophils, these may be present in lichen planus-like keratosis. The remnants of a solar lentigo may be seen at the periphery. These features, plus the clinical information that it represents a solitary lesion, suggest the correct diagnosis. Clinical



Fig. 29-8 Lichen planus-like keratosis.

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correlation is essential, as similar histologic findings may be seen in lichenoid drug eruptions, acral lupus erythematosus, and lichenoid regression of melanoma. Direct immunofluorescence is positive, with clumped deposits of IgM in a lichen planus-like pattern at the dermoepidermal junction. This differs from the continuous granular immunoglobulin deposition of acral lupus erythematosus. Cryotherapy with liquid nitrogen is effective.

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ARSENICAL KERATOSES

Arsenical keratoses are keratotic, pointed, 2- to 4-mm wartlike lesions on the palms, soles, and sometimes ears of persons who have a history of drinking contaminated well water or taking medications containing arsenic trioxide, usually for asthma (Fowler's solution, Bell's Asthma Mixture), atopic dermatitis, or psoriasis, often years previously (Fig. 29-9). These lesions resemble palmar pits, but may have a central hyperkeratosis. When the keratosis is picked off with the fingernails, a small dell-like depression is seen.

Bowen disease and invasive arsenical SCC may be present, with the latent period being 10 and 20 years, respectively. The profound increase in Bowen disease and SCC appears to be characteristic of patients with arsenic



Fig. 29-9 Arsenical keratosis in a patient who had been exposed to arsenic in drinking water.

exposure from well water. In patients exposed to arsenic via elixirs, BCCs are more characteristically seen. The latency period for development of BCC is also 20 years. Lesions are most common on the scalp and trunk. Internal carcinoma also occurs with increased frequency, after an average latent period of 30 years, with pulmonary and genitourinary carcinoma being most common. Arsenic has also been implicated in causing Merkel cell carcinoma.

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NONMELANOMA SKIN CANCERS AND THEIR PRECURSORS

Nonmelanoma skin cancers (NMSCs) are the most common form of cancer diagnosed in the US, with 1.3 million cases diagnosed annually. One in two men and one in three women in the US will develop NMSC in their lifetime, usually after the age of 55. While these result in only about 2000 to 2500 deaths annually, due to their sheer numbers NMSCs represent about 5% of all Medicare cancer expenditures. Those at risk for skin cancer are fair-skinned individuals who tan poorly and who have had significant chronic or intermittent sun exposure. Red hair phenotype with loss-of-function mutations in the melanocortin-1 receptor may be a risk factor as well. Additional risk factors include a prior history of skin cancer, prior radiation therapy, PUVA treatment, arsenic exposure, and systemic immunosuppression (Fig. 29-10). Once an individual has developed a NMSC, his/her risk for a second is increased 10-fold. Over the 3-year period following the initial NMSC diagnosis, more than 40% of BCC and SCC patients develop a BCC, and 18% of SCC patients develop another SCC. By 5 years as many as 50% of women and 70% of men will develop a second NMSC. The rate of developing NMSCs is not different 3 years or 10 years after the initial NMSC diagnosis. Patients with a history of NMSC should be examined for NMSCs on a regular basis.

Ultraviolet radiation (UVR) is the major cause of nongenital NMSCs and actinic keratoses. The effect of UVR appears to be mediated through mutation of the p53 gene, which is found mutated in a substantial percentage of NMSCs and actinic keratoses. Most skin cancers are highly immunogenic, but the immune response is suppressed by continued actinic exposure. Both chronic sun exposure and intermittent intense exposure are risk factors for the development of NMSCs. It is believed that avoiding sun exposure reduces the risk for NMSC. The use of sunscreens in the prevention of NMSCs has been controversial, as they may inadvertently



Fig. 29-10 Actinic keratosis/Bowen disease in a transplant recipient.

lead to prolonged intentional sun exposure, negating their possible beneficial effect. Nonetheless, dermatologists and their societies recommend a program of sunscreen use together with sun avoidance to patients at risk for skin cancer. This includes avoiding midday sun, seeking shade, wearing protective clothing, and regularly applying a sunblock of sun protection factor (SPF) 15 to 30 with both UVB and UVA coverage. This program, which was pioneered in Australia, has led to improvements in some skin cancer rates in that country. Lack of standards for label claims of UVA blockade remains a problem, but superior UVA-blocking sunscreen ingredients, such as avobenzone zinc oxide and titanium dioxide, are gaining consumer recognition.

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ACTINIC KERATOSIS (SOLAR KERATOSIS)

Actinic keratoses represent in situ dysplasias resulting from sun exposure. They are found chiefly on the chronically sun-exposed surfaces of the face, ears, balding scalp, dorsal hands, and forearms. They are usually multiple, discrete, flat or elevated, verrucous or keratotic, red, pigmented, or skin colored. Usually the surface is covered by an adherent scale, but sometimes it is smooth and shiny. On palpation the surface is rough, like sandpaper, and at times lesions are more easily felt than seen. The patient may complain of tenderness when the lesion is rubbed or shaved over with a razor. The lesions are usually relatively small, measuring 3 mm to 1 cm in diameter, most being less than 6 mm. Rarely, lesions may reach 2 cm in size, but a lesion larger than 6 mm should only be considered an actinic keratosis if confirmed by biopsy or if it completely resolves with therapy. The hypertrophic type, which may lead to cutaneous horn formation, is most frequently present on the dorsal forearms and hands.

Actinic keratoses are the most common epithelial precancerous lesions. While lesions typically appear in persons over 50 years of age, actinic keratoses may occur in the 20s or 30s in patients who live in areas of high solar irradiation and are fair-skinned. Patients with actinic keratoses have a propensity for the development of nonmelanoma cutaneous malignancies, with estimates ranging from 0.25% to 20%. Actinic keratoses can be prevented by the regular application of sunscreen and by a diet low in fats. Beta-carotene is of no benefit in preventing actinic keratoses.

Six types of actinic keratoses can be recognized histologically: hypertrophic, atrophic, bowenoid, acantholytic, pigmented, and lichenoid. The epidermis may be acanthotic or atrophic. Keratinocyte maturation may be disordered with overlying parakeratosis sometimes present. The basal cells are most frequently dysplastic, although in more advanced lesions dysplasia may be seen throughout the epidermis, simulating Bowen disease (bowenoid actinic keratosis).

The clinical diagnosis of actinic keratosis is usually straightforward. Early lesions of chronic cutaneous lupus erythematosus and pemphigus foliaceus are sometimes confused for actinic keratoses. Seborrheic keratoses, even when they lack pigmentation, are usually more “stuck on” in appearance and more sharply margined than actinic

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keratoses. Magnification may aid in this distinction. It is difficult to distinguish hypertrophic actinic keratoses from early SCC and a low threshold for biopsy is recommended. Similarly, actinic keratoses, which present as red patches, can not easily be distinguished from Bowen disease or superficial BCC. If there is a palpable dermal component, or if on stretching the lesion there is a pearly quality, a biopsy should be considered. Any lesion larger than 6 mm, and any lesion which has failed to resolve with appropriate therapy for actinic keratosis should also be carefully evaluated for biopsy.

Since some percentage of actinic keratoses will progress to NMSC, their treatment is indicated. There are many effective therapeutic modalities. Cryotherapy with liquid nitrogen is most effective and practical when there are a limited number of lesions. A bulky cotton applicator dipped into liquid nitrogen or a handheld nitrogen spray device can be used. If the cotton-tip applicator method is used, the liquid nitrogen into which the applicator is dipped should be used for only one patient, as there is theoretical risk of cross-contamination from one patient to another. Infectious agents are not killed by freezing. For this reason, many dermatologists now use the spray devices. We recommend using a small opening tip with continuous bursts of nitrogen spray in a circular motion, depending on the size of the lesion, attempting an even frosting. Only the lesion should be frosted and the duration of cryotherapy must be carefully controlled. A long freeze that results in significant epidermal-dermal injury produces white scars, which are easily seen on the fair skin of those at risk for actinic keratoses. When correctly performed, healing usually occurs within a week on the face, but may require up to 4 weeks on the arms and legs. Caution should be exercised when treating below the knee, since wound healing in these regions is particularly poor and a chronic ulcer can result. Also, use caution in persons at risk for having a cryoprotein (hepatitis C virus-infected patients, and patients with connective tissue disease or lymphoid neoplasia). They may have an excessive reaction to cryotherapy. It is better on the first visit to "under-treat" until the tolerance of a patient's skin to cryotherapy is known. Application of 0.5% 5-FU for 1 week prior to cryotherapy improves the response to cryotherapy.

For extensive, broad, or numerous lesions, topical chemotherapy is recommended. The two agents most commonly used are 5-FU cream, 0.5% to 5%, or imiquimod 5% cream. Topical tretinoin and adapalene do not have the efficacy of these two agents, but can be used for prolonged periods and represent an option for patients with a few early lesions. Three percent diclofenac in 2.5% hyaluronan gel when used for 60 days can also be effective for actinic keratoses.

The frequency and duration of treatment are determined by the individual's reaction and the anatomic site of application. 5-FU is applied once a day in most cases. For the face, 0.5% 5-FU tends to give a predictable response, which is a bit less severe than that produced by the 1% to 5% concentrations. Some patients prefer the stronger concentration for a briefer period, while others favor a slower onset of the reaction and a more prolonged course. For the 5% cream, treatment duration rarely needs to exceed 2 to 3 weeks. For the 0.5% cream, the treatment course is usually 3 to 6 weeks. Usually the central face will respond more briskly than the temples and forehead, which may require a longer

duration of treatment. If the reaction is brisk, the treatment can be stopped and restarted at a lower concentration. Depending on the individual's sensitivity, an erythematous burning reaction will occur within several days. Treatment is stopped when a peak response occurs characterized by a change in color from bright to dusky-red, by reepithelialization, and by crust formation. Healing usually occurs within another 2 weeks after treatment has been stopped, depending on the treatment site. Certain areas of the face are prone to intense irritant dermatitis when exposed to 5-FU and tolerance can be improved if the patient avoids application to the glabella, melolabial folds, and chin. For the scalp, the 0.5% concentration may be adequate, but often prolonged or multiple treatment courses are required if this low concentration is used. The 5% cream produces a more predictable, albeit brisk, reaction. A thick cutaneous horn can prevent penetration of 5-FU and hypertrophic actinic keratoses on the scalp, dorsal hand, and forearm may respond poorly unless the area is pretreated with an agent to remove excessive keratin overlying the lesions. Pretreatment with tretinoin for 2 to 3 weeks can improve efficacy and shorten the duration of subsequent 5-FU treatment. It has been observed that 5-FU "seeks out" lesions that may not be clinically apparent. Clinically inapparent BCCs may be detected during or on completion of the treatment. Rarely, patients who have had multiple courses of 5-FU topical chemotherapy will develop a true allergic contact dermatitis to the 5-FU. This is manifested by the redness, edema or vasculature extending beyond the area of application and by the patient developing pruritus rather than tenderness on the treated areas. Patch testing can be confirmatory.

Imiquimod is an interferon inducer and apparently eradicates actinic keratoses by producing a local immunologic reaction against the lesion. The ideal protocol for application of imiquimod may not yet be determined. About 80% of patients respond to imiquimod and 20% may not respond at all, perhaps due to the fact that they lack some genetic component required to induce an inflammatory cascade when imiquimod is applied. If applied three times a week, patients develop an inflammatory reaction similar to that seen with daily application of 5-FU. It is somewhat unpredictable how severe the reaction will be, with a small subset of patients (especially fair-skinned women) developing a severe burning and crusting reaction after only one or a few applications. In others, no reaction at all occurs. With twice a week application, the treatment course is prolonged, up to 16 weeks. Severe erythema occurs in 17.7% and scabbing/crusting in 8.4% of patients so treated. The median percent reduction in actinic keratoses is 83.3% with this treatment protocol. Overall, while the reaction is less predictable from imiquimod, it is also typically less severe than with high concentrations of 5-FU. The adverse event rates are similar to those with low concentration (0.5%) 5-FU. Another regimen is to apply imiquimod for long periods at a reduced frequency (once or twice a week). Applications can be in alternating 1-month cycles or continuous for many months. This may allow some patients who require treatment but cannot tolerate any significant changes in appearance to be managed. In the end, the choice between topical 5-FU and imiquimod will be based on patient preference, prior physician and patient experience with the modalities, and the cost of the medication. Imiquimod is significantly

more expensive per gram than any form of 5-FU. A paired comparative trial would be of great value in determining the optimal and most cost-effective strategy for the treatment of extensive actinic keratoses. Surgical management of actinic keratoses with chemical peels, laser resurfacing, and photodynamic therapy is discussed in Chapters 37 and 38.

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CUTANEOUS HORN (CORNU CUTANEUM)

Cutaneous horns are encountered most frequently on the face and scalp. Lesions may also occur on the hands, penis, and eyelids. They are skin-colored, horny excrescences, 2 to 60 mm long, sometimes divided into several antler-like projections.

These lesions are most often benign, with the hyperkeratosis being superimposed on an underlying seborrheic keratosis, verruca vulgaris, angiokeratoma, molluscum contagiosum or trichilemmoma about 60% of the time. However, 20% to 30% may overlie premalignant keratoses and 20% may overlie SCCs or BCCs. The risk for a cutaneous horn overlying a malignancy is much higher in elderly fair-complexioned persons. Hyperkeratotic actinic plaques less than 1 cm in diameter on the dorsum of the hand, wrist, or forearms in white patients have been shown to have a malignancy rate of 50%. One-third of penile horns are

associated with underlying malignancies. Excisional biopsy with histologic examination of the base is necessary to determine the best therapy, which would be dictated by the diagnosis of the underlying lesion and by the apparent adequacy of removal.

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KERATOACANTHOMA

*Clinical Features

There are four types of keratoacanthomas: solitary, multiple, eruptive, and keratoacanthoma centrifugum marginatum. The exact biologic behavior of keratoacanthoma remains controversial. In the past it had been considered a reactive condition or pseudomalignancy which could be treated expectantly. Now the favored view is that keratoacanthomas are malignant tumors, which in many cases will regress. The regression may be partially mediated by immunity, but takes the form of terminal differentiation. The course of these tumors is unpredictable. Even those that ultimately involute can cause considerable destruction before they regress. Any lesions with the histologic features of keratoacanthoma and which appear in an immunosuppressed host should be managed as an SCC, with complete eradication.

Sunlight appears to play an important role in the etiology, especially in the solitary types. In addition, light-skinned persons are more apt to develop keratoacanthoma than dark-skinned persons. Instances of keratoacanthomas following trauma and surgical excisions suggest an isomorphic phenomenon may occur. Lesions histologically identical to keratoacanthomas can be seen rarely in patients with hypertrophic lichen planus and discoid lupus erythematosus. The biologic behavior of these lesions is unknown, but they have added to the controversy of keratoacanthoma as a reactive versus a malignant process. In Muir-Torre syndrome, sebaceous tumors and keratoacanthomas occur in association with multiple internal malignancies. A second, less common cancer syndrome is the keratoacanthoma visceral carcinoma syndrome (KAVCS). Only a handful of cases have been reported. Patients have multiple or large keratoacanthomas which appear at the same time as an internal malignancy, always of the genitourinary tract. The relationship of Muir-Torre to KAVCS awaits identification of the genetic basis of both syndromes.

Solitary Keratoacanthoma

This type of keratoacanthoma is a rapidly growing papule that enlarges from a 1-mm macule or papule to as large as



Fig. 29-11 Keratoacanthoma.

25 mm in 3 to 8 weeks. When fully developed it is a hemispheric, dome-shaped, skin-colored nodule in which there is a smooth crater filled with a central keratin plug (Fig. 29-11). The smooth shiny lesion is sharply demarcated from its surroundings. Telangiectases may run through the lesion. Subungual keratoacanthomas are tender subungual tumors which usually cause significant nail dystrophy. Subungual lesions often do not regress spontaneously and induce early underlying bony destruction, characterized on radiograph as a crescent-shaped lytic defect without accompanying sclerosis or periosteal reaction.

The solitary keratoacanthoma occurs mostly on sun-exposed skin, with the central portion of the face, backs of the hands, and arms being the most commonly involved sites. Less frequently, other sites are involved, such as the buttocks, thighs, penis, ears, and scalp. Elderly fair-skinned individuals most commonly develop keratoacanthomas. Lesions of the dorsal hands are more common in men and keratoacanthomas of the lower legs are more common in women. The most interesting feature of this disease is the rapid growth for some 2 to 6 weeks, followed by a stationary period for another 2 to 6 weeks, and finally a spontaneous involution over another 2 to 6 weeks to leave a slightly depressed scar. The stationary period and involuting phase are variable; some lesions may take 6 months to a year to completely resolve. It has been estimated that some 5% of treated lesions recur. Invasion along nerve trunks has been documented and may result in recurrence after a seemingly adequate excision.

Histopathology

The histologic findings of keratoacanthoma and a low-grade SCC are so similar that it is frequently difficult to make a definite diagnosis on the histologic findings alone. When a properly sectioned specimen is examined under low magnification, the center of the lesion shows a crater filled with eosinophilic keratin. Over the sides of the crater, which seems to have been formed by invagination of the epidermis, a “lip” or “marginal buttress” of epithelium extends over the keratin-filled crater. At the base and sides of the crater, the epithelium is acanthotic and composed of keratinocytes which are highly keratinized and have an eosinophilic, glassy cytoplasm. Surrounding the keratinocyte proliferation, a dense inflammatory infiltrate is frequently seen. Neutrophilic microabscesses are common within the tumor and trapping

of elastic fibers is commonly identified at the periphery of the tumor. These features favor a diagnosis of keratoacanthoma. The most definitive histologic feature is evidence of terminal differentiation, where the scalloped outer border of the tumor has lost its infiltrative character and is reduced to a thin rim of keratinizing cells lining a large keratin-filled crater. The presence of acantholysis within the tumor is incompatible with a diagnosis of keratoacanthoma. It is also important to distinguish keratoacanthoma from marked pseudoepitheliomatous hyperplasia as seen in prurigo nodularis.

Treatment

Although keratoacanthomas spontaneously involute, it is impossible to predict how long this will take. The patient may be faced with destructive growth of a tumor for as long as a year. More importantly, clinically SCC cannot always be excluded. Therefore, excisional biopsy of the typical keratoacanthoma of less than 2 cm in diameter should be considered in most cases. If the history is characteristic or multiple lesions have appeared simultaneously, less aggressive interventions may be considered. Nonsurgical therapy may also be considered in certain sites to preserve function or improve cosmetic outcome.

Intralesional injections of 5-FU solution, 50 mg/mL (undiluted from the ampule) at weekly intervals; bleomycin 0.5 mg/mL; or methotrexate 25 mg/mL can be effective. For a typical lesion, four injections along the base at each pole are recommended. Low-dose systemic methotrexate can be considered if multiple lesions are present and there is no contraindication. For clinically typical lesions these modalities may be tried before resorting to surgical removal, especially if the latter presents any problem. Excision is recommended if there is at least 50% involution of the lesion is not complete after 3 weeks. Radiation therapy may also be used on giant keratoacanthomas when surgical excision or electrosurgical methods are not feasible.

Multiple Keratoacanthomas (Ferguson Smith Type)

This type of keratoacanthoma is frequently referred to as the *Ferguson Smith type of multiple self-healing keratoacanthomas*. These lesions are identical clinically and histologically to the solitary type. There is frequently a family history of similar lesions. This condition has been traced to two large Scottish kindreds. Affected families from other countries have also been reported. Beginning on average at about the age of 25, but as early as the second decade, patients develop crops of keratoacanthomas that begin as small red macules and rapidly become papules which evolve to typical keratoacanthomas. Lesions may number from a few to hundreds but generally only 3 to 10 lesions are noted at any one time. Sun-exposed sites are favored, especially the ears and nose, and in most cases scalp lesions occur. In addition, these patients typically develop keratoacanthomas at sites of trauma. Lesions grow over 2 to 4 weeks reaching a size of 2 to 3 cm, then remain stable for 1 to 2 months before slowly involuting. They leave a prominent crateriform scar. If the early lesions are aggressively treated with cryotherapy, shave removal, or curettage, the scar may be less marked than that induced by spontaneous involution. Treatment with etretinate can be effective in stopping the appearance of new lesions and causing involution of existing ones.

Generalized Eruptive Keratoacanthomas (Grzybowski Variant)

This type of keratoacanthoma is very rare and sporadic, with most patients having no affected family members. The usual age of onset is between 40 and 60. The patients are usually in good health and are not immunosuppressed. The cause of this condition is unknown. Human papilloma viruses have not been detected in most cases in which it was sought. The clinical features are characteristic and unique. Grzybowski type of multiple keratoacanthomas is characterized by a generalized eruption of numerous dome-shaped, skin-colored papules from 2 to 7 mm in diameter. Multiple larger typical keratoacanthomas may also appear. Thousands of lesions may develop. The eruption is usually generalized, but spares the palms and soles. The oral mucous membranes can be involved. Severe pruritus may be a feature. Clinically, pityriasis rubra pilaris or widespread lichen planopilaris are often considered. Bilateral ectropion, narrowing of the oral aperture, and severe facial disfigurement can result. Linear arrangement of some lesions, especially over the shoulders and arms, has also been noted. Despite the multiplicity of lesions, no case of "metastasis" from a skin lesion or increased risk of internal malignancy has been reported in the Grzybowski variant of keratoacanthoma. Dr Grzybowski's original patient died 16 years after diagnosis of a myocardial infarction. Treatment with oral retinoids may improve the larger keratoacanthomas but they are at best partially beneficial for the widespread lesions.

There are reports of multiple keratoacanthomas appearing after surgical procedures in the setting of immunosuppression and after treatment with infliximab. These cases of "eruptive" keratoacanthomas are considered multiple "solitary" keratoacanthomas, rather than the Grzybowski variant of keratoacanthoma.

Keratoacanthoma Centrifugum Marginatum

This uncommon variant of keratoacanthoma is most commonly solitary, but multiple lesions can occur. Keratoacanthoma centrifugum marginatum is characterized by progressive peripheral expansion and concomitant central healing leaving atrophy. Spontaneous involution, as may be seen in other variants of keratoacanthoma, does not occur. Lesions range from 5 to 30 cm in diameter (Fig. 29-12). The dorsum of the hands and pretibial regions are favored sites. Treatment with oral etretinate and oral methotrexate with prednisone have been effective in isolated cases.



Fig. 29-12
Keratoacanthoma centrifugum marginatum.

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BASAL CELL CARCINOMA

BCC is the most common cancer in the US, Australia, New Zealand, and many other countries with a largely white, fair-skinned population with the opportunity to expose their skin to sunlight. Intermittent intense sun exposure, as identified by prior sunburns; radiation therapy; a positive family history of BCC; immunosuppression; a fair complexion, especially red hair; and easy sunburning (skin types I or II); and blistering sunburns in childhood are risk factors for the development of BCC. Of interest, actinic elastosis and wrinkling are not risk factors for the development of BCC. In fact, BCCs are relatively rare on the dorsal hand, where sun exposure is high, and actinic keratoses and SCCs abound. SCC is three times more common than BCC on the dorsum of the hand. These findings suggest that the mechanism by which UVR induces BCC is not related solely to the total amount of UVR received.

Many clinical morphologies of BCC exist. Clinical diagnosis is dependent on the clinician being aware of the many forms BCC may take. Since these clinical types may also have different biologic behavior, histologic classification of the type of BCC may also influence the form of therapy chosen.

Nodular Basal Cell Carcinoma (Classic Basal Cell Carcinoma)

The classic or nodular BCC comprises 50% to 80% of all BCCs. Nodular BCC is composed of one or a few small, waxy, semitranslucent nodules forming around a central depression that may or may not be ulcerated, crusted, and



Fig. 29-13 Basal cell carcinoma.



Fig. 29-14 Basal cell carcinoma, nodular type.

bleeding (Fig. 29-13). The edge of larger lesions has a characteristic rolled border. Telangiectases course through the lesion. Bleeding on slight injury is a common sign.

As growth progresses, crusting appears over a central erosion or ulcer, and when the crust is knocked or picked off, bleeding occurs and the ulcer becomes apparent. This ulcer is characterized by chronicity and gradual enlargement over time. The lesions are asymptomatic and bleeding is the only difficulty encountered. The lesions are most frequently found on the face (85–90% are found on the head and neck) and especially on the nose (25–30%). The forehead, ears (Fig. 29-14), periocular areas, and cheeks are also favored sites. Any part of the body may be involved, however.

Cystic Basal Cell Carcinoma

These dome-shaped, blue-gray cystic nodules are clinically similar to eccrine and apocrine hidrocystomas (Fig. 29-15).

Morpheic, Morpheaform, or Cicatricial Basal Cell Carcinoma

This type of BCC presents as a white sclerotic plaque. Ninety-five percent of these BCCs occur on the head and neck. Ulceration, a pearly rolled border, and crusting are usually absent. Telangiectasia is variably present. For this reason, the lesion is often missed or misdiagnosed for some time. The differential diagnosis includes desmoplastic trichoepithelioma, a scar, microcystic adnexal carcinoma, and



Fig. 29-15 Basal cell carcinoma, cystic.



Fig. 29-16 Basal cell carcinoma, plaque with central regression.

desmoplastic melanoma. The unique histologic feature is the strands of basal cells interspersed amid densely packed, hypocellular connective tissue. Morpheic BCCs constitute 2% to 6% of all BCCs.

Infiltrative Basal Cell Carcinoma

Infiltrative BCC is an aggressive subtype characterized by deep infiltration of spiky islands of basaloid epithelium in a fibroblast rich stroma. Clinically, it lacks the scarlike appearance of morphoeic BCC. Histologically, the stroma is hypercellular, the islands are jagged in outline and squamous differentiation is common.

Micronodular Basal Cell Carcinoma

These tumors are not clinically distinctive, but the micronodular growth pattern makes them less amenable to curettage.

Superficial Basal Cell Carcinoma

Superficial BCC is also termed *superficial multicentric BCC*. This is a very common form of BCC, comprising at least 15% of BCCs. This form favors the trunk (45%) or distal extremities (14%). Only 40% occur on the head and neck. The multicentricity is merely a histologic illusion created by the passing of the plane of section through the branches of a single, multiply branching lesion.

This type of BCC most frequently presents as a dry, psoriasiform, scaly lesion. They are usually superficial flat growths, that in many cases exhibit little tendency to invade or ulcerate. They enlarge very slowly and may be misdiagnosed as patches of eczema or psoriasis. These lesions may grow to be 10 to 15 cm in diameter. Close examination of the edges of the lesion will show a thread-like raised border (Figs 29-16 and 29-17). These erythematous plaques with telangiectasia may show atrophy or scarring occasionally. Some lesions may develop an infiltrative component in their deeper aspect and grow into the deeper dermis. When this occurs they may induce dermal fibrosis and multifocal ulceration, forming a “field of fire” type of large BCC. Sometimes the lesion will heal at one place with a white atrophic scar and then spread actively to the neighboring skin. It is not uncommon for a patient to have several of these lesions simultaneously or with time. This form of BCC is the most common pattern seen in patients with human immunodeficiency virus (HIV) infection and BCC.



Fig. 29-17 Basal cell carcinoma, superficial.



Fig. 29-18 Basal cell carcinoma, pigmented.

Pigmented Basal Cell Carcinoma

This variety has all the features of nodular BCC, but in addition, brown or black pigmentation is present (Fig. 29-18). When dark-complexioned persons such as Latin Americans, Hispanics, or Asians develop BCC, this is the type they tend to develop. Pigmented BCCs comprise 6% of all BCCs. In the management of these lesions it should be known that if

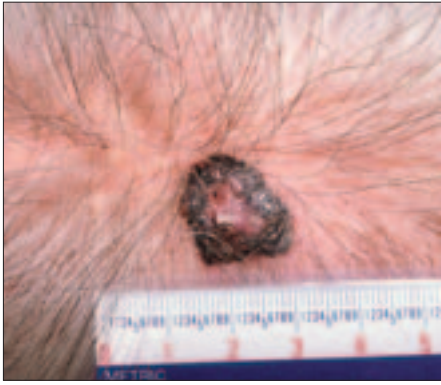


Fig. 29-19 Basal cell carcinoma, rodent ulcer.

ionizing radiation therapy is chosen as the therapeutic modality, the pigmentation remains at the site of the lesion.

Rodent Ulcer

Also known as *Jacobi ulcer*, rodent ulcer is a neglected BCC which has formed an ulceration (Fig. 29-19). The pearly border of the lesion may not be recognized. If it occurs on the lower extremity it may be misdiagnosed as a vascular ulceration.

Fibroepithelioma of Pinkus

First described by Pinkus as premalignant fibroepithelial tumor, the tumor is usually an elevated, skin-colored, sessile lesion on the lower trunk, the lumbosacral area, groin, or thigh and may be as large as 7 cm. The lesion is superficial and resembles a fibroma or papilloma.

Histologically, there are interlacing basocellular sheets that extend downward from the surface to form an epithelial meshwork enclosing a hyperplastic mesodermal stroma. Like infundibulocystic BCC, fibroepithelioma is composed of pink epithelial strands with blue basaloid buds. Fibroepitheliomas has a more prominent fibromucinous stroma and lacks the horn cysts characteristic of infundibulocystic BCC. Fibroepithelioma often demonstrates sweat ducts within the pink epithelial strands. A slight inflammatory infiltrate may also be present. Simple removal by excision or electro-surgery is the treatment of choice.

Polypoid Basal Cell Carcinoma

These tumors present as exophytic nodules of the head and neck.

Pore-Like Basal Cell Carcinoma

Patients with thick sebaceous skin of the central face may develop a BCC that resembles an enlarged pore or stellate pit. The lesions virtually always occur on the nose, melolabial fold, or lower forehead. Affected patients are generally men and the majority are smokers. Many years pass from the appearance of the lesion until a diagnostic biopsy is taken because the lesion is considered inconsequential.

Aberrant Basal Cell Carcinoma

Even in the absence of any apparent carcinogenic factor, such as arsenic, radiation, or chronic ulceration, BCC may occur in odd sites, such as the scrotum, vulva, perineum, nipple, and axilla.

Solitary Basal Cell Carcinoma in Young Persons

These curious lesions are typically located in the region of embryonal clefts in the face and are often deeply invasive. Complete surgical excision is much safer than curettage for their removal. Cases in children and teenagers, unassociated with the basal cell nevus syndrome or nevus sebaceous, are well-documented.

Natural History

BCCs run a chronic course as the lesion slowly enlarges and tends to become more ulcerative. As a rule, there is a tendency for the lesions to bleed without pain or other symptoms. Some of the lesions tend to heal spontaneously and to form scar tissue as they extend. Peripheral spreading may produce configurate, somewhat serpiginous, patches. The ulceration may burrow deep into the subcutaneous tissues or even into cartilage and bone, causing extensive destruction and mutilation. At least half of the deaths that occur from BCC result from direct extension into a vital structure rather than metastases.

Metastasis

Metastasis is extremely rare, occurring in 0.0028% to 0.55% of BCCs. This low rate is believed to be due to the fact that the tumor cells require supporting stroma to survive. The following criteria are now widely accepted for the diagnosis of metastatic BCC:

1. The primary tumor must arise in the skin
2. Metastases must be demonstrated at a site distant from the primary tumor and must not be related to simple extension
3. Histologic similarity between the primary tumor and the metastases must exist
4. The metastases must not be mixed with SCC

Metastatic BCC is twice as common in men as in women. Immunosuppression does not appear to increase the risk of metastasis of BCC. Most BCCs which metastasize arise on the head and neck, and tend to be large tumors that have recurred despite multiple surgical procedures or radiation therapy. The histologic finding of perineural or intravascular BCC increases the risk for metastasis. The regional lymph nodes are the most frequent site of metastasis, followed by the lung, bone, skin, liver, and pleura. Spread is equally distributed between hematogenous and lymphatic. An average of 9 years elapses between the diagnosis of the primary tumor and metastatic disease, but the interval for metastasis ranges from under 1 year to 45 years. Although the primary tumor may be present for many years before it metastasizes, once metastases occur the course is rapidly downhill. Fewer than 20% of patients survive 1 year and less than 10% will live past 5 years after metastasis.

Association with Internal Malignancies

Frisch et al reported a series of 37,674 patients with BCCs followed over 14 years. Comparison of cancer rates for the general population was remarkable for 3663 new cancers compared with 3245 in the control population. Malignant melanoma and lip cancers were the most frequently found; however, internal malignancies were also noted to be excessive, involving the salivary glands, larynx, lung, breast, kidney, and lymphatics (non-Hodgkin lymphoma). The rate

of non-Hodgkin lymphoma was particularly high. Patients receiving the diagnosis of BCC before the age of 60 were found to have a higher rate of breast cancer, testicular cancer, and non-Hodgkin lymphoma.

Immunosuppression

Immunosuppression for organ transplantation increases the risk for the development of BCC by about 10-fold. Some increased risk for BCC is considered also to occur in HIV infection and in persons on immunosuppressive medications for other reasons. Patients with chronic lymphocytic leukemia are also at increased risk for BCC. In the immunosuppressed population, a history of blistering sunburns in childhood is a strong risk factor for the development of BCC following immunosuppression.

Etiology and Pathogenesis

It appears that BCCs arise from immature pluripotential cells associated with the hair follicle. Mutations that activate the hedgehog signaling pathway, which controls cell growth, are found in most BCCs. The affected genes are sonic hedgehog, Patched 1, and Smoothened genes. Inactivation of the Patched 1 gene is most common.

Histopathology

There is a general belief that there is a correlation between histologic subtype of BCC and biologic behavior. BCCs are considered low or high risk, depending on their probability of causing problems in the future: subclinical extension, incomplete removal, aggressive local invasive behavior, and local recurrence. Therefore, the dermatopathology report of a BCC should include a subtype descriptor when possible. Unfortunately, many shave biopsy specimens do not allow for accurate typing and the presence of an indolent growth pattern superficially does not exclude the possibility of a more aggressive deeper growth pattern. The common histologic patterns are nodular, superficial, infiltrative, morphoeic, micronodular, and mixed. The nodular type is a low-risk type. High-risk types include the infiltrative, morphoeic, and micronodular types, due to aggressive local invasive behavior and a tendency to recurrence. Superficial BCC is prone to increased recurrence due to inadequate removal. When evaluating the histologic margin of superficial BCC, tumor stroma involving the margin should be considered a positive margin.

The early lesion shows small, dark staining, polyhedral cells resembling those of the basal cell layer of the epidermis, with large nuclei and small nucleoli. These occur within the epidermis as thickenings or immediately beneath the epidermis as downgrowths connected with it. After the growth has progressed, regular compact columns of these cells fill the tissue spaces of the dermis and a connection with the epidermis may be difficult to demonstrate. At the periphery of the masses of cells, the columnar cells may be characteristically arranged like fence posts (palisading). This may be absent when the tumor cells are in cord arrangement or in small nests. Cysts may form. The interlacing strands of tumor cells may present a lattice-like pattern. The dermal stroma is an integral and important part of the BCC. The stroma is loose and fibromyxoid with a sparse lymphoid infiltrate commonly present. The stroma can be highlighted by metachromatic toluidine blue staining, which can be useful during Mohs surgery.



Fig. 29-20 Basal cell carcinoma, accentuation of the pearly border when the skin is stretched.

Differential Diagnosis

Distinguishing between small BCCs and small SCCs is largely an intellectual exercise. Both are caused chiefly by sunlight; neither is likely to metastasize; and both will have to be removed, usually by simple surgical excision or curettage. A biopsy is always indicated, but may be performed at the time of the definitive procedure when the likelihood of the diagnosis of NMSC is high and the patient is fully informed and gives consent.

A waxy, nodular, rolled edge is fairly characteristic of BCC (Fig. 29-20). The SCC is a dome-shaped, elevated, hard, and infiltrated lesion. The early BCC may easily be confused with sebaceous hyperplasia, which has a depressed center with yellowish small nodules surrounding the lesion. These lesions never bleed and do not become crusted.

Bowen disease, Paget disease, amelanotic melanoma, and actinic and seborrheic keratoses may also simulate BCC. Ulcerated BCC on the shins is frequently misdiagnosed as a stasis ulcer and a biopsy may be the only way to differentiate the two. Pigmented basal cell epithelioma is frequently misdiagnosed as melanoma or as a pigmented nevus. The superficial BCC is easily mistaken for psoriasis or eczema. The careful search for the rolled edge of the peripheral nodules is important in differentiating BCC from all other lesions.

Treatment

Each lesion of BCC must be thoroughly evaluated individually. Age and sex of the patient as well as the size, site, and type of lesion are important factors to be considered when choosing the proper method of treatment. No single treatment method is ideal for all lesions or all patients. The choice of treatment will also be influenced by the experience and ability of the treating physician in the various treatment modalities. A biopsy should be performed in all cases of suspected BCC, to determine the histologic subtype and to confirm the diagnosis.

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The aim of treatment is for a permanent cure with the best cosmetic results. This is important because the most common location of BCC is the face. Recurrences result from inadequate treatment and are usually seen during the first 4 to 12 months after treatment. A minimum 5-year follow-up is indicated, however, to continue a search for new lesions, since the development of a second BCC is common.

Treatment of BCC is usually surgical (see Chapter 37), but some forms of BCC are amenable to medical treatment.

Topical Therapy

Topical treatment appears to be most effective in the treatment of superficial BCC. For nodular BCCs the cure rates are only 65% which is unacceptable given the other options available. On the other hand, superficial BCCs may be cured 80% of the time with topical treatment. Topical 5-FU is not extraordinarily effective and recurrence rates are high. Imiquimod applied three times a week with occlusion or five times a week without occlusion is the favored form of topical, patient-applied treatment for superficial BCC. Duration of treatment is for 6 weeks, but may be extended if the lesion does not appear to have been eradicated. Cosmetic results are excellent, especially for lesions of the anterior chest and upper back where significant scarring usually results from surgical procedures. Photodynamic therapy has also emerged as a treatment option for BCC.

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NEVOID BASAL CELL CARCINOMA SYNDROME (GORLIN SYNDROME)

*Clinical Features

The nevoid BCC syndrome or basal cell nevus syndrome (BCNS) is an autosomal-dominantly inherited disorder characterized by the development of multiple BCCs (Fig. 29-21); odontogenic cysts of the jaws; pitted depressions on the hands and feet; osseous anomalies of the ribs, spine, and skull; and multiple other disorders. Keratin cysts are frequently seen and calcium deposits in skin, especially in the scalp, may be present. A characteristic facies is present with frontal



Fig. 29-21 Basal cell nevus syndrome (Gorlin syndrome), multiple milia.

bossing, a hypoplastic maxilla, a broad nasal root, and true ocular hypertelorism being features.

Of 105 patients reported in one series, 80% were white and 38% were black. The first tumor developed by the mean age of 23 years for white patients. Palmar pits were seen in 87%. Jaw cysts were found in 74%, with 80% manifested by the age of 20. The total number of cysts ranged from 1 to 28. Medulloblastomas developed in four patients and three had cleft lip or palate. Physical findings in this series included "coarse face" (54%), macrocephaly (50%), hypertelorism (42%), frontal bossing (27%), pectus deformity (13%), and Sprengel deformity (11%). Previously described features not found in this series include short fourth metacarpal, scoliosis, cervical ribs, and spina bifida occulta.

Skin Tumors

The BCCs occur at an early age or any time thereafter as multiple lesions, usually numerous. The usual age of appearance is between 17 and 35 years. Although any area of the body may be affected, there is a marked tendency toward involvement of the central facial area, especially the eyelids, periorbital area, nose, upper lip, and cheeks. Any variety of BCC may be present. In children there may be pigmented papules resembling skin tags.

Jaw Cysts

Jaw cysts occur in 70% of patients. Both the mandible and the maxilla may show cystic defects by x-ray, with mandibular involvement occurring twice as often. The patient may complain of jaw pain and tenderness, fever, difficulty in closing the mouth, and swelling of the jaw. The cysts are uni- or multi-ocular and may occur anytime during life, with the first decade being the most common time of appearance. They may have a keratinized lining and some are ameloblastomas.

Pits of Palms and Soles

An unusual pitting of palms and soles is a distinguishing feature of the disease. They usually become apparent in the second decade of life. Up to 87% of patients with nevoid BCC syndrome will have pits. Histologically, they show basaloid proliferation, but the lesions do not progress or behave like a BCC.

Skeletal Defects

Numerous skeletal defects are easily detected by roentgenograms. Such defects may be spina bifida; bifid, fused missing or splayed ribs; scoliosis; and kyphosis. An interesting finding is shortened fourth metacarpal and metatarsal bones. The shortened fourth metacarpal results clinically in a dimple over the fourth metacarpophalangeal joint (Albright's sign). Radiographic evidence of multiple lesions is highly suggestive of this syndrome and since most are present congenitally, roentgenograms may be useful in diagnosing this syndrome in patients too young to manifest other abnormalities. Seventy to 75% of patients manifest skeletal abnormalities. Flame-shaped lucencies of the phalanges, metacarpal, and carpal bones of the hands were found in 30% of 105 patients. Other radiographic findings in this series include bifid ribs (26%), hemivertebra (15%), and fusion of the vertebral bodies (10%).

Disorders of the Central Nervous System

Important radiographic signs include calcification of the falx cerebri (65%), of the tentorium cerebelli (20%), and of

the bridged sella (68%). On computed tomography (CT) the calcification of the falx is distinctly lamellar. Varying mental problems may be encountered in patients.

Other Defects

Ophthalmologic abnormalities and mesenteric, ovarian, and mammary cysts, as well as uterine fibromas, lipomas, epithelial cysts, milia, and renal calculi are known to occur at times in these patients. Calcified multinodular ovarian fibromas are characteristic.

Etiology

This is a genetic disorder with an autosomal-dominant pattern. Penetrance may be as high as 95%. The mutation is located on chromosome 9q22.3. Mutations in the Patched 1 (PTCH1) tumor suppressor gene and less commonly in the sonic hedgehog (SHH) or Smoothed (SMOH) genes are responsible for this syndrome.

Histopathology

The histology of BCCs arising in syndrome patients is identical to those arising in non-syndrome patients, with the solid and superficial types being most common.

Differential Diagnosis

Several other unique types of presentation of BCCs should not be confused with BCNS. One is the linear unilateral BCC syndrome, in which a linear arrangement of close-set papules, sometimes interspersed with comedones, is present at birth. Biopsy reveals basal cell epitheliomas; however, they do not increase in size with the age of the patient. The second type, referred to as Bazex syndrome, is an X-linked dominantly inherited disease comprising follicular atrophoderma of the extremities, localized or generalized hypohidrosis, hypotrichosis, and multiple BCCs of the face, which often arise at an early age. The third is the syndrome of multiple hereditary infundibulocystic BCCs, which is also an autosomal-dominant syndrome. It is distinguished from BCNS by the absence of palmar pits and jaw cysts in most cases. Clinically, patients appear to have multiple trichoeplitheliomas. Numerous skin-colored pearly papules affect the center face, accentuated in the nasolabial folds. The generalized basaloid follicular hamartoma syndrome differs from BCNS by having basaloid follicular hamartomas instead of BCCs. It is reported from a large kindred in the southeastern US (see below). Tiny palmar pits are present. Histologically, infundibulocystic BCC and basaloid follicular hamartoma may be indistinguishable, so the two familial syndromes may be difficult to separate. Rombo syndrome, reported in one large Swedish family, has multiple BCCs and vermiculate atrophoderma and hypotrichosis. A patient with multiple BCCs and myotonic dystrophy has been reported, suggesting yet another genodermatosis associated with multiple BCCs.

Treatment

Genetic counseling is essential. Strict sun avoidance is essential and maximum sun protection, as recommended for xeroderma pigmentosa patients, is recommended. Treatment involves very regular monitoring and biopsying of suspicious lesions. Topical therapy with tazarotene and imiquimod may find some use in preventing and treating the superficial tumors. Surgical treatments are used for most lesions. One

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case with intractable lesions responded to systemic chemotherapy with paclitaxel. Oral retinoid therapy may reduce the frequency of new BCCs.

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SQUAMOUS CELL CARCINOMA

SCC is the second most common form of skin cancer. Most cases of SCC of the skin are induced by UVR. Chronic, long-term sun exposure is the major risk factor and areas which have had such exposure (the face, scalp, neck, and dorsal hands) are favored locations. SCC is relatively more common as the annual amount of UVR increases, so SCC is more common in Texas than in Minnesota, for example. Immunosuppression greatly enhances the risk for the development of SCC. Etanercept treatment has been associated with the appearance of cutaneous SCC in patients with rheumatoid arthritis also being treated with methotrexate. Human papilloma viruses (HPV-16, -18, -31, and -35 primarily) play a role in SCCs that develop on the genitalia and perianally. A chronic ulcer, hidradenitis suppurativa, prior X-radiation exposure, PUVA treatment, recessive dystrophic epidermolysis bullosa, lesions of discoid lupus, and erosive lichen planus are all risk factors for the development of SCC. Metastasis, with a mortality rate of 18%, is very uncommon for SCCs arising in sites of chronic sun damage, whereas it is relatively high (20–30%) in SCCs occurring in the various scarring processes. Patients with epidermodysplasia verruciformis (EDV) also develop SCCs on sun-exposed sites, associated with unique HPV types. These unique EDV HPV types (HPV-5, -8, and others) may also play a role in SCCs which develop in immunosuppressed persons. SCC of the

oral mucosa is discussed in Chapter 34. Because the vast majority of cutaneous SCCs are induced by UVR, sun protection with avoidance of the midday sun, protective clothing, and the regular application of a sunblock of SPF 15 to 30 is recommended. Some researchers have suggested that smoking is also a risk factor for cutaneous SCC, but this is controversial.

Clinical Features

Frequently, SCC begins at the site of actinic keratosis on sun-exposed areas such as the face and backs of the hands. BCCs far outnumber SCCs on the facial skin, but SCCs on the hand occur three times more commonly than BCCs. The lesion may be superficial, discrete, and hard, and arises from an indurated, rounded, elevated base (Figs 29-22 and 29-23). It is dull-red and contains telangiectases. In the course of a few months the lesion becomes larger, deeply nodular, and ulcerated. The ulcer is at first superficial and is hidden by a crust. When this is removed, a well-defined, papillary base is seen and on palpation a discrete hard disk is felt. In the early phases this tumor is localized, elevated, and freely movable on the underlying structures; later it gradually becomes diffuse, more or less depressed, and fixed. The growth eventually invades the underlying tissues. The tumor above the level of the skin may be dome-shaped, with a core-like center that later ulcerates. The surface in advanced lesions may be cauliflower-like, composed of densely packed, filamentous



Fig. 29-22 Squamous cell carcinoma, ulcerating tumor in an area of chronic sun exposure.



Fig. 29-23 Squamous cell carcinoma, preauricular ulceration in a patient with AIDS.

projections, between which are clefts filled with a viscid, purulent, malodorous exudate.

In black patients SCCs are 20% more common than BCCs. The most common sites are the face and lower extremities, with involvement of non-sun-exposed areas more common. Elderly women (mean age, 77) are primarily affected in cases involving the lower legs. Prior direct heat exposure from open fireplaces may be the predisposing factor. In contrast, in white patients the frequent predisposing conditions are scarring processes, such as burns, leg ulcers, and hidradenitis suppurativa.

On the lower lip, SCC often develops on actinic cheilitis. From repeated sunburn the vermilion surface becomes dry, scaly, fissured, and actinic cheilitis develops. Cancer usually arises on fissure or keratosis. At the beginning only a local thickening is noticeable. This then becomes a firm nodule. It may grow outward as a sizable tumor or inward with destructive ulceration. A history of smoking is also frequent and a significant predisposing factor. Lower lip lesions far outnumber upper lip lesions, men far outnumber women (12:1), and the median age is the late 60s. SCCs occurring on the lower lip metastasize approximately 10% to 15% of the time. SCC of the lip may also occur in areas of discoid lupus (DLE) in black patients. Neoplastic transformation into SCC may develop in 0.3% to 3% of patients with DLE of the lip.

Periungual SCC frequently presents with signs of swelling, erythema, and localized pain. It commonly arises in the nailfolds of the hands and initially resembles a periungual wart. Fifty percent of those x-rayed show changes in the terminal phalanx. There is a low rate of metastases (3%), but local excision with Mohs microsurgery is recommended as it reduces the risk of recurrence. Periungual SCC is strongly associated with genital HPV types, primarily 16, 18, 31, and 35.

Given the numerous presentations of SCC on the skin, there should be a low threshold for biopsy of any suspicious lesions, especially in the background of chronic sun exposure.

Histopathology

SCC is characterized by irregular nests of epidermal cells invading the dermis to varying degrees. The degree of cell differentiation has been used to grade SCC. Although interpretations vary, it is believed that the greater the differentiation, the less the invasive tendency, and therefore the better the prognosis. In grade I SCC, most of the cells are well-differentiated, whereas in grade IV most are undifferentiated or anaplastic. The anaplastic type of tumors may be difficult to differentiate from other tumors such as melanoma, lymphoma, and mesenchymal tumors. This is true also when the tumor is of the spindle cell type. Immunoperoxidase staining for keratins is very useful in this setting. Desmoplastic SCCs by light microscopy have prominent trabecular growth patterns, narrow columns of atypical epithelial cells, and marked desmoplastic stromal reaction. Acantholytic SCC is a recognized histologic subtype, but its behavior parallels that of cutaneous SCC. The finding of perineural and vascular invasion are bad prognostic features for recurrence and metastasis in any form of cutaneous SCC.

Differential Diagnosis

The differentiation of SCC from keratoacanthoma is of academic interest in most cases as simple surgical excision is

performed on most of these lesions. However, if nonsurgical modalities are contemplated, a biopsy confirming the diagnosis of keratoacanthoma is recommended. In the setting of immunosuppression, keratoacanthoma-like lesions should be managed as SCCs. The rapid growth and presence of a rolled border with a keratotic central plug suggest the diagnosis of keratoacanthoma, as does explosive growth. An early SCC may be confused with a hypertrophic actinic keratosis and indeed the two may be indistinguishable clinically. Biopsy to include the base of the lesion is necessary to make the diagnosis.

Pseudoepitheliomatous hyperplasia must be distinguished histologically from true SCC. Marked pseudoepitheliomatous hyperplasia may be seen in granular cell tumor, bromoderma, blastomycosis, granuloma inguinale, and chronic stasis ulcers, ulcerations occurring in thermal burns, lupus vulgaris, leishmaniasis, and even in sporotrichosis. Pseudoepitheliomatous hyperplasia (PEH) arises from adnexal structures as well as the surface epidermis. Hyperkeratosis and hypergranulosis of adjacent hair follicles is often present. Strands of epidermal cells may extend into the reticular dermis and commonly trap elastic fibers, a finding also seen in keratoacanthoma, but rarely in conventional SCCs. A potential diagnostic pitfall is the presence of benign PEH adjacent to and overlying invasive SCC. This is particularly common in lesions that have been picked or scratched.

Metastases

The rate of SCC metastasis from all skin sites ranges from 0.5% to 5.2%. Careful attention should be paid to regional lymph nodes draining the site of the SCC. These should be examined at the time of the initial evaluation when the suspicious lesion is identified and at the regular visits which follow the treatment of the SCC. Risk factors for local recurrence and metastasis include: 1) treatment with a modality that does not check the margins of the specimen (such as curettage and desiccation, cryotherapy or radiation); 2) recurrence after prior treatment; 3) location (temples, scalp, ear, lip); 4) size; 5) depth; 6) histologic differentiation; 7) histologic evidence of perineural invasion; 8) histologic evidence of desmoplastic features; 9) precipitating factors other than UV light; and 10) host immunosuppression. In reference to metastatic disease, the highest rates occur from scars (37.9%), the lip (13.7%), and the external ear (8.8%). Risk of metastasis rises for lesions larger than 2 cm in diameter, skin lesions deeper than 4 mm, and lip lesions deeper than 8 mm. Patients with perineural spread have a local recurrence rate of 47.2% and a metastatic rate of 34.8%. Desmoplastic SCCs are six times more likely to metastasize than other histologic patterns, excluding neurotropic forms.

Patients with SCC are at increased risk of developing other malignancies, such as cancers of the respiratory organs, buccal cavity, pharynx, small intestines (in men), non-Hodgkin lymphoma, and leukemia.

Treatment

The primary treatment of SCC of the skin is surgical (see Chapter 37). Oral retinoids may be useful as a preventive strategy in patients with immunosuppression who develop frequent cancers.

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VERRUCOUS CARCINOMA (CARCINOMA CUNICULATUM)

Verrucous carcinoma is a distinct, well-differentiated variety of SCC. It affects mostly elderly men. The primary characteristic of these lesions is their close resemblance, clinically and histologically, to a wart. The lesions present as a bulbous mass with a soft consistency and often multiple sinuses opening to the surface, resembling "rabbit burrows." Lesions of this type are most common on the sole, but also occur in the genital area (giant condyloma of Buschke and Lowenstein), on the sacrum, and in the oral mucosa. In some cases, as in the Buschke-Lowenstein tumor, verrucous carcinomas are induced by HPV. These HPV may be of the "low-risk" types, such as HPV-6 or -11, or the high-risk types, such as HPV-16. In other cases no HPV can be found and pressure or other factors (but not UV light) are felt to play a role. The natural history is of a slow-growing and invading mass that over years may invade the bony structure beneath the tumor.

Histologically, the lesion shows a characteristic picture of bulbous rete ridges that are topped by an undulating keratinized mass. The squamous epithelium is well-differentiated and cytologic atypia is minimal. The cytoplasm is often apple pink and may have a glassy appearance. The tumor border is smooth and bulldozing, rather than spiky and infiltrative.

Excision is the best treatment and Mohs micro-surgery may be a helpful technique. Radiotherapy may induce anaplastic transformation and is best avoided if other treatment options exist. Lymph node metastasis is rare and the prognosis is favorable when complete excision is accomplished. In SCC of the penis derived from verrucous forms, the prognosis is much better than other causes of penile SCC.

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BOWEN DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Bowen disease is an intraepidermal SCC that probably arises from adnexal epithelium and invades the adjacent epidermis. It may ultimately become invasive. When it does, it tends to behave like an anaplastic adnexal carcinoma.

Clinical Features

Bowen disease may be found on any part of the body as an erythematous, slightly scaly and crusted, noninfiltrated patch from a few millimeters to many centimeters in diameter (Figs 29-24 to 29-26). The lesion is sharply defined. The scale may be pronounced enough for the lesions to be mistaken for



Fig. 29-24 Bowen disease.



Fig. 29-25 Bowen disease.

psoriasis or the plaque may have a stuck-on appearance and may be mistaken for a broad sessile seborrheic keratosis.

As the lesion slowly enlarges, spontaneous cicatrization may develop in portions of the lesion. When the intraepithelial growth becomes invasive, the lesion may appear ulcerated and fungating. The squamous carcinoma that evolves from Bowen disease tends to be more aggressive than SCC arising in actinic dermatoses. When SCC in situ occurs as a velvety plaque on the glans penis it is referred to as *erythroplasia of Queyrat*.

Etiology

Bowen disease affects mostly older white men in whom the lesions occur primarily on sun-exposed surfaces. Most patients with Bowen disease have chronic sun damage. Chronic arsenism produces Bowen disease in non-sun-exposed sites and a history of exposure to arsenic should be sought when Bowen disease is found on the palms, soles, and covered nongenital sites. High-risk HPV types (HPV-16, -18, -31, and -35) have been implicated in lesions involving the periungual and genital regions.

Histopathology

The atypical keratinocytes may invade the adjacent epidermis in a buckshot or clonal nested pattern. With time, they may replace the entire epidermis, often with deep full-thickness involvement of adnexal structures. The epidermis shows hyperkeratosis, parakeratosis, and broad acanthosis or anastomosis of adjacent rete ridges. Epidermal maturation is absent, so the epidermis appears disorganized, and individually keratinizing cells and atypical cells are seen at all levels of the epidermis. There is, however, a sharp delineation between dermis and epidermis, and the basement membrane is intact. The upper dermis usually shows a chronic inflammatory infiltrate. Although the cells tend to be anaplastic with a high nuclear-to-cytoplasmic ratio, variants with smaller nuclei and abundant cytoplasm exist and transitional areas between the patterns may be seen.

Differential Diagnosis

Bowen disease is frequently misdiagnosed as psoriasis, superficial multicentric BCC, tinea corporis, nummular eczema, seborrheic keratosis, and actinic keratosis. Paget disease, especially the extramammary type, not only clinically but also histologically may mimic Bowen disease. There is no dyskeratosis in Paget disease and the intervening nonvacuolated epidermal cells are not atypical in Paget



Fig. 29-26 Bowen disease.

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disease. Stains for mucin and carcinoembryonic antigen are positive in Paget disease and negative in pagetoid Bowen disease. Bowen disease may be heavily pigmented, especially when occurring in the anogenital region. Lesions of bowenoid papulosis show a histologic spectrum from genital warts with buckshot atypia to full-thickness atypia indistinguishable from Bowen disease. If the lesions are multicentric and behave like genital warts, the term bowenoid papulosis may be applied. Treatment is guided completely by the clinical pattern. Since genital SCC is induced by high-risk HPV, bowenoid papulosis represents the initial clinical lesion in the progression from HPV infection to carcinoma. There is no clear boundary where bowenoid papulosis stops and SCC in situ begins.

Treatment

Topical treatment of SCC in situ with cryotherapy and topical 5-FU has been disappointing due to a high rate of recurrence. Iontophoresis will enhance the response to 5-FU, but is not commonly performed by dermatologists. Imiquimod 5% cream applied once a day for up to 16 weeks seems to be effective enough to recommend it as a therapeutic option. Response rates have been as high as 90% in limited series. It may allow treatment of large lesions which might be difficult to approach surgically. The combination treatment with imiquimod 5% cream three times a week and 5% 5-FU twice a day (except at the times of the imiquimod application) has also been reported as effective.

Simple excision of small lesions is a reasonable treatment option. Large, ill-defined lesions, or lesions in which preservation of normal tissue is critical, are indications for Mohs microsurgery. Other surgical techniques to treat SCC in situ are described in Chapter 37. Curettage and desiccation may also be performed, but recurrence may occur if the extension down the follicles is not eradicated. Lesions of the lower legs are particularly problematic, as they are often multiple, and in the elderly are often found in conjunction with significant venous insufficiency. Any form of therapy may result in chronic leg ulceration in this setting. Consideration should be given to using a compression bandage after surgery identical to one applied to a chronic leg ulcer. This may prevent ulceration.

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ERYTHROPLASIA OF QUEYRAT

Erythroplasia of Queyrat is SCC in situ of the glans penis or prepuce. SCC in situ on the penile shaft also occurs and is probably similar. Both conditions are caused by high-risk HPV types (16, 18, 31, 35). Clinically, erythroplasia of Queyrat is characterized by single or multiple fixed, well-circumscribed, erythematous, moist, velvety or smooth, red-surfaced plaques on the glans penis (Fig. 29-27). Uncircumcised men, usually over age 40 are most commonly affected, and when Bowen disease affects the penile shaft it is usually distally under the foreskin. The differential diagnosis includes Zoon balanitis, candidiasis, penile psoriasis, irritant balanitis, and Paget disease. A biopsy is usually indicated to confirm the diagnosis. Since red lesions on the glans of elderly uncircumcised men are common, the following factors suggest a biopsy is indicated: 1) the lesion is fixed (does not move or resolve); 2) the patient lacks other stigmata of psoriasis or another skin disease that could affect the glans penis; 3) the patient's sexual partner has cervical dysplasia; and 4) the lesion does not resolve with effective topical therapy for irritant balanitis, candidiasis, and psoriasis. Once the diagnosis of SCC in situ of the penis is made, the patient's sex partner(s) should be referred for evaluation. Sexual partners of men with SCC of the penis are more likely to develop preinvasive and invasive cancer of the cervix or anus.

Progression to invasive SCC is more common in erythroplasia of Queyrat than in Bowen disease of the nongenital



Fig. 29-27
Erythroplasia of Queyrat.

skin, and the resulting SCCs are more aggressive and tend to metastasize earlier than those that develop in Bowen disease of the nongenital skin. There is no evidence of an increase in internal malignancy in patients with erythroplasia.

Topical therapy can be effective in the treatment of erythroplasia of Queyrat and has the advantage that it can identify and treat areas not visible clinically. Topical 5% 5-FU cream applied once a day under occlusion (with the foreskin or a condom) can be effective. It will induce a brisk reaction and superficial erosion, which can be uncomfortable. Treatment is continued for 3 to 12 weeks, depending on the response. Imiquimod cream 5% applied between once a day and three times a week will similarly induce a significant reaction, but after 3 to 12 weeks may clear the lesion. Careful follow-up is required, especially for the first few years. Surgical modalities such as excision, laser treatments, and photodynamic therapy are reserved for cases failing topical treatments. Radiation therapy can also be effective.

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BALANITIS PLASMACELLULARIS (ZOON)

Balanitis plasmacellularis is also known as *balanoposthitis chronica circumscripta plasmacellularis*. It is a benign inflammatory lesion characteristically with a plasma cell infiltrate. The plasma cell infiltrate, while characteristic, may not be present in all lesions of this type, and in fact, some researchers feel there is a spectrum of histology in idiopathic, benign, nonscarring balanitis, from lesions containing few plasma cells to lesions containing many plasma cells. Clinically, Zoon balanitis is characterized by a red patch, which is usually sharply demarcated and usually on the inner surface of the prepuce and the glans penis (Fig. 29-28). The lesion is erythematous, moist, and shiny. It occurs as a single lesion,



Fig. 29-28 Zoon balanitis, fixed red papule on the glans penis indistinguishable from erythroplasia of Queyrat.

but it may consist of several confluent macules. It is asymptomatic and does not produce inguinal adenopathy. Uncircumcised men from ages 24 to 85 are most often affected.

Vulvitis chronica plasmacellularis is the counterpart of balanitis in women. The vulva shows a striking lacquer-like luster. Erosions, punctate hemorrhage, synechiae, and a slate-to-ochre pigmentation may supervene.

Plasmacytosis circumorificialis is the same disease on the oral mucosa, lips, cheeks, and tongue, clinically suggestive of SCC.

Histologically, the epidermis is atrophic with flattened diamond-shaped keratinocytes and mild spongiosis. In the papillary dermis a band of infiltrate consisting almost exclusively of plasma cells is present. Dilated vessels are also seen. This picture is strikingly different from that of the main clinical differential diagnosis, erythroplasia of Queyrat, in which the epidermis is principally involved, with atypia of keratinocytes throughout the entire epithelium. HPV has not been detected. Topical steroids, alone or in combination with anticandidal treatment, are helpful. Circumcision may be curative. Laser ablation can also be effective.

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PSEUDOEPITHELIOMATOUS KERATOTIC AND MICACEOUS BALANITIS

Pseudoepitheliomatous keratotic and micaceous balanitis was described by Lortat-Jacob and Civatte in 1966. The lesions occurring on the glans penis are verrucous excrescences with scaling. Ulcerations, cracking, and fissuring on the surface of the glans frequently are present. The keratotic scale is usually micaceous and resembles psoriasis. Most patients are over the age of 50 and frequently have been circumcised for phimosis in adult life.

Histologically, there is marked hyperkeratosis and parakeratosis, as well as pseudoepitheliomatous hyperplasia. Acanthotic masses give rise to a crater-like configuration. HPV has not been detected. This is probably best considered as a form of verrucous carcinoma. The treatment is usually surgical and might include Mohs microsurgery. Topical 5-FU has been effective, but the hyperkeratotic scale may make penetration suboptimal. If topical chemotherapy is utilized, post-treatment biopsies are recommended.

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Fig. 29-29 Paget disease of the breast.

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PAGET DISEASE OF THE BREAST

*Clinical Features

Paget disease of the nipple is characterized by a unilateral, sharply marginated, erythematous, and at times a crusted patch or plaque affecting the nipple and occasionally the areola (Figs 29-29 and 29-30). In the course of months or years it may become infiltrated and ulcerated. The nipple may or may not be retracted. A subjacent mass and ipsilateral axillary adenopathy may be palpable. There is virtually always an invasive or in-situ ductal adenocarcinoma of the affected breast.

Histopathology

Paget disease is characterized by the presence of Paget cells: large, round, pale-staining cells with large nuclei. Inter-cellular bridges are absent. The cells appear singly or in small nests between the squamous cells. Usually, acanthosis is present, the granular layer is preserved, and there is no parakeratosis, but atypical cells may be "spat out" into the stratum corneum. Frequently a layer of basal cells separates the Paget cells from the basement membrane and is seen crushed beneath the nests of Paget cells. This histologic feature helps to distinguish Paget disease from pagetoid melanoma and Bowen disease. In the dermis an inflammatory reaction is often present.

The Paget cell is PAS positive, diastase resistant, CEA positive, almost always HER-2/neu positive, EMA positive, and stains with CAM 5.2 and CK 7. This staining profile and negativity for S-100 and cytokeratins 5/6 allow clear distinction from pagetoid melanoma and pagetoid Bowen disease. The Toker cell, a normal clear cell of the breast, stains similarly and is proposed as the precursor cell of Paget disease. Clear cell papulosis is an intraepidermal proliferation of benign Toker cells. Lack of atypia distinguishes it from Paget disease.

Diagnosis

The presence of unilateral eczema of the nipple recalcitrant to simple treatment is suspicious for Paget disease and the



Fig. 29-30 Paget disease of the breast.

lesion should be biopsied. The presence of bilateral lesions suggests a benign process, usually atopic dermatitis. Papillary adenoma of the nipple clinically resembles Paget disease, but on biopsy shows a papillary and adenomatous growth in the dermis with connection to the surface. There is a lining of apocrine-type secretory epithelium. Hyperkeratosis of the nipple and areola may occasionally be unilateral, but histologically reveals only hyperkeratosis, acanthosis, and papillomatosis. Clear cell papulosis of the skin presents with scattered, white, flat-topped lesions distributed on the lower abdomen and along the milk line in otherwise healthy children (adult cases are very rare). Histologic examination reveals benign pagetoid clear cells in the basal layer. The clear cells are AE1 positive and CAM5.2 positive, suggesting they derive from glandular secretory cells.

Treatment

Patients with Paget disease of the breast should be referred to a center with expertise in the management of breast cancer.

Brummer O, et al: HER-2/neu expression in Paget disease of the vulva and the female breast. *Gynecol Oncol* 2004;95:336.

Gianotti R, et al: Clear cell papulosis (pagetoid papulosis) in a non-Asian patient. *Dermatology* 2001;203:260.

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Marucci G, et al: Toker cells are probably precursors of Paget cell carcinoma: a morphological and ultrastructural description. *Virchows Arch* 2002;441:117.



Fig. 29-31 Extramammary Paget disease.

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EXTRAMAMMARY PAGET DISEASE

Extramammary Paget disease (EMPD) presents most commonly as a unifocal process, but multifocal lesions may occur. Lesions typically affect apocrine sites, including the groin (vulva, scrotum, perianal, penis, inguinal folds) (Fig. 29-31) and axilla, but rare cases can affect other anatomic locations. EMPD typically affects persons older than 50. The lesions of extramammary Paget disease are clinically similar to those of Paget disease, but often go undiagnosed longer as they are initially misdiagnosed as pruritus ani, a fungal infection, or intertrigo. A nonhealing banal eczematous patch persisting in the anogenital or axillary region should raise concern for EMPD. Intense pruritus is common. Bleeding is a late sign. Lesions may simulate lichen simplex chronicus or leukoplakia.

Extramammary Paget disease can be divided into four forms: 1) primary EMPD (arising intraepidermally); 2) EMPD associated with an underlying apocrine carcinoma; 3) EMPD associated with an underlying gastrointestinal malignancy; and 4) EMPD associated with an underlying carcinoma of the genitourinary tract. The majority of patients with EMPD do not have underlying carcinoma and the process apparently begins as an intraepidermal neoplasm, which can then invade (invasive EMPD). The clinical appearance of all types of EMPD is identical.

Histologically, the findings are similar to those found in mammary Paget disease: hyperkeratosis, parakeratosis, acanthosis, and the pale, vacuolated Paget cells in suprabasilar levels of the epithelium. Histologic staining cannot distinguish Paget disease of the breast and EMPD due to intraepidermal

or underlying apocrine carcinoma. Cytokeratin staining is unable to clearly distinguish forms of EMPD, except that CK 20 stains cases of EMPD with underlying transitional carcinoma (but not cases of primary EMPD), and PSA (prostate specific antigen) may stain cases of EMPD due to underlying prostate cancer. The mucin core proteins may be used to distinguish other forms of EMPD. Mammary Paget disease stains positively for MUC1 (mammary type apomucin), but negative for MUC2 (intestinal type mucin) and MUC5AC (gastric surface mucin). Vulvar EMPD with underlying apocrine carcinoma stains in a pattern similar to mammary Paget disease (some of these cases may represent "extramammary breast cancer"). Patients with perianal EMPD and underlying gastrointestinal adenocarcinomas stain with MUC2, but only variably with MUC1 or MUC5AC. EMPD with no underlying carcinoma (primary EMPD) are MUC1+, MUC2-, and MUC5AC+.

EMPD can remain within the epithelium or "invade" the dermis. "Invasive" EMPD has a high rate of metastases and a very poor prognosis. Sentinel node examination of patients with "invasive" EMPD should be considered as it predicts the risk for metastases.

Surgical removal is the treatment of choice, which may require Mohs microsurgery. Despite what appears to be adequate margins, recurrence rates are high because of the multifocal nature of extramammary Paget disease. The recurrence rate following micrographic surgery exceeds 25%. One case of scrotal EMPD responded to imiquimod 5% cream applied daily. Radiation therapy, photodynamic therapy, and laser treatments have also been used.

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Merkel Cell Carcinoma (Trabecular Carcinoma)

Merkel cell carcinoma (MCC) was first described by Toker in 1972. The cell of origin is felt to be the Merkel cell, a slow-acting mechanoreceptor in the basal layer of the epidermis. MCC is a rare tumor with an incidence of about 2 in a million per year in the white population and about 1 in 20 in black populations. Ninety-five percent of cases occur in persons over the age of 50 years (mean age 69 years). Men outnumber women by more than 2:1. MCC are felt to be induced by sun exposure since 90% of cases occur on sun-exposed sites, 50% on the head and neck, and 40% on the extremities. PUVA therapy and arsenic exposure may also be potential causes. Immunosuppression by organ transplantation, chronic lymphatic leukemia, and HIV infection all substantially increase the risk for developing MCC.

Clinically, it presents as a rapidly growing, red-to-violaceous nodule with a shiny surface and overlying telangiectasia. Most lesions are diagnosed when they are less than 2 cm in size, but the diagnosis is rarely suspected at the time of biopsy. MCC is an aggressive tumor with a propensity for dermal and nodal spread. At presentation about one-third of cases have regional node involvement and hematogenous spread will eventuate in 50% of cases. Spontaneous remissions occur, and between 10% and 20% of cases present with no primary tumor evident.

Patients should be staged for therapy and prognosis. Physical examination and CT scanning of the relevant nodal region, chest, and liver should be performed. Stage I, or localized disease, represents 70% to 80% of patients at presentation. Five-year survival is 64%. Stage II patients have locoregional disease and are 10% to 30% of patients at diagnosis. Five-year survival is 47%. Stage III disease is distant metastases, and accounts for 1% to 4% of patients at presentation. Median survival is 9 months. Lymph node involvement at presentation is the major predictor of survival. Lesions on the legs are particularly difficult to control because wide excisions and complete courses of radiation therapy are hard to perform on the lower extremity in elderly patients. Undertreatment of lower leg lesions is common, resulting in a poor outcome.

The treatment of MCC should be directed by persons with expertise in managing this rare tumor. Therapy may need to

be individualized, depending on various risk factors present. The goal of treatment for patients with stage I and II disease is cure and local control. This involves the combined use of surgery and radiation therapy in most cases. For stage I patients, local removal (by standard surgery with 2-3-cm margins on the trunk or Mohs micrographic surgery on the head and neck) is recommended. Comparative trials are not available to demonstrate the benefit of radiation therapy following excision. However, since radiation therapy alone has induced sustained remissions, MCC is radiosensitive. Radiation therapy added to surgery may provide additional benefit. Both the local area with 3- to 5-cm margins and the draining lymph nodes should be treated. Untreated lymph nodes experience recurrence from 46% to 76% of the time. Even after Mohs surgery, radiation therapy seems to provide additional benefit. Prophylactic lymph node dissection enhances local control, but does not improve survival. Stage II patients are treated with the same principals as stage I patients. The affected nodal masses are either removed surgically then the area radiated, or treated with radiation alone. It is unclear if surgery improves outcome. Adjunctive chemotherapy may provide some benefit in patients with high-risk disease, using synchronous chemoradiotherapy and adjuvant chemotherapy. Treatment of patients with stage III disease is palliative.

Histologically, MCC is a dermal tumor that may extend into the subcutaneous tissue. The cells are about 15 μ m in diameter and have very scanty cytoplasm and hyperchromatic nuclei with a distinctive smudged chromatin pattern. Mitoses and apoptotic cells are numerous. The cells are arranged in sheets and cords. MCC must be distinguished from small cell lung cancer, lymphoma, neuroblastoma, small cell endocrine carcinoma, Ewing sarcoma, melanoma, and even BCC. While electron microscopy may detect the dense core granules, this is rarely used diagnostically. Instead, immunoperoxidase markers with characteristic staining for both keratins such as CK 20, CK 7, CAM 5.2 (in a perinuclear "dot" pattern) and neuroendocrine markers (neuron-specific enolase, neurofilament protein, neuropeptides, chromogranin, synaptosyn) are the primary method used to confirm the diagnosis of MCC. MCC is S-100 and leukocyte common antigen (LCA) negative.

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Fig. 29-32 Nevus sebaceus.



Fig. 29-33 Nevus sebaceus in a prepubescent child.

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SEBACEOUS NEVI AND TUMORS

*Nevus Sebaceus (Organoid Nevus)

Nevus sebaceus of Jadassohn occurs in approximately 3 in 1000 neonates. It presents as a sharply circumscribed, yellow–orange, hamartoma varying from a few millimeters to several centimeters in size. These lesions are usually solitary, congenital, and linear in configuration. The scalp is the most common location (50%), but other areas of the head and neck (45%) are also common. The trunk is involved in 5% or less of cases. The lesions persist throughout life and are usually alopecic. In childhood they are slightly papillated or velvety, but in adulthood, with hyperplasia of the sebaceous elements, the lesions become more elevated and cerebriform (Figs 29-32 and 29-33). Numerous neoplasms, most of them adnexal, have been described arising in nevus sebaceus. The most common tumors are trichoblastoma and syringocystadenoma papilliferum, each occurring in about 5% of nevus sebaceus. Both of these tumors present as new, often pigmented, papules or nodules arising in the nevus sebaceus. BCC is uncommon, occurring in less than 1% of lesions. Many cases previously diagnosed as BCC are actually trichoblastomas. Many of the tumors are difficult to classify precisely as a well-described entity. Development

of benign tumors occurs in less than 5% of nevus sebaceus before the age of 16 and malignant tumors are rare in childhood or adolescence. The risk for tumor development increases with age. Rarely, aggressive malignant adnexal neoplasms may arise. Familial cases have been described and a paradigmatic pattern of transmission has been suggested.

Nevus sebaceus may be associated with multiple internal abnormalities, making it one of the cutaneous abnormalities to be included within the epidermal nevus syndrome (see above). In cases of nevus sebaceus syndrome, the nevus sebaceus is usually on the scalp, linear, and of larger size (several centimeters).

Histologically, in prepubertal lesions, the epithelium is acanthotic and papillomatous. Pilosebaceous structures are immature and resemble the fetal pilar germ. After puberty, the epidermis is more hyperplastic and at times papillomatous. It may resemble a seborrheic keratosis, acanthosis nigricans, or have features of an epidermal nevus. Sebaceous glands are usually abundant, placed high in the dermis, and connect directly to the epidermal surface, but may be partially lipidized near puberty. Follicular structures, if present are usually vellus or partially formed. Apocrine glands are present in about half of the lesions. The dermis is thickened with increased vascularity and fibrous connective tissue. Mature lesions have been described as broad, bald, bumpy (papillomatous), and bubbly (sebaceous).

Although the risk of development of malignancy exists, it is small, and virtually always occurs after adolescence. For this reason, surgical removal can be delayed until adulthood, when the patient can make an informed decision regarding removal. If the lesion leads to disfigurement, stigmatization, or symptomatology, it may be removed at any age.

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Sebaceous Hyperplasia

This condition is especially common in persons with significant chronic sun exposure. The age of onset is usually past 40. The areas of predilection are the forehead, infra-orbital regions, and temples. The lesions are small, cream-colored or yellowish umbilicated papules 2 to 6 mm in diameter. Unusual sites may be affected, such as the areolas, nipples, penis, neck, and chest, where they occur as solitary lesions, clustered papules or beaded lines. Prominent sebaceous hyperplasia occurs in 10% to 15% of patients taking cyclosporin and may involve ectopic sites such as the oral mucosa. It often appears many years after the cyclosporin is begun. Histologically, the sebaceous glands are hypertrophied, with normal-appearing acini. The glands are multilobulated, each dividing into other lobules to produce a cluster resembling a bunch of grapes. Clinically, they may mimic an early BCC.

Premature sebaceous hyperplasia, also known as *familial presenile sebaceous hyperplasia*, presents with extensive sebaceous hyperplasia with onset at puberty and worsening with age. Familial patterns have been reported, inherited in an autosomal-dominant fashion. It involves the face, neck, and upper thorax but spares the periorificial regions.

Treatment is solely for cosmetic purposes and employs electrosurgery, laser treatment, photodynamic therapy, or even shallow shave biopsy. Isotretinoin will reduce lesions, but they immediately recur when it is stopped, so it is probably not indicated for this condition.

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Sebaceous Adenoma

This slow-growing tumor usually presents as a pink, flesh-colored, or yellow papule or nodule. It occurs primarily on the head and neck in the elderly. Histologically, the tumor is composed of multiple sharply marginated sebaceous lobules. Each lobule has a basal layer of darker germinative cells, but the maturation is not as well-developed as in a normal sebaceous gland. Multiple openings directly to the overlying epidermis may be found. Sebaceous adenoma may be a cutaneous marker of the Muir-Torre syndrome and immunohistochemical staining for MLH-1 and MSH-2 may be used to demonstrate microsatellite instability.

Sebaceoma (Sebaceous Epithelioma)

Clinically, sebaceomas have the same morphologic characteristics as BCCs. They appear as yellow or orange papules, nodules, or plaques, usually on the scalp, face, and neck. They may be associated with Muir-Torre syndrome. Histologically, the tumor consists of oval nests of irregularly shaped basaloid cells with differentiation toward sebaceous cells. Also, there may be cystic spaces containing vacuolated amorphous material.

Sebaceous Carcinoma

This rare carcinoma most frequently arises on the eyelids from the meibomian or Zeis glands. It usually appears in the tarsal region of the upper eyelids (75%) and represents 1% or more of eyelid malignancies. It frequently is misdiagnosed as a chalazion, delaying appropriate treatment. The scalp, other areas of the face, and the trunk are the next most common areas involved. Rarely, it has been reported to involve foot, external genitalia, and the oral mucosa. Fatal metastatic disease occurs in up to 30% of eyelid cases and the 5-year survival for this tumor is 80%. Sebaceous carcinomas arising in nonocular locations can also metastasize, usually to regional lymph nodes. Sebaceous carcinoma may be seen in Muir-Torre syndrome (Fig. 29-34).



Fig. 29-34 Sebaceous carcinoma in a patient with Muir-Torre syndrome.

Histologically, the tumor is composed of lobules or sheets of cells which extend deeply into the dermis, subcutaneous fat, or muscle. The tumor cells are pleomorphic and show various degrees of sebaceous differentiation, manifested by a vacuolated rather than clear cytoplasm. Undifferentiated cells with mitotic figures can be found. The cells vary greatly in size and shape. A characteristic feature in ocular tumors is pagetoid or bowenoid spread of the tumor onto the overlying conjunctiva or skin. Sebaceous differentiation may be minimal in this in situ component, leading to the misdiagnosis of SCC in situ. Treatment is surgical with Mohs' microsurgery having had good results in some cases. Given their extent, oculoplastic reconstruction is usually required. In extraocular cases, complete excision, as for an adnexal carcinoma, and careful follow-up is recommended.

Muir-Torre Syndrome

Sebaceous tumors of the skin were first reported by Muir in 1967 and Torre in 1968 to be associated with the development of internal malignancy, a combination that has been called the Muir-Torre syndrome. The internal tumors often occur a decade or two before the cutaneous lesions, but may occur before or simultaneously with the internal malignancies. The age of presentation of the internal tumors is variable, even within the same kindred. Exacerbation of the syndrome occurs with immunosuppression.

The most common malignancy is colonic adenocarcinoma, but neoplasms of the genitourinary tract may also occur. The visceral tumors are malignant or premalignant, but may not behave as aggressively as predicted. Muir-Torre syndrome is allelic to hereditary nonpolyposis colorectal cancer syndrome. The cutaneous lesions may be sebaceous adenomas, sebaceomas, sebaceous carcinomas, or keratoacanthomas. Cystic sebaceous neoplasms are seen only in patients with Muir-Torre syndrome. Since these sebaceous neoplasms are very uncommon, even the presence of one of these lesions should trigger an evaluation for Muir-Torre syndrome. In one study, 60% of patients with a sebaceous neoplasm were found to have Muir-Torre syndrome.

The genetic basis of Muir-Torre syndrome is an inactivating germline mutation of the DNA mismatch repair genes, very commonly MSH-2 and at times MLH-1, resulting in microsatellite instability. Loss of expression of MSH-2 or MLH-1 can be demonstrated in associated neoplasms by means of immunohistochemical staining. Since the genetic defects and the presence of microsatellite instability can be detected in routinely processed pathology specimens, the diagnosis can be confirmed from both skin biopsies and any visceral tumors removed from the patient. Once the diagnosis is confirmed, the patient and his/her genetically-related family members should be appropriately screened for the presence of the mutation and for underlying malignancies. Genetic counseling should be provided.

Surgical excision of cutaneous lesions is recommended. Grossly involved lymph nodes should also be excised. Patients have responded well to 40 mg/day of isotretinoin and may continue to experience good results with doses as low as 10 mg/day. Patients with this syndrome should have regular examinations for gastrointestinal and genitourinary cancer, including annual colonoscopy beginning at age 25 and first morning urine for cytology. Asymptomatic relatives should also be counseled and evaluated.

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SWEAT GLAND TUMORS

*Syringoma

Syringoma are very common neoplasms demonstrating sweat duct differentiation. They present as small papules 1 to 3 mm in diameter. They may be yellow, brown, or pink. They are virtually always multiple and most frequently occur on the eyelids and upper cheeks (Fig. 29-35). They are disproportionately common in these sites in Japanese women. Other sites of involvement include the axillae, abdomen, forehead, penis, and vulva. Genital syringomas may cause genital



Fig. 29-35 Syringomas.

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pruritus and be mistaken for genital warts. Rarely they may be unilateral or linear. Symmetrical distal extremity involvement has also been reported. Eruptive syringomas are histologically identical to syringomas of the eyelid, but appear suddenly as numerous lesions on the neck, chest, axillae, upper arms, and periumbilically, usually in young persons (Fig. 29-36). Many individual case reports document unusual clinical variants of syringomas. These include types limited to the scalp, associated with alopecia; a unilateral linear or nevoid distribution; those limited to the vulva or penis; those limited to the distal extremities; and the lichen planus- and milia-like types.

Familial cases of syringomas occur. In general, except in eruptive cases, syringomas develop slowly and persist indefinitely without symptoms. Syringomas occur in 18% of adults with Down syndrome, particularly females. This is approximately 30 times the frequency seen in patients with other mental disabilities.

Histologically, syringomas are characterized by dilated cystic spaces lined by two layers of cuboidal cells and epithelial strands of similar cells. Some of the cysts have small comma-like tails to produce a distinctive picture, resembling tadpoles or the pattern of a paisley tie. There is a dense fibrous stroma. At times the cells of the syringoma have abundant clear cytoplasm which represents accumulated glycogen. This has been called "clear cell syringoma" and is often associated with diabetes mellitus. Syringomas stain positive for EKH-6 and CEA, a pattern similar to normal eccrine ducts, but are negative for EKH-5 and SKH1, which label the ductal portions of the eccrine glands. The microscopic differential diagnosis of "paisley tie" epithelial islands embedded in a sclerotic stroma includes microcystic adnexal carcinoma (sclerosing sweat duct carcinoma), desmoplastic trichoepithelioma, and morphoeiform BCC.

Treatment is difficult, but many lesions respond to very light electrodesiccation or shave removal. For larger lesions, surgical removal may be considered.



Fig. 29-36 Syringomas.

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Hidrocystomas

Hidrocystomas are 1 to 3 mm translucent papules that occasionally have a bluish tint (Fig. 29-37). They usually are solitary, occur on the face or scalp, and are more common in women. In some patients, multiple lesions may be present (Fig. 29-38) and they may be pigmented. They may become more prominent during hot weather. Multiple hidrocystomas of the eyelids may be found in Schopf-Schulz-Passarge syndrome, an adult-onset form of focal dermal hypoplasia. Microscopically, a single cystic cavity lined by two layers of small cuboidal epithelial cells is present. Apocrine differentiation in the form of decapitation secretion is common. Lesions with papillary proliferations of the lining are classified as cystadenomas. Treatment, if desired, is by excision for solitary lesions. Laser treatment may be effective. Topical atropine ointment 1% or scopolamine cream 0.01% (1.2 mL of 0.25% scopolamine



Fig. 29-37
Hidrocystoma.



Fig. 29-39 Poroma.



Fig. 29-38 Hidrocystoma.

eyedrops in 30 g of Eucerin) once daily, have been used with variable success in patients with multiple lesions. Pupil size may increase with these agents. Botulinum toxin may also be effective.

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Acrospiromas (Poroma, Hidroacanthoma Simplex, Dermal Duct Tumor, Nodular Hidradenoma, Clear Cell hidradenoma)

Acrospiromas are benign tumors with acrosyringial differentiation. A poroma presents as a slow-growing, 2- to 12-mm, slightly protruding, sessile, soft, reddish tumor that occurs most often on the sole (Fig. 29-39) or side of the foot. Palmar lesions may also occur and more rarely lesions appear wherever sweat glands are found. The lesion will bleed on slight trauma. A distinctive finding is the cup-shaped shallow depression from which the tumor grows and protrudes. Poromas tend to occur singly, but multiple lesions may also occur. A rare variant is called eccrine poromatosis, in which more than 100 lesions may involve the palms and soles and may be associated with hidrotic ectodermal dysplasia. These may represent acrosyringial nevi. Dermal duct tumors present deep nodules that may involve any part of the body. Nodular and clear cell hidradenomas are larger nodules that often involve the head or neck, but may occur anywhere. Hybrid combinations of different patterns of acrospiroma are very common.

Histologically, poromas demonstrate solid masses of uniform, cuboidal epithelial cells with ample cytoplasm and focal duct differentiation. The cells are smaller than those in the contiguous epidermis and tend to arrange themselves in cords and broad columns extending downward from the normal epidermis. Areas of clear cell and cystic degeneration may be present, and an underlying dermal duct tumor or hidradenoma may be present. The surrounding stroma is highly vascular with telangiectatic vessels. Hidroacanthoma simplex represents an intraepidermal eccrine poroma. They resemble clonal seborrheic keratoses except for the presence of focal duct differentiation. Dermal duct tumors are composed of the same small acrosyringial cells as other acrospiromas. The cells form small dermal islands with ductal differentiation. When the cells form a large nodule, the tumor is referred to as a nodular hidradenoma. When clear cells and cystic degeneration are prominent, the tumor is referred to as a clear cell hidradenoma. A distinctive feature of the latter two tumors is the presence of areas of eosinophilic hyalized stroma. These areas represent a degenerative change of vascular walls, and always contain small endothelial-lined lumens. The appearance of these areas has been likened to that of osteoid stroma. Much of this unique stroma appears to represent massive reduplication of the vascular basement membrane.

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The clinical differential diagnosis includes porocarcinoma, granuloma pyogenicum, melanoma (amelanotic and melanotic), Kaposi sarcoma, BCC, and seborrheic keratosis. The lesions are benign, but often recur following inadequate excision. Malignant degeneration may occur, as atypia is sometimes minimal within tumors that have metastasized. For these reasons, simple complete excision is recommended when feasible.

Malignant Acrospiroma (Malignant Poroma, Porocarcinoma)

This represents the most common form of sweat duct carcinoma. Most malignant acrospiromas appear clinically similar to poromas, but may also manifest as a blue or black nodule, plaque, or ulcerated tumor. Porocarcinoma affects men and women equally at an average age of 70 years. The most frequent sites of involvement are the legs (30%), feet (20%), face (12%), thighs (8%), and arms (7%). Of interest is the rare involvement of the palms and soles, despite these having the greatest concentration of sweat glands. The average age from onset to treatment is 8 years. These tumors are of intermediate aggressiveness, with metastases usually occurring to regional lymph nodes and less commonly hematogenously.

Histologically, the tumor may be seen adjoining benign acrospiroma. Atypia may be marked or minimal, with pleomorphic or monomorphous nuclei and abundant or scant eosinophilic cytoplasm. Most commonly, the cells are smaller and more basophilic than those in benign acrospiromas with a high mitotic rate. Just as in benign acrospiromas, clear cell and cystic degeneration may be present. The degree of ductal differentiation is variable. The tumors can be deeply infiltrative.

Mohs surgery can be a valuable technique, particularly on the face. As with other cutaneous neoplasms, margins should be free of tumor islands and tumor stroma to be considered negative.

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Spiradenoma

Spiradenoma clinically presents as a solitary, 1-cm, deep-seated nodule occurring most frequently on the ventral surface of the body, especially over the upper half. Normal-appearing skin covers the nodule, which may be skin-colored, blue, or pink. Occasionally, multiple lesions may be present and may occur in a linear or segmental pattern. Lesions may be painful, but not universally. Spiradenoma has a generally benign clinical course and occurs most frequently between the ages

of 15 and 35, although it has also been reported in infancy and childhood. Familial cases have been described. Rarely, malignant transformation occurs and the subsequent tumor may also have features of a cylindroma (spiradenocylindrocarcinoma).

Microscopically, it demonstrates either a single nodule or multiple basophilic nodules within the dermis. Tumor cells have little to no visible cytoplasm. They are often arranged in characteristic small rosettes. Three cell types are present: cells with large, pale gray nuclei; those with smaller, darker gray nuclei; and jet-black lymphocytes peppered throughout the nodule. Duct-like structures are often present, as are large pink hyaline globules that resemble the bright red hyaline basement membrane material that outlines the islands of cylindromas. In fact, spiradenomas and cylindromas commonly occur together in the same patient and hybrid collision tumors are quite common.

When painful, eccrine spiradenoma may be mistaken for leiomyoma, glomus tumor, neuroma, and angioliopoma. Treatment is simple excision.

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Cylindroma

Cutaneous cylindroma, also known as dermal eccrine cylindroma, occurs predominantly on the scalp and face as a solitary lesion. The tumor is firm, but rubber-like, pinkish to blue, and ranging from a few millimeters to several centimeters. The solitary cylindroma is considered to be nonhereditary and may at times be found in areas other than the head and neck. Women are affected more than men.

The dominantly inherited form, Brooke-Spiegler syndrome, appears soon after puberty as numerous rounded masses of various sizes on the scalp. The lesions resemble bunches of grapes or small tomatoes. Sometimes they cover the entire scalp like a turban and are frequently associated with trichoepitheliomas and milia. In the familial form the cylindromas may be widespread. This syndrome is due to a mutation in the *CYLD1* gene on chromosome 16q12-13.

Histologically, these are cylindrical masses of epithelial cells surrounded and segmented by thick bands of a hyaline

material. Cylindroma may be mistaken for pilar cyst, but the distinctive appearance and consistency makes diagnosis easy, especially in the multiple type. Treatment is surgical.

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Mixed Tumor (Chondroid Syringoma)

Cutaneous mixed tumor is an uncommon skin tumor, representing about 1 in 1000 skin lesions electively removed. It favors men between the ages of 25 and 65. Mixed tumor presents clinically as a firm intradermal or subcutaneous nodule, virtually always located on the head and neck. These tumors are usually asymptomatic and measure 5 to 30 mm in diameter.

Histologically, nests of cuboidal or polygonal epithelial cells in the dermis give rise to tubuloalveolar and ductal structures and occasionally, keratinous cysts. These structures are embedded in a matrix varying from a faint, bluish chondroid substance to an acidophilic hyaline material. This tumor may be of apocrine or eccrine origin. Myoepithelial and lipomatous elements may also be found in the tumor, in addition to the chondroid stroma. Ossification may occur. The treatment is surgical. Mixed tumors may also occur in other organs, especially salivary glands. Tumors with only focal glandular elements, or with no epithelial elements, have been called "cutaneous myoepitheliomas." They are tumors of the myoepithelial cells. Myoepithelial cells surround the sweat glands and by their contraction help deliver the product of the glands to the surface.

Malignant Mixed Tumor (Malignant Chondroid Syringoma)

This rare tumor favors the trunk and extremities (whereas benign mixed tumor of the skin favors the head and neck). At presentation the masses range from 1 to 10 cm, with a median size of 4 cm, and often grow rapidly. The chance of metastasis is more than 50%, with a predilection for visceral spread. Metastases are usually as an adenocarcinoma and the chondroid stroma found in primary lesions is often not found. Histologic features that distinguish it from chondroid syringoma include cytologic atypia, pleomorphism, increased mitotic activity, and focal necrosis. Treatment is surgical.

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Ceruminoma

Ceruminous glands, modified apocrine glands of the external ear, may give rise to both benign and malignant tumors. Their distinction may be very difficult, hence both the malignant and benign tumors have been termed ceruminomas. The tumors present as a firm papule or nodule in the external auditory canal. Ulceration and crusting may occur and continued growth may obstruct the meatus.

Histologically, glands and cysts are present, lined by a tuboglandular proliferation with two layers—an inner layer of ceruminous cells (containing cerumen and with decapitation secretion) and a basal spindled or cuboidal myoepithelial layer. Treatment is excision, which is curative if margins are clear.

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Hidradenoma Papilliferum

Hidradenoma papilliferum is a benign apocrine adenoma that is located almost exclusively in the vulvar and perianal areas. The tumor is covered by normal skin. On palpation it is a firm papule less than 1 cm in diameter.

Microscopically, it is encapsulated and lies in the dermis, and has no connection with the epidermis. There is a cyst-like cavity lined with villi. The walls of the cavity and the villi are lined, occasionally with a single layer, but usually a double layer of cells—luminal secretory cells and myoepithelial cells. Electron microscopy shows hidradenoma and

myoepithelial cells, confirming the apocrine origin of hidradenoma papilliferum. This is a benign lesion and the diagnosis and treatment are accomplished by excisional biopsy.

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Vang R, et al: Ectopic hidradenoma papilliferum: a case report and review of the literature. *J Am Acad Dermatol* 1999;41:115.

Syringadenoma Papilliferum (Syringocystadenoma Papilliferum)

This lesion develops in a nevus sebaceus of Jadassohn on the scalp (Fig. 29-40) or face in about one-third of cases. About half are present at birth and approximately 25% arise on the trunk and genital and inguinal regions during adolescence. The lesions are rose-red papules of firm consistency; they vary from 1 to 3 mm and may occur in groups. Vesicle-like inclusions are seen, pinpoint to pinhead in size, filled with clear fluid. Some of the papules may be umbilicated and simulate molluscum contagiosum. Extensive verrucous or papillary plaques may also be present.

Histologically, the tumor shows ductlike structures that extend from the surface epithelium. Numerous papillary projections may extend into the lumina, which may be cystic. The papillary projections are lined by glandular epithelium, often consisting of two rows of cells. The tumor cells stain positively for carcinoembryonic antigen. The dermal stroma contains numerous plasma cells. Rarely, malignant transformation may occur. Verrucous carcinoma may develop in syringocystadenoma papilliferum. Excision is recommended and radiation therapy is ineffective.

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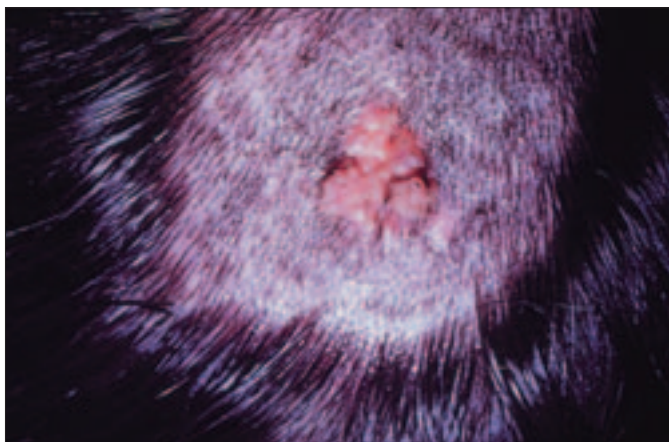


Fig. 29-40 Syringocystadenoma papilliferum.

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Papillary Eccrine Adenoma (Tubular Apocrine Adenoma)

This uncommon benign sweat gland neoplasm presents clinically as dermal nodules located primarily on the extremities of black patients, especially on the dorsal hand or foot. Histologic findings consist of a well-circumscribed, dermal, unencapsulated growth composed of dilated ductlike structures lined by two or more layers of cells. Intraluminal papillations may project into the cystic spaces. Because of its tendency to recur locally, complete surgical excision with clear margins is recommended.

Jackson EM, Cook J: Mohs micrographic surgery of a papillary eccrine adenoma. *Dermatol Surg* 2002;28:1168.

Syringofibroadenoma (Acrosyringal Nevus of Weedon and Lewis)

First described by Mascaro in 1963, four variants of eccrine syringofibroadenoma (ESFA) are now recognized: 1) the solitary variant; 2) multiple in Schopf syndrome; 3) multiple without other skin manifestations; and 4) nonfamilial unilateral linear type. The solitary type presents frequently as a hyperkeratotic nodule or plaque involving the extremities. The linear type may be linear, blaszkoid, or zosteriform in appearance and some cases may represent an acrosyringal nevus. Multiple lesions have been termed *eccrine syringofibroadenomatosis* and occur in both variants of hidrotic ectodermal dysplasia, Schopf syndrome, and Clouston syndrome. The multiple eccrine syringofibroadenomas may appear in a mosaic pattern. In Clouston syndrome, HPV-10 has been detected in the tumors. Multiple lesions have also been reported without any other associated cutaneous findings. Many cases represent a reactive epithelial proliferation, whereas others represent a true neoplasm of acrosyringal cells. Histologically, the pike strands resemble those of the fibroepithelial tumor of Pinkus, but with broader anastomosing cords without the basaloid buds. "Reactive eccrine syringofibroadenoma" most commonly occurs on the lower leg and

may show adjacent changes of an associated dermatosis. Carcinomatous transformation of ESFA has been reported.

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- Trauner MA, et al: Eccrine syringofibroadenoma treated with a dual pulse width flashlamp pumped pulsed dye laser. *Dermatol Surg* 1999;25:418.
- Utani A, et al: Reactive eccrine syringofibroadenoma: an association with chronic foot ulcer in a patient with diabetes mellitus. *J Am Acad Dermatol* 1999;41:650.

Microcystic Adnexal Carcinoma (Sclerosing Sweat Duct Carcinoma)

The tumor generally presents as a very slow-growing plaque or nodule. It occurs most commonly on the upper lip (Fig. 29-41) or face. Microcystic adnexal carcinomas have occurred at sites of prior therapeutic radiation. It is very locally aggressive, with local recurrences in 50% of cases. Metastasis probably does not occur. Histologically, the superficial part of the tumor is composed of ducts, keratinous cysts, and small cords of cells, superficially resembling a syringoma. The deeper component consists of nests and strands in a dense stroma. Perineural invasion is common and may be extensive. This explains the frequent recurrence after initial excision. Mohs microsurgery is the treatment of choice. Radiation treatment of the tumor is ineffective and may lead to recurrence with more aggressive behavior.

- Callahan EF, et al: Microcystic adnexal carcinoma (MAC) of the scalp with extensive pilar differentiation. *Dermatol Surg* 2002;28:536.
- Culhaci N, et al: Microcystic adnexal carcinoma: report of a case. *J Oral Maxillofac Surg* 2003;61:723.
- Hodgson TA, et al: Microcystic adnexal carcinoma: an unusual cause of swelling and paraesthesia of the lower lip. *Oral Oncol* 2003;39:195.



Fig. 29-41 Microcystic adnexal carcinoma.

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- Ozbek C, et al: Microcystic adnexal carcinoma of the external ear canal. *Otolaryngol Head Neck Surg* 2004;130:148.
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“Eccrine” Carcinoma (Syringoid Carcinoma)

Eccrine carcinoma is rare and presents as a plaque or nodule on the scalp (Fig. 29-42), trunk, or extremities. Local recurrence is common, but metastases are rare. It is composed of ducts and tubules with atypical basaloid cells. A more cellular tumor with numerous tubules and ducts has been termed *polymorphous sweat gland carcinoma*. Overlap features with microcystic adnexal carcinoma occur, but in general eccrine carcinoma has a less desmoplastic stroma.

Mucinous Carcinoma

This tumor is commonly a round, elevated, reddish, and sometimes ulcerated mass, usually located on the head and neck (75%). Forty percent occur on the eyelid. It grows slowly and is usually asymptomatic. Local recurrence is seen in 36%, but the rate of metastasis and widespread dissemination is low (15%). Rare tumors on the eyelid (derived from the glands of Moll) may express estrogen and progesterone receptors, analogous to mucinous carcinoma of the breast. Mucinous gut carcinomas may also metastasize to skin; therefore, metastatic breast cancer must be excluded before diagnosing a primary cutaneous mucinous carcinoma.

Histologically, tumors are characterized by the presence of large areas of mucin in which small islands of basophilic epithelial cells are embedded (blue islands floating in a sea of mucous). Basaloid cells in a cribiform pattern, with duct-like structures, is typical. The recommended treatment is local surgical excision.

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- Mitsui H, et al: Mucinous carcinoma of the skin could have either an eccrine or an apocrine origin. *Br J Dermatol* 2004;151:1285.

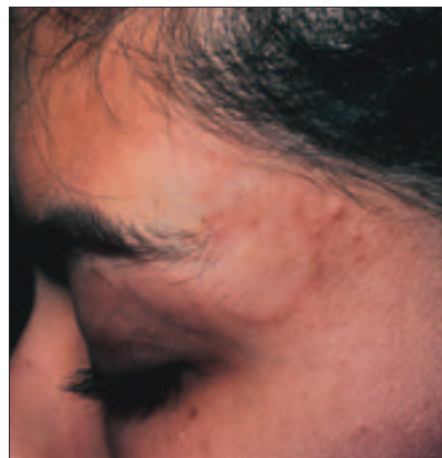


Fig. 29-42 Eccrine carcinoma.

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Terada T, et al: Primary cutaneous mucinous carcinoma initially diagnosed as metastatic adenocarcinoma. *Tohoku J Exp Med* 2004;203:345.

Wako M, et al: Mucinous carcinoma of the skin with apocrine-type differentiation: immunohistochemical studies. *Am J Dermatopathol* 2003;25:66.

Aggressive Digital Papillary Adenocarcinoma (Digital Papillary Adenocarcinoma)

This aggressive malignancy involves the digit between the nailbed and the distal interphalangeal joint spaces in most cases, or just proximal to this region. It presents as a solitary cystic nodule. Ulceration and bleeding can occur and rarely the malignancy may be fixed to underlying tissues. Most patients are men in their 50s. Metastases occur in about 15% of cases, particularly pulmonary. The tumor is poorly circumscribed and composed of tubuloalveolar and ductal structures with areas of papillary projections. The tumor is positive for S-100, and the cystic contents are positive for CEA and EMA. Complete excision is the treatment of choice. Cases previously called aggressive digital papillary "adenoma" are best regarded as adenocarcinoma.

Duke WH, et al: Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). *Am J Surg Pathol* 2000;24:775.

Mori O, et al: Aggressive digital papillary adenocarcinoma arising on the right great toe. *Eur J Dermatol* 2002;12:491.

Primary Cutaneous Adenoid Cystic Carcinoma

This rare cutaneous tumor presents usually on the chest, scalp, or vulva of middle- to older-aged persons. It is similar histologically to adenoid cystic carcinoma of the salivary gland, with a proliferation of small duct-like islands and larger islands with a "Swiss cheese" or cribriform pattern. It may recur locally or rarely metastasizes. Surgical excision, perhaps with Mohs micrographic surgery, is the treatment of choice.

Doganay L, et al: Primary cutaneous adenoid cystic carcinoma with lung and lymph node metastases. *J Eur Acad Dermatol Venereol* 2004;18:383.

Krunic AL, et al: Recurrent adenoid cystic carcinoma of the scalp treated with Mohs micrographic surgery. *Dermatol Surg* 2003;29:647.

Marback EF, et al: Eyelid skin adenoid cystic carcinoma: a clinicopathological study of one case simulating sebaceous gland carcinoma. *Br J Ophthalmol* 2003;87:118.

Apocrine Gland Carcinoma

Apocrine gland carcinoma, unrelated to Paget disease, is rare. The axilla or anogenital region are the most common sites, but occasionally other areas with apocrine glands may be involved. Lesions present as a mass. Widespread metastases occur in at least 40% of cases.

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Chintamani, et al: Metastatic sweat gland adenocarcinoma: A clinico-pathological dilemma. *World J Surg Oncol* 2003;1:13.

Kiyohara T, et al: Apocrine carcinoma of the vulva in a band-like arrangement with inflammatory and telangiectatic metastasis via local lymphatic channels. *Int J Dermatol* 2003;42:71.

Kuno, Y, et al: Adenocarcinoma with signet ring cells of the axilla: two case reports and review of the literature. *J Dermatol* 1999;26:390.

Shintaku M, et al: Apocrine adenocarcinoma of the eyelid with aggressive biological behavior: report of a case. *Pathol Int* 2002;52:169.

Sugita K, et al: Primary apocrine adenocarcinoma with neuroendocrine differentiation occurring on the pubic skin. *Br J Dermatol* 2004;150:371.

Paridaens D, Mooy CM: Apocrine sweat gland carcinoma. *Eye* 2001;15:253.

HAIR FOLLICLE NEVI AND TUMORS

*Pilomatricoma (Calcifying Epithelioma of Malherbe)

Also known as *Malherbe calcifying epithelioma* and *pilomatricoma*, this benign tumor is derived from hair matrix cells. It usually occurs as a single lesion which is most commonly found on the face, neck, or proximal upper extremity. Lesions may also be located on the scalp, trunk, and lower extremities. Pilomatricoma is an asymptomatic, deeply seated, 0.5- to 7.0-cm, firm nodule, covered by normal or pink skin, which on stretching may show the "tent sign," with multiple facets and angles (Fig. 29-43). Overlying epidermal atrophy is common, leading to an appearance that may resemble anetoderma or striae. In a review of 209 patients, the youngest was 18 months and the oldest 86 years. There is a bimodal age distribution, in the first and sixth decades. Girls are more commonly affected than boys.

Multiple pilomatricomas are uncommon. They are usually seen in association with myotonic dystrophy—Steinert syndrome. They may also occur in Ruinstein-Taybi syndrome and Turner syndrome. Patients with Gardner syndrome have epidermoid cysts with focal areas of pilomatricoma-like changes. Rarely, multiple pilomatricomas will be inherited in an autosomal-dominant pattern with no other association.

The histopathology shows an encapsulated mass. Basophilic cells with little cytoplasm resemble those of the hair matrix. They evolve into eosinophilic "shadow" cells. Calcification occurs commonly. Ossification, melanin deposits, and foreign-body reaction with giant cells may all be present.



Fig. 29-43
Pilomatricoma.

Activating mutations in β -catenin are present in the majority of pilomatricomas. It is expressed in the basophilic but not the shadow cells. "Melanocytic matricoma" is a rare lesion presenting as a small papule which histologically is composed of metrical cells, some shadow cells, and numerous dendritic melanocytes containing melanin.

Clinical differential diagnosis is usually impossible in the adult, but in children, since epidermoid cysts are rare, this diagnosis should be considered for any firm cystic mass of the face and upper body. When palpated, pilomatricomas are firmer and more faceted than epidermoid and pilar cysts. Fine needle aspiration has led to misdiagnosis, with the basophilic cells being interpreted as carcinoma. Treatment is surgical excision.

Malignant Pilomatricoma (Pilomatrix Carcinoma, Pilomatrical Carcinoma)

Malignant pilomatricomas are rare tumors. Described as being locally aggressive, but with limited metastatic potential, many cases described as "malignant" may actually have been "proliferating" pilomatricomas. Metastases to regional lymph nodes are most frequent. Mohs micrographic surgery may be considered to obtain clear margins.

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- Bassarova A, et al: Pilomatrix carcinoma with lymph node metastases. *J Cutan Pathol* 2004;31:330.
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- Waxtein L, et al: Malignant pilomatricoma: a case report. *Int J Dermatol* 1998;37:538.
- Yiqun J, Jianfang S: Pilomatricoma with a bullous appearance. *J Cutan Pathol* 2004;31:558.

Trichofolliculoma

Trichofolliculoma is a benign, highly-structured tumor of the pilosebaceous unit, characterized by a small, dome-shaped nodule some 5 mm in diameter on the face or scalp. From the center of the flesh-colored nodule a small wisp of fine, vellus hairs protrudes through a central pore (Fig. 29-44). It may occur at any age but mostly affects adults.

Histologically, the tumor consists of one or more large follicles with smaller radiating secondary follicular structures (sometimes referred to as the mother follicle with her babies). The secondary follicles range from an immature rudimentary matrix to well-formed follicles with papillae, matrix, trichohyaline, and fine hairs ("fingers of fully formed follicles forming fiber"). The tumor may have little stroma or may be embedded in a fibrous orb. Sebaceous glands may be prominent, a variant termed "sebaceous trichofolliculoma." The follicular structures in trichofolliculomas transition through phases of the hair cycle. In telogen, they may resemble fibrofolliculomas. The presence of hair shafts helps distinguish the two. Folliculosebaceous cystic hamartoma may represent a sebaceous trichofolliculoma in telogen. Treatment is surgical removal.

- Kurokawa I, et al: Trichofolliculoma: case report with immunohistochemical study of cytokeratins. *Br J Dermatol* 2003;148:593.
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Multiple Familial Trichoepithelioma (Epithelioma Adenoides Cysticum, Brooke-Spiegler Syndrome)

This autosomal-dominant condition usually presents in childhood or around puberty. Multiple cystic and solid nodules appear on the face, favoring the upper lip, nasolabial folds, and eyelids. The individual lesions are small, round, smooth, shiny, slightly translucent, firm, circumscribed



Fig. 29-44
Trichofolliculoma.

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Fig. 29-45
Trichoepithelioma.



Fig. 29-47
Trichoepithelioma,
desmoplastic type.



Fig. 29-46
Trichoepithelioma.

papules or nodules (Fig. 29-45). The individual lesions average 2 to 4 mm in diameter. The center may be slightly depressed. Most frequently the lesions are grouped but discrete. On the face they are often symmetrical (Fig. 29-46). Other sites may be the scalp, neck, and trunk. Multiple linear and dermatomal trichoepitheliomas may rarely be seen. Cylindromas and multiple spriadenomas may occur in association with multiple trichoepitheliomas. Multiple trichoepitheliomas was originally associated with mutations on the long arm of chromosome 9, near or in the PTCH gene. Recently, mutations of the CYLD gene on 16q12–q13 have been described in families with multiple trichoepitheliomas and cylindromas. Some individuals in these families have primarily trichoepitheliomas and resemble patients with Brooke-Spiegler syndrome.

Solitary Trichoepithelioma

The single occurring trichoepithelioma is nonhereditary and occurs mostly on the face; however, it may also be found on the scalp, neck, trunk, and proximal extremities. It presents as a firm dermal papule or nodule and must be distinguished from BCC.

Giant Solitary Trichoepithelioma

The lesions may be several centimeters in diameter, occurring most commonly on the thigh or perianal regions. They are found in older adults.

Desmoplastic Trichoepithelioma

This lesion, which is difficult to differentiate from morpheiform BCC, histologically occurs as solitary or multiple lesions on the face. Desmoplastic trichoepitheliomas are firm, slightly indented (central dell sign), and have a raised, annular border (Fig. 29-47). Young women are most commonly affected and familial solitary and multiple desmoplastic trichoepitheliomas have been described.

Histology

Trichoepitheliomas are dermal tumors with multiple nests of basaloid cells, some of which show abortive follicular differentiation. Keratinous cysts, calcification, and amyloid may all be seen. The stroma in most trichoepitheliomas resembles the fibrous sheath of a normal hair follicle. It contains many fine collagen fibers and fibroblasts that surround the tumor islands in a concentric array. Clusters of plump nuclei resembling the cells of the follicular papilla (papillary mesenchymal bodies) are common. In the desmoplastic variety, the tumor is composed of small cords of epithelium embedded in a dense eosinophilic stroma with fewer fibroblasts. The islands often present a “paisley tie” appearance, and the microscopic differential diagnosis includes morpheiform BCC, syringoma, and microcystic adnexal carcinoma. The clinical features may distinguish these entities. Focal calcification, horn cysts, and a central dell favor desmoplastic trichoepithelioma. In desmoplastic trichoepithelioma, clefts form between collagen fibers in the stroma, while in BCC, clefts form between the tumor islands and stroma. Trichoepitheliomas are best classified as benign tumors of the hair germ. As such, they may be considered variants of trichoblastoma. Histologically, trichoepithelioma must be differentiated from keratotic BCC, for which it is frequently confused.

Treatment

Solitary lesions can be treated by surgical excision. Multiple lesions can be smoothed down by resurfacing the skin with laser, dermabrasion, or electrosurgery. This procedure must be repeated at regular intervals, as the lesions recur gradually.

Harada H, et al: The gene for multiple familial trichoepithelioma maps to chromosome 9p21. *J Invest Dermatol* 1996;107:41.

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Trichoblastoma

These benign neoplasms of follicular germinative cells usually present as asymptomatic nodules greater than 1 cm in size in the deep dermis or subcutaneous tissue. The scalp is the most common location. They occur in male and female adults. The lesions may be pigmented. Trichoblastomas arise in organoid nevi and represent the majority of basaloid neoplasms described as “basal cell carcinomas” in nevus sebaceus. Histologically, trichoblastoma is a dermal or subcutaneous tumor composed of basaloid cells with areas of follicular differentiation of the tumor. The islands may connect with the overlying epidermis, especially in the setting of an organoid nevus. The stroma is identical to that seen in trichoepithelioma and typically contains papillary mesenchymal bodies. Merkel cells may be prominent within the tumor and amyloid can be found. Cutaneous lymphadenoma is a variant of trichoblastoma with extensive infiltration of the tumor islands by lymphocytes and histiocytes. The stroma resembles that of other trichoblastomas. A single or double row of basaloid tumor cells is seen at the periphery of each island, while the center is composed of pale histiocytes and lymphocytes. Surgical excision is curative.

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Trichilemmoma and Cowden Syndrome (Cowden Disease, Multiple Hamartoma Syndrome)

Trichilemmoma is a benign neoplasm that differentiates toward cells of the outer sheath. It may occur as a small solitary papule on the face, particularly the nose and cheeks. Most lesions are clinically misdiagnosed as BCC or benign keratosis.

Trichilemmomas may also occur as multiple facial lesions. When they do, it is a specific cutaneous marker for Cowden syndrome, an autosomal-dominantly inherited condition. Diagnostic criteria for Cowden syndrome have been established and certain of the mucocutaneous manifestations are considered “pathognomic.” The trichilemmomas are generally limited to the head and neck; however, unusual sites may be involved. Eighty-seven percent of patients with Cowden syndrome have these facial papules (Fig. 29-48). Most consider all the facial papules variants of trichilemmoma, but some contend that some of the facial lesions are trichilemmomas and others are HPV-induced and contain epidermodysplasia- verruciformis HPV types. Since not all facial papules have characteristic histology, the presence of “papillomatous” lesions is a diagnostic criteria. The other pathognomic mucocutaneous benign features include oral mucosal papillomas and acral keratotic papules. Some patients may lack cutaneous findings. Malignancies develop in up to 40% of patients with Cowden syndrome. They are major criteria for the diagnosis and include breast, endometrial, and thyroid carcinoma. Macrocephaly and Lhermitte-Duclos disease are other major criteria. Although not criteria for the diagnosis, gastrointestinal malignancies also occur. Minor criteria included thyroid lesions (adenomas or goiter), mental retardation, fibrocystic disease of the breast, lipomas, fibromas (multiple sclerotic fibromas), and genitourinary tumors. The adult form of Lhermitte-Duclos disease, or dysplastic gangliocytoma of the cerebellum, may represent



Fig. 29-48 Cowden syndrome.

the neurologic manifestation of Cowden disease. A number of mucocutaneous malignancies have been found in patients with Cowden disease, including melanoma, BCC, SCC, Merkel cell carcinoma, and trichilemmal carcinoma. Mutations in a tumor suppressor gene (called PTEN) are responsible for Cowden syndrome. Another disorder caused in 60% of cases by mutations in PTEN is Bannayan-Riley-Ruvalcaba syndrome (autosomal-dominantly inherited, macrocephaly, genital lentiginosities, motor and speech delay, mental retardation, hamartomatous polyps, myopathies, lipomas, and hemangiomas). Some patients with a Proteus-like syndrome also have mutations in PTEN. These diseases have been called the "PTEN hamartoma tumor syndrome."

Microscopically, trichilemmomas show variable hyperkeratosis and parakeratosis. Tumor lobules extend downward from the epidermis and demonstrate glycogen-rich clear cells, peripheral palisading, and a thick hyalinized basement membrane.

Some have advocated bilateral simple mastectomies in affected females to prevent the development of subsequent malignancies. Women with the syndrome who have lost many loved ones to breast cancer have not regarded this recommendation as excessive. With better screening techniques, this recommendation may be modified. Isotretinoin has been used to treat the cutaneous lesions, but even those that regress tend to recur when it is discontinued. Facial papillomas can be removed with surgical procedures, but new lesions continue to appear throughout life. Some patients get satisfactory cosmetic results from dermabrasion or CO₂ laser.

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Trichilemmal Carcinoma

Trichilemmal carcinomas are reported to arise on sun-exposed areas, most commonly the face and ears. They present as a slow-growing papule, indurated plaque, or nodule with a tendency to ulcerate. They may arise in the association of immunosuppression. It may be difficult to distinguish trichilemmal carcinoma from invasive Bowen disease (which often shows adnexal differentiation) or a clear cell SCC. Surgical removal is recommended; Mohs micrographic surgery has been used successfully.

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Trichodiscoma, Fibrofolliculoma, Perifollicular Fibromas, Mantleomas and Birt-Hogg-Dubé Syndrome

These benign tumors form a spectrum of neoplasms combining a follicular element and the specialized periadventitial dermis of the upper portion of the hair follicle. They may represent variations of the same tumor cut in different planes of section. All these lesions clinically appear as 2- to 4-mm, asymptomatic, skin-colored, dermal papules, affecting the face and upper trunk. They may be single, but are frequently multiple. When multiple, they are often numerous and are a marker for Birt-Hogge-Dubé syndrome (BHD). The histomorphology of these hair follicle tumors is identical in patients with BHD and in cases unassociated with BHD. Fibrofolliculoma demonstrates cords and strands of two to four cef epithelium emanating from a follicular structure. The epithelial elements may anastomose and sebaceous elements may be present. This follicular structure is surrounded by a collagenous or fibromucinous orb. Trichodiscomas represent a sectioning artifact that demonstrates only the tumor stroma.

BHD syndrome is caused by a mutation in the gene folliculin (FLCN) which is located on chromosome 17p. Many of the mutations occur in a hypermutable region of the gene. This gene is conserved in many species and expressed in many tissues, especially those with secretory function. Homozygous loss of function of the folliculin gene is embryonically lethal, suggesting it has important functions. In addition to the cutaneous lesions noted above, patients are at risk for the development of renal tumors and spontaneous pneumothorax. The renal tumor risk is seven times the general population and especially affects men (at twice the risk) and those over 40. Almost 12% of BHD patients over the age of 40 develop renal tumors. Renal tumors may be multiple and bilateral. BHD patients develop renal oncocytomas and chromophobe renal carcinomas, otherwise rare renal cancers. Persons with BHD have greater than 50 times the risk of developing a spontaneous pneumothorax compared to unaffected persons. Pneumothorax is inversely related to

age and young persons with BHD have a high risk of pneumothorax—17% of BHD patients under 40 will have a spontaneous pneumothorax. Spontaneous pneumothorax results from multiple pulmonary cysts, which affect 83% of BHD patients. Familial spontaneous pneumothorax is also an autosomal-dominant disorder and in at least one kindred was associated with a deletion in the folliculin gene. Colonic polyps and neoplasms, which were initially reported to be associated with BHD syndrome, have been shown *not* to be increased in BHD syndrome. However, microsatellite stable colonic polyps and carcinomas frequently have loss of heterozygosity for the region of chromosome 17p where the BHD gene is located. The BHD gene may thus be involved in colorectal tumor progression in sporadic colorectal carcinomas. BHD mutations have also been reported in spontaneous renal tumors. Inherited renal cancer in the German shepherd dog and rat is due to mutation in the BHD gene. Although they are often small and not cosmetically problematic, larger lesions in patients with BHD may be treated with laser therapy or shave excisions.

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Fig. 29-49 Dilated pore of Winer.

Other Hair Follicle Tumors

***Dilated Pore (Winer)** This lesion typically presents as a solitary, prominent, open comedo on the face or upper trunk of an elderly individual (Fig. 29-49). Histologically, it is composed of a markedly dilated follicular pore lined by outer root sheath epithelium. Multiple short bulbous, acanthotic projections extend from the central infundibulum-like pore.

Pilar Sheath Acanthoma Most often found on the face, particularly above the upper lip in adults, patients present with a solitary 5- to 10-mm skin-colored nodule with a central keratinous plug. Histologically, pilar sheath acanthoma differs from a dilated pore by having larger tumor lobules radiating from the central infundibulum-like pore.

Trichoadenoma Presenting as a solitary growth ranging from 3 to 15 mm in diameter, clinically it may be mistaken for a seborrheic keratosis, having a vegetative or verrucous appearance. Although most frequently found on the face, it may occur at other sites, especially the buttock, which is the second most common location. Trichoadenomas also differentiate towards the follicular infundibulum. Histologically, they are quite distinctive, being composed of a collection of ring-like eosinophilic structures that often occur in pairs (resembling spectacles). No hair shafts are present.

Basaloid Follicular Hamartoma Basaloid follicular hamartoma (BFH) is a distinctive benign adnexal tumor that has four described variants: solitary papule, localized plaque of alopecia, linear or Blaschkoid unilateral plaque, and generalized papules. This latter form has also been termed “generalized hair follicle hamartoma.” Most often affecting the skin of the face and scalp, BFHs are solitary or multiple skin-colored 2- to 3-mm papules or infiltrating plaques associated with progressive hair loss in the affected areas. Congenital and adult appearance has been described. In some generalized cases there is an association with alopecia, myasthenia gravis, and/or circulating autoantibodies (antinuclear and anti-acetylcholine receptor antibodies). Cystic fibrosis and generalized follicular hamartomas have been reported in three siblings, suggesting a possible genetic linkage. A familial, autosomal-dominant form with numerous milia; comedo-like lesions; hyperpigmented papules of the face, scalp, ears,

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neck and trunk; hypotrichosis; hypohidrosis; and pinpoint palmar pits has been described. It presents in early childhood.

Histologically, basaloid follicular hamartomas may be indistinguishable from infundibulocystic basal cell carcinoma. They are characterized by thin, branching eosinophilic strands and thick cords with associated basaloid buds and keratin cysts. Unlike most other pilar tumors, the stroma is loose, fibrillar, or mucinous. In nevoid and generalized forms, apparently normal skin may also demonstrate small islands of basaloid cells. Trichoblastomas may occur within nevoid lesions. PTCH gene signaling is upregulated in the cells contacting the dermis in BFH. Generalized basaloid follicular hamartoma syndrome must be distinguished from Bazex-Dupre-Christol syndrome, Brown-Crounse syndrome, Rombo syndrome, basal cell nevus syndrome, and Brooke-Spiegler syndrome. Its differentiation from multiple hereditary infundibulocystic basal cell carcinoma syndrome may be difficult.

Folliculosebaceous Cystic Hamartoma Folliculosebaceous cystic hamartoma is a benign hamartoma of epithelial and mesenchymal elements. It presents as a solitary 0.5- to 1.5-cm papule or nodule virtually always on the head, with two-thirds occurring on or adjacent to the nose. Rare giant lesions up to 15 cm in diameter have been reported. Age of onset ranges from infancy to the sixth decade. Histologically, the lesion is composed of three elements: an intradermal cystic structure lined by squamous epithelium identical to that of the infundibulum; numerous sebaceous lobules radiating from the cystic structure; and a surrounding stroma with fibrous, adipose, vascular, and neural tissues. Stromal spindle cells are positive for CD34. The tumor may represent a sebaceous trichofolliculoma biopsied during telogen phase.

Tumors of the Follicular Infundibulum These flat, keratotic papules of the head and neck are usually solitary but may be multiple. They appear in adulthood. The term eruptive infundibulomas and infundibulomatosis has been used to describe the cases with multiple lesions. In the rare generalized cases there is a strong clinical resemblance to Darier disease, with accentuation on the neck, central chest, groin, and axillae. Histologically, the solitary and multiple cases are identical. There is a platelike proliferation of epidermal cells growing parallel to the epidermis and connecting to it at multiple sites. Clear glycogenated cells like that of a trichilemmoma, sebaceous differentiation, cystic and ductal structures, and papillary mesenchymal bodies may be seen.

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EPITHELIAL CYSTS AND SINUSES

*Epidermal Cyst (Epidermal Inclusion Cyst, Infundibular Cyst)

Epidermal inclusion cyst is one of the most common benign skin tumors. It presents as a compressible, but not fluctuant, cystic mass from a half to several centimeters in diameter (Fig. 29-50). The surface of the overlying skin is usually smooth and shiny from the upward pressure. These nodules are freely movable over underlying tissue and are attached to the normal skin above them by a comedo-like central infundibular structure or punctum. The pasty contents of the cysts are formed mostly of macerated keratin which has a cheesy consistency and pungent odor. Epidermal inclusion cysts occur most commonly on the face, neck, and trunk, but may be found almost anywhere. They frequently result from plugging of the follicular orifice, often in association with acne vulgaris. They may also occur by epidermal implantation. Deep penetrating injuries, such as with a sewing machine needle or stapler, may result in epidermoid cysts growing within bone. In pigmented races, the lining of the epidermoid cyst and its contents may be pigmented. Epidermoid

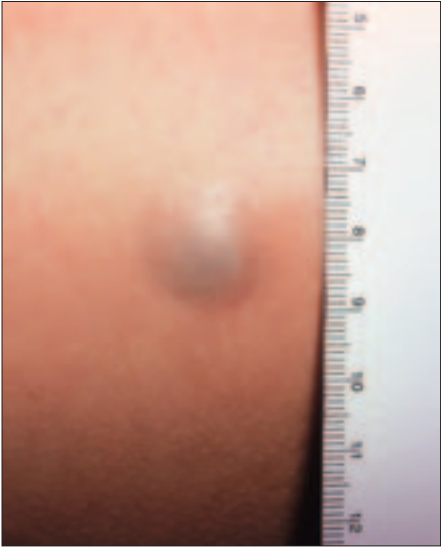


Fig. 29-50
Epidermal inclusion
cyst.

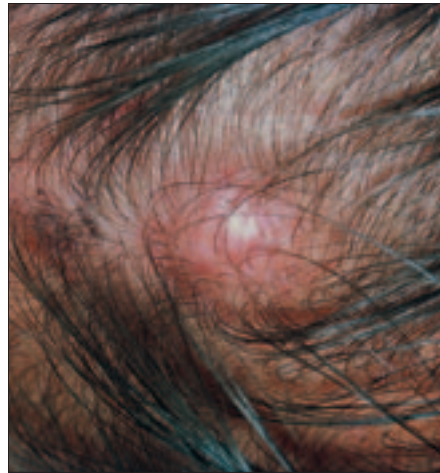


Fig. 29-51 Pilar
cyst.

cysts rarely appear before puberty and earlier onset should suggest an alternative diagnosis (e.g. pilomatrixoma, dermoid cyst, or Gardner syndrome). Lesions of the scalp are usually trichilemmal cysts. Rare cysts of the soles are due to infection by HPV-60.

Epidermoid cysts may rupture and induce a vigorous foreign body inflammatory response, after which they are firmly adherent to surrounding structures and are more difficult to remove. Rupture is associated with the sudden onset of redness, pain, swelling, and local heat, simulating an abscess. Incision and drainage will confirm the diagnosis of inflamed cyst, when the smelly, cheesy material is evacuated. This will also lead to rapid resolution of symptoms. These episodes are often misdiagnosed as “infection” of the cyst, but cultures are usually negative and antibiotic treatment is not required. Intralesional triamcinolone may hasten resolution of the symptoms.

The epidermoid cyst is a keratinizing cyst the wall of which is stratified squamous epithelium containing keratohyalin granules. It is differentiated from the pilar cyst by the different pattern of keratinization. Idiopathic scrotal calcinosis is the end stage of calcification of epidermoid cysts of the scrotum. Pilomatrical differentiation within an epidermoid cyst should raise a suspicion of Gardner syndrome.

Surgical excision is curative, but the complete cyst and any associated “daughter” cysts must be removed. Enucleation of the cyst through a small incision or a hole made with a 4- or even a 2-mm biopsy punch may be attempted. A curette may be used to scrape out and snag all the fragments of the cyst wall. Inflamed cysts may also be treated in this way, but the inflammation makes complete removal of the cyst more difficult. If any fragment of the cyst wall is left behind, the cyst may recur.

Proliferating Epidermoid Cyst

These tumors derived from epidermoid cysts occur more commonly in men (64%) and the most frequent sites are the pelvic/anogenital areas (36%), scalp (21%), upper extremities (18%), and trunk (15%). Carcinomatous changes on histology, with anaplasia, high mitotic rate, and deep invasion occur in up to 20% of cases. They are locally aggressive, but distant metastasis is rare. Malignant onycholemmal

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Pilar Cyst (Trichilemmal Cyst, Isthmus-Catagen cyst)

The trichilemmal cyst, also known as a *wen*, is similar clinically to the epidermoid cyst except that about 90% of pilar cysts occur on the scalp (Fig. 29-51) and inheritance by the autosomal-dominant mode is common. It may be found rarely on the face, trunk, and extremities. An overlying punctum is not present and lesions tend to be more mobile and firmer than epidermoid cysts. Hereditary trichilemmal cysts link to the short arm of chromosome 3, but not to β -catenin or MLH1.

The trichilemmal cyst is lined by stratified squamous epithelium which is derived from the outer root sheath. The lining cells demonstrate trichilemmal keratinization, increasing in size as they approach the cyst cavity and abruptly keratinizing without forming a granular cell layer. The cyst contents are homogenous and commonly calcify. Hybrid cysts with features of both an epidermoid cyst and pilar cyst can be seen.

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Treatment is the same as that for the epidermoid cyst. They are much more easily enucleated, so more limited incision is required to remove the lesion.

Proliferating Trichilemmal Cyst/Malignant Trichilemmal Cyst

There is a spectrum of lesions from typical pilar cysts with focal areas of epithelial proliferation to solid proliferating growths with atypia that are best considered SCCs. They are large (up to 25 cm), exophytic neoplasms confined almost exclusively to the scalp and back of the neck. They are approximately five times more common in women and the mean age of patients is 65 years. They gradually enlarge and may undergo ulceration (Fig. 29-52). The vast majority of lesions are cured by local excision. Some lesions may recur and less commonly be locally aggressive. In rare cases, local invasion or metastases occurs, resulting in death.

Proliferating trichilemmal cysts are composed of proliferations of squamous cells with trichilemmal differentiation forming scroll-like structures or small cysts. Lesions are usually well-circumscribed. Focal cellular atypia, mitoses, and necrosis may be present and do not necessarily predict aggressive behavior. Cases with aggressive growth and metastases usually have cytologic atypia as well as an invasive growth pattern. The presence of a clearly benign component and a second anaplastic component growing outward suggests the development of a carcinoma. Proliferating pilar cysts and their malignant counterparts express hair cytokeratins (cytokeratin 7) and malignant trichilemmal tumors express CD34, suggesting fetal hair root phenotype and trichilemmal differentiation.

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Fig. 29-52 Pilar cyst, proliferating type.

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Dermoid Cyst

Cutaneous dermoid cysts, also called congenital inclusion dermoid cysts, result from local anomalies in embryonic development and occur along embryonic closure zones. On the face they occur above the lateral end of the eyebrow (external angular dermoid) (Fig. 29-53), at the nasal root, along the midline of the forehead, over the mastoid process on the floor of the mouth, and anywhere along the midline of the scalp from the frontal to the occipital region. They may also be found on the chest, back, abdomen, and perianally. Nasal and external angular dermoids may be seen in multiple members of a family, suggesting a genetic component. Lesions usually present within the first year of life, although only 70% of lesions have been identified by age 5 years. The typical lesion is a few millimeters to several centimeters in diameter and located in the subcutaneous fat. A tethering to the underlying tissues and an underlying bony defect may be noted. They are nonpulsatile, firm, and cystic, and do not transilluminate. A punctum or opening to the skin surface may sometimes be present, but they are commonly not attached to the overlying skin. Inflammation of the cyst due to rupture or infection may first bring the patient to the physician. Since the dermoid may connect to underlying structures, including the pleura and CNS, infection may spread to the CNS or lungs, causing potentially serious infections. Patients with spina bifida frequently develop dermoid cysts of the repaired portion of their spinal column. Dermoids overlying the lower spine may be associated with tethered cord and late development of ambulating difficulties.



Fig. 29-53 Dermoid, cystic nodule of the lateral eyebrow.

Histologically, the cyst wall is lined with keratinizing stratified squamous epithelium containing skin appendages, including lanugo hair. Portions of the cyst lining may demonstrate a wavy eosinophilic (shark tooth) pattern like that of a steatocystoma.

In a child, attempts at surgical removal or biopsy of a cyst over cleavage planes (including along the midline of the back) should not be attempted without proper assessment to rule out a potential intracranial communication. A CT scan or magnetic resonance imaging (MRI) is required to rule this out. Any underlying bony changes detected by CT scan should be followed up with an MRI scan, since the cranial penetration by the cyst may at times be difficult to identify by CT scan. If an intracranial connection is detected, the patient should be referred to a neurosurgeon.

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Pilonidal Sinus

Pilonidal cyst or sinus occurs in the midline sacral region at the upper end of the cleft of the buttocks. A pit may be all that is visible before puberty. Pilonidal cysts/sinuses usually become symptomatic during adolescence. The lesion becomes inflamed due to rupture or, less commonly, infection. Pilonidal sinus/cyst often occurs with nodulocystic acne, dissecting cellulitis, and hidradenitis suppurativa (the acne tetrad). Histologically, the cyst/sinus is lined by stratified squamous epithelium of the type seen in normal epidermis or follicular infundibulum. Some pilonidal cysts/sinuses are composed of epithelium which keratinizes without formation of a granular cell layer, analogous to outer root sheath. Referral to a general surgeon is recommended, as recurrences following simple cystectomy and marsupialization. SCCs have been reported to arise from chronic inflammatory pilonidal disease.

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Steatocystoma Simplex

Solitary steatocystoma (simple sebaceous duct cyst, steatocystoma simplex) occurs with equal frequency in adult women and men and can occur on the face, trunk or extremities. The oral mucosa may also be involved. It is not familial, and solitary lesions are much less common than multiple ones. The cysts are usually 0.5 to 1.5 cm in size, although rarely solitary steatocystomas over 8 cm have been reported. The cyst contains an oily, yellow fluid and may contain vellus hairs. Histologically, the cyst is lined by stratified squamous epithelium. Small, mature, sebaceous lobules are present along the cyst wall and empty into the cyst. The luminal surface of the cyst is eosinophilic, wavy (shark tooth pattern), and ribbon-like, analogous to the sebaceous duct. "Hybrid" cysts may have portions of their lining of the steatocystoma type, with the other portions resembling pilar cyst, epidermoid cyst, or even pilomatrixoma. Simple excision is curative.

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Steatocystoma Multiplex

Steatocystoma multiplex consists of multiple, uniform, yellowish, cystic papules 2 to 6 mm in diameter, located principally on the upper anterior portion of the trunk (Fig. 29-54), upper arms, axillae, and thighs. The lesions lack a punctum. Lesions usually appear in adolescence or early adulthood, when sebaceous activity is at its peak. In severe cases, the lesions may be generalized, with sparing only of the palms and soles. At times the lesions may be limited to the face or scalp, a distinct form termed the facial papular variant. Congenital and adolescent onset linear lesions have rarely been reported. Steatocystoma may be larger (up to 2 cm) and prone to rupture and suppuration (steatocystoma multiplex suppurativum). If these lesions are widespread, the condition can be very disfiguring. Steatocystomas contain a syrup-like, yellowish, odorless, oily material. In the suppurative type, as in hidradenitis suppurativa, colonization with bacteria can occur, leading to foul odor and social isolation.

Histologically, the lining of the cyst is stratified squamous epithelium with the cyst lining containing mature sebaceous

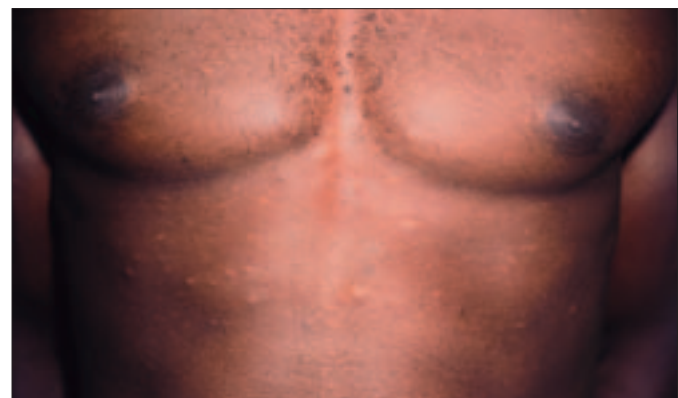


Fig. 29-54 Steatocystoma multiplex.

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glands. The epithelial lining is identical to the sebaceous duct. In some instances, hair follicles occur in the cyst wall and vellus hairs may be present in the cavity. A relationship with eruptive vellus hair cysts has been suggested because of a similar clinical appearance, time of onset, and overlapping histologic features. It has been proposed that these clinical entities are a spectrum of the same disease process and should be classified as multiple pilosebaceous cysts.

Steatocystoma multiplex is often familial, demonstrating an autosomal-dominant mode of inheritance. Sporadic cases are not uncommon, however. Keratin 17 missense mutations occur in familial (but not sporadic) steatocystoma multiplex, usually in a hypermutable site of exon 1 of the gene (the helix initiation motif). Keratin 17 is specialization keratin expressed in the nailbed, hair follicles, and sebaceous glands. This same genetic mutation also causes pachyonychia congenita type 2 (PC-2). This form of pachyonychia congenita has milder keratoderma, but also natal teeth, pili torti, angular chelosis, and hoarseness. These patients have multiple cysts, some of which are steatocystomas and some eruptive vellus hair cysts. Milia, flexural abscesses identical to hidradenitis, and scrotal and vulvar cysts can also be seen in these kindreds. Hybrid cysts may occur. It is unclear why patients with hereditary steatocystoma multiplex and keratin 17 mutations identical to those seen in PC-2 have no other stigmata of PC-2.

The definitive treatment of individual lesions is excision. However, the sheer number of the cysts usually precludes this type of treatment. In such instances, incision and through expression of the cyst contents or aspiration using an 18-gauge needle may be effective in temporarily reducing the lesions. Laser incision of the cysts may also be effective. They may remain clinically improved for many months; however, eventual recurrence is the rule. For inflammatory and non-inflammatory lesions, cryotherapy has been reported as beneficial. Isotretinoin orally at a dose of 0.75 to 1 mg/kg has been reported to benefit the suppurative variant of steatocystoma. Long-term follow-up has not been reported.

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Eruptive Vellus Hair Cysts

Eruptive vellus hair cysts (EVHCs) appear as multiple (up to hundreds) of 1- to 4-mm skin-colored or hyperpigmented dome-shaped papules of the mid-chest and proximal upper extremities. They may be congenital but usually have their onset between ages 17 and 24. Disseminated lesions have been reported. Hidrotic and anhidrotic ectodermal dysplasia have been associated with EVHC. As noted above, there is debate as to whether steatocystoma multiplex and EVHC are distinct entities. Clinically, EVHCs tend to be smaller than steatocystomas and may have an area of central hyperkeratosis or umbilication, a feature lacking in steatocystoma. Histologically, the cystic epithelium is of the stratified squamous type; the cyst contents are composed of laminated keratin and multiple vellus hairs, and follicle-like invaginations may be present in the cyst wall. Treatment is surgical, with laser or needle evacuation.

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Milia

Milia are white keratinous cysts, 1 to 4 mm in diameter, appearing chiefly on the face, especially on the eyelids. They are white and easily seen as cystic through the overlying attenuated skin. Multiple lesions are common, especially in middle-aged women. They occur in up to 50% of newborns.

Primary milia develop without a predisposing condition and are most commonly found in adults or during the newborn period. Secondary milia can develop as a consequence of blistering skin diseases, such as epidermolysis bullosa, pemphigus, bullous pemphigoid, porphyria cutanea tarda, herpes zoster, and contact dermatitis. They also tend to occur after trauma, such as dermabrasion. Long-term topical corticosteroid therapy and the use of occlusive moisturizers may result in the appearance of milia.

Multiple milia have been reported in a number of genodermatoses, such as congenital ectodermal defect; reticular pigmented genodermatosis with milia (Naegeli-Franceschetti-Jadassohn syndrome); congenital absence of dermal ridges,



Fig. 29-55 Milia en plaque.

syndactyly, and facial milia; Rombo syndrome; and Bazex syndrome.

Idiopathic multiple eruptive milia describes the appearance of multiple widespread milia over weeks to months. Rare familial cases have been reported. The etiology of this condition is unknown. Milia en plaque presents with grouped milia forming a plaque. It can affect the face (especially the periauricular area) (Fig. 29-55), trunk, or extremities. Milia en plaque has been reported in association with pseudoxanthoma elasticum, renal failure and chronic cutaneous lupus erythematosus. The cause of Milia en plaque is unknown.

Primary milia are small epidermoid cysts, derived from the infundibulum of the vellus hair. Like epidermoid cysts, they are fixed and persistent. Secondary milia may be derived from eccrine ducts or hair follicles as they attempt to re-epithelialize eroded epidermis. They are often transient and spontaneously disappear. Milia must be distinguished from milia-like idiopathic calcinosis cutis, military osteomas, syringomas with milia-like structures, trichoepitheliomas, comedonal acne, flat warts, and xanthelasma. Lesions of cutaneous T-cell lymphoma with prominent follicular mucinosis may have many milia. Milia can occur on the nasal crease in preadolescent children with allergic rhinitis who frequently rub their noses. These milia may rupture and simulate acne vulgaris. This has been termed "*pseudoacne of the nasal crease*."

Treatment is incision and expression of the contents with a beveled cutting tipped hypodermic needle, 11 blade, or comedo extractor. No anesthesia is needed for most patients. Topical tretinoin (Retin-A) has been reported as effective in treating milia en plaque and more generalized forms of milia involving the face. Minocycline has been used to treat milia en plaque.

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Verrucous Cysts (Cystic Papillomas)

Verrucous cysts resemble epidermoid cysts, except that the lining demonstrates papillomatosis and coarse hypergranulosis. Koilocytes may be present. On the sole, red granules resembling those in myrmecia are commonly seen. They have been shown to contain HPV and probably form as a result of HPV infection of a follicular unit or sweat duct (see Chapter 19).

Pseudocyst of the Auricle (Auricular Endochondral Pseudocyst)

Pseudocyst of the auricle clinically presents as a fluctuant, tense, noninflammatory swelling on the upper half of the ear. Most affected persons are between the ages of 20 and 45 and up to 90% are male. While it may be associated with trauma, especially rubbing due to pruritus, patients frequently deny trauma. Microtrauma or an embryologic defect in the cartilage may play a role. The fluid collection is between the two layers of the bilaminar cartilage of the pinna. There is no cyst lining, with the affected cartilage showing focal degeneration and granulation tissue. Needle aspiration yields serous or bloody fluid. Simple aspiration is ineffective. Aspiration or drainage followed by the application of a bolster or pressure dressing for several weeks is usually effective. Since application of pressure for several weeks is required, a sutured-on bolster with buttons or gauze is easier for the patient than an externally applied dressing. Intracystic injections of corticosteroids, fibrin glue, or minocycline have been used in recurrent cases. Surgical intervention involves removal of the thinner anterior portion of the cyst.

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Cutaneous Columnar Cysts

Five types of cysts that occur in the skin are lined by columnar epithelium. *Bronchogenic cysts* are small, solitary cysts or sinuses, most typically located in the region of the suprasternal notch or over the manubrium sterni. They also can occur on the chin, neck, shoulder region, and abdominal wall. Boys are four times more commonly affected than girls. Lesions are typically subcutaneous and rarely connect to deeper structures. Histologically, the cyst is composed of a wall lined by respiratory epithelium and may contain seromucinous glands and underlying fibromuscular connective tissue or cartilage.

Branchial cleft cysts present as cysts, sinuses, or skin tags along the anterior border of the sternocleidomastoid muscle or near the angle of the mandible (Fig. 29-56). Branchial cysts

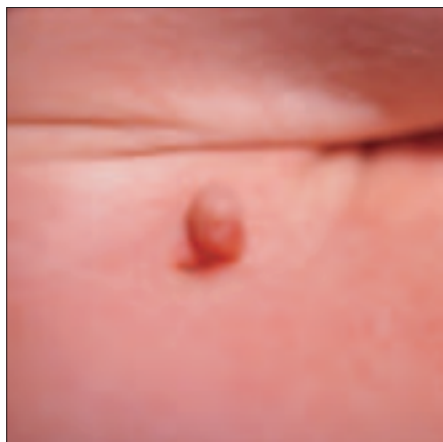


Fig. 29-56 Branchial cleft cyst.

are lined primarily with stratified squamous epithelium. Lymphoid follicles are often present and smooth muscle is absent, distinguishing them from bronchogenic cysts, although some evidence suggests that these cysts are related.

Thyroglossal duct cysts virtually always occur on the anterior portion of the neck, near the hyoid bone. They present as a sinus, cyst, or recurrent abscess of the neck. They are the most common cause of congenital neck anomalies in childhood. Presentation in adult life can occur. Malignancies (papillary adenocarcinoma, follicular adenocarcinoma, mixed papillary/follicular adenocarcinoma, adenocarcinoma, and SCCs) arising from cysts have been reported in 1% of cases. Clinically, thyroglossal duct cysts are deep to subcutaneous tissue and usually are not managed by dermatologists.

Cutaneous ciliated cysts are usually solitary and located on the legs of females. Men account for only 10% of cases. They have also been described in the perineum and vulva (vulvar ciliated cysts). The epithelium lining the cysts is cuboidal to columnar with pseudostratified areas. Cilia are seen and the lining cells stain strongly for dynein. This histology is similar to the normal fallopian tube, suggesting the cysts are of müllerian origin. Ciliated metaplasia of eccrine duct has been proposed for those lesions occurring on the upper half of the body and in men. Like the median raphe cyst, the cavity is often filled with debris.

Median raphe cysts of the penis are developmental defects lying in the ventral midline of the perineum from the anus to the urethra, but most commonly on the distal shaft near the glans. They most commonly present as less than 1-cm dermal lesions in young men and may appear suddenly after sexual intercourse-associated trauma. These cysts are lined by pseudostratified columnar epithelium with focal areas of mucin secreting epithelium present. Ciliated cells may be present and, like ciliated cysts in females, the cavity is typically filled with debris. Melanocytes may occasionally be present in the cyst wall giving the cysts a pigmented appearance. Median raphe cysts do not stain with human milk fat globulin 1, distinguishing them from apocrine cystadenomas. All these forms of cysts are treated with surgical excision.

CONGENITAL PREAURICULAR FISTULA

This anomaly occurs as a pit in the preauricular region, often in several members and generations of a family. On each side, just anterior to the external ear, there is a small dimple, pore, or fistulous opening that may extend even into the middle ear. Most are benign and do not require surgery. Complications of surgery are frequent, and complete excision of both the pit and sinus tract should be the goal if surgery is attempted.

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