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Review article

Cutaneous paraneoplastic syndromes

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ABSTRACT

A variety of cutaneous abnormalities can be seen in patients with malignant diseases, some of which are infectious, with others representing direct involvement of the skin by the underlying disorder. Yet another group of lesions can be regarded as associated markers of the malignant process, and, as such, are termed "paraneoplastic." This review considers the latter collection of conditions, grouping them by the generic type of malignancy that is usually linked to the paraneoplasia. Some of the processes show a predominant association with alimentary tract malignancies (acanthosis nigricans, acrodermatitis paraneoplastica, florid cutaneous papillomatosis, necrolytic migratory erythema, palmoplantar keratoderma, pancreatic fat necrosis, and pityriasis rotunda). Others are usually linked to a hematolymphoid malignancy (acquired ichthyosis, exfoliative erythroderma, necrobiotic xanthogranuloma, pemphigus paraneoplastica, plane xanthoma, pyoderma gangrenosum, scleromyxedema, Sweet syndrome, and leukocytoclastic vasculitis). Finally, yet another collection of paraneoplastic skin disorders can associate themselves with anatomically-diverse malignancies (Leser–Trelat syndrome, Trousseau syndrome, dermatomyositis, erythema gyratum repens, hypertrichosis lanuginosa acquisita, papuloerythroderma of Ofuji, tripe palms, and multicentric reticulohistiocytosis). Recognition of these processes by the pathologist can be a valuable step in the characterization of underlying malignant diseases.

The word "paraneoplastic" is derived from the Greek roots *para*, meaning "to, at, or from the side of,' *neo*, meaning "new," and *plasma*, meaning "formation," and it is used to refer to changes in tissues that are remote from a tumor or its metastases.[1] As commonly used, the term "paraneoplastic" usually refers to syndromes that are associated with malignant tumors, although that is not universally true. The focus in this particular discussion is on conditions that are, or can be, associated with malignancies.

Paraneoplastic conditions of the skin are particularly important. From an academic standpoint, they can provide insights into basic tumor biology. In more practical terms, and in contrast to most internal disorders, changes involving the skin are often readily identifiable at an early stage. Consequently, cutaneous lesions can serve as the harbingers of a malignant process, allowing for earlier detection and treatment of the latter (Table 1). Although it is uncommon for the pathologist to make a definitive diagnosis of a paraneoplastic condition based upon biopsy findings alone, it can occur, as in the case of necrolytic migratory erythema (linked to glucagonoma), acanthosis nigricans (gastrointestinal adenocarcinoma), or paraneoplastic pemphigus (non-Hodgkin's lymphoma). Because the microscopic changes of paraneoplastic lesions in the skin can also be seen in the absence of neoplasia, the more common role of the pathologist is to suggest heightened surveillance for a malignant process when they are observed.

Part I: conditions that are usually linked to malignant alimentary tract neoplasms

Necrolytic migratory erythema (NME; glucagonoma syndrome)

Clinical findings

This syndrome features anemia, weight loss, glossitis, and adult-onset diabetes mellitus. The characteristic cutaneous feature is a migrating annular erythema with erosions and crusting. It is concentrated in intertriginous areas of the trunk, groin, buttocks, and thighs, and perioral lesions may occur.[2–5] Necrolytic migratory erythema is most often associated with a glucagon-secreting neuroendocrine tumor of the pancreas.[3] In a typical case, elevated glucagon levels and reduced plasma amino acids are detected.[2,4,6,7] Identical skin changes have also been seen in association with neuroendocrine hepatic tumors, hepatic cirrhosis, jejunal and rectal adenocarcinoma, myelodysplastic syndromes, inflammatory bowel disease, pancreatitis, and malabsorption disorders.[3,4,8] Skin lesions resolve with treatment of the underlying tumor and correction of nutritional deficiencies. There appears to be no

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Table 1
Cutaneous paraneoplastic syndromes—associations with visceral malignancies.

Conditions that are usually linked to malignant neoplasms of the alimentary tract
-Acanthosis nigricans
-Acrodermatitis paraneoplastica (Bazex syndrome)
-Florid cutaneous papillomatosis
-Necrolytic migratory erythema (glucagonoma syndrome)
-Palmoplantar keratoderma
-Pancreatic fat necrosis
-Pityriasis rotunda
Conditions that are usually linked to hematolymphoid malignancies
-Acquired ichthyosis
-Exfoliative erythroderma
-Necrobiotic xanthogranuloma
-Paraneoplastic pemphigus
-Plane xanthoma
-Pyoderma gangrenosum
-Scleromyxedema
-Sweet syndrome (aseptic neutrophilic dermatosis)
-Vasculitis
Conditions that are linked to anatomically diverse malignancies
-Birt–Hogg–Dube syndrome (renal cell carcinomas]
-Cowden syndrome (thyroid, genitourinary, gastrointestinal, and breast carcinomas]
-Dermatomyositis [ovarian, lung, breast, and gastrointestinal carcinomas]
-Erythema gyratum repens [lung, esophageal, and breast carcinomas]
-Gardner syndrome [thyroid and gastrointestinal carcinomas]
-Hypertrichosis lanuginosa acquisita [gastrointestinal, lung, and breast carcinomas]
-Leser–Trelat syndrome (eruptive seborrheic keratoses) [gastrointestinal tumors and hematolymphoid malignancies]
-Multicentric reticulohistiocytosis [hematolymphoid malignancies; breast and genitourinary carcinomas]
-Muir Torre syndrome [gastrointestinal and genitourinary carcinomas]
-Papuloerythroderma of Ofuji [hematolymphoid malignancies; hepatic and gastrointestinal carcinomas]
-Superficial thrombophlebitis (Trousseau syndrome) [pancreatic, gastric, and lung carcinomas]
-Tripe palms [lung and gastric carcinomas]

clear consensus regarding the pathogenesis of necrolytic migratory erythema, but amino acid, zinc, and fatty acid deficiencies, caused by the catabolic effects of elevated glucagon levels, may all play a part[2,6,7].

Histopathology

The cutaneous lesions of NME show acanthosis, which may range from mild to marked. Confluent parakeratosis overlies distinctly vacuolated keratinocytes in the upper portion of the epidermis (Fig. 1). Necrosis may be superimposed, with the coalescence of vacuoles and neutrophil accumulation, at times producing spongiform pustulation. Subcorneal pustules occasionally may be the principal histopathologic finding.[9,10] Within the superficial to mid dermis, there is a perivascular infiltrate comprised mainly of lymphocytes but sometimes including neutrophils.

Specificity of findings and differential diagnosis

The presence of confluent parakeratosis overlying vacuolated superficial keratinocytes is quite characteristic of NME and should raise suspicions of that diagnosis. However, several other nutritional deficiency disorders can have similar microscopic changes. The clinical presentations of biotin deficiency, pellagra, and childhood acrodermatitis enteropathica should be sufficiently distinctive, but adult onset zinc deficiency could be difficult to distinguish from necrolytic migratory erythema in the absence of laboratory data.

Psoriasiform varieties of necrolytic migratory erythema could be difficult to distinguish from true psoriasis, but vacuolization of superficial keratinocytes is not typical of psoriasis.

Acrokeratosis paraneoplastica (Bazex syndrome)

Clinical findings

Individuals with this condition have psoriasiform or eczematous lesions that are concentrated on acral surfaces, including the hands, feet, knees, ears, nose, and cheeks. Brittle nails with surrounding psoriasis-like changes can also occur. The skin lesions often have a distinctly violaceous color.[11–19] Acrokeratosis paraneoplastica (AKP) is associated with malignancies in virtually all cases, particularly associated with the aerodigestive tract. Examples include carcinomas of the tongue, pharynx, soft palate, esophagus, and lung.[13,17,19] The development of AKP typically precedes initial symptoms of the underlying malignancy by an average of 11 months.[13] In most cases, cutaneous lesions improve following treatment of the associated malignancy. Possible causes of AKP include an immune response directed toward particular tumor antigens, or tumor-induced inflammatory mediators such as transforming growth factor-alpha.[15,16]

Histopathology

Microscopic findings in AKP include focal parakeratosis, hyperkeratosis, and acanthosis (Fig. 2).[15,16,18] Varying degrees of vacuolar keratinocyte alteration and apoptosis have been detected as well. Within the superficial dermis one sees a mild perivascular lymphocytic infiltrate.

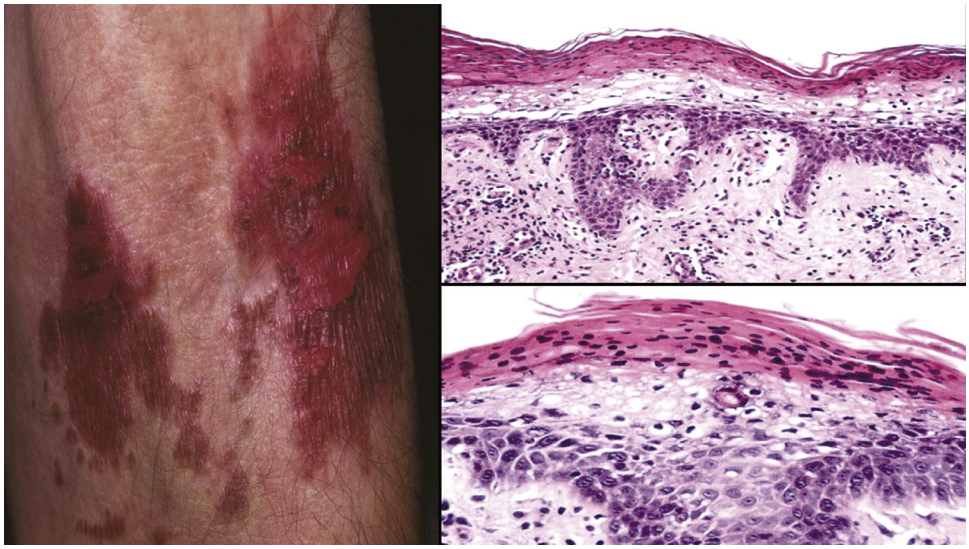

Fig. 1. Necrolytic migratory erythema. This patient with a pancreatic glucagonoma has erythematous, crusted erosions on the extremities (left panel). Microscopically, they are typified by confluent parakeratosis over an attenuated epidermis with superficial cytoplasmic pallor (right panels).

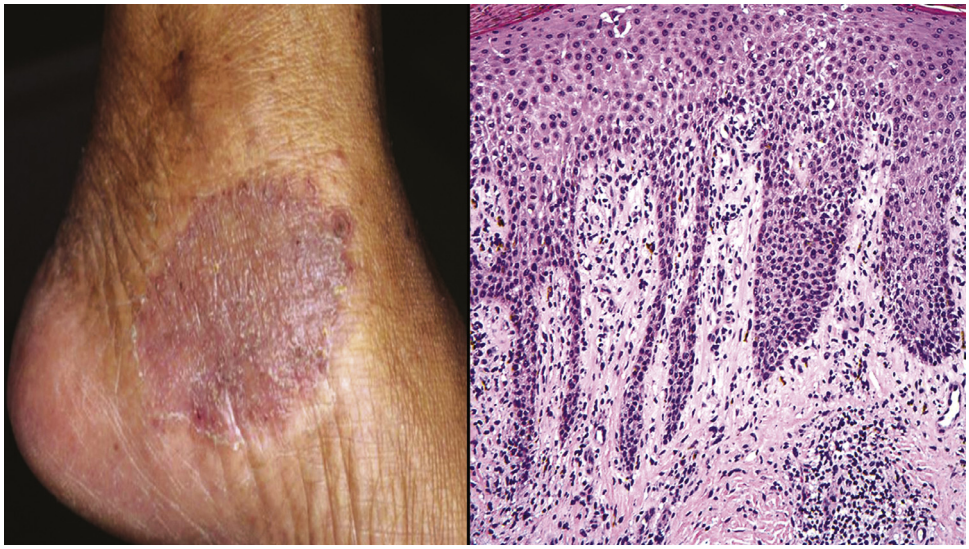

Fig. 2. Bazex syndrome. Well-demarcated, violaceous, eczematoid lesions are seen on the distal extremities (left panel). Microscopically, they have the appearance of subacute or chronic spongiotic dermatitis (right panel).

Specificity of findings and differential diagnosis

In the absence of a clinical history, the microscopic findings in AKP are nonspecific. The described constellation of histologic features would ordinarily raise the differential diagnosis of psoriasis versus psoriasiform spongiotic dermatitis, a common issue in diagnostic dermatopathology. However, neutrophil accumulations within the stratum corneum, as seen in psoriasis, have not been observed in AKP. The clinical presentation of AKP is quite characteristic, and in that context, the microscopic findings can be strongly supportive of the diagnosis.

Acanthosis nigricans

Clinical findings

Acanthosis nigricans (AN) is perhaps best known as a sign of malignancy, but it also accompanies a group of endocrinologic disorders, particularly those associated with insulin resistance and obesity.[20,21] It may likewise be seen as an autosomal dominant familial disorder or may be caused by certain medications, including corticosteroids, nicotinic acid, and triazinate.[22,23] "Malignant" acanthosis nigricans (so-called because of its association with malignancy) is mainly a disorder of adults. It is most closely associated with gastrointestinal carcinomas, but has been seen with carcinomas of the lung, kidney, and bladder, mycosis fungoides, and carcinomas of the ovary and pancreas.[24–28] AN may precede the detection of malignancy in roughly 20% of cases, whereas it appears simultaneously with the cancer in 60% and follows the tumor diagnosis in another 20% of cases. The condition can regress, at least temporarily, when the tumor has been resected. It appears that growth factors produced by the tumors may be responsible causally for the development of AN.[27] All forms of the disorder feature pigmented, velvety plaques that are concentrated in flexures, such as the neck, axillae, and groin.[26,27] The palms may be hyperkeratotic and develop a "honeycomb" appearance. Cases have been reported in which AN coexisted with tripe palms, mucosal papillomas, and the sign of Leser–-Trelat (eruptive seborrheic keratoses).

Histopathology

The findings in acanthosis nigricans are characteristic, if not pathognomonic, and include marked papillomatosis with "finger-like" projections of rete ridges, associated with hyperkeratosis that tends to be basket-woven rather than compact (Fig. 3). Acanthosis is mild, usually limited to the valleys between papillomatous formations.[22] Basilar melanization is often mild, except in dark-skinned individuals, and it is believed that in most instances, the pigmentation perceived clinically is primarily due to hyperkeratosis.[27]

Specificity of findings and differential diagnosis

The changes of acanthosis nigricans are characteristic but not entirely specific. Similar combinations of hyperkeratosis and papillomatosis can be seen in confluent and reticulated papillomatosis (a hyperkeratotic condition most commonly seen on the trunk of younger individuals, unassociated with malignancy), some seborrheic keratoses, and epidermal nevi. Seborrheic keratoses may also have horn cysts and a greater degree of acanthosis, while the changes in confluent and reticulated papillomatosis are generally less pronounced. Obviously, the clinical history and physical examination have a great bearing on the diagnosis in many cases. Once a diagnosis of acanthosis nigricans is established, there is still a need to determine the underlying cause. In the absence of a family history, endocrinologic syndrome, obesity, or relevant medications, the development of this condition in an adult should prompt a search for malignancy, particularly of the gastrointestinal tract.

Florid papillomatosis (FP; Schwartz–Burgess syndrome)

Clinical findings

FP begins with the abrupt appearance of many cutaneous papillomas that clinically simulate the image of viral warts.[29–33] The lesions are 1–3 mm in diameter, and usually are first seen in acral skin. With time, they become disseminated. Pruritus accompanies the lesions in roughly 50% of cases. The suddenness of the eruption and the multiplicity of papillomas facilitates distinction from verrucae and epidermodysplasia verruciformis. FP is associated with underlying cancer of the stomach (in the majority of cases) as well as carcinomas of the breast, bladder, ovary, uterus, prostate, and lung.[30–32] Uncommonly, squamous cell carcinoma or lymphoma also may represent the underlying malignancy. Individuals with FP sometimes show a clinical continuum of lesions that also have the appearance of acanthosis nigricans or eruptive seborrheic keratosis. FP tends to remit, at least in part, with successful treatment of the associated neoplasm.

Histopathology

Histologically, the lesions of FP show hyperkeratosis, epidermal acanthosis, and papillomatosis (Fig. 4). There is no vacuolization of keratinocytes, and parakeratosis and viral inclusions are absent.[29,30]

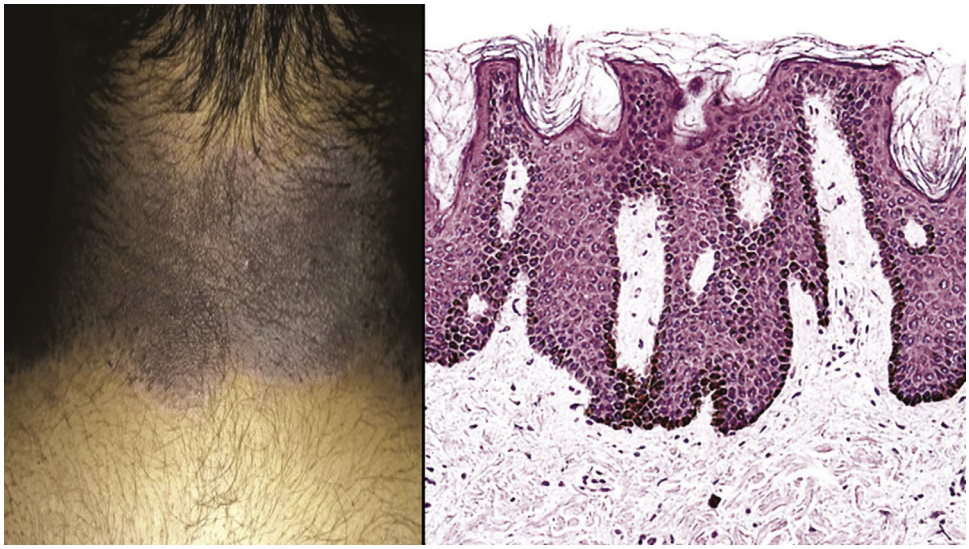

Fig. 3. Acanthosis nigricans. Pigmented, velvety plaques are seen on the posterior neck (left panel). Histologically, epidermal papillomatosis is present with hyperkeratosis and slight basilar hyperpigmentation (right panel).

Specificity of findings and differential diagnosis

For practical purposes, a diagnosis of FP always equates with the presence of an underlying malignant neoplasm.

Pityriasis rotunda

Clinical findings

Pityriasis rotunda is characterized by ovoid, scaly, pigmented patches that principally affect the trunk and extremities. Two types of the disorder have been described. Type I is seen in adult Asian or black patients, and it is often associated with an underlying malignancy, usually gastric or hepatocellular carcinoma.[34–40]

Type II pityriasis rotunda occurs before the age of 40 years, and is often familial. It has not been associated with internal diseases or malignant neoplasms.[36] The clinical images of types I and II lesions are identical. They are represented by circular pink or light brown patches that are sharply defined with dry scaling, ranging between 0.5 and 20 cm in greatest dimension. The lesions tend to be hyperpigmented in patients with dark skin and hypopigmented in those with light skin.[36,37]

Histopathology

Type I pityriasis rotunda may be a biological variant of paraneoplastic ichthyosis vulgaris. Accordingly, the histologic appearance of lesions features compact orthokeratosis, a lack of spongiosis, and minimal dermal inflammation. The granular cell layer of the epidermis is often attenuated or absent, mimicking the microscopic image of hereditary ichthyosis vulgaris.[35–37]

Specificity of findings and differential diagnosis

The appearance of pityriasis rotunda in an older adult, in the absence of a family history of that condition, has a strong association with an underlying carcinoma. It usually arises in the stomach or liver.

Pancreatic panniculitis (PP)

Clinical findings

The lesions of PP are predominantly distributed over the legs, trunk, and buttocks, as violaceous or erythematous nodules and plaques in the subcutis. They may ulcerate spontaneously and drain viscous, oily fluid.

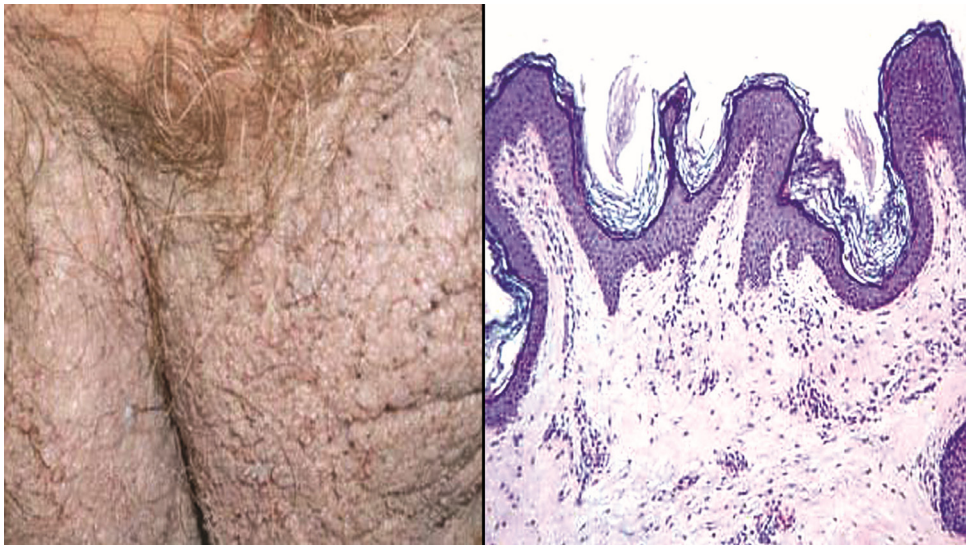

Fig. 4. Florid papillomatosis. Numerous and confluent squamous papillomas are present in the skin of the upper legs (left panel). Microscopically, epidermal papillomatosis is accompanied by orthokeratosis, scant dermal chronic inflammation, and an attenuated granular layer (right panel).

Patients with paraneoplastic PP are typically older adults with no prior history of pancreatic disease.[41–44] The lesions may antedate discovery of a malignant neoplasm by 1–7 months, or, conversely, they may develop months after the tumor is identified.

Laboratory studies usually reveal elevations in serum lipase, amylase, and trypsin levels, although that finding is not universal. The blood level of carcinoembryonic antigen also may be above normal.[42,44] The most common pancreatic malignancy in this setting is acinar cell adenocarcinoma, but conventional ductal adenocarcinoma and neuroendocrine pancreatic carcinoma sometimes cause PP as well. The clinical evolution is almost always adverse, owing to the aggressive nature of the associated pancreatic tumors.

Histopathology

Skin and subcuticular biopsies in PP show lobular fat necrosis, associated with anuclear adipocytes (ghost cells), microcalcifications, and a neutrophilic inflammatory infiltrate.[44]

Specificity of findings and differential diagnosis

The microscopic features of PP, as just described, serve to distinguish it from other forms of panniculitis such as erythema nodosum or erythema induratum. Patients with acute or chronic pancreatitis may also develop the syndrome, but differences in the clinical presentation of those disorders and that of paraneoplastic PP facilitate the distinction between them.

Tylosis (palmoplantar keratoderma)

Clinical findings

Tylosis, or keratosis palmaris et plantaris, can occur in a wide variety of genetic disorders. It can also arise as an acquired disease in a number of ways, e.g., following arsenic exposure, as keratoderma climactericum, or as an accompaniment of other dermatoses such as pityriasis rubra pilaris. Clinically the hyperkeratosis can be diffuse, focal or nummular, or punctate.[45–52] Acquired tylosis can also be associated with internal malignancies of varying types, ranging from lymphoma to bronchogenic carcinoma.[45,48,53] In fact, tripe palms may be regarded as a variant of palmar keratoderma. Tylosis has also been associated with gastrointestinal carcinoma as part of a familial syndrome. The best known is the Howel–Evans syndrome, associating tylosis with the development of esophageal carcinoma.[46] The genetic locus for tylosis with esophageal cancer has been mapped to a 500 kb region on chromosome 17q2S.[47] In 1984, Bennion and Patterson reported on a family with punctate keratoderma of palms and soles and carcinomas of the colon and pancreas.[48]

Histopathology and specificity of findings

Microscopically, all forms of keratoderma show orthokeratosis, variable parakeratosis, hypergranulosis, and acanthosis (Fig. 5). In punctate variants, a degree of keratin plugging can also be observed.[49,51] Underlying malignancy should be included in the differential diagnosis of conditions associated with acquired keratoderma of palms and soles, though it is not the most common. Although Howel–Evans keratoderma begins in childhood, it tends to be later in onset than is the case for benign hereditary keratoderma.

Part II: conditions that are usually linked to hematolymphoid malignancies

Paraneoplastic pemphigus

Clinical findings

In 1990, Anhalt et al. defined the disorder that is now known as paraneoplastic pemphigus.[54] Patients with that condition develop erosions of the lips and oropharynx, pseudomembranous conjunctivitis, and pruritic, polymorphous skin lesions with blisters and erosions. Some lesions have a target-like configuration, and these, combined with the mucous membrane changes can erroneously suggest the diagnosis of erythema multiforme. Paraneoplastic pemphigus has a strong association with lymphoproliferative disorders, including non-Hodgkin lymphomas, thymoma, chronic lymphocytic leukemia, and Castleman's disease.[54–56] Other tumors are present in roughly 15% of all cases, including carcinomas, sarcomas, and malignant melanoma. In typical cases that are associated with lymphoma, the neoplastic process is already established at the time of onset of paraneoplastic pemphigus. Unusual cases have also been reported in which no tumor was detected.[57] Patients with paraneoplastic pemphigus have been shown to develop circulating antibodies to a variety of keratinocyte-derived proteins, particularly desmoplakin I (250 kd), bullous pemphigoid antigen (230 kd), envoplakin (210 kd), and periplakin (190 kd).[58,59] Presumably, autoantibodies which are directed toward the underlying tumors cross-react with native epithelia that contain related antigens.[54,60]

Histopathology

The microscopic image of paraneoplastic pemphigus combines features of erythema multiforme with those of pemphigus vulgaris. There is vacuolar alteration of the basilar layer, apoptotic keratinocytes can be found at all levels of the epidermis, and a superficial dermal infiltrate is present comprising mainly lymphocytes, but with some eosinophils and neutrophils (Fig. 6). All of those changes can be seen in erythema multiforme. In addition, suprabasilar acantholysis with cleft formation is often present.[61,62] It is possible that the exposure of antigens resulting from lichenoid dermatitis could promote the development of autoimmunity and the subsequent acantholytic changes of pemphigus; this could be considered an example of a phenomenon termed “epitope spreading”.[63]

Direct immunofluorescence shows a combination of intercellular epidermal deposits of IgG and C3 and linear-granular basement membrane zone staining for C3 and/or IgG, a combination of findings that is also observed in pemphigus erythematosus.[64] Positive intercellular IgG is also found by indirect immunofluorescence using monkey esophagus substrate, as would also be the case for non-paraneoplastic forms of pemphigus. In addition, sera from patients with paraneoplastic pemphigus show antibody binding to simple epithelia such as that found in murine bladder, a finding not encountered in ordinary pemphigus.

Specificity of findings and differential diagnosis

Microscopic findings in paraneoplastic pemphigus are potentially diagnostic in and of themselves. The best opportunity for a specific diagnosis arises when interface (lichenoid) changes, sometimes resembling erythema multiforme, coexist with suprabasilar acantholysis. Supportive evidence is provided by direct immunofluorescent studies, as described above. The histologic differential diagnosis includes a variety of interface or lichenoid dermatoses, particularly erythema multiforme but also graft versus host disease and fixed drug eruption. At times, biopsy findings may show only suprabasilar acantholysis without lichenoid tissue changes, a circumstance that has been reported in 27% of cases.[65–71]

Papuloerythroderma of Ofuji

Clinical findings

First described by Ofuji in 1984,[72] papuloerythroderma is another clinically distinctive dermatosis, but one that lacks specific histopathologic features. This condition typically presents in elderly men. Widespread erythema and solid, red–brown papules develop, with dramatic sparing of flexural folds-a finding often termed the “deck chair sign.” Eosinophilia and lymphopenia may accompany the skin eruption. Papuloerythroderma has a strong association with malignancy, especially lymphoma. The most common lymphoproliferative disorder is T-cell lymphoma, particularly cutaneous T-cell lymphoma.[73,74]

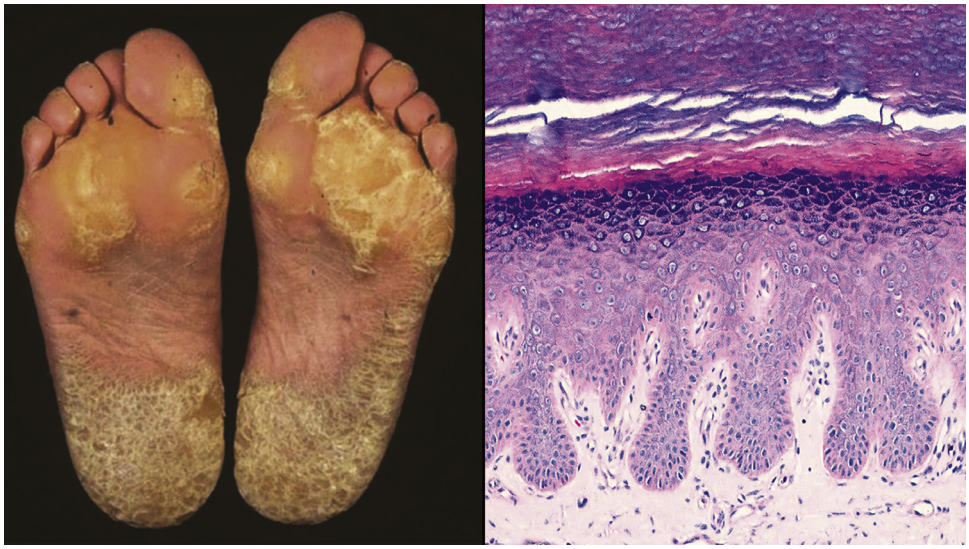

Fig. 5. Tylosis (palmoplantar keratoderma). Dense hyperkeratosis is present on the weight-bearing portions of the soles (left panel). Microscopically, the lesions show marked orthokeratosis, hypergranulosis, and acanthosis (right panel).

Nonepidermotropic peripheral T-cell lymphoma, Hodgkin's disease, and acute myeloid leukemia have also been reported. Solid tumors have included gastric carcinoma,[75] adenocarcinoma of the colon, and hepatocellular carcinoma.[76] Despite the apparently strong cancer association, some patients have not developed malignancy during a limited period of follow-up, and sporadic cases have been related to HIV infection[77] and choledocholithiasis with secondary sepsis.[78]

Histopathology

Microscopic findings include parakeratosis, variable acanthosis, and spongiosis (Fig. 7). A moderately intense perivascular and interstitial inflammatory infiltrate is seen in the upper to mid dermis, comprised mainly of lymphocytes, with scattered eosinophils and plasma cells.[72–75]

Specificity of findings and differential diagnosis

None of the microscopic changes just described are considered to be specific. In fact, they can be observed in a variety of spongiotic dermatitides, including forms of eczematous dermatitis and erythroderma. In the authors' experience, the diagnosis is largely a clinical one, with histopathology playing mainly a supportive role. Clinically, the “deck chair sign” is far more distinctive than any of the histopathologic features.

Exfoliative dermatitis with erythroderma

Clinical features

Exfoliative dermatitis, or erythroderma, has been reported in association with lymphomas, leukemias, and Hodgkin's disease.[79] However, the best-documented association with malignancy is with cutaneous T-cell lymphoma, in which erythroderma is an integral part of the Sezary syndrome.[80] In fact, it has been argued that cases of erythroderma linked to “chronic lymphocytic leukemia” were most likely examples of the Sezary syndrome.[81] Associations also exist with solid tumors (rarely), including carcinomas of the stomach, liver, prostate, lung, thyroid, and gallbladder.[82] Exfoliative dermatitis can precede, follow, or present concomitantly with an underlying malignancy.

Exfoliative dermatitis also develops in patients who do not have malignancies. In fact, it is most often associated with drug reactions or a preexisting dermatosis, such as psoriasis, contact dermatitis, or stasis dermatitis.

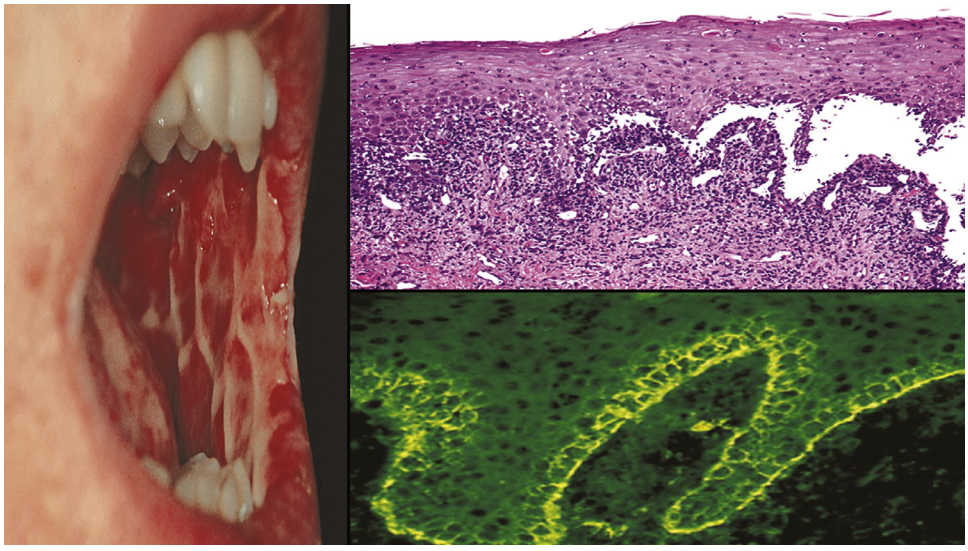

Fig. 6. Paraneoplastic pemphigus. Erosive lesions of the oral mucosa and perioral skin are similar to those of erythema multiforme (left panel). Microscopically, basal epidermal vacuolization is apparent with keratinocyte apoptosis, as well as suprabasilar acantholysis (top right panel). Direct immunofluorescence studies show circumferential labeling of keratinocytes and linear labeling of the epidermal basement membrane for IgG (bottom right panel).

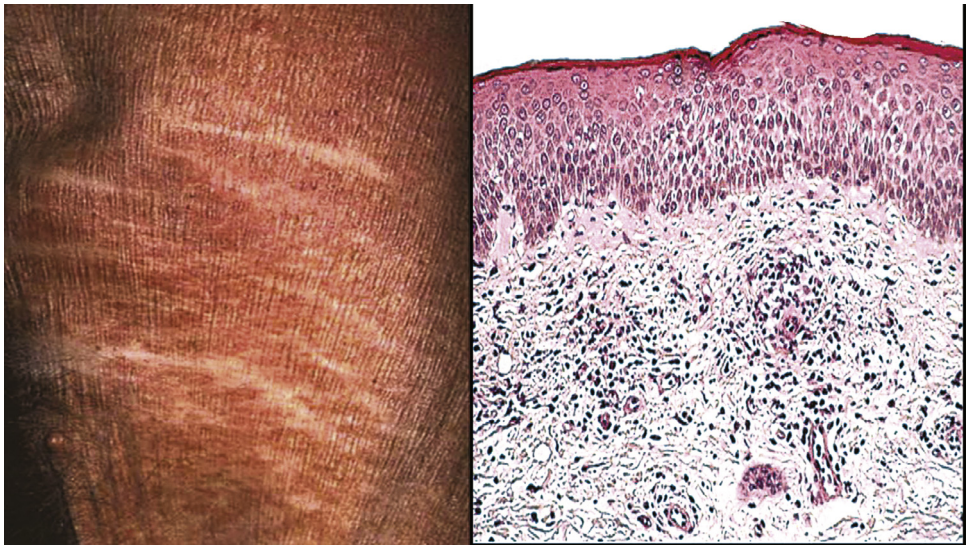

Fig. 7. Ofuij's papuloerythroderma. Generalized erythema is present with sparing of the flexural folds (the "deck-chair" sign) (left panel). Histologically, the lesions have a resemblance to those of eczematoid dermatitis (right panel).

Histopathology and specificity of findings

Microscopically, one usually sees parakeratosis, acanthosis with mild spongiosis, vasodilatation, and a chronic inflammatory infiltrate (Fig. 8). Those findings are suggestive of exfoliative dermatitis but are otherwise nonspecific. Occasionally, a lichenoid tissue reaction pattern can be identified. Atypical lymphocytes and Pautrier microabscesses would provide a clue to the diagnosis of Sezary syndrome, or, alternatively, histologic changes may be sufficiently specific to suggest an underlying dermatosis such as psoriasis.

Dermatomyositis

Clinical findings

Dermatomyositis is a well-known condition that combines the features of polymyositis with inflammatory skin lesions. Some patients present with identical skin lesions in the absence of clinical and laboratory findings of myositis. When this situation lasts for over 2 years, it is called "amyopathic dermatomyositis".[83] Internal malignancy has been reported in 15%–25% of cases of dermatomyositis.[84,85] On the other hand, polymyositis alone does not appear to have an increased risk for malignancy.[86] The neoplastic process may precede, develop concurrently with, or follow the onset of dermatomyositis, with approximately equal frequencies.[87] Carcinomas of breast and lung are among the most common, but several other tumors have also been encountered, including lymphomas, melanoma, and sarcomas.

The literature suggests that a diagnosis of dermatomyositis should not, by itself, prompt a detailed evaluation for malignancy. Instead, such an assessment should be guided by the history, results of physical examination, and/or routine laboratory studies.[88]

The most common clinical features include violaceous erythema and scale, particularly on the head and neck or over the extensor surfaces of the extremities, often with poikiloderma (variegated pigmentation and telangiectasia) and a degree of atrophy. "Heliotrope" eyelids are classic signs but are not always found. Papules or plaques involving skin over the interphalangeal joints (Gottron's papules) are often seen, and there may be nailfold telangiectasias or ragged-appearing cuticles (Samitz's sign). Photosensitivity, sometimes with a burning sensation, and plaque-like cutaneous calcifications may also occur.[89]

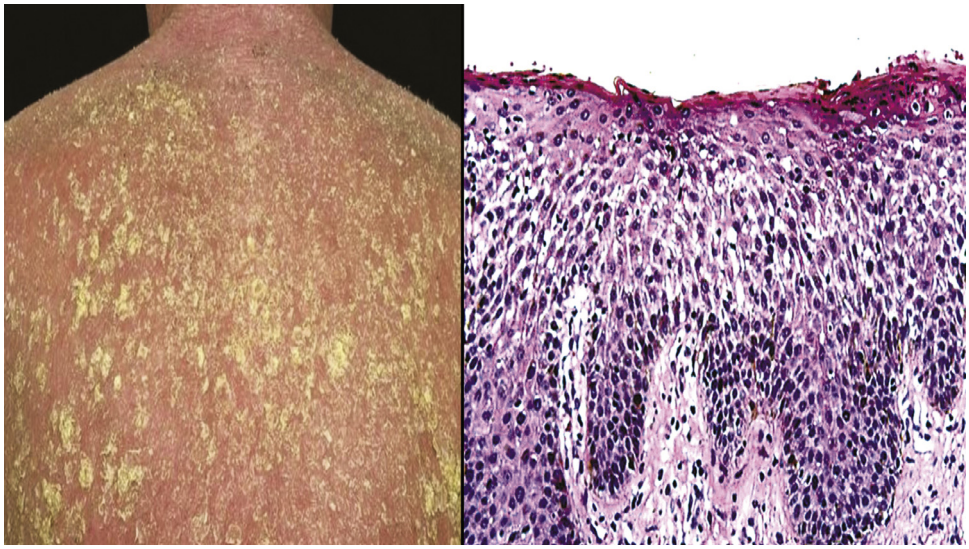

Fig. 8. Exfoliative erythrodermatitis. Diffuse erythroderma is present, with numerous crusted plaques (left panel). The microscopic image is again that of spongiotic dermatitis (right panel).

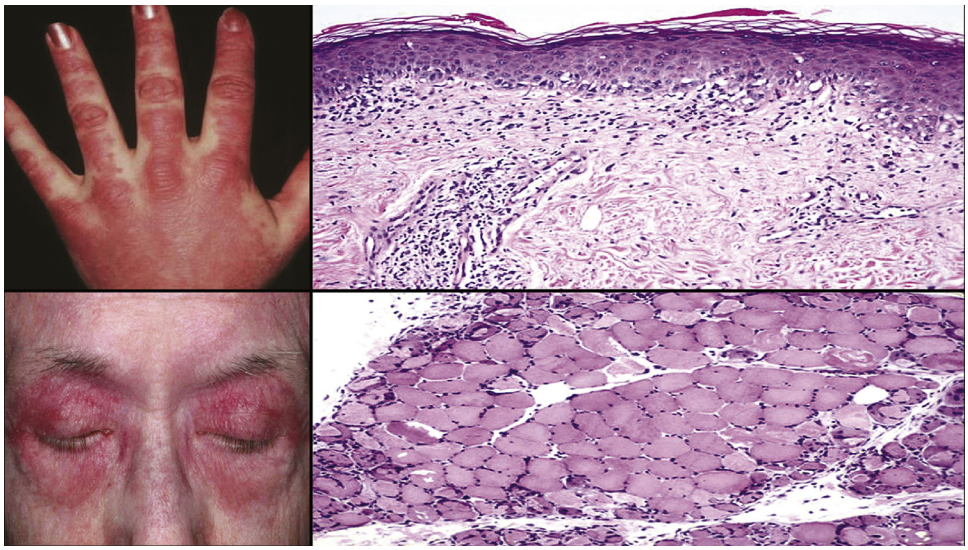

Fig. 9. Dermatomyositis. Confluent erythematous papules and plaques are present over the doral hands (top left panel) and in the periocular skin (bottom left panel). A skin biopsy shows epidermal atrophy, basal vacuolization, interface dermatitis, and pigment incontinence (top right panel). A striated muscle biopsy demonstrates numerous infiltrates of lymphocytes (bottom right panel).

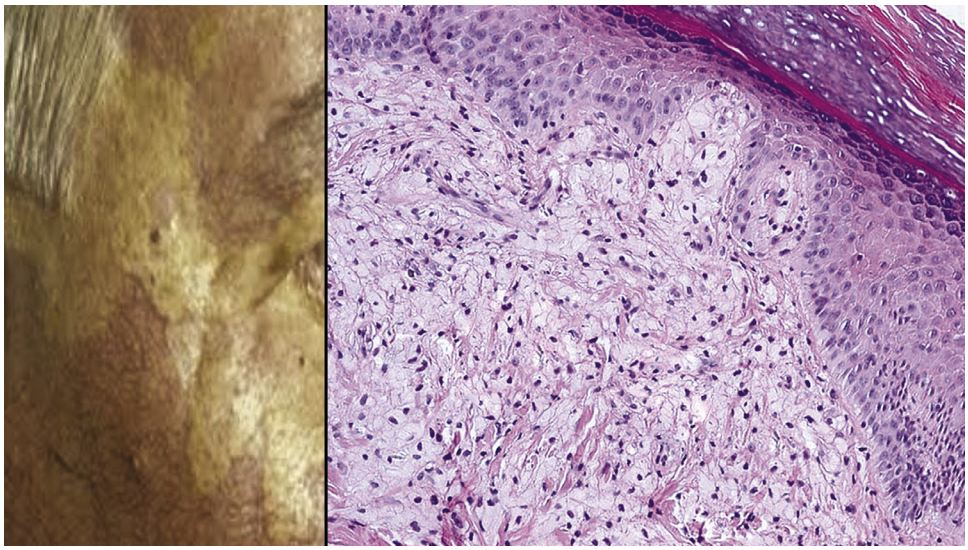

Fig. 10. Normolipemic (plane) xanthoma. Diffuse yellow–orange discoloration of the facial skin is present (left panel), represented by diffuse infiltration of the dermis by markedly xanthomatized histiocytes (right panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Histopathology

The most typical presentation is that of a lichenoid tissue reaction, with vacuolar alteration of the basilar layer of the epidermis and formation of apoptotic keratinocytes. Often the features are those of poikiloderma atrophicans vasculaire: basilar vacuolar change in an atrophic epidermis, vasodilatation, and pigmentary incontinence (Fig. 9). The superficial dermal infiltrate seen in dermatomyositis tends to be mild, lymphocytic, and perivascular. A lymphoplasmacytic panniculitis can be seen, but in the authors' experience, it is uncommon. Dermal mucin deposition is frequently identified with colloidal iron or alcian blue staining.[90] Direct immunofluorescent studies tend to be negative, except for the presence of apoptotic (Civatte) bodies in the basal epidermis that stain positively for IgM and C3.

Specificity of findings and differential diagnosis

Lesions that manifest interface dermatitis raise a broad differential diagnosis, but the presence of poikiloderma atrophicans vasculaire in an adult suggests three major possibilities—dermatomyositis, lupus erythematosus, and the poikilodermatous phase of mycosis fungoides. A distinct separation between them is not always possible. However, in addition to epidermal changes, lupus erythematosus often shows a prominent perivascular and perifollicular lymphoid infiltrate accompanied by vacuolar alteration of the outer root sheath epithelium. Thinning of lateral follicular walls occurs in discoid lupus erythematosus. Direct immunofluorescence of skin biopsies can be helpful because only lupus erythematosus is expected to show basement membrane deposits of complement and immunoglobulin. Mycosis fungoides would be expected to show atypical lymphocytes, exocytosis with formation of haloed intraepidermal cells or Pautrier microabscesses, possibly with an abnormal immunophenotype or positive T-cell receptor gene rearrangement studies.

Diffuse (normolipemic) plane xanthoma

Clinical findings

Plane xanthomas manifest with patchy or diffuse orange–yellow discoloration of the skin on the face and trunk, and particularly in intertriginous areas such as the axillae.[91,92] Most patients with these lesions are normolipemic, but plane xanthomas can certainly occur in hyperlipoproteinemias of types 2 through 4. This condition has a strong association with multiple myeloma.[91] There have also been reports of plane xanthomatosis associated with chronic lymphocytic leukemia[93] and rectal adenocarcinoma.[94] Clinical and histopathologic links have been suggested between diffuse plane xanthoma and necrobiotic xanthogranuloma (see below)[95,96].

Histopathology

Microscopic findings include clusters of foamy macrophages scattered throughout the dermis, in the absence of fibrosis (Fig. 10). Lymphocytic inflammation is typically sparse or absent.[97–100]

Specificity of findings and differential diagnosis

The distribution of foamy macrophages, minimal inflammation, and a lack of fibrosis are suggestive of plane xanthoma. Clinical correlation is necessary to confirm the "diffuseness" of the process. In addition to the hyperlipoproteinemias mentioned above, plane xanthomas can also accompany biliary cirrhosis. Cases showing foci of degenerate connective tissue or multinucleated cells can resemble the histologic image of necrobiotic xanthogranuloma.

Acquired ichthyosis

Clinical findings

Acquired ichthyosis in adults is frequently associated with malignancy. The malignant process is most often a lymphoma, Hodgkin's disease being more common than non-Hodgkin's lymphomas.[101] It has also been reported in association with lymphomatoid papulosis,[102] multiple myeloma,[103] and, uncommonly, with solid tumors such as carcinomas of the breast or lung.[104,105] Ichthyosis in this setting usually arises in patients with established malignant disease, although it may occasionally be the initial manifestation. However, there are other potential causes of acquired ichthyosis, including malnutrition, hypothyroidism, sarcoidosis, and drugs such as nicotinic acid and clofazimine.

Histopathology

Microscopically, skin biopsies show compact orthokeratosis, a lack of spongiosis unless secondary eczematization has occurred, and minimal dermal inflammation (Fig. 11). The granular cell layer is often attenuated or absent, mimicking the image of ichthyosis vulgaris.[103,104] Some cases of ichthyosis associated with myeloma have also presented with follicular keratotic spicules; biopsy of such lesions has demonstrated intercellular deposition of cryoproteins.[103] Certainly, ichthyosiform biopsy changes in adults, in the absence of a long-term or familial history, should raise the possibility of underlying malignancy, though as noted above, there are other possible explanations for this finding.

Necrobiotic xanthogranuloma

Clinical findings

Necrobiotic xanthogranuloma (NXG) is a rare granulomatous disease that is typified by yellowish indurated cutaneous plaques and nodules that coalesce into indurated plaques.[106–111] They are usually 0.5–2.0 cm in greatest dimension, often with superficial telangiectasias, potential ulceration, and scarring. Incisional biopsy is recommended to establish the diagnosis. Most NXG lesions (60%−70%) first affect the trunk or extremities and then involve the periorbital skin.[110] However, periocular lesions are neither pathognomonic nor required diagnostically. Blepharoptosis, restricted ocular motility, and proptosis are seen in 50%–80% of patients. NXG also may involve various extracutaneous sites, including the lung, myocardium, larynx, pharynx, skeletal muscle, kidney, ovary, and intestine.[107–109]

The association between NXG and paraproteinemias is well documented. Most patients (80–90%) with NXG have a serum monoclonal gammopathy, usually of the IgG κ type, but only 10% of patients develop plasmacytic myeloma.[109,111] The skin lesions in NXG represent reactive inflammatory infiltrates and are not associated with the presence of monoclonal plasma cells. Other lymphoproliferative and hematologic disorders may also be associated with NXG.[108]

Histopathology

Microscopically, the lesions of NXG show marked necrobiosis alternating with foci of xanthogranulomatous infiltration in the reticular dermis and subcutis (Fig. 12).[106,107,110] In the latter location, a septal distribution may be present which imitates panniculitis. The inflammatory infiltrate features the presence of epithelioid and xanthomatized histiocytes, multinucleated giant cells, lymphocytes, plasma cells, and cholesterol clefts. Focal vasculitis may be observed as well. The lymphocytes and plasma cells in NXG are polytypic.[107]

Specificity of findings and differential diagnosis

As mentioned earlier, the great majority of individuals with NXG have paraproteinemias, but these may eventuate months or years after appearance of the skin lesions. Histologic differential diagnosis principally centers on infectious granulomas, but no microorganisms are demonstrable by culture or histochemical staining in NXG.

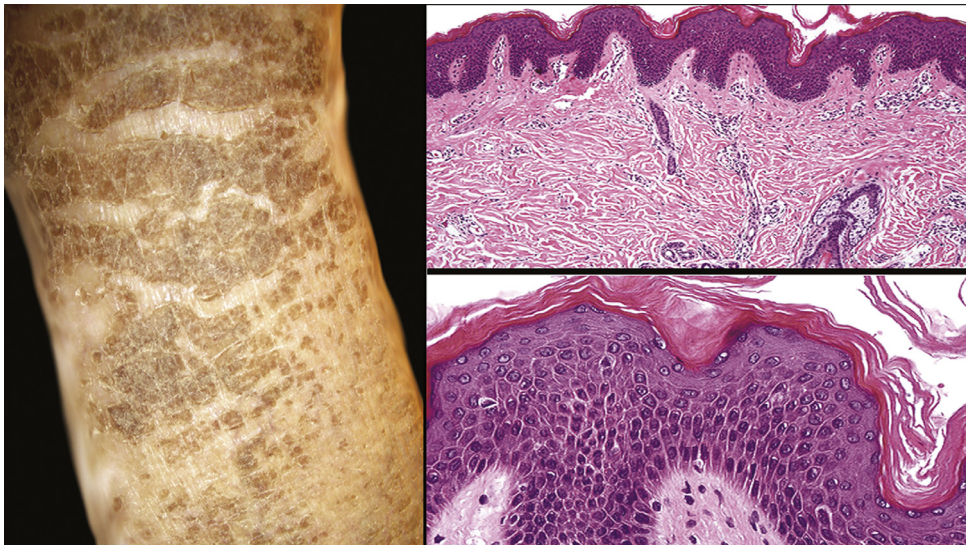

Fig. 11. Acquired ichthyosis. Plate-like scales are present over the forearm, resembling the appearance of a fish (left panel). Compact orthokeratosis with attenuation of the epidermal granular layer is seen histologically (right panel).

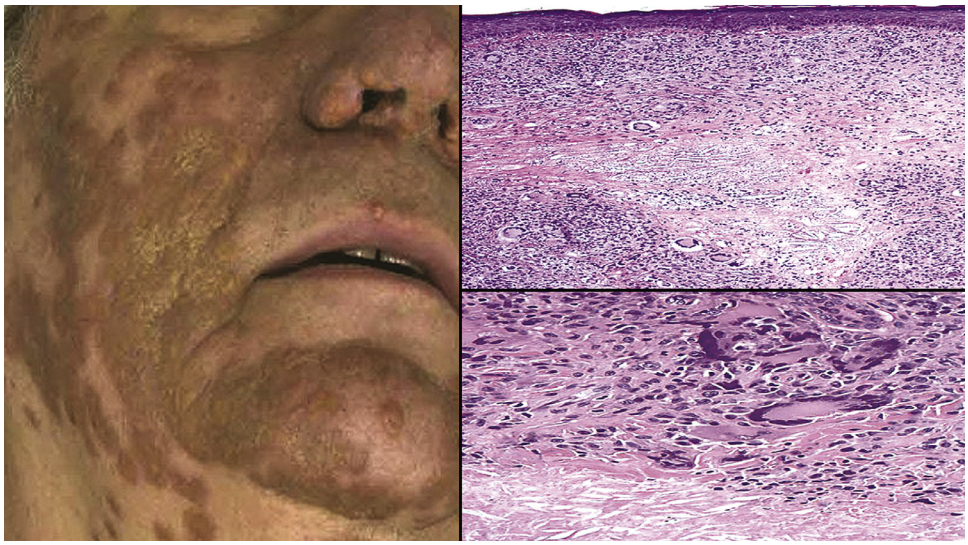

Fig. 12. Necrobiotic xanthogranuloma. Indurated, coalescent brown–red plaques are present in the facial skin (left panel). Histologically, marked necrobiosis is seen in the corium, with infiltrates of epithelioid, multinucleated, and xanthomatized histiocytes with polarized nuclei (right panels). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Paraneoplastic scleromyxedema

Clinical findings

The characteristic cutaneous manifestation of scleromyxedema is the widespread eruption of 2–3 mm, firm, waxy, closely-spaced, dome-shaped or flat-topped papules involving the hands, forearms, head, neck, upper trunk, and thighs.[112,113] Papules are often arranged in linear arrays and the surrounding skin is shiny and indurated. The glabella is typically involved with formation of deep furrows that produce the characteristic leonine faces. Cutaneous furrowing also is seen on the trunk or limbs, producing the "Shar-Pei sign".[113]. Erythema, edema, and a brownish discoloration may be seen in the involved skin, and pruritus is relatively common. Eyebrow, axillary, and pubic hair may be sparse in patients with scleromyxedema. The mucous membranes are spared.

As the condition progresses, erythematous and infiltrated plaques may appear with skin stiffening, sclerodactyly, and decreased motility of the mouth and joints.[112,113] On the proximal interphalangeal joints, a central depression surrounded by an elevated rim (caused by skin thickening) can be seen and is called the "doughnut sign".[112,113] Patients with scleromyxedema can also have internal lesions that involve the neurologic, rheumatologic, cardiovascular, and gastrointestinal systems, as well as the lungs and kidneys.[114]

Scleromyxedema is associated with paraproteinemias. The monoclonal gammopathy is usually represented by IgG with a predominance of lambda light chains, but IgG kappa dominance also may be seen.[111–113] Patients with scleromyxedema in the absence of a paraproteinemia are considered to have an atypical form of the disease. The disease progresses to outright multiple myeloma in $<10\%$ of cases. Anecdotal associations with other hematologic malignancies such as Hodgkin and non-Hodgkin lymphomas,[115] Waldenström macroglobulinemia, and myelomonocytic leukemia, or visceral carcinomas have been reported as well.

Histopathology

Scleromyxedema features the presence of a triad of microscopic features that includes diffuse deposition of dermal mucin, dermal fibrosis, and a proliferation of randomly arranged fibroblasts in the corium (Fig. 13). The epidermis may be normal or thinned, hair follicles may be atrophic, and a slight perivascular dermal lymphoplasmacytic infiltrate is often present. Elastic fibers are often fragmented and decreased quantitatively. An interstitial, granuloma annulare-like pattern has been described in some cases of scleromyxedema, typified by a diffuse proliferation of histiocytes, giant cells, and lymphocytes in the upper dermis.[116] Those elements form loose granulomas that disrupt dermal collagen fibers.

Specificity of findings and differential diagnosis

The histological appearance of scleromyxedema is similar to that of cutaneous myxedema in thyroid disease, scleroderma (systemic sclerosis), scleredema of Buschke, and nephrogenic fibrosing dermopathy.[112] Therefore, attention to laboratory data pertaining to thyroid function, serum glucose levels, and renal function is crucial to differential diagnosis in this setting. The presence of a paraproteinemia would be selective for scleromyxedema.

Sweet's syndrome (acute febrile neutrophilic dermatosis)

Clinical findings

Although it is often described as an uncommon entity, Sweet's syndrome (SS) is not rare, particularly in academic and referral centers. In this condition, erythematous and potentially painful plaques and nodules develop over the face, trunk, or extremities. Characteristically, the lesions arise suddenly, are accompanied by fever and leukocytosis, and are particularly responsive to treatment with systemic corticosteroids. Several disease associations have been reported, represented by autoimmune-inflammatory, infectious, iatrogenic, and pregnancy-related conditions.[117–120] Idiopathic cases also occur.

The other significant disease linkage is with malignancy, seen in roughly 10% of SS cases.[121–128] Leukemia has been the most frequent condition in that category, particularly acute myeloid or myelomonocytic leukemia[121]. SS has also accompanied chronic myeloid leukemia.[122] Other hematologic dyscrasias seen with SS have included hairy cell leukemia and myelodysplastic syndrome.[123] There have also been reports of SS occurring with non-Hodgkin lymphoma,[124] myeloma,[125] and solid tumors.[126,127] Most examples in the latter category are carcinomas of the bladder, prostate, and uterine cervix.

Histopathology

Microscopic findings in SS include pronounced papillary dermal edema and a dense neutrophilic infiltrate in the upper to mid-corium. Leukocytoclasis is usually apparent, but leukocytoclastic vasculitis typically cannot be demonstrated (Fig. 14).[128] A neutrophil-poor variant has been described,[129] but it is sufficiently unusual that reconsideration of the diagnosis would be warranted. A "histiocytoid" variant of SS is, in fact, caused by dermal infiltrates of immature myeloid cells.[130]

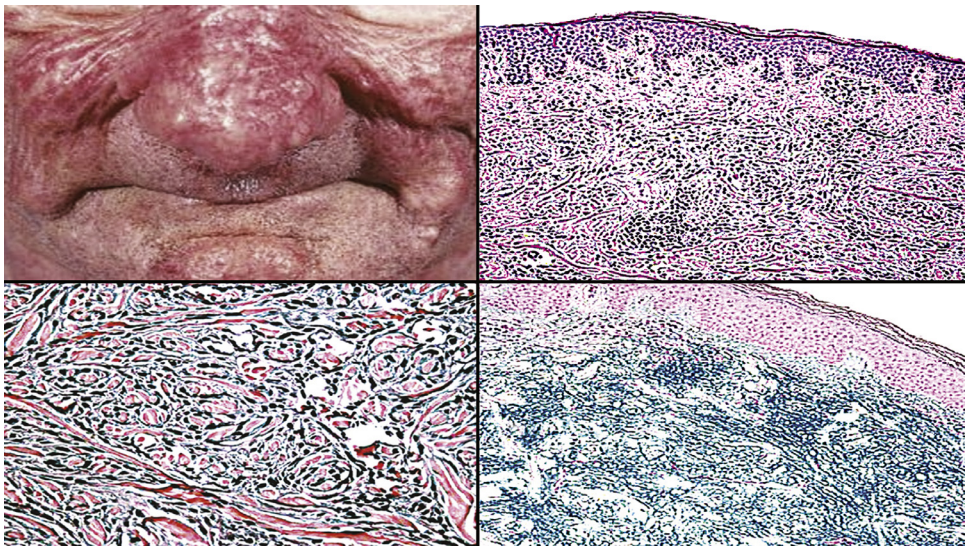

Fig. 13. Scleromyxedema paraneoplastica. Confluent papules and nodules are present in the upper facial skin, with prominent involvement of the nose (left upper panel). Dermal hypercellularity (top right panel) with a random proliferation of fibroblasts (bottom left panel) and mucin deposition (bottom right panel—colloidal iron stain) are seen.

Specificity of findings and differential diagnosis

The microscopic findings in SS are characteristic, and often diagnostic. Its histologic image does overlap to some extent with that of early pyoderma gangrenosum, and those disorders may, in fact, be part of a single continuum.[131,132] However, early lesions of "classic" pyoderma gangrenosum often show the presence of acute folliculitis,[128] whereas SS does not. Moreover, it is not typical for SS lesions to be ulcerated, as seen in pyoderma gangrenosum. The lesions of erythema elevatum diutinum can have overlapping microscopic features. Another condition termed "rheumatoid neutrophilic dermatosis" also bears a close resemblance to SS microscopically, but in the authors' experience, it shows deep as well as superficial dermal inflammation with a lesser degree of karyorrhexis, and may be associated with the changes of interstitial granulomatous dermatitis.[133] The majority of SS cases are not associated with malignancy, but the detection of primitive myeloid forms in the infiltrate should always prompt an investigation for possible underlying leukemia.

Paraneoplastic pyoderma gangrenosum (PPG)

Clinical findings

Pyoderma gangrenosum starts as a painful papule or pustule that develops into a nodule; this then ulcerates and forms violaceous borders with purulent exudates and a necrotic base. Classical PG is more frequently located on the lower limbs, and the bullous variant occurs is seen chiefly on the arms.[134–136] The pathergy phenomenon has been frequently described in PPG, in regard to the development of new lesions or worsening of pre-existing lesions after different types of trauma, such as debridement, intradermal injections, vaccinations, or surgical scars.[134] This phenomenon is found in up to 50% of patients. Bullous or atypical pyoderma gangrenosum is associated with an underlying hematological malignancy (acute myelogenous leukemia, myelodysplasia, myeloproliferative disorders, non-Hodgkin lymphomas, and multiple myeloma) in 7% of cases.[136–141]

Histopathology

Histopathological findings of pyoderma gangrenosum in general are not specific, encompassing areas with abscess, zones of neutrophilic and lymphocytic infiltrate, and moderate vasculitis with fibrinoid necrosis. In bullous PPG, which is more often associated with an underlying malignancy, one sees diffuse neutrophilic dermal inflammation without vasculitis. Direct immunofluorescence studies may demonstrate positive perivascular labeling for C3, IgM, IgA, or IgG.[134]

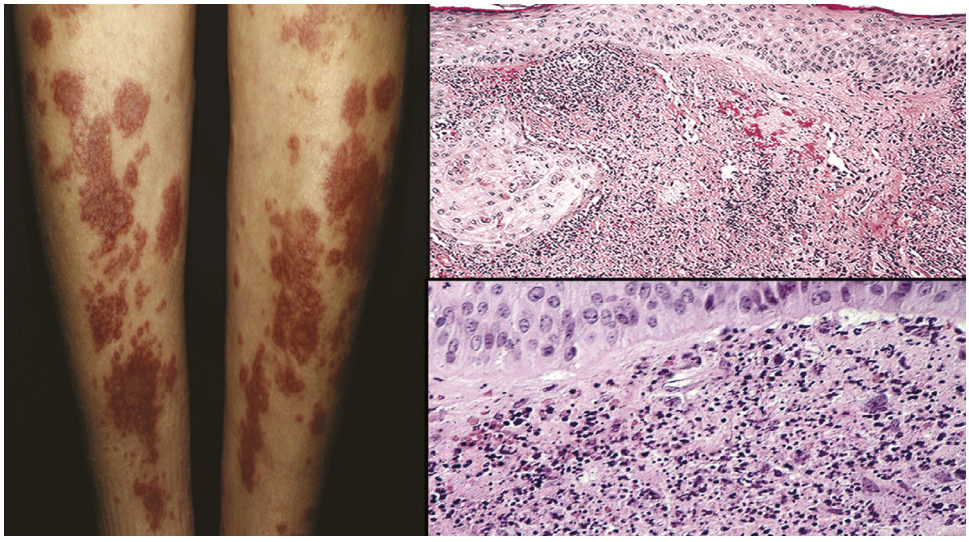

Fig. 14. Sweet syndrome. Red–brown plaques and nodules are present in the pretibial skin (left panel). Diffuse dermal neutrophilia is apparent (top right panel) with karyorrhexis (bottom right panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Specificity of findings and differential diagnosis

The principal differential diagnostic considerations in cases of PPG include infectious cellulitis, leukocytoclastic vasculitis, and Sweet syndrome. Cultures and histochemical stains for microorganisms are negative in PPG, and vasculitis is not expected in Sweet syndrome. The clinical presentation of pyoderma, especially the bullous variant, is quite dissimilar to that of leukocytoclastic vasculitis.

Paraneoplastic cutaneous vasculitis

Clinical findings

In 1986, Longley et al.[142] suggested that malignant neoplasms might produce tumor-related antigens that consequently cause paraneoplastic vasculitis. Concurrently, two criteria were advanced to establish the presence of a paraneoplastic vasculitis: first, the simultaneous appearance of vasculitis and a neoplasm; and second, their parallel course. The pathogenetic mechanisms for the development of paraneoplastic vasculitis remain unknown, but it appears to represent approximately 4% of all cases of cutaneous vasculitis in adults.[143–152] Moreover, it is not understood why there is a stronger association between vasculitis and hematologic malignancies (e.g., myelodysplasia, leukemia, non-Hodgkin lymphoma) as compared with solid tumors (such as carcinomas of the head and neck, breast, lung, and urinary bladder).[149,150]

The most frequently-seen skin lesions are represented by palpable purpura, leg ulcers, urticaria, and macular erythema. The cutaneous lesions are usually located on the legs. Fever, general malaise, and arthralgias also may be present.[142,145,149] Paraneoplastic vasculitis can remit after successful treatment of the underlying malignant tumor, but it otherwise persists despite appropriate treatment of the skin lesions.

Histopathology

Skin biopsies show small-vessel neutrophilic vasculitis, with the variable presence of fibrinoid change in vessel walls (Fig. 15). Extravasated erythrocytes are seen surrounding the inflamed vessels, which may extend into the deep corium and subcutis. In florid cases, epidermal microinfarction and necrosis may be apparent.[153]

Specificity of findings and differential diagnosis

Microscopically, paraneoplastic cutaneous vasculitis shows no definable differences from vasculitis that is unassociated with an underlying malignancy. However, the presence of recalcitrant vasculitis in an elderly patient should prompt consideration of the possibility that it is tumor-related.

Part III: conditions that are linked to anatomically-diverse malignancies

Superficial thrombophlebitis

The association between superficial migratory thrombophlebitis and malignancy was first described by Trousseau in 1865, and therefore it is sometimes referred to as Trousseau's syndrome.[154] Nodules or cords appear on the lower legs or elsewhere, conveying the impression of “migration.” Although an association with Behcet's or Buerger's diseases is known, there is also often an association with an underlying cancer, particularly involving the pancreas, stomach, lung, prostate, or hematopoietic system.[155] The hypercoagulable state associated with these malignancies likely predisposes patients to the syndrome.[156,157]

Histopathology and specificity of findings

Microscopically, a vein at the dermal-subcutaneous interface shows thrombosis, with an inflammatory infiltrate consisting mainly of neutrophils at first, followed by lymphocytes and granulomatous elements. The infiltrates are concentrated in the immediate vicinity of the involved vessel (Fig. 16).[156,157] Although veins are traditionally distinguished from arteries by the finding of an internal elastic lamina in the latter, veins can also possess an elastic lamina. A paper by Dalton et al. indicates that the smooth muscle pattern of the vessel wall may be diagnostic: arteries have a circumferential smooth muscle pattern, while that in veins is more haphazard and “cobblestoned” in appearance.[158] In the absence of another explanation, biopsy changes of superficial thrombophlebitis should at least prompt the consideration of internal malignancy, particularly carcinoma of the body or tail of the pancreas.

Hypertrichosis lanuginosa (Malignant Down)

Clinical findings

This acquired condition consists of extensive growth of lanugo hairs that cover the face and can progress to the neck, trunk, and extremities.[159,160] Most reported patients have had a malignancy, usually carcinoma. These have included carcinomas of the lung, colon, gallbladder, rectum, uterus, breast, endometrium, and prostate; lymphoma has also been reported.[160–163] In the majority of reported patients, the

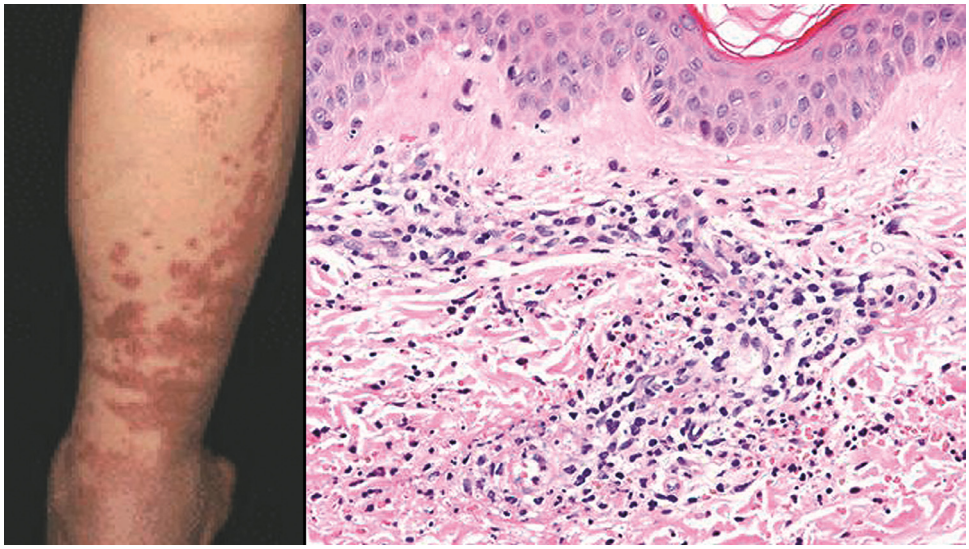

Fig. 15. Leukocytoclastic small-vessel vasculitis. Palpable purpuric lesions are present in the skin of the lower legs (left panel). Destructive intravascular infiltrates of neutrophils are present in the dermis, with erythrocyte extravasation and karyorrhexis (right panel).

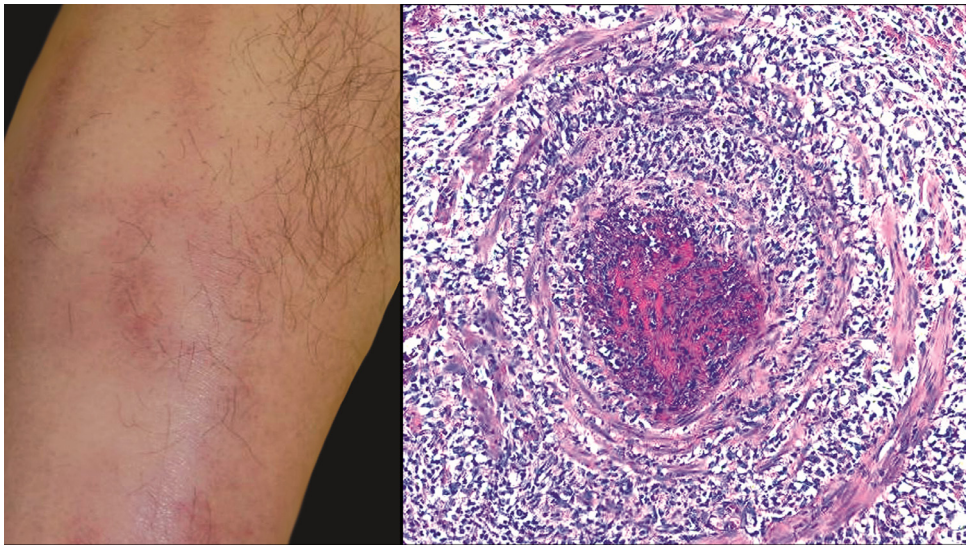

Fig. 16. Trousseau syndrome. Erythematous, firm cords are present in the skin of the forearm, representing superficial thrombophlebitis (left panel). Transmural and perivascular infiltration of superficial veins by neutrophils is present histologically (right panel).

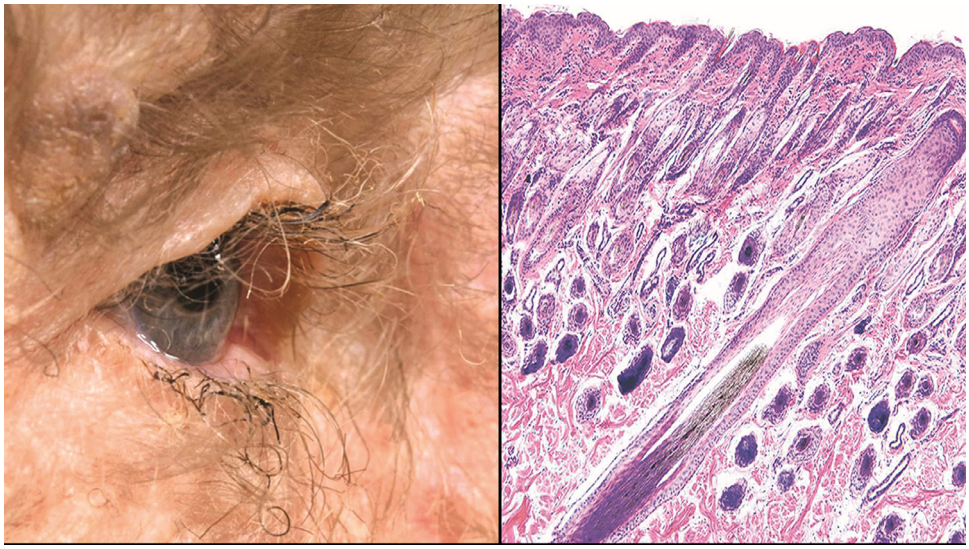

Fig. 17. Hypertrichosis lanuginosa acquisita. A profuse growth of lanugo hair is seen in the periocular facial skin (left panel). A skin biopsy of this condition shows numerous small hair follicles with the appearance of "mantle" hairs (right panel).

malignancy was known to be present when the lanugo hair growth occurred, but in a few cases, hair growth preceded identification of the cancer. Resolution of the condition has occasionally been reported to follow treatment of the underlying malignancy.[161] The pathogenesis of hypertrichosis lanuginosa is unclear, and an endocrinologic mechanism has not been discovered.

Histopathology

A histopathologic study by Hegedus and Schorr described the presence of mantle hair follicles in hypertrichosis lanuginosa. The follicular mantle is a poorly recognized structure championed by Pinkus.[163] It consists of cords of basaloid cells that extend downward around the follicular infundibulum with a resemblance in tissue sections to a set of parentheses (Fig. 17). They sometimes contain sebaceous cells and are believed to give rise to sebaceous glands. Most reported cases of hypertrichosis lanuginosa have not included histopathologic descriptions, so it remains to be seen if this is truly a characteristic finding of the disorder.

Specificity of findings and differential diagnosis

Mantle hair follicles can occasionally be seen as an incidental finding in biopsies done for other reasons, so their identification does not "make" a diagnosis of hypertrichosis lanuginosa. The condition is so striking clinically that the diagnosis is often made without resorting to histopathology. However, the pathologist might be called upon to support the diagnosis, which could be accomplished by finding increased numbers of lanugo hairs per unit area (best accomplished with horizontal sectioning of a biopsy specimen), together with the detection of mantle hair follicles (best identified in vertically oriented sections).

Tripe palms

Clinical findings

"Tripe palms" represents a form of acquired palmar keratoderma in which the palms take on what is most commonly described as a rugose (wrinkled) appearance, resembling the luminal surface of the small bowel. It is sometimes observed together with acanthosis nigricans or the sign of Leser–Trelat,[164–167] but it can also appear as an isolated

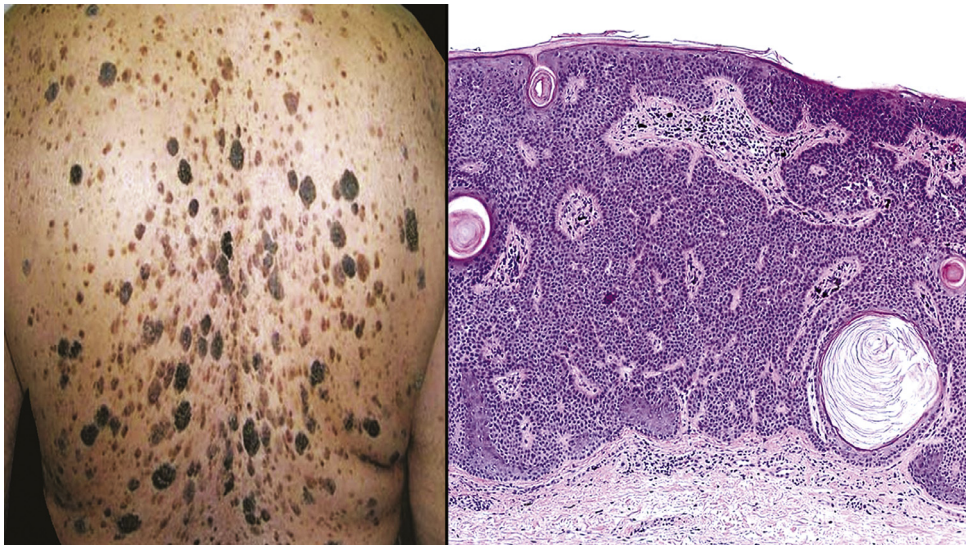

Fig. 18. Leser–Trelat syndrome. Numerous, eruptive seborrheic keratoses are present in the skin of the trunk (left panel). The lesions comprise interlocking cords and nests of cytologically-bland keratinocytes, with pigmentation and formation of squamous "horn cysts" (right panel).

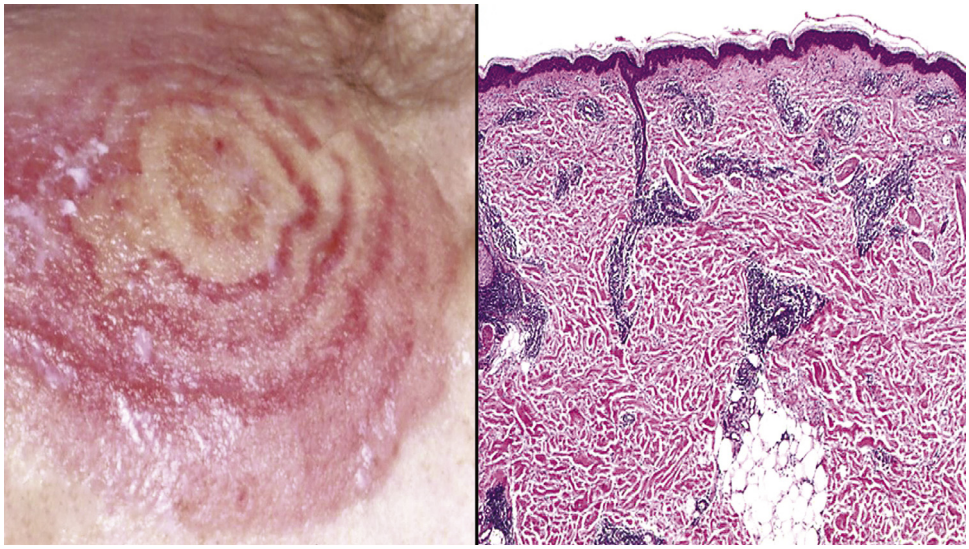

Fig. 19. Erythema gyratum repens. Arcuate erythematous bands are seen on the trunk, resembling wood grain (left panel). Dense superficial and deep perivascular lymphoid infiltrates are present microscopically (right panel).

finding. Despite some earlier literature contaminated with cases of acanthosis nigricans and keratoderma not necessarily featuring the typical "tripe palm" appearance, the evidence suggests that tripe palms constitute an independent sign of internal malignancy. Carcinomas of the lung and stomach appear to be the most common.[166]

Histopathology

Little has been written about the histopathology of tripe palms. In some instances, only "hyperkeratosis" has been emphasized.[168] However, a study by Requena et al. demonstrated an undulant (wavy) epidermis featuring hyperkeratosis, papillomatosis, and acanthosis.[169]

Specificity of findings and differential diagnosis

Additional histopathologic studies will be necessary to determine if the changes that have been described are specific for the diagnosis of tripe palms. It certainly seems likely that there would be considerable overlap with other forms of palmar keratoderma, most of which are not associated with malignancy. However, an appreciation of undulation of the epidermis could be diagnostically useful.

Proper evaluation of this feature would require sufficient sampling to enable inspection of a reasonable stretch of epidermis, and it might also be dependent upon the orientation of the specimen (i.e., whether parallel or perpendicular to the surface undulation). Again, clinical correlation would be decisive in most cases.

The sign of Leser–Trelat

Clinical findings

The sign of Leser–Trelat consists of the rapid increase in the number and/or size of seborrheic keratoses, particularly on the trunk, in association with an internal malignancy. Inflammation of seborrheic keratoses may be a part of this process,[170] and it is conceivable that a host inflammatory response directed toward existing but subtle seborrheic keratoses could account for the "rapid increase" of lesions seen in some cases. Since multiple seborrheic keratoses are prevalent, among older adults, and rapidity of onset may be questionable in any given case, a determination that the sign is present may be problematic. In addition, purists do not accept the development of multiple keratoses in the

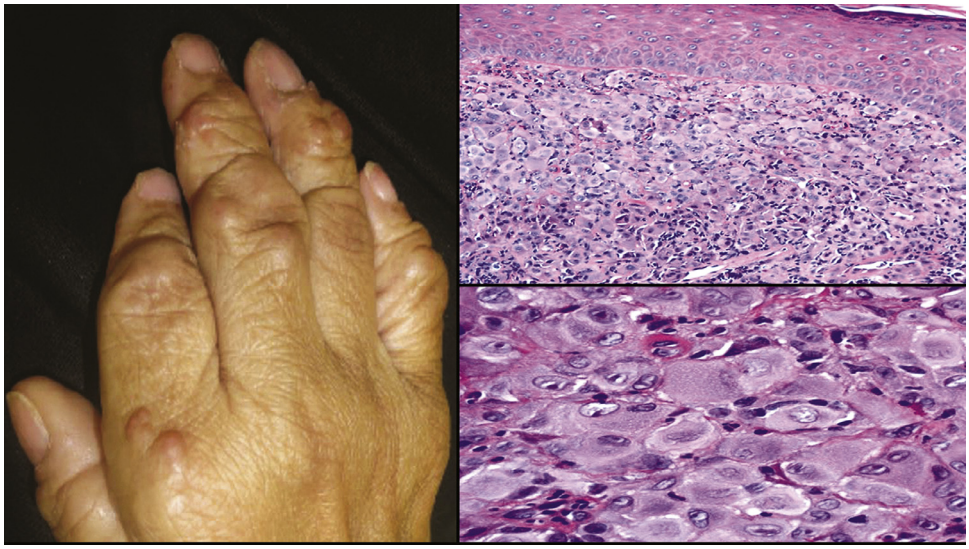

Fig. 20. Multicentric reticulohistiocytosis. Several nodules are present in the juxtaarticular skin of the hands (left), with deformative arthritis. The dermis contains a confluent infiltrate of large polygonal histiocytes with "glassy" cytoplasm (right panels).

setting of erythroderma, even if that erythroderma is a manifestation of cutaneous T-cell lymphoma, i.e., Sezary syndrome. As mentioned previously, coexistence of this sign with acanthosis nigricans has been reported.

The malignancies associated with the sign of Leser–Trelat include gastrointestinal or pancreatic carcinomas and lymphomas.[171–174] The eruption of seborrheic keratoses can precede recognition of the cancer, or it can follow or develop concurrently.[174] The seborrheic keratoses may resolve following treatment of the primary tumor. A role for growth factors in the production of these lesions has been suggested, including epidermal growth factor and *TGF-a*.[175]

Histopathology

The microscopic findings have differed somewhat from case to case, ranging from typical seborrheic keratoses to foci of hyperkeratosis with variable degrees of papillomatosis (Fig. 18).[174,176] Inflammation may be an integral part of the development of Leser–Trelat seborrheic keratoses, at least in some cases.

Specificity of findings and differential diagnosis

Unfortunately, seborrheic keratoses, including inflamed seborrheic keratoses, are quite common, and this histopathologic finding by itself is not diagnostic of the sign. However, in the context of rapidly eruptive seborrheic keratoses (particularly if other changes, such as acanthosis, nigricans or tripe palms, are also present), the microscopic features can be supportive of the diagnosis of the sign of Leser–Trelat.

Erythema gyratum repens

Clinical findings

Erythema gyratum repens is surely one of the most dramatic clinical presentations in all of dermatology. In this condition, arcuate erythematous bands, sometimes with a trailing edge of scale, migrate over the skin surface. In some cases, this produces intricate patterns resembling the grain of wood.[177–183] Involvement is concentrated over the trunk and proximal extremities. This condition has a strong association with cancers, including those in the lung, breast, and other anatomic sites.[179,181,183] However, though they are most strongly associated with malignancy, the same changes have accompanied non-neoplastic conditions such as cystic hypertrophy of the breast and pulmonary tuberculosis, and they have rarely arisen in apparently normal individuals. When linked with malignancy, the cutaneous eruption may arise either before or after the detection of the tumor.

Histopathology

The microscopic findings include foci of parakeratosis and spongiosis and a moderately intense, perivascular infiltrate concentrated around vessels of the superficial to mid-dermis, comprised of lymphocytes and macrophages (Fig. 19).[180,181] The infiltrates may rarely be more diffuse or contain eosinophils.[180] On direct immunofluorescence, granular IgG and C3 deposition can be seen along the dermal-epidermal junction,[184] the significance of which is not entirely clear.

Specificity of findings and differential diagnosis

The histopathologic image of this entity is non-specific. Basically, a diagnosis of erythema gyratum repens depends upon the clinical presentation, which, as mentioned, is usually quite striking. However, the microscopic findings can be supportive of the diagnosis. The combination of focal parakeratosis, spongiosis, and a superficial perivascular lymphocytic and macrophagic infiltrate can also be seen in the superficial variant of erythema annulare centrifugum (EAC), another less complex annular eruption that is not usually associated with internal cancer. It is interesting to note that in some case reports, erythema gyratum repens has begun as a more localized annular erythema with the clinical features of EAC.

Multicentric reticulohistiocytosis

Clinical findings

This uncommon histiocytic proliferative disorder is associated with a widespread papulonodular eruption and a severe arthritis, involving particularly the interphalangeal joints of the hands. Malignancies have been reported in up to 25%–30% of cases.[185–189] There have been a variety of types, including mesotheliomas and carcinomas of various organs.[186]

Histopathology

Microscopically, the cutaneous lesions show a dermal infiltrate of mononuclear and multinucleated cells with eosinophilic "ground glass" cytoplasm and nuclei with distinct chromatin rims and prominent nucleoli (Fig. 20). These cells express macrophage markers such as CD68 and CD163, and are sometimes factor XIIIa positive.[190] Spontaneous regression may occur after a period of years, though residual damage to joints may persist.

Other skin lesions related to visceral malignancies—the genodermatoses

The genodermatoses are inherited syndromes that feature the presence of various cutaneous marker lesions. They include Gardner's syndrome, in which unique epidermal inclusion cysts and soft tissue fibromas are associated with gastrointestinal carcinomas[191,192]; Cowden syndrome, featuring the presence of trichilemmomas and sclerotic cutaneous fibromas together with malignant tumors of various organs[193,194]; Muir–Torre syndrome, in which multiple sebaceous skin tumors or "keratoacanthomas" are linked to malignancies of the alimentary or genitourinary tracts[195,196]; and Birt–Hogg–Dube' syndrome, a disorder that shows an association between cutaneous fibrofolliculomas and various visceral malignant neoplasms.[197,198] Because these conditions are not truly paraneoplastic, but are rather genetically-driven multisystem diseases, they have not been considered in this discussion.

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