Benign Epithelial Tumors

Benign cutaneous epithelial neoplasms are common tumors that are derived from the keratinizing stratified squamous epithelium of the epidermis and hair follicles and the ductular epithelium of cutaneous glands. They often recapitulate the structures from which they arise. Their appearance sometime raises a concern of malignancy, particularly when they are pigmented or inflamed, and biopsy is frequently required to establish a definitive diagnosis. In very rare instances they are a telltale sign of syndromes associated with potentially life-threatening visceral malignancies, such as multiple trichilemmomas in Cowden syndrome or multiple sebaceous neoplasms in Muir-Torre syndrome. Diagnosis of epithelial tumors in these instances may facilitate recognition of the underlying syndrome and implementation of appropriate clinical interventions.

Seborrheic Keratoses

These common epidermal tumors occur most frequently in middle-aged or older individuals. They arise spontaneously and are particularly numerous on the trunk, although the extremities, head, and neck may also be involved. In people of color, multiple small lesions on the face are termed *dermatosis papulosa nigra.*

Pathogenesis. Activating mutations in the fibroblast growth factor receptor-3 (FGFR3), a receptor tyrosine kinase, are found in many sporadic seborrheic keratoses and are thought to drive the growth of the tumor. Seborrheic keratoses may suddenly appear in large numbers as part of a paraneoplastic syndrome *(Leser-Trélat sign)*, possibly due to stimulation of keratinocytes by transforming growth factor-α produced by tumor cells, most commonly carcinomas of the gastrointestinal tract.

MORPHOLOGY

Seborrheic keratoses characteristically appear as round, flat, coinlike, waxy plaques that vary in diameter from millimeters to several centimeters (Fig. 25-9, *inset*). They are uniformly tan to dark brown and usually have a velvety to granular surface. Inspection with a hand lens usually reveals small, round, pore-like ostia impacted with keratin, a feature helpful in differentiating these pigmented lesions from melanomas.

On histologic examination, these neoplasms are exophytic and sharply demarcated from the adjacent epidermis. They are composed of sheets of small cells that most resemble basal cells of the normal epidermis (Fig. 25-9). Variable melanin pigmentation is present within these basaloid cells, accounting for the brown coloration. Exuberant keratin production (hyperkeratosis) occurs at the surface, and small keratin-filled cysts (horn cysts) and invaginations of keratin into the main mass (invagination cysts) are characteristic features. If irritated and inflamed, seborrheic keratoses develop whirling foci of squamous differentiation resembling eddy currents in a stream.

Acanthosis Nigricans

Acanthosis nigricans may be an important cutaneous sign of several underlying benign and malignant conditions. It is a condition marked by thickened, hyperpigmented skin with a "velvet-like" texture that most commonly appears in the flexural areas (axillae, skin folds of the neck, groin, and anogenital regions). It is divided into two types based on the underlying condition.

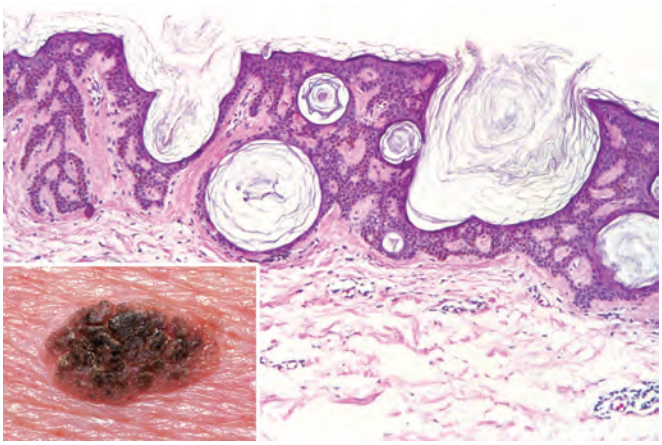

Figure 25-9 Seborrheic keratosis. A well-demarcated coinlike pigmented lesion containing dark keratin-filled surface plugs *(inset)* is composed of benign basaloid cells associated with prominent keratin-filled "horn" cysts, some of which communicate with the surface (pseudohorn cysts).

- In 80% of cases, acanthosis nigricans is associated with benign conditions and develops gradually, usually during childhood or puberty. It may occur (1) as an autosomal dominant trait with variable penetrance, (2) in association with obesity or endocrine abnormalities (particularly with pituitary or pineal tumors and diabetes), and (3) as part of several rare congenital syndromes. The most common associations are with obesity and diabetes.
- In the remaining cases, acanthosis nigricans arises in association with cancers, most commonly *gastrointestinal adenocarcinomas*, usually in middle-aged and older individuals. In this setting, acanthosis nigricans is best viewed as a paraneoplastic phenomenon that is likely caused by growth factors released from tumors.

Pathogenesis. **The unifying feature in all types of acanthosis nigricans is a disturbance that leads to increased growth factor receptor signaling in the skin.** The familial form is associated with germline activating mutations in the receptor tyrosine kinase FGFR3, the same receptor that is frequently mutated in seborrheic keratoses. Depending on the mutation, acanthosis may be an isolated finding or be seen together with skeletal deformities, including achondroplasia and thanatophoric dysplasia. Why in some cases FGFR3 mutation gives rise to seborrhic keratosis and in others acanthosis nigricans is not clear. In those with type 2 diabetes, hyperinsulinemia is believed to provoke increased stimulation of insulin-like growth factor receptor-1 (IGFR1), another receptor tyrosine kinase that activates the same signaling pathways as FGFR3. Factors responsible for paraneoplastic acanthosis nigricans are uncertain; some cases have been linked to high levels of transforming growth factor-alpha (TGF-α), which may result in excessive activation of epidermal growth factor receptor (EGFR), yet another receptor tyrosine kinase, in the skin.