Detection and Diagnosis of Skin Cancer

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Although people have become increasingly conscious of cancer through the mass media, some physicians still forget to include in the routine physical a careful examination of the skin. This is unfortunate for several reasons: (1) cancers may go unnoticed until extensive radical treatment is required and may then be only palliative; and (2) the cure frequencies for patients with skin tumors, although quite high, could be higher if more lesions were diagnosed in their early stages.[1]

After a brief discussion of factors influencing the development of skin cancer, we will turn to a description of common types of precancerous and cancerous lesions, as well as other common skin tumors important in the differential diagnosis.

Factors Influencing the Development of Skin Cancer

Skin cancers develop on exposed skin much more often than on unexposed skin, a fact plainly evident in the South and Southwest where sunlight is more intense and actinic damage more severe.

Epidemiologic studies have convincingly demonstrated that sunlight is a major factor in skin cancer, confirmed for example, by the rare occurrence of skin cancer in Negroes and other dark-skinned people whose abundant quantities of melanin give them natural protection against harmful solar rays.[2] There is a direct correlation between the total amount of ultraviolet exposure and the degree of skin damage and ultimate number of skin cancers.[3]

Most adult men who live in the South and Southwest have a sharp line of demarcation between exposed and unexposed skin, such as at the collar line and wrists. This line becomes more noticeable with age and continued exposure. Most women are spared severe damage because they wear make-up regularly and avoid exposing themselves to the intense midday sun.

In a histologic study with human volunteers, actinic degeneration of the dermis was more severe in older individuals; in those who had been exposed to sunlight excessively; and on areas of skin receiving the most exposure.[4] Surprisingly, actinic degeneration of collagen was evident and occasionally severe in young adults in their 20's. Rete ridges of epidermis from exposed regions were effaced even in young Caucasian adults, whereas no such effacement was seen on covered areas of Caucasians and Negroes or even on exposed areas of Negroes. Although we did not find a significant correlation between complexion and degeneration, such a correlation has been observed by others.

After determining micrometrically

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the depth of sebaceous glands, it was apparent these glands were more superficial in actinically damaged skin. This indicated thinning of the damaged portion of the dermis. Chronic sun damage is associated with degradation of collagen, increased elastic staining and mucopolysaccharides.[5,6] When exposed, actinically damaged skin was transplanted to an unexposed site in the same individual, collagen degenerated and elastosis regressed during 9 months of observation.

The ultraviolet wave lengths between 2,900 and 3,200 A° are the injurious ones. Fortunately, the atmosphere's ozone layer removes many of these wave lengths, and moisture and dust particles scatter ultraviolet light.[7] Noonday sun traverses the thinnest layer of atmosphere and is filtered the least. When the sun's angle is low, e.g., during winter, dawn or dusk, its filtering effects are exaggerated since a greater thickness of atmosphere must be traversed.

Urbach recently amplified these findings, using a solid chemical dosimeter to demonstrate the distribution of natural sunlight radiation under varying atmospheric and environmental conditions.[8] Ultraviolet light measured by this technique is received in one of several ways: directly from the sun, indirectly after being scattered by atmospheric particles, or indirectly by reflection from nearby objects.

Each type of irradiation is distributed differently on the skin's surface. Direct irradiation received as parallel rays is most intense on the cheeks, nose, forehead, lower lip, and rim of the ear, with some variation depending on the angle of the sun. Scattered rays fall on the skin's surface from many directions with more uniform distribution and without "hot spots." The distribution of rays reflected from the side or from below varies greatly with the nature of the reflecting surface, but usually it is in a diffuse manner over most exposed areas and some ordinarily protected areas, such as eyelids and undersurfaces of chin, nose, upper lip, and ears. Sand and shiny metal surfaces are very efficient reflecting surfaces but, contrary to popular notion, water is not highly reflective.

These factors apply to squamous and probably to basal type cancers, although their role in melanomas is uncertain.

Many environmental and physical factors influence the quantity of ultraviolet light reaching the earth and the biologic effect of that light. Studies have shown that latitude is important because skin cancers are more common at latitudes near the equator.[2,7,9] In El Paso, Texas, the sun's rays are more direct, undergo less filtration by the atmosphere, and are more intense for longer periods of each year than in a more temperate climate, for example, in New England.

Why frequency of skin cancers varies with the same latitudes is not yet fully understood. However, results of a recent experimental study showed that heat enhances ultraviolet damage.[10] Albino mice heated and then exposed to ultraviolet light were burned more severely than other mice cooled and irradiated. Mice subjected to continuous ultraviolet exposure died more rapidly at 90°F. than at 70°F., and less rapidly at 50°F. Mice kept continuously at 90°F. and given small daily exposures of ultraviolet light developed squamous cell carcinomas of the skin more rapidly and more frequently than mice which were kept at 70°F. and given identical ultraviolet exposures.

While the outcome of this animal experiment cannot be applied directly to man, it is interesting that the temperature of an adult Caucasian's skin rises 10°F. within 3 minutes after he moves from a 70°F. office to the 90°F. summer outdoors. Thus, a significant change in skin temperature occurs with a change

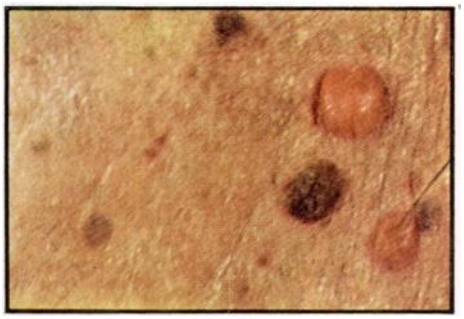

Fig. 1. Two pigmented nevi and several seborrheic keratoses. The nevi are smooth, raised and flesh-colored in contrast to the darkly pigmented and rough keratoses.

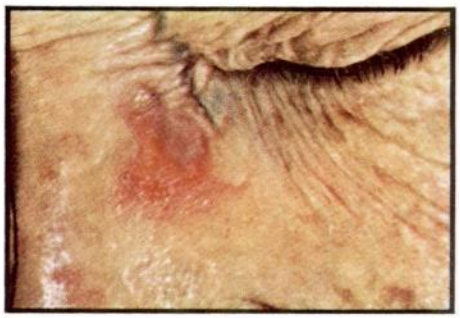

Fig. 4. Red crusted area on side of nose represents moderately well-developed actinic keratosis.

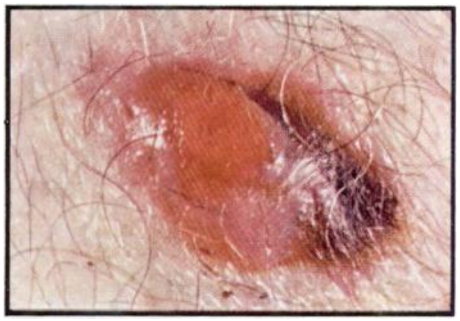

Fig. 2. Nonpigmented melanoma arising from pre-existing pigmented nevus. Ulceration and erythema have developed.

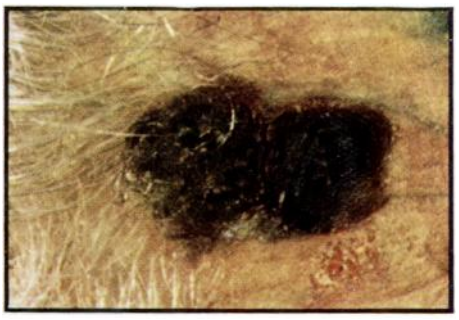

Fig. 3. Deeply pigmented seborrheic keratosis may be mistaken for a mole or melanoma.

in environmental temperature. Similar studies are in progress to evaluate the effect of wind velocity and humidity.

Nevi and Malignant Melanomas

Nevi are the most prevalent of all skin tumors, young adults having an average of 40.[11] They vary from light yellow to chocolate brown or even bluish black. They may be as small as a pinhead or larger than the palm of the hand. Some are raised, smooth and pedunculated; others are verrucous and covered with a greasy scale, resembling seborrheic keratoses. (Fig. 1.)

The most common type of nevus is soft, slightly elevated, and moderately pigmented. It is usually found on the face, neck, trunk, thighs, buttocks or external genitalia. Nevi on the palms or soles and those between the fingers or toes are usually flat and conform with the concept of the junction nevus.

According to one school of thought, most malignant melanomas originate *de novo* with no pre-existing nevus.[12] About 25% of melanomas are known to develop from benign nevi, usually from nevi manifesting junctional activity. Some investigators believe that pregnancy stimulates the rate of growth and adds to the poor prognosis, but recent reports tend to negate this concept.[13]

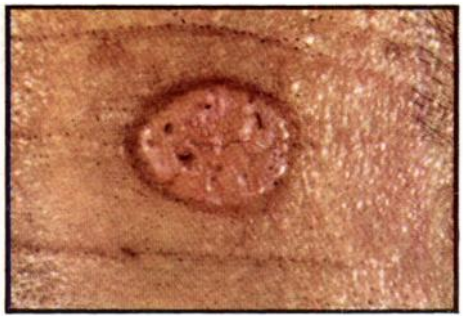

Fig. 5. This basal cell epithelioma has a typically rounded and translucent border and telangiectasia.

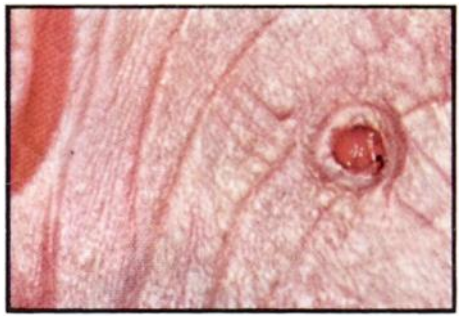

Fig. 6. Squamous cell carcinoma with elevated border. Crust has been removed, revealing a red, granular ulcer.

The appearance of malignant melanomas varies greatly, and their frequent resemblance to other skin tumors often leads to delay in recognition. A melanoma may be macular, papular or nodular and is usually pigmented, smooth, and non-hairy. The full extent of spread may not be detectable by ordinary inspection, and in its early stages it may superficially resemble other lesions. In late stages, superficial ulceration as well as crust formation may occur.

Physicians who have a particular interest in nevi or special training in recognizing skin lesions, can with a high degree of accuracy differentiate between benign nevi and malignant melanomas.[14] To substantiate this statement, records for the past 5 years at Baylor were reviewed. During this period, more than 3,000 benign nevi and 46 malignant melanomas were sent to the laboratory for study. The clinical diagnosis submitted with the specimen was accurate in 97% of the cases. The most common diagnostic error was that of classifying a benign tumor as a possible malignant melanoma. Such an error is justified.

It would be impractical to remove all nevi routinely; however, there are 3 basic indications for removal. The fore-

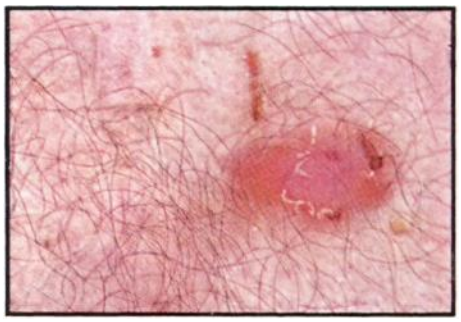

Fig. 7. Lesion of Bowen's disease must be differentiated from eczema. superficial basal cell epithelioma and Paget's disease.

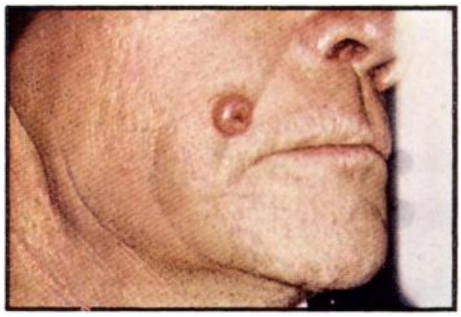

Fig. 8. Keratoacanthoma which developed in two months, has typically rounded edges and keratin-filled crater.

most reason is the development of signs or symptoms suggesting cancer. Next is the potentiality of the nevus for developing into a malignant melanoma because of type, location, or growth rate. Last is the patient's desire to improve his appearance.

There are several indications that a nevus is malignant or potentially so: (1) increase in pigment or size; (2) radical extension or peripheral halo of pigmentation; (3) ulceration (Fig. 2); (4) hemorrhage or serous exudation; and (5) local satellite nodules.[15]

When no signs suggest cancer, how can the physician determine which nevi should be removed for prophylactic reasons? Such decisions are not always easily made. In general, lesions at sites of trauma, nevi of the nail beds, and unusual or atypical nevi are considered for prophylactic removal. Nevi of the hands and feet are not thought as ominous as they once were; yet they still deserve special attention.[16]

Histopathologic examination of all removed nevi protects both patient and physician. The literature contains no proven examples of an inadequately removed, histologically benign nevus developing into a malignant melanoma.[17] Lesions incompletely removed and later identified as malignant melanomas almost certainly were malignant from the beginning. Nevi occurring after incomplete removal do not manifest junctional activity unless this activity were present at the time of removal.

Seborrheic Keratoses

These common and benign lesions are circular, brown, flat, or heaped-up masses of thick, folded epithelium productive of greasy flaking. They are set upon the skin rather than in it, looking something like pigmented moles. (Fig. 3.) Most are 1 to 2 cm. in diameter but their sizes range from a few millimeters to several centimeters or more. Their pigmentation ranges from pale tan to black. The base is usually wide but may be constricted to form a pedicle. They may be located anywhere on the head, neck, trunk, or extremities, but not on the palms, soles, or mucous membranes. Great numbers of them are often seen on the upper trunk, front and back, or beneath pendulous breasts. Seborrheic keratoses are asymptomatic although they may be irritated by trauma, etc. Patients complain mainly of their unsightliness or of the possibility of cancer.

These lesions do not disappear spontaneously. They slowly increase in size and number, behaving as if perhaps inoculable. The cause is unknown. Old people tend to have many, young people few. They are epidermal lesions, the dermal papillae elongated into the epithelial folds.

Seborrheic keratoses do not become cancerous, although occasionally they resemble a skin cancer. Since they are seen in older people who frequently have skin cancers, their differentiation from cancer may be troublesome clinically. The decision of removing these lesions depends largely on the desire of the patients. For a more complete description of these lesions, see Sutton's handbook, "The Skin."[18]

Premalignant Keratoses

Of the premalignant keratoses, the actinic (solar or senile) type is the most common. It appears as a scaly, dry, often erythematous, irregular area on an area of aged, wrinkled, and actinically damaged exposed skin. (Fig. 4.) Larger, thicker and more infiltrative lesions are usually the most advanced microscopically, although ulceration, infection, hyper-keratosis and other secondary changes may be misleading. Some of these lesions remain quiescent and noninvasive for years and may even fade. Approximately 20% eventually invade the dermis as squamous cell carcinomas.

Actinic keratoses develop almost exclusively on areas of the body repeatedly exposed to sunlight: the face, neck, ears, hands, and arms. The incidence is proportional to the total amount of exposure, and inversely proportional to the degree of cutaneous pigment. Therefore, the fair-skinned person working out-of-doors in a region of intense sunshine is more likely to develop these lesions.

Histologically, an actinic keratosis is a squamous carcinoma, grade ½. In other words, malignant change has occurred but is confined to the epidermis and there is no invasion. Invasion signifies more aggressive behavior and is a sign of overt cancer.[19]

Patients with a predilection for actinic keratoses can protect themselves by avoiding unnecessary exposure to sunlight and by using clothing and sunscreens. A broad-brimmed hat and long-sleeved garments should be worn. Excellent sun-screens are 10% para-aminobenzoic acid in vanishing cream (Dermovan®), or a 10% benzophenone cream or lotion. Red veterinary petrolatum is also effective, although less acceptable cosmetically.

Leukoplakia

Leukoplakia, which by definition is limited to mucous membranes, is closely related to actinic keratosis. Early lesions may occasionally be cured by simple measures. Tobacco in all forms should be discontinued. All pathologic conditions of the teeth and mouth should be corrected. Dental hygiene must be excellent. Any source of irritation, including strong tooth paste and mouth rinses, should be eliminated. Vitamin A (Vi-Dom-A® buccal tablets 75,000 to 150,000 units daily) may be helpful. When the lips are involved, dryness can be avoided by using A-Fil® sunstick or other sun-screen agent such as red veterinary petrolatum. Lipstick also provides good protection.

Advanced leukoplakia requires more vigorous treatment. Carcinoma frequently develops and carries a serious prognosis. All measures recommended for early lesions should be instituted. If there is erosion, ulceration, fissuring or pronounced thickening in any of the involved sites, a biopsy is indicated to rule out actual cancer.

Basal Cell Epithelioma

Basal cell epitheliomas occur almost exclusively on hair-bearing skin; seldom are they found on the palms or soles. The face is by far the most common site. The mucous membranes are never affected. Although basal cell epithelioma usually develops as a single lesion, multiple lesions are not infrequently observed.

Clinically, there are 6 types of basal cell epitheliomas:

Nodulo-ulcerative basal cell epithelioma is the most common type. (Fig. 5.) It appears first as a small waxy nodule, often with a few telangiectatic vessels on its surface. The nodule increases slowly in size and undergoes central ulceration. A typical lesion then consists of a slowly enlarging ulcer surrounded by a pearly, rolled border. This represents the rodent ulcer.

Pigmented basal cell epithelioma differs from the nodulo-ulcerative type only by the dark pigmentation of the lesion.

Morphea-like or *fibrosing basal cell epithelioma* manifests itself as a slightly elevated, firm, yellowish plaque with an ill-defined border, over which the skin remains intact for a long period of time. Finally, ulceration occurs.

Superficial basal cell epithelioma consists of one or several erythematous, scaling, slightly infiltrated patches surrounded by a fine, thread-like pearly border. The patches usually have small areas of superficial ulcer-

ation and crusting. Their centers may have smooth, atropic scarring.

Premalignant fibroepithelioma (Pinkus) consists of one or several raised, flat, moderately firm, often slightly pedunculated nodules with a pale red smooth surface. Clinically they resemble fibromas. The most common location is the trunk. Occasionally they undergo ulceration.

Basal cell nevi begin developing in childhood or puberty. New lesions continue to appear during adult life, accumulating to the hundreds. The lesions consist of elevated firm smooth nodules which are either the color of normal skin or slightly pigmented. Some of the nodules increase gradually in size and eventually may ulcerate. Basal cell nevi may be associated with various congenital anomalies—such as jaw cysts, bifid rib, agenesis of the corpus callosum or scoliosis, etc.

Basal cell epitheliomas can develop after the prolonged administration of inorganic arsenic, and they can arise in areas of radiodermatitis. Furthermore, as with squamous cell carcinomas, basal cell epitheliomas of the face occur much more frequently in areas of the world with much sunshine. As a rule, these lesions do not metastasize.

Usually it is not difficult to differentiate clinically basal from squamous cell carcinomas but sometimes it is impossible. Biopsy material should be submitted to a pathologist for definitive diagnosis. Although the histologic differentiation between basal cell epithelioma and squamous cell carcinoma is usually clear cut, at times it is so difficult that many authors have decided that intermediary forms occur (basal-squamous cell epithelioma). The cells of basal cell epithelioma stain deeply basophilic, and palisading about the periphery of tumor is characteristic, whereas most cells of squamous cell carcinoma have an eosinophilic tint which is due to partial or near complete keratinization.

A complete histopathologic description of basal cell epitheliomas and squamous cell carcinomas can be found in Lever's "Histopathology of the Skin."[20]

Squamous Cell Carcinoma

Squamous cell carcinoma, a true invasive carcinoma, may develop anywhere on the skin or on mucous membranes. It may begin as such or develop from a precancerous condition such as actinic keratosis or leukoplakia. Most commonly, the lesion consists of a shallow ulcer surrounded by a wide, elevated and indurated border. (Fig. 6.) Often the ulcer is covered by a crust that conceals a red, granular base. Occasionally, raised, fungoid, verrucous lesions without ulceration occur. These usually are of a low grade of malignancy, whereas ulcerated lesions may grow more rapidly and metastasize within a short time.

Histologic examination reveals irregular masses of epidermal cells which proliferate downward and invade the dermis. These invading masses are composed in varying proportions of differentiated squamous cells and of dedifferentiated (anaplastic, atypical) squamous cells. The more malignant the tumor, the greater the number of atypical squamous cells. Atypicality of squamous cells expresses itself in such changes as great variation in the size and shape of the cells, hyperplasia and hyperchromasia of the nuclei, absence of prickles, keratinization of individual cells, prevalence of mitotic figures, and presence of atypical mitotic figures.

Differentiation in squamous cell carcinoma is in the direction of keratinization. Keratinization often takes place in the form of horn pearls, very characteristic structures composed of concentric layers of squamous cells showing gradually increasing keratinization toward the center. The center may or may not

show complete keratinization. Single cells also may keratinize.

The diagnosis of squamous cell carcinoma, although easily made in atypical cases, may be difficult at times. It must be differentiated from senile keratosis, pseudocarcinomatous hyperplasia and basal cell epithelioma.

The difference between squamous cell carcinoma and senile keratosis is in the degree of changes rather than in the type of changes. In both conditions one finds atypicality of the cells with dyskeratosis of individual cells and downward proliferation of the epidermis. However, in squamous cell carcinoma these changes are more advanced. Yet, no sharp line of separation exists between the two conditions. In lesions resembling actinic keratosis, serial sections often reveal one or several areas in which the changes have progressed to squamous cell carcinoma.

In differentiating squamous cell carcinoma from pseudocarcinomatous hyperplasia, clinical data may be necessary. The considerable thickening and irregular proliferation of the skin which clinically and histologically resembles carcinoma occur not infrequently in chronic granulomas, such as bromoderma, blastomycosis and granuloma inguinale; at the edges of chronic ulcers, such as develop after burns; in stasis dermatitis; decubitus ulcers; basal cell epithelioma; lupus vulgaris; scrofuloderma: gumma and pyoderma gangrenosum. To compound the difficulty in the differential diagnosis, actual carcinoma can develop in these chronic ulcerating disease processes.

A complete description of squamous cell carcinomas is in Lever's textbook.[20]

Bowen's Disease

Bowen's disease is an intra-epidermal squamous cell carcinoma, or a squamous cell carcinoma in situ, not a "precancerous dermatosis," the title used by Bowen in his original description.

It usually manifests itself as a single lesion, and is characterized by a dull-red to brownish-red patch of sharp but irregular outline, showing little or no infiltration. (Fig. 7.) Within the patch are areas of crusting, beneath which may be a granular and oozing surface. The patch spreads slowly by peripheral extension and shows no tendency to heal in its center.

The epidermis shows hyperkeratosis with parakeratosis and acanthosis. The rete ridges are elongated and thickened, often to such a degree that papillae located between them are reduced to thin strands or are obliterated. However, the basal layer is intact, and no true invasion can be seen. Throughout the stratum malpighii, the cells lie in complete disorder. Many of them are atypical showing large and hyperchromatic nuclei.

The upper dermis usually shows a moderate amount of inflammatory infiltration composed chiefly of lymphocytes and plasma cells. In true Bowen's disease the basal layer is intact. However, the basal layer is ultimately broken through and an invasive squamous cell carcinoma results. At first, this may happen in only one or a few areas. In order not to miss such areas, representative sections should be examined throughout the entire tissue block, giving particular attention to nodules or areas of erosion.

As long as Bowen's disease remains in the true, intra-epidermal stage, metastases do not occur. However, when invasion of the dermis has taken place, metastasis becomes likely. This is due to the fact that if Bowen's disease changes into an invasive carcinoma, it usually is Grade 2, or even Grade 3, with atypicality of the cells and little tendency to keratinization.

In the differential diagnosis, senile keratosis and arsenical keratosis must be considered. Because the bowenoid type of senile keratosis has the same

histological picture as Bowen's disease, differentiation both clinically and histologically may be difficult, if not impossible. Arsenical keratosis may closely resemble Bowen's disease or senile keratosis, but usually shows more vacuolization of the squamous cells than these two diseases.[21]

Paget's Disease

Paget's disease of the nipples develops usually in women only. The lesion is always unilateral. Extramammary Paget's disease, which is uncommon, occurs on or near the male and the female genitals, in the perianal region and in the axillae.

The lesion of Paget's disease consists of a sharply defined, slightly infiltrated area of dusky erythema showing scaling, oozing and crusting. On the breast, the process begins in the nipple or the areola and slowly extends to the surrounding skin. There may be retraction of the nipple.

It is generally accepted that Paget's disease of the nipple is a cancer from the outset and that the initial lesion is a carcinoma *in situ*, arising in one or more mammary ducts near their outlets. Paget cells from the epidermis do not invade the underlying dermis.

Paget's disease must be differentiated from Bowen's disease and from early malignant melanoma. In Bowen's disease, large, vacuolated epidermal cells also may develop but, in contrast to Paget cells, they often possess prickles. Although the vacuolated cells of Bowen's disease, like Paget cells, may contain PAS-positive material, it is not diastase resistant as in Paget cells. Furthermore, there is in Bowen's disease, but not in Paget's disease, clumping of nuclei within multinucleated epithelial giant cells and individual cell keratinization.

An early superficial malignant melanoma may be difficult to rule out in cases of Paget's disease in which the Paget cells are concentrated in the lower epidermis, since in both diseases the characteristic cells are large and vacuolated. Difficulty in differentiating the two diseases is enhanced by the fact that Paget cells also may contain melanin. The most important points of differentiation are: (1) Paget cells often are separated from the dermis by flattened basal cells, while melanoma cells border directly on the dermis; (2) Paget cells never invade the dermis, while melanoma cells may do so; and (3) Paget cells are PAS-positive, while melanoma cells are not.[22]

Keratoacanthomas

Since these lesions are benign and self-healing, it is important to distinguish them from squamous cell carcinomas to avoid unnecessary treatment. A keratoacanthoma grows rapidly for 4 to 8 weeks, then remains stationary for several weeks. When fully developed, it is usually elevated, 1 to 2 cm. in diameter, and has rounded edges and a central keratin-filled crater. (Fig. 8.) Spontaneous regression ensues, sometimes requiring as long as 4 to 6 months, and leaving a faint, slightly depressed scar. These lesions are usually solitary but may be multiple as well as widespread.

In several large reported series, keratoacanthomas comprised approximately 18% of all squamous type tumors.[23] Although they might be expected to comprise a higher percentage of tumors in northern latitudes where sunlight-induced cancers are infrequent, surveys from different latitudes yield similar ratios of keratoacanthomas to squamous cell carcinomas. This suggests a common etiologic factor—sunlight. Exposure to sunlight is further implicated by the fact that keratoacanthomas usually develop on exposed skin.[24] In one series, 71% of the lesions developed on the face, 19% on the hand

or forearm, the remaining 10% on other areas of the body.[23]

Histologic criteria for the diagnosis of keratoacanthoma are characteristic.[25] A keratin-filled crater with overhanging edges of epidermis is surrounded by acanthotic epithelium with cohesive rounded epithelial masses. The basal cell layer is usually intact.

The degree of dyskeratosis varies in the acanthotic prickle cell layer but true invasion does not occur. A study of lesions by serial sections demonstrates that isolated epithelial nests may simulate invasion but in reality are pseudopods continuous with the main tumor. These distinctive features, when supported by the typical clinical picture, make a diagnosis of keratoacanthoma almost certain.

During the period of rapid growth, atypical pathologic changes may prevent differentiating the lesion from an early squamous cell carcinoma. Epithelial proliferation and dyskeratosis are common features of both tumors. More characteristic of keratoacanthoma are the crater-shaped configuration, cohesiveness of the down-growing epithelial masses, and retention of the basal cell layer. In addition, the dyskeratosis and atypical cellular changes usually are not as pronounced in patients with keratoacanthoma. The histologic picture during regression appears progressively more benign. Eventually the lesion may resemble an epidermal cyst.

While not enough keratoacanthomas of mucous membranes have been observed to know whether they characteristically resemble lesions on the skin, this unique tumor should be considered when confronted with an unusual-appearing mucosal lesion, or with mucosal lesions accompanied by spontaneously involuting skin tumors.

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