16
Acquired Ichthyosis, Acanthosis Nigricans, and Palmar Hyperkeratosis

■ Synonyms:	AI—Pityriasis rotunda AN—None PH—Tylosis, Howel-Evans syndrome, tripe palms, acrokeratosis of Bazex
■ Etiology:	Unknown
■ Associations:	AI—Lymphoma AN—Gastric carcinoma PH—Esophageal carcinoma
■ Clinical:	AI—Diffuse xerosis AN—Axillary pigmentation PH—Palmar/plantar hyperkeratosis
■ Histology:	AI—Hypogranulosis with hyperkeratosis AN—Acanthosis with hyperkeratosis PH—Acanthosis with hyperkeratosis and hypergranulosis
■ IHC repertoire:	N/A
■ Staging:	N/A
■ Prognosis:	Generally poor, associated with advanced internal malignancy
■ Adverse variables:	Dependent upon underlying malignancy type and stage of disease
■ Treatment:	Dependent upon tumor type and stage

Serious systemic diseases, including visceral cancer, may be indirectly signaled by the development of distinctive cutaneous eruptions. Important aspects of these eruptions include the development of the rash concurrent with the diagnosis of the neoplasm and the fact that the two entities, though individually uncommon, are commonly seen together and pursue a similar clinical course. The more important, albeit uncommon, dermatoses that develop in conjunction with visceral cancer involve disorders of the epithelium and entail alterations in keratinization. This chapter will deal with the clinical and pathologic attributes of acquired ichthyosis, acanthosis nigricans, and paraneoplastic palmar/plantar keratoderma as they relate to underlying malignancy.

Ichthyosis refers to the presence of fish-like (Latin, *ichthus*) or scaly skin. The characteristic clinical appearance is due to an inherited defect in keratinization involving the epithelium that with rare exception represents little more than a lifelong cosmetic nuisance. Acquired ichthyosis, however, referring to the sudden development of scaly dry skin in the adult, may herald the presence of a serious underlying malignancy. The eruption usually develops over the extensor aspects of the extremities and scalp resembling the appearance of the most common autosomal dominant form, *ichthyosis vulgaris* [1]. The rash typically spares the flexural folds. Erythema may be seen between the scaly fissures. The most common underlying malignancy is Hodgkin's lymphoma, occurring in conjunction with an

D.R. Crowe et al. (eds.), *Deadly Dermatologic Diseases*, DOI 10.1007/978-3-319-31566-9_16

estimated 70 % of all cases of acquired ichthyosis with the severity of the rash reflecting the progression of disease [2, 3]. The rash may, however, presage the malignancy by many years. Important systemic illnesses that may also produce or be associated with acquired ichthyosis include malnutrition, HIV disease, hypothyroidism, leprosy, sarcoidosis, lupus erythematosus, dermatomyositis, bone marrow transplant in the setting of graft-versus-host disease, and eosinophilic fascitis and may follow exposure to certain medications such as nicotinic acid, triparanol, butyrophenone, dixyrazine, nafoxidine, clofazimine, and cetrimide [4, 5]. Among HIV-positive individuals, its development may be a marker for concomitant infection by the *human T-cell leukemia/lymphoma virus (HTLV-II)* [6]. In dark-skinned races, the rash may produce sharply demarcated round-to-oval scaly patches termed *pityriasis rotunda* [7]. The histopathology is distinctive and consists of a normally thickened epithelium with compacted hyperkeratosis. The epidermal granular layer is characteristically absent. The altered keratin layer may also extend down the adjacent follicular ostia (acrotrichia). Supportive therapy is directed toward hydration of the skin (bathing, high ambient humidity) and the application of lubricants (creams and ointments). Investigation for the possibility of underlying malignancy, particularly hematologic cancer, with appropriate imaging studies and consideration for bone marrow examination is indicated.

Acanthosis nigricans (AN) is a common cutaneous malady associated with myriad unrelated systemic diseases including underlying cancer [8, 9]. The most common association involves obesity with or without insulin resistance and hyperinsulinemia. In most instances, the eruption begins as gray-black thickening of the flexural areas and, in particular, the axillae (Fig. 16.1). Palpation of the involved areas yields a textural change likened to velvet. The eruption may rarely spread to involve the non-flexural areas and even the oral and anogenital mucosa. Certain demographic groups are overrepresented, including Hispanics and African-Americans. Rare familial tendencies have also been identified, suggestive of an underlying genetic predisposition. The pathogenesis is thought to involve a patterned response of the skin to increased serum levels of trophic epithelial hormones and cytokines, presumably released in conjunction with the underlying endocrinologic or neoplastic dyscrasia. In the setting of hyperinsulinemia and diabetes mellitus, it has been shown that excess binding of insulin to IGF receptors located on keratinocytes and fibroblasts results in increased proliferation. Similarly, increased transforming growth factor (TGF) released by neoplastic cells has been shown to increase keratinocyte proliferation via surface epidermal growth factor receptors. Other important disease associations include *h*yper*a*ndrogen states with *i*nsulin *r*esistance and *a*canthosis *n*igricans (*HAIR-AN syndrome*). Certain medications including nicotinic acid, glucocorticoids, and triazinate and the sex hormones including estrogen have also been implicated in its development. AN associated with underlying malignancy, alternatively referred to as *malignant* AN, is morphologically similar yet characterized by rapid onset and progression [10–13]. It more commonly is associated with keratoderma or rugose-like thickening of the palms in which there is accentuation of the fingerprints, otherwise known as pachydermatoglyphy (or *tripe palm*) [14, 15]. Other important associations include oral involvement and the presence of multiple eruptive seborrheic keratosis (the sign of *Leser-Trelat*) (Fig. 16.2). The most common internal malignancy is visceral adenocarcinoma of the stomach, intestines, or lung. Bladder, renal, and esophageal carcinoma and lymphoma have also been reported. In most instances, the lesions are discovered in conjunction with internal malignancy diagnosis. The eruption, however, may precede or follow diagnosis of internal malignancy. The histopathology yields slight epidermal acanthosis with papillomatosis and hyperkeratosis (Fig. 16.3). Although the basilar layer keratinocytes may show increased amounts of cytoplasmic melanin, the clinical appearance of hyperpigmentation is largely due to the epidermal hyperkeratosis.

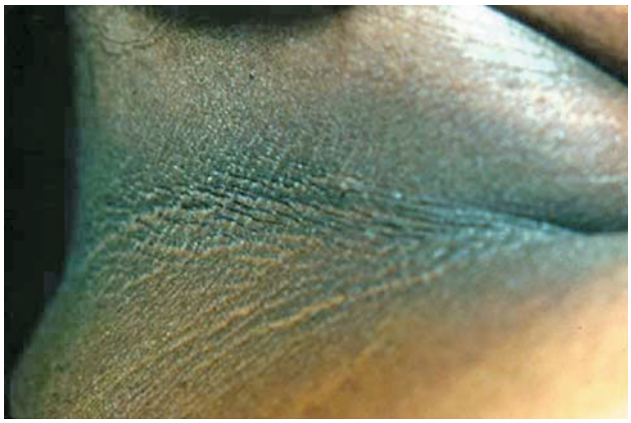

Figure 16.1. Velvety hyperpigmented intertriginous plaque in acanthosis nigricans.

The acquired *palmar/plantar keratodermas* comprise a heterogeneous group of keratinizing disorders characterized by thickening of the palms and soles that in many instances are associated with the development of visceral cancer (Fig. 16.4) [16]. These conditions are distinct from the more common forms of inherited palmoplantar keratoderma that typically manifest in children and are associated with inherited defects in keratinization. The acquired keratodermas can be broadly separated into three categories that involve diffuse thickening, punctate areas of thickening, or additional areas of the non-acral skin. The most well-documented form of diffuse acquired keratoderma was described by Dr. Howel-Evans in 1958 among two kin-

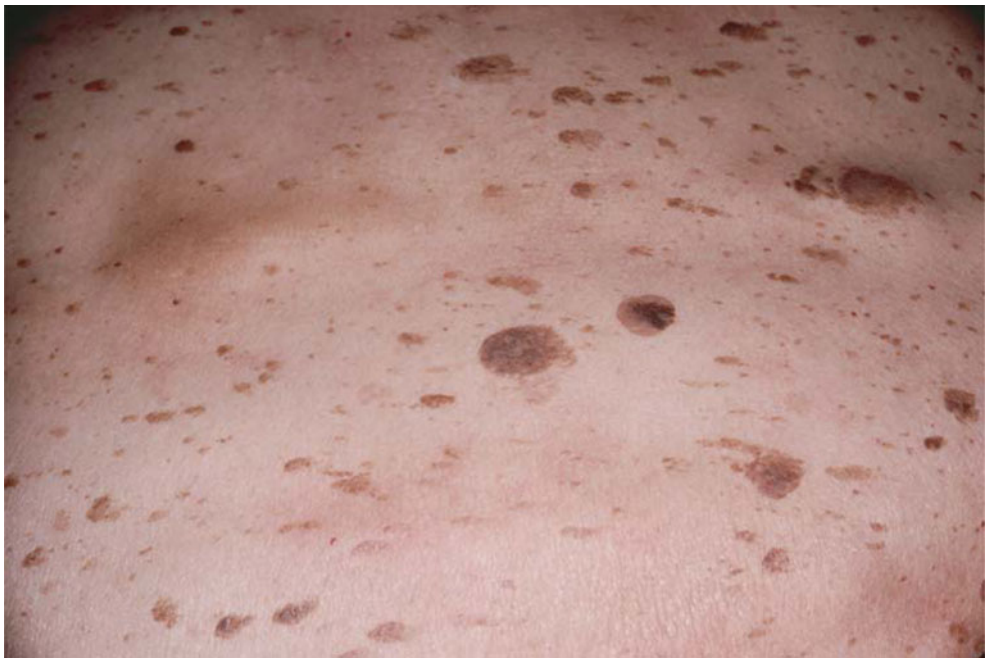

Figure 16.2. Sign of Leser-Trelat. Multiple seborrheic keratosis on the trunk of patient with metastatic colorectal carcinoma.

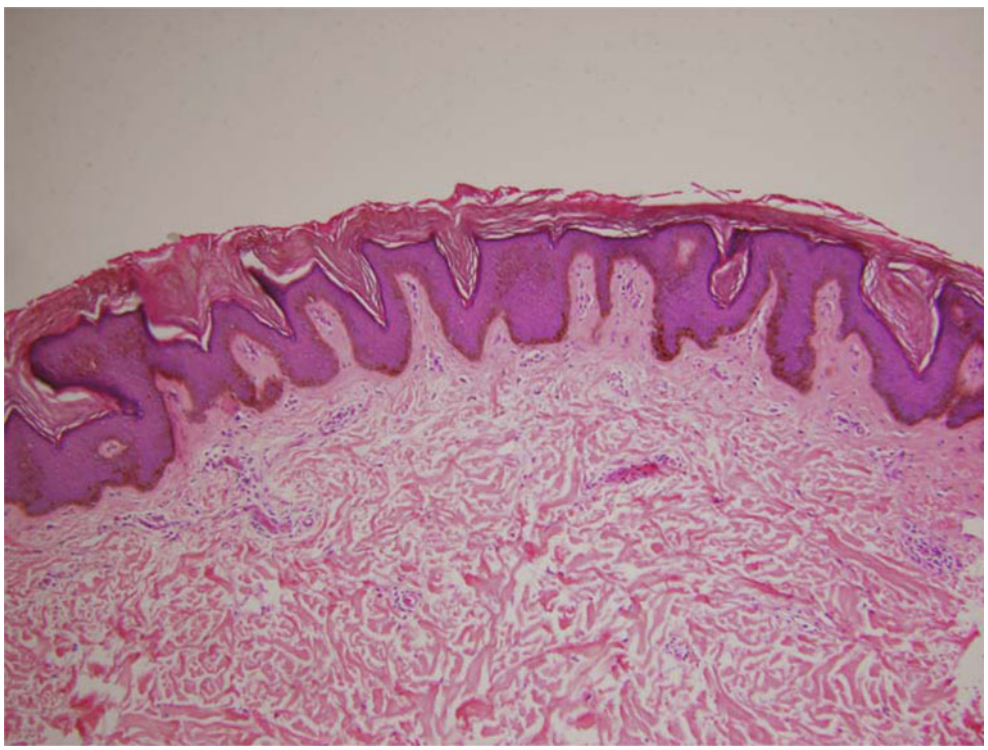

Figure 16.3. Medium-power photomicrograph depicting dome-like epidermal acanthosis with hyperpigmented basilar layer keratinocytes seen in acanthosis nigricans.

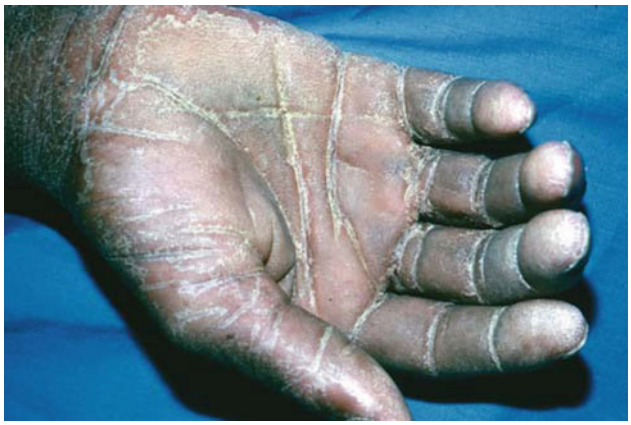

Figure 16.4. Hyperkeratosis of the palmar skin seen in the keratodermas. Note the accentuated palmar creases.

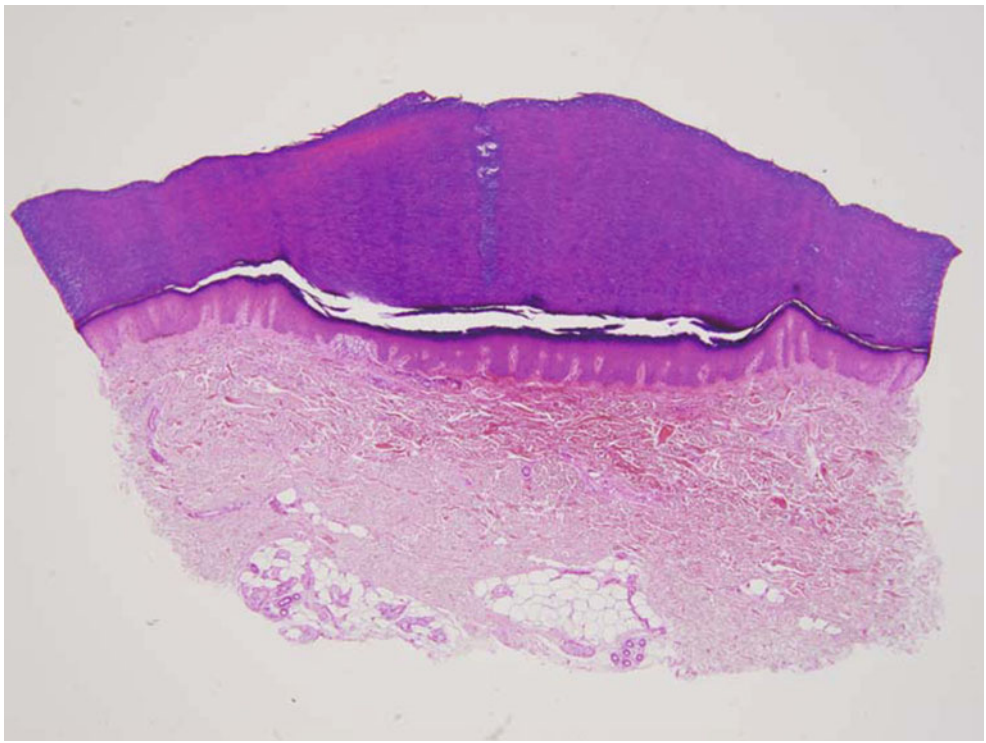

Figure 16.5. Low-power photomicrograph depicting the exaggerated hyperkeratosis with central swelling observed in punctate keratoderma.

dreds afflicted with esophageal carcinoma [17, 18]. This condition, alternatively referred to as *tylosis* or *Howel-Evans* syndrome, involves the development of poorly demarcated and irregular areas of palmar or plantar thickening in children who later develop esophageal carcinoma as adults [19]. The gene responsible for this condition has been linked adjacent to the keratin type I gene cluster (17q24) [20]. The punctate form of acquired keratoderma is associated with the development of breast and gynecologic malignancies. Finally, acquired keratoderma may be associated with an erythematous and psoriasiform dermatitis involving the non-acral skin. Referred to as *acrokeratosis of Bazex,* patients with this entity are typically male and are predisposed to develop carcinoma of the upper and lower aerodigestive tracts [21]. The thickened areas of the palms and soles often appear erythematous or violaceous.

Keratoderma has also been described among patients with hematologic malignancies including multiple myeloma, lymphoma, and mycosis fungoides. Nonneoplastic conditions including myxedema, arsenic exposure, menopause (*keratoderma climactericum*), water exposure (*aquagenic keratoderma*), and following ingestion of certain medications including glucan, tegafur, and fluorouracil have been shown to also produce acquired keratoderma [16]. The diffuse form of keratoderma histologically shows epidermal acanthosis and orthokeratotic hyperkeratosis with occasional epidermolytic hyperkeratosis. The punctate form shows a dense keratin plug of the stratum corneum with underlying depression of the stratum malpighi and adjacent pitting of the stratum corneum (Fig. 16.5). Biopsy changes observed in conjunction with acrokeratosis of Bazex include acanthosis, hyperkeratosis, and exocytosis of lymphocytes with accompanying spongiosis and epidermal dyskeratosis.

References

Acquired ichthyosis

1. Aram H. Acquired ichthyosis and related conditions. Int J Dermatol. 1984;23:458.
2. Patel N, Spencer LA, English III JC, Zirwas MJ. Acquired ichthyosis. J Am Acad Dermatol. 2006;55:647–56.
3. Word AP, Cayce R, Pandya AG. Beware of underlying malignancy: acquired ichthyosis. Am J Med. 2014;127(3):202–4.
4. Dykes P, Marks R. Acquired ichthyosis: multiple causes for an acquired generalized disturbance in desquamation. Br J Dermatol. 1977;97:327.
5. Spleman L, Strutton G, Robertson I, et al. Acquired ichthyosis in bone marrow transplant recipients. J Am Acad Dermatol. 1996;35:17.
6. Kaplan M, Sadick N, McNutt N, et al. Acquired ichthyosis in concomitant HIV-1 and HTLV-11 infection: a new association with intravenous drug abuse. J Am Acad Dermatol. 1993;29:701.
7. Aste N, Pau M, Aste N, et al. Pityriasis rotunda: a survey of 42 cases observed in Sardinia, Italy. Dermatology. 1997;194:32.

Acanthosis nigricans

8. Lee SS, Jung NJ, Im M, Lee Y, Seo YJ, Lee JH. Acral-type malignant acanthosis nigricans associated with gastric adenocarcinoma. Ann Dermatol. 2001;23 Suppl 2:S208–10.
9. Schwartz R. Acanthosis nigricans. J Am Acad Dermatol. 1994;31:1.
10. Phiske MM. An approach to acanthosis nigricans. Indian Dermatol Online J. 2014;5(3):239–49.
11. Andreev V. Malignant acanthosis nigricans. Semin Dermatol. 1984;3:265.
12. Rigel D, Jacobs M. Malignant acanthosis nigricans: a review. J Dermatol Surg Oncol. 1980;6:923.
13. Brown J, Winkelman R. Acanthosis nigricans: a study of 90 cases. Medicine. 1968;47:33.
14. Stawczyk-macieja M, Szczerkowska-dobosz A, Nowicki R, Majewska H, Dubowik M, Sokołowska-wojdyło M. Malignant acanthosis nigricans, florid cutaneous papillomatosis and tripe palms syndrome associated with gastric adenocarcinoma. Postepy Dermatol Alergol. 2014;31(1):56–8.
15. Breathnach S, Wells G. Acanthosis Palmaris: tripe palms. Clin Exp Dermatol. 1980;5:181.

Palmoplantar keratoderma

16. Zemtsov A, Veitschegger M. Keratodermas. Int J Dermatol. 1993;32:493.
17. Howel-Evans W, McConnell R, Clarke C, et al. Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis). Q J Med. 1958;27:413.
18. Marger R, Marger D. Carcinoma of the esophagus and tylosis. A lethal genetic combination. Cancer. 1993;72:17.
19. Ilhan M, Erbaydar T, Akdeniz N, Arslan S. Palmoplantar keratoderma is associated with esophagus squamous cell cancer in Van region of Turkey: a case control study. BMC Cancer. 2005;5:90.
20. Stevens H, Kelsell D, Bryant S, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Arch Dermatol. 1996;132:640.
21. Bazex A, Griffiths A. Acrokeratosis paraneoplastica: a new cutaneous marker of malignancy? Br J Dermatol. 1980;102:301.