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CONTINUING MEDICAL EDUCATION

Cutaneous deposition diseases. Part I

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The cutaneous deposition disorders are a group of unrelated conditions characterized by the presence of either endogenous or exogenous substances within the dermis or the subcutis. Part I of this two-part series will focus on metabolic processes involved in the endogenous deposition in the various forms of amyloidosis, porphyria, colloid milium, and lipoid proteinosis. We will also review the clinical, histologic, biochemical, and ultrastructural findings relevant to each disorder. Basic mechanisms of pathogenesis, diagnostic modalities, and treatment options are also discussed. (J Am Acad Dermatol 1998;39: 149-71.)

Learning objective: After reading this article, participants should be familiar with the deposition disorders. On the basis of the clinical and histologic findings discussed for each disorder, clinicians should be able to distinguish between these often-confusing entities.

The cutaneous deposition disorders are a group of unrelated conditions characterized by the accumulation of either endogenous or exogenous substances within the skin. In this discussion, we review the clinical and laboratory findings in several of the endogenous deposition disorders of the skin.

AMYLOIDOSIS

Amyloidosis refers to the extracellular deposition of any of a group of unrelated proteins, leading to changes in tissue architecture and function.[1,2] The term was coined in 1838 by Schleiden, a German botanist, to describe the cellulose-like substance of plants.[2] With light microscopy, amyloid appears as an eosinophilic amorphous substance, which on Congo red staining with polarized light, demonstrates apple-green birefringence. Eelectron microscopy shows that all amyloid subtypes are composed of 7.5 to 10 nm wide linear, nonbranching tubular fibrils loosely arranged in a meshwork.[1] Each fibril is composed of several filaments arranged in a beta-pleated sheet configuration.[2] Most physiologic proteins exist in the alpha (or helical) tertiary form; the beta or pleated-sheet form is abnormal in human tissue. The quaternary structure is still hypothetic for amyloid of all types.[3]

The clinical type of amyloidosis depends on the amyloid fibril protein and the pathogenic mechanism of deposition (Table I). Amyloidosis can present with either systemic or localized deposits.

Systemic amyloidosis can be classified into a primary type caused by an occult plasma cell dyscrasia, and a myeloma-associated type. There is considerable overlap between these two in the literature.[2] Secondary or reactive amyloidosis occurs in association with chronic inflammatory systemic disease or chronic dermatoses. The various underlying disorders are listed in Table II. Other systemic forms include hemodialysis-related[4,5] and multiple heredofamilial forms, including familial Mediterranean fever, Muckle-Wells syndrome, and familial amyloid polyneuropathy.

From the Dermatology Service, Walter Reed Army Medical Center.
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Table I. Classification of amyloidosis and amyloid fibril proteins

Clinical type of amyloidosis	Amyloid fibril proteins
Systemic	
Primary	AL
Myeloma associated	AL
Secondary	AA
Heredofamilial	
Familial Mediterranean fever	AA
Muckle-Wells syndrome	AA
Familial nephropathic, polyneuropathy, cardiac	Prealbumin (transthyretin)
Hemodialysis associated	β_2-Microglobulin
Localized	
Organ limited	
Lungs, larynx	AL
Diabetes mellitus associated	Amylin
Thyroid	?Precalcitonin
Senile cerebral/Alzheimer's associated	ACPC
Hereditary cerebral	Cystatin C
Primary cutaneous	
Nodular	AL
Macular amyloidosis	Altered keratin
Lichen amyloidosis	Altered keratin
Secondary cutaneous	
Cutaneous tumors	Altered keratin

Modified from Breathnach SM (J Am Acad Dermatol 1988;18:1-16) and Vogelgesang SA, Klipple GL. (Postgrad Med 1994;96:119-27).
AA, Amyloid A; *AL*, amyloid L; *APCP*, amyloid plaque core protein.

These subtypes and organ-limited forms rarely have cutaneous manifestations and will only be mentioned briefly.

Localized cutaneous amyloidosis can be either primary or secondary. Primary cutaneous amyloidosis consists of three types: nodular, macular, and lichenoid. Secondary cutaneous amyloid deposits are found as incidental findings in multiple benign and malignant cutaneous tumors and after PUVA therapy.[1]

Noncutaneous, organ-limited forms also exist but will not be discussed.

Pathogenesis

Amyloid deposits contain a nonfibrillar protein called amyloid-P, identical to a normal circulating plasma globulin, known as serum amyloid P (SAP).[3] It constitutes up to 14% of the dry weight of amyloid and is an integral constituent of the microfibrillar sheath of normal elastic fibers.[1] SAP is closely related to the acute phase reactant C-reactive protein and has been shown to be an elastase inhibitor.[6] Although its function in amyloidosis is unknown, both SAP and the beta-pleated sheet configuration seem to protect amyloid deposits from degradation and phagocytosis, contributing to the progressive and irreversible course of amyloidosis.[7]

Primary and myeloma-associated systemic amyloidosis have immunoglobulin light chains as precursors to the amyloid fibril protein, termed *amyloid L* (AL). Most of these immunoglobulins are of the lambda type,[3] derived from serum immunoglobulins originating from a clonal plasma cell dyscrasia,[1] either overt in myeloma or occult in the primary form. Although identical light chains are usually found in the urine and serum of both groups of patients, they are distinguished by bone marrow plasma cell counts, the amount of monoclonal protein in serum and urine, and radiographic surveys.[2] Of all the patients with myelomatosis, amyloidosis occurs in about 15%.[1]

In secondary systemic amyloidosis, familial Mediterranean fever, and Muckle-Wells syndrome, a serum precursor protein (serum amyloid A [SAA]) forms the fibrils of the amyloid deposited.[1] SAA is a high-density lipoprotein and an acute-phase reactant in healthy patients.[1] The SAA is thought to be cleaved proteolytically by macrophages to amyloid A protein and excreted extra-

cellularly.[8] Although the mechanism of amyloid formation is not clearly understood, the chronic elevation of SAA in these patients seems to be linked to chronic inflammation with subsequent activation of the acute-phase response.[9]

Hemodialysis-associated amyloidosis results from high levels of β_2-microglobulin, a protein not cleared by cellulose or cuprophane dialysis membranes.[10] This is a limited form of amyloidosis that usually involves only the articular structures. The use of a different membrane can improve the primary complaint of these patients, carpal tunnel syndrome.[10] The pathogenesis of this variant remains unclear, however, because many patients who receive dialysis therapy with high β_2-microglobulins never experience the development of carpal tunnel syndrome.[10] Deposition of articular amyloid usually develops after 8 to 9 years of dialysis.[5] Skin manifestations are unusual. Recent cases include "wrinkling" of the fingers[5,11] and lichenoid truncal lesions[4] that reveal amyloid by biopsy.

Nodular amyloidosis is considered a cutaneous plasmacytoma, locally producing immunoglobulin light chains as precursors to the AL-type fibril proteins.[1,12,13] These amyloid deposits are indistinguishable from those of primary systemic amyloidosis. In one recent study,[14] the nodular amyloid fibril protein was characterized as polyclonal, suggesting that, at least in this case, the nodular amyloid deposit could be a reactive, rather than a neoplastic process .

The exact characterization of the amyloid fibers in macular and lichen amyloidosis remains to be determined. The immunoglobulins and complement present are believed to be passively absorbed.[1] Ultrastructural and immunohistochemical findings point toward degenerated keratin as the substrate (Hashimoto's "fibrillar body theory").[15] The necrotic epidermal cells (colloid bodies) are transformed into amyloid by dermal macrophages and fibroblasts. No clear explanation of how the alpha type of keratin tertiary structure is degraded and converted into the beta pleated-sheet configuration of amyloid exists.[1,16,17]

Another hypothesis, the "secretion theory" of Yamagihara et al.[18] suggests that the amyloid in macular amyloidosis may be secreted by disrupted basal cells and assembled at the dermoepidermal junction. One study[16] found electron microscopic evidence of lamina densa disruption above the amyloid deposits in patients with lichen and macular amyloidosis. The deposits contained types IV and VII collagen, laminin, lamina densa–like substance and LDA-1 antigen (a basement membrane component). Whether lamina densa abnormalities contribute to these amyloid deposits remains to be determined.

Table II. Diseases associated with secondary amyloidosis

Infectious diseases
Tuberculosis
Lepromatous leprosy
Osteomyelitis
Schistosomiasis
Autoimmune diseases
Rheumatoid arthritis
Ankylosing spondylitis
Behçet's syndrome
Sjögren's syndrome
Polymyalgia rheumatica
Inflammatory bowel disease
Malignant diseases
Hypernephroma
Hodgkin's lymphoma
Other lymphomas
Solid tumors
Miscellaneous diseases
Diabetes mellitus
Cystic fibrosis
Bronchiectasis
Drug abuse
Cutaneous diseases
Recurrent venous ulcer
Generalized psoriasis and psoriatic arthritis
Hidradenitis suppurativa
Chronically infected burns
Ulcerated basal cell carcinoma
Epidermolysis bullosa dystrophica
Epidermolysis bullosa acquisita
X-linked anhidrotic ectodermal dysplasia

Clinical features

Systemic. Primary and myeloma-associated amyloidosis most commonly occur in elderly men.[3] Patients may have nonspecific constitutional symptoms, macroglossia, carpal tunnel syndrome, or edema. Less common presentations include sicca syndrome,[14] the "shoulder pad sign"[19] (amyloid deposits in soft tissues around the shoulders), and a rheumatoid arthritis–like deposition in small joints.[3] Gastrointestinal bleeding, peripheral neuropathies, and cardiac involvement

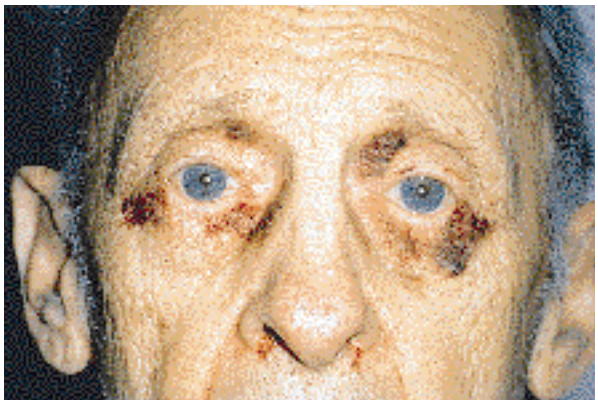

Fig. 1. Systemic amyloidosis seen as periorbital purpura. (From the files of Walter Reed Army Medical Center [WRAMC].)

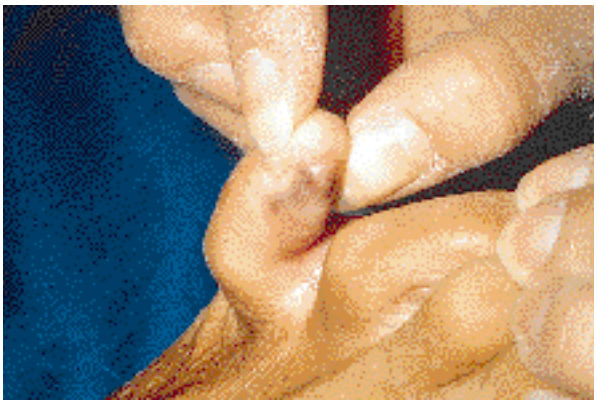

Fig. 2. Nodular cutaneous amyloidosis seen as a firm subcutaneous nodule of the toe with purplish discoloration caused by hemorrhage.

also occur.[3] Congestive heart failure or arrhythmias account for death in about 40% of patients with systemic amyloid.[20]

Skin or mucous membrane lesions are seen in 40% or less of cases.[21] The most common lesion is purpura, seen in 15% to 17% of patients.[3] It occurs after minor trauma (pinch purpura) particularly in areas such as eyelids, axilla, umbilicus, and anogenital regions. Facial purpura can occur after a Valsalva maneuver or proctoscopy (Fig. 1). Purpura results from amyloid deposition in vessel walls; the deposits can leave cutaneous vessels thickened and cordlike.[22] Other factors include coagulopathies caused by amyloid infiltration of the liver, decreased vitamin K absorption, urinary losses of clotting factors, and acquired factor IX and X deficiency.[23] Impaired platelet function also can exist.[23] Asymptomatic papules, plaques, and nodules with a waxy, hemorrhagic appearance occur less commonly and are located in flexural areas, the central area of the face, the retroauricular fold, and the oral cavity, especially the tongue.[1] Facial plaques may coalesce, resulting in a leonine appearance; a sclerodermatous infiltration may occur.[24] Bullous lesions,[25] alopecia,[26] and cutis laxa[27] have also been reported in association with systemic amyloidosis.

Localized. Nodular (tumefactive) cutaneous amyloidosis may be seen with lesions similar to those described for primary cutaneous amyloidosis[1] or with firm, subcutaneous nodules (Fig. 2) up to several centimeters in diameter.[3] They are brown-pink, waxy nodules often with overlying telangiectasias.[28,29] They occur on the face, extremities, and trunk or genitalia and can appear atrophic, anetodermic, or bullous, possibly from dermal destruction of elastic and collagen fibers.[30] The nodular variant is the rarest of the cutaneous amyloidosis.[28] Women are affected twice as often as men, usually in the sixth and seventh decades of life.[28] There is an infrequent (less than 15%) progression of nodular-localized lesions to systemic amyloidosis.[31] The condition should be investigated with radiographic examination,[3] biopsies, and evaluation of immunoglobulins[31] to detect a latent paraproteinemia and systemic disease.

Lichen amyloidosis commonly is seen as red-brown pruritic hyperkeratotic papules on the shins (Fig. 3) with a subsequent spread to the dorsa of the feet and thighs. It occurs more commonly in persons of Chinese ancestry.

Macular amyloidosis is seen as gray-brown pruritic patches anywhere on the trunk or extremities, but especially on the upper the back (Fig. 4). Small papules may coalesce into a rippled pattern. Macular amyloidosis occurs more commonly in Central and South American, Asian, and Middle Eastern populations.[3]

Variants of primary localized amyloidosis include periorbital hyperpigmentation,[33] "nylon-brush" amyloidosis,[34] and a whorled biphasic form following Blaschko's lines.[35] Macular amyloidosis has been reported in association with notalgia paraesthetica.[36] Neither macular nor lichen amyloidosis has, to our knowledge, been reported to progress to systemic disease.

Rare variants of localized cutaneous amyloid include poikiloderma-like cutaneous amyloid

Fig. 3. Lichen amyloidosis reveals multiple hyperkeratotic papules on anterior leg.

(PCA)[37], biphasic amyloidosis, and a familial form.[38] PCA occurs in either a focal or generalized distribution. It may occur in association with the "PCA syndrome," an autosomal-dominant disease with poikiloderma, lichenoid papules, photosensitivity, blistering, and short stature.[29] Biphasic amyloidosis consists of both macular and lichen amyloidosis in the same patient. It may represent an evolution of lesions believed to be caused by scratching[29,39] or two separate entities. A familial form of primary cutaneous amyloidosis is characterized by swirled pigmentation of the trunk or extremities. The disease begins in childhood and is associated with pruritus.[38]

Amyloidosis of the auricular concha[40] is a rare variant of primary cutaneous amyloidosis. The lesions are described as papules grouped on the concha and are typically not pruritic. The amyloid is derived from keratinocytes and gives a positive reaction with monoclonal antikeratin antibodies.

Fig. 4. Macular amyloidosis shows small hyperpigmented papules on the upper back with coalescence into a rippled pattern. (From the files of Walter Reed Army Medical Center [WRAMC].)

Other unusual variants of localized amyloidosis include nodular deposits in the respiratory[41] or urinary tract,[1] amyloidosis associated with certain neoplastic and degenerative disorders of endocrine glands,[10] and aging and Alzheimer's disease.[10,42]

Nodular amyloidosis has been reported in association with Sjögren's syndrome.[14,43] These amyloid deposits are localized or organ limited to dermis and lung and are of immunoglobulin light chains derived from plasma cells in the area surrounding the amyloid nodules.

Localized secondary cutaneous amyloidosis consists of clinically insignificant microscopic deposits of amyloid occurring as a secondary phenomenon in association with several skin tumors.[1,12,44] This form has most commonly been reported in association with skin lesions of epithelial origin that include basal cell carcinoma, Bowen's disease, squamous cell carcinoma, seborrheic keratosis, and disseminated superficial actinic porokeratosis. The mechanism of amyloid formation is these tumors is thought to be analogous to that which occurs in lichen and macular amyloidosis.

Histology

A variety of stains can demonstrate amyloid deposits in skin biopsy specimens. The best known is the Congo red stain, which under polarizing light reveals "apple-green" birefringence of amyloid deposits (Fig. 5). Secondary amyloidosis (amyloid A) loses its staining with Congo red after pretreatment with potassium permanganate,[2]

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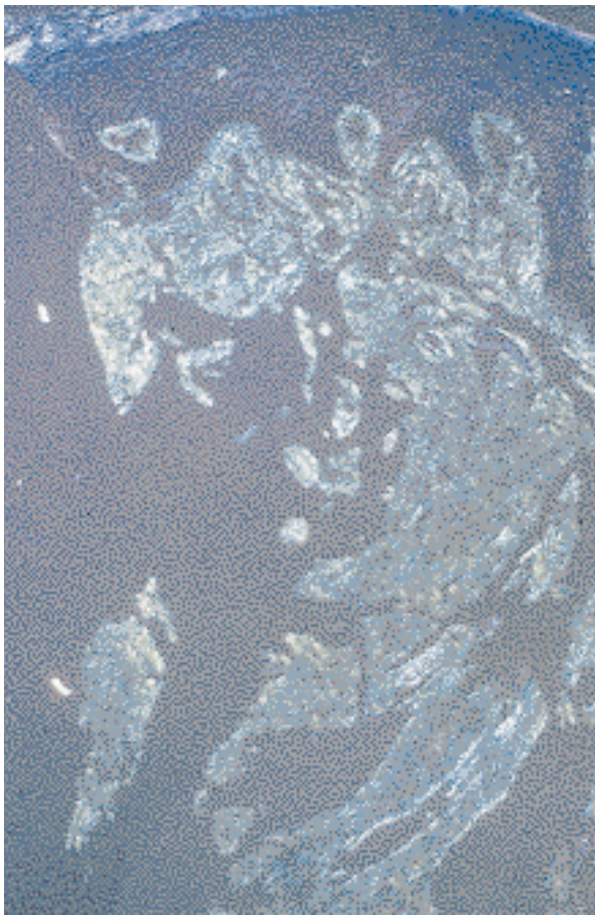

Fig. 5. Amyloid deposits in systemic amyloidosis reveals apple-green birefringence on polarization. (Congo Red stain; original magnification ×25.)

whereas primary systemic, myeloma-associated, and localized amyloid deposits are resistant to potassium permanganate. A more sensitive method is the use of antisera to the fibril proteins κ, λ, protein A, prealbumin, and β_2-microglobulin, and the universal stain, antiSAP. Other stains include the periodic acid–Schiff (PAS), methyl violet, crystal violet, various cotton dyes (sirius red, pagoda red, dylon stain), and the fluorescent dyes, thioflavin-T and phorwhite BBU.[3]

Formalin-fixed tissue may be processed for electron microscopy (EM). On EM, amyloid deposits consist of 6 to 10 nm wide, straight, nonbranching, nonanastomosing filaments arranged in a loose meshwork (Fig. 6). Research on the tertiary structure of various amyloid proteins is being carried out with both radiographic diffraction and infrared spectroscopy.[1,17]

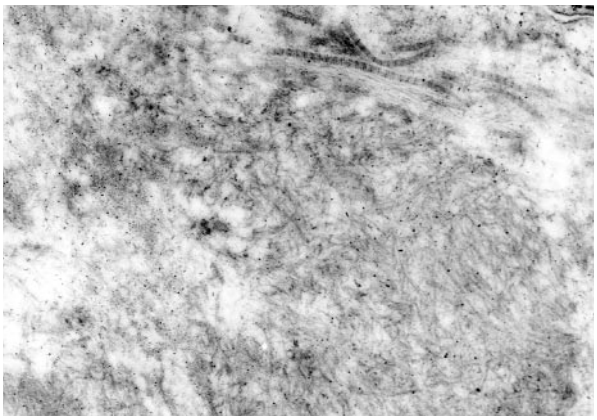

Fig. 6. Electron micrograph shows amyloid filaments. Collagen fibers are seen at the top. (EM; original magnification ×37,700.)

Systemic. In primary systemic and myeloma-associated amyloidosis, dermal and subcutaneous masses of amyloid appear pink, fissured, and amorphous with hematoxylin and eosin stain. Deposits may be seen in blood vessel walls, subcutaneous fat, and the membrana propria surrounding eccrine glands and other mesenchymal tissues (Fig. 7). Amyloid deposits around individual fat cells (amyloid rings) are distinctive; they often cause the fat to be brittle and the specimen to be fragmented on aspiration.[3] Multiple organs including the peripheral vessels, tongue, gastrointestinal tract, heart, and kidney may also show deposits.

The deposits are not usually associated with an inflammatory infiltrate.[1] A biopsy specimen of clinically normal forearm skin has been reported to reveal amyloid in 55% or less of primary and myeloma-associated amyloidosis.[21] More sensitive is the fine-needle aspirate of the abdominal fat pad; 95% or less of cases are reported to be positive in these types.[45] About 66% of secondary (amyloid A) cases are positive.[45] A rectal biopsy specimen is positive in approximately 75% of primary systemic amyloidosis, but only if submucosa is included.[20] Histologic patterns identical to those seen in lichen and nodular amyloidosis can also be seen in systemic amyloidosis.[3]

Although the skin is grossly uninvolved in secondary amyloidosis; amyloid deposits in the deep dermis around adnexae, blood vessels, and fat cells can be seen in approximately 50% of patients.[21] Indirect immunofluorescence with anti-amyloid A

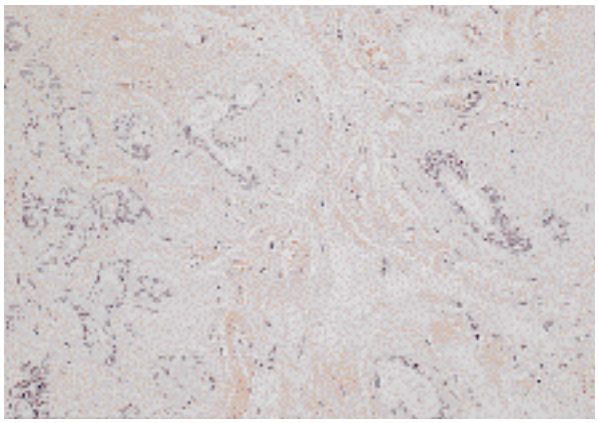

Fig. 7. Systemic amyloidosis reveals amorphous pink fissured dermal masses surrounding adnexae and blood vessels. (Hematoxylin-eosin stain; original magnification ×50.)

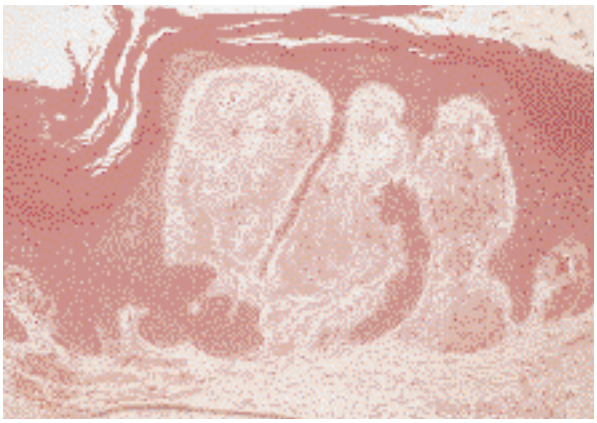

Fig. 8. Lichen amyloidosis reveals papillary dermal deposits of pink, amorphous amyloid. (Hematoxylin-eosin stain; original magnification ×25.)

antiserum and potassium permanganate reaction can distinguish amyloid A protein from AL protein.[46]

Localized. In nodular cutaneous amyloidosis, an atrophic epidermis overlies large, amorphous, clefted masses of amyloid, extending from the papillary and reticular dermis into the subcutaneous fat. Deposits can also be seen around adnexa, blood vessels, and fat cells.[8] An inflammatory infiltrate with prominent plasma cells is seen; Russell bodies and giant cells are also noted.

On EM, mature plasma cells are seen at the periphery of amyloid deposits. Within their cytoplasm, amyloid can be seen in proximity to intermediate filaments of the plasma cells. Their cytoplasm stains histochemically with anti-Ig light chains. Amyloid synthesis and secretion by plasma cells in situ appears likely, although the mechanism remains unknown.[47]

In contrast to nodular amyloidosis, in which deposits are found throughout the dermis and subcutaneous fat, lichen and macular amyloidosis have deposits in the papillary dermis (Fig. 8), usually within the dermal papillae.[48] Lichen amyloidosis can sometimes be distinguished from the macular form by the presence of hyperkeratosis, acanthosis, and larger deposits. The amyloid may be circumscribed and globular, consistent with colloid bodies, and may be in contact with basal cells at the basement membrane zone. Identical structures can be seen in the epidermis but fail to stain as amyloid. Pigmentary incontinence, hemorrhage, and hemosiderin can also be seen in the papillary dermis.

On EM, the amyloid of lichen and macular amyloidosis is composed of amyloid filaments, normal and degenerated tonofilaments, and lysosomes. Direct immunofluorescence in primary localized cutaneous amyloidosis reveals IgM, C3, and light chains, believed to be passively absorbed.[49] Monoclonal antikeratin antibodies are often reactive with these deposits in lichen and macular forms of amyloidosis.

Treatment

Systemic. Most reports on the treatment of primary and myeloma-associated amyloidosis have been anecdotal, and responses to treatment are difficult to assess because of poor correlation between amyloid load and organ function.[50] A comprehensive review of recent chemotherapy trials has recently been published.[50] Cytotoxic chemotherapy is the mainstay of treatment and is aimed at controlling the aberrant plasma cell population and the amount of amyloid precursor light chains. Melphalan, prednisone, colchicine, penicillamine, azathioprine, vincristine and cyclophosphamide have been used to control systemic disease. Melphalan combined with prednisone and possibly colchicine appears to offer possible benefit in the treatment of AL. However, significant bone marrow toxicity limits the value of this treatment. Disease regression and prolonged survival were seen in a small number of patients treated with alkylating-agent–based chemotherapy.

Supportive therapy, cardiac and renal transplantation, and dialysis have also been described. Colchicine was found to improve life expectancy in one study of 53 patients with AL-type amyloidosis.[51,52] Experimental disaggregation of primary AL amyloid λ chain fibrils was performed in vitro in a recent report[7] that used α_1-antitrypsin and may have future therapeutic implications.

Future treatment approaches may include more aggressive chemotherapy, myeloablation, and autologous bone marrow transplantation.[51] Recent investigations into the treatment of systemic amyloidosis include immunotoxins directed against the precursors of the amyloidogenic plasma cells.[51] Conflicting evidence exists concerning vitamin C[50] and vitamin E.[50] A recent study[53] that showed a doxorubicin derivative enhancing resorption of AL amyloid in vitro and in murine models holds promise.

Dimethyl sulfoxide (DMSO) was one of the earliest treatments for amyloidosis. It is a dipolar industrial solvent used as a chemical solubilizing agent.[54] It is a nontoxic, antiinflammatory drug with a major side effect of halitosis. Topical use may result in erythema, pruritus, and urticaria. DMSO in vitro was found to solubilize amyloid A fibrils and enhance excretion of amyloid-like substance in mice.[54] Although the benefit in systemic disease is not clearly established, the skin lesions of both primary and myeloma-associated amyloidosis have responded to oral DMSO.[11,55] It may inhibit amyloid synthesis or act to promote amyloid degradation.[56]

Renal function improvement has been reported with DMSO in secondary AA amyloidosis and was believed to be secondary to its antiinflammatory properties.[1] Treatment of the underlying inflammatory or infectious process can often result in clinical improvement of the secondary systemic amyloid deposits. Amyloidosis secondary to juvenile rheumatoid arthritis has responded to chlorambucil in some patients.[57] Colchicine is the treatment of choice in familial Mediterranean fever.[58]

Localized. Lichen amyloidosis may respond to dermabrasion,[1,59] topical DMSO,[50] and etretinate,[60,61] although these were anecdotal reports. One etretinate failure has also been reported.[62] Anecdotal reports of improvement in pruritus and flattening of papules[63,64] with topical DMSO for lichen amyloidosis have been published, but failure has also been reported.[65] Topical steroids and antipruritics have not provided relief to most patients. Macular amyloidosis was treated with UVB[66] with some symptomatic relief. Well-controlled studies are limited in number, and satisfactory treatment overall is lacking at present for all forms of cutaneous amyloidosis. Nodular lesions of primary localized cutaneous amyloidosis have been treated with excision[67] and the carbon dioxide laser,[68] although recurrences can be expected with both. Electrodesiccation and curettage provided an acceptable cosmetic result in one case report.[67]

PORPHYRIAS

The porphyrias are a group of inherited or acquired disorders resulting from excessive production of porphyrins or their precursors during heme synthesis. The synthesis of heme occurs primarily in the liver and bone marrow.[69] These sites can serve as the basis for a classification scheme of the various porphyrias, in conjunction with the enzyme deficiency. The heme biosynthetic pathway, clinical types of porphyrias, and associated enzyme deficiency are shown in Fig. 9. Porphyrias are classified into erythropoietic, hepatic, and erythrohepatic types based on the tissue in which the biochemical defect is localized. Congenital erythropoietic porphyria (CEP) or Gunther's disease is the erythropoietic type. The hepatic type includes acute intermittent porphyria (AIP), variegate porphyria (VP), porphyria cutanea tarda (PCT), and hereditary coproporphyria (HCP). Erythropoietic protoporphyria (EPP), erythropoietic coproporphyria and hepatoerythrocytic porphyria (HEP) are the erythrohepatic type.

Pathogenesis

Enzymatic defects in the heme synthetic pathway result in elevated intermediates called porphyrinogens, which, in a critical step, are oxidized to photosensitizing porphyrins. Porphyrins principally absorb radiation in the Soret band of 400 to 410 nm,[70] which converts them to an unstable, excited state. On transfer of this energy to oxygen, the molecule returns to ground state, creating excited-state oxygen molecules. The reactive oxygen species (singlet O_2, superoxide radical, H_2O_2) finally transfer their energy to the water or lipids of plasma membranes, DNA, or membrane-bound structures, causing tissue damage, and ultimately,

Table III. Classification of porphyria and laboratory abnormality

Clinical types	Site of metabolic expression	Predominant porphyrins			
		RBC	Plasma	Urine	Feces
Congenital erythropoietic porphyria	Erythroid cells	URO I > COPRO I stable fluorescence	URO I > COPRO I	URO I > COPRO I	COPRO I > URO I
Acute intermittent porphyria	Hepatocytes	Negative	Negative	ALA + PBG continuously	Negative
Hereditary coproporphyria	Hepatocytes	Negative	Negative	COPRO; ALA + PBG during attack	COPRO
Variegate porphyria	Hepatocytes	Negative	COPRO PROTO	ALA + PBG during attack; COPRO > URO	PROTO > COPRO
Porphyria cutanea tarda	Hepatocytes	Negative	URO I	URO I > III; 7-COOH-PIII > I continuous fluorescence	ISOCOPRO
Hepatoerythropoietic porphyria	Erythroid cells and hepatocytes	PROTO	URO COPRO	URO ISOCOPRO	COPRO ISOCOPRO
Erythropoietic protoporphyria	Erythroid cells and hepatocytes	PROTO COPRO transient fluorescence	PROTO	Negative	PROTO COPRO

Modified from Meola T, Lim HW. Dermatol Clin 1993;11:583-96; Young JW, Conte ET. Int J Dermatol 1991;30:339-406; and Moore MR, McColl KEL, Fitzsimons EJ, Goldburg SA. Blood Rev 1990;4:88-9.
ALA, δ Aminolevulinic acid; *COPRO*, coproporphyrin; *ISOCOPRO*, isocoproporphyrin; *PBG*, porphobilinogen; *PROTO*, protoporphyrin; *URO*, uroporphyrin; *7-COOH-P*, 7-carboxyl-porphyrin.

clinical lesions as seen in the skin, liver, and erythrocytes of the various porphyrias.[71] UV-induced complement activation,[72] mast cell degranulation,[73] and neutrophil superoxides[74] may also play a role in skin injury, although the exact mechanism is still unclear. The cellular damage in porphyria is partially dependent on the solubility properties of the accumulated porphyrins. As the pathway progresses, the number of carboxyl side groups decrease. This in turn decreases the water solubility and correlates to some extent with the clinical and laboratory differences among the porphyrias. The classification and laboratory abnormalities are shown in Table III.

Clinical features

Congenital erythropoietic porphyria. Congenital erythropoietic porphyria (CEP), or Gunther's disease, is a rare autosomal recessive disorder usually occurring between birth and 5 years of age. The defective enzyme is uroporphyrinogen III cosynthase. An overproduction of uroporphyrin I occurs via the nonenzymatic pathway. The predominant porphyrins found are uroporphyrin and coproporphyrin in urine, feces, erythrocytes, and plasma. Uroporphyrin I is a toxic compound that accumulates in erythrocytes causing hemolysis[75] and turns the urine pink-red. Pink-staining diapers allows early diagnosis in infancy.

Clinically, patients have erythema, stinging, and blistering after UV exposure to exposed sites. Ulcerations and mutilating scarring of the ears and nose can occur. Ocular involvement can lead to blindness. Other findings include erythrodontia, alopecia, splenomegaly, and hemolysis.[71]

Acute intermittent porphyria. Acute intermittent porphyria (AIP) is inherited as an autosomal dominant trait and, in both acute and latent cases, is characterized by a deficiency of porphobilinogen deaminase. The gene defect alone does not induce disease unless the precipitating factors discussed later are present. There are no cutaneous findings. Patients have severe abdominal pain with or without peripheral neuropathy and psychiatric

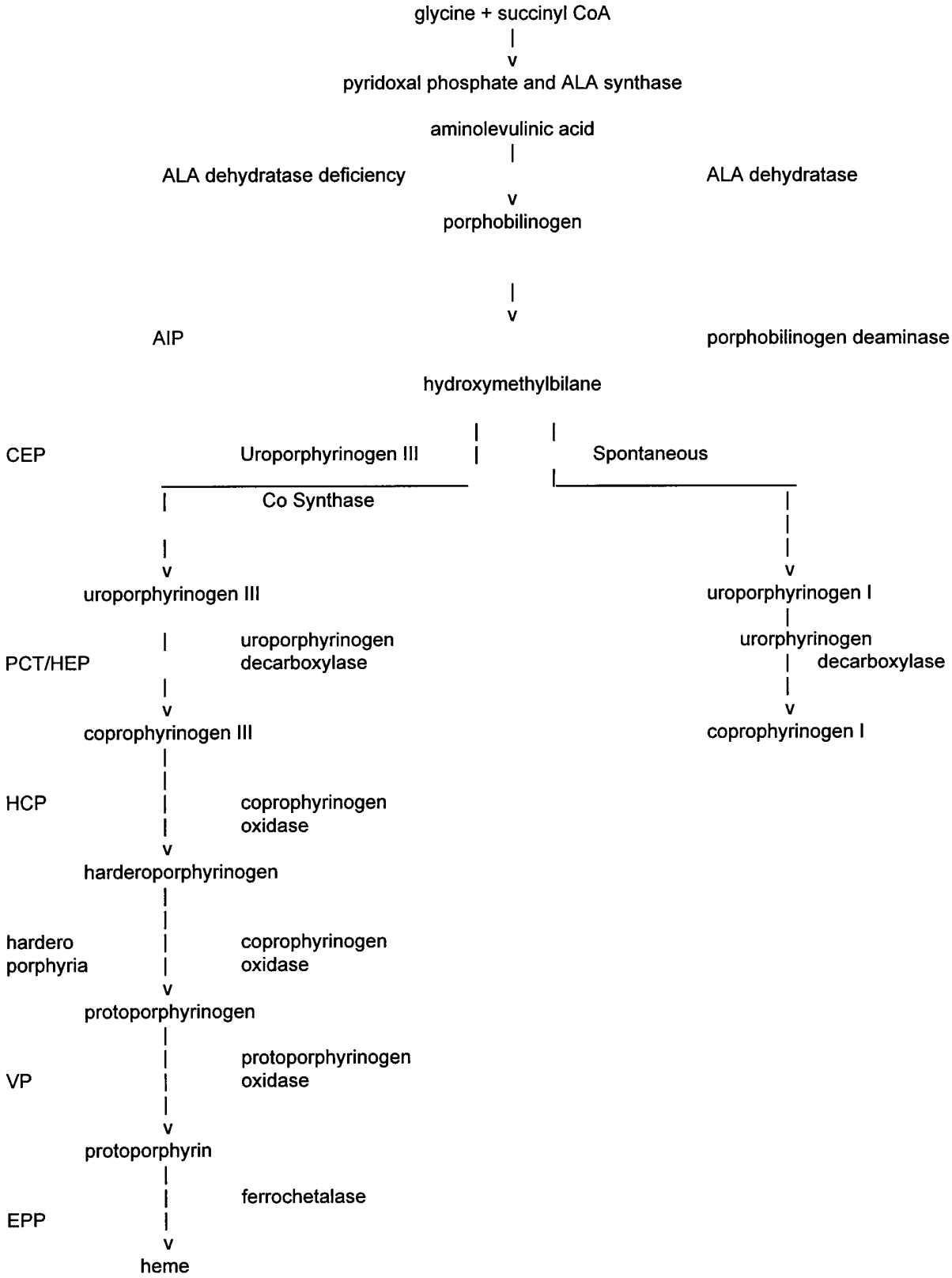

Fig. 9. Pathway of heme synthesis, clinical types of porphyria, and associated enzyme deficiency. (Modified from Meola T, Lim HW. Dermatol Clin 1993;11:583-96; Young JW, Conte ET. Int J Dermatol 1991;30:339-406; and Moore MR, McColl KEL, Fitzsimons EJ, Goldburg SA. Blood Rev 1990;4:88-9.)

symptoms.[76] The mechanism appears to be a central, peripheral, or autonomic nervous system dysfunction. This dysfunction is likely caused by a deficiency of heme within neural tissue[71] or to the neurotoxic properties of δ aminolevulinic acid (ALA) or porphobilinogen (PBG).[71] Attacks may be triggered by drugs (oral contraceptives, barbiturates, sulfonamides, enzyme-inducing anticonvulsants, antidepressants, griseofulvin), infections, alcohol, fasting, and hormonal changes.[70,76]

The primary laboratory abnormalities, urinary ALA and PBG, are markedly elevated during acute attacks and mildly elevated during remissions.[70]

Hereditary coproporphyria. Hereditary coproporphyria (HCP), also known as harderoporphyria in the homozygous state, is a rare autosomal dominant disorder of heme synthesis. The deficient enzyme is coproporphyrinogen oxidase, which leads to an accumulation of coproporphyrin. Clinically, acute attacks may mimic AIP, although cutaneous findings mimic PCT. Photosensitivity with blistering is present in about 30% of patients.[70] Drugs that induce AIP also can precipitate acute attacks of HCP, probably through induction of ALA synthase activity with subsequent precursor buildup.[70] These are neurotoxic and likely produce the acute neurovisceral symptoms.

Laboratory evaluation in acute attacks reveals elevated urinary coproporphyrin, ALA, and PBG. Chronic elevation of fecal coproporphyrin is also seen.

Variegate porphyria. Variegate porphyria (VP), or mixed porphyria, is an autosomal dominant disorder most prevalent in South Africans of Dutch ancestry. It is characterized by decreased protoporphyrinogen oxidase activity. Like HCP, the lack of enzyme activity in the distal heme pathway results in loss of negative feedback of ALA synthase and the accumulation of ALA and PBG. Neurologic and laboratory abnormalities consistent with AIP are present, as well as photocutaneous lesions similar to those in PCT. The skin lesions result from the accumulated distal substrates, protoporphyrin, and protoporphyrinogen.

Laboratory evaluation reveals increased urinary excretion of ALA, PBG, uroporphyrin, and coproporphyrin. Stool samples contain elevated coproporphyrin and protoporphyrin levels.

PCT. PCT, the most common form of porphyria in North America and Europe, represents a group of disorders either inherited in an autosomal dominant fashion or acquired. The acquired form may occur sporadically or may be induced by toxins or drugs. In all these forms, there is decreased activity of uropophyrinogen decarboxylase. The homozygous inherited form is called hepatoerythropoietic porphyria. Both erythrocyte and liver-enzyme activity are reduced in the inherited forms; in the sporadic forms only the liver enzyme is deficient. Precipitating agents in the acquired forms include alcohol, estrogen, polychrorinated hydrocarbons, iron, and hepatic neoplasms.[76]

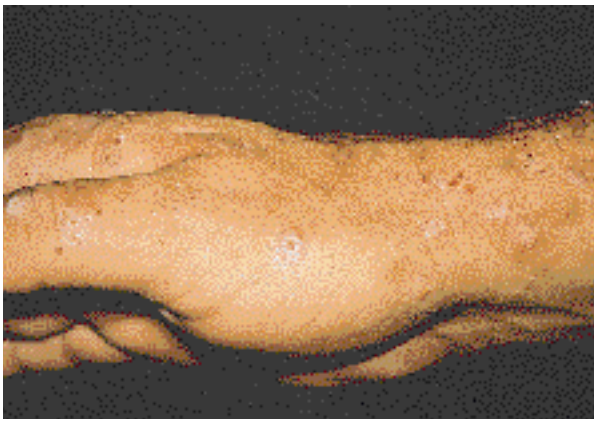

Fig. 10. Scarring, erosion, and milia on the hand of a patient with PCT.

Clinically, erosions, vesicles, and bullae occur in exposed areas after even minor trauma. Skin fragility, milia, and scarring are often present (Fig. 10). Malar and upper extremity hypertrichosis can be present, with patchy hyperpigmentation and sclerodermoid plaques.[71]

Laboratory findings include increased urine porphyrins that fluoresce under Wood's lamp. Uroporphyrins are present in the urine, and isocoproporphyrins are found in both the urine and stool.[71]

A high prevalence (70.7% or less) of hepatitis B virus (HBV) has been found in association with PCT.[77,78] PCT has also been frequently associated with other viruses, namely HIV[79,80,81] and hepatitis C virus (HCV).[82,83] In two recent reports,[79,80] 24 cases of an association of HIV infection with PCT have been described. The usual risk factors for HIV infection were present in most of these patients. PCT was diagnosed either before, concurrent with, or after the diagnosis of HIV infection. Patients were younger than the usual age for the sporadic PCT. Many patients also had associ-

ated HBV infection. Liver damage by viral hepatitis, alcoholism, and drugs is probably linked to the pathophysiologic finding of PCT.[79,80] However, hepatitis may not account for the development of PCT in all cases. HIV infection predisposes patients to photosensitivity, and this may play a pathogenic role.[81] Patients with nonfamilial PCT should be routinely assessed for the presence of HIV infection.

The initial reports from Italy, France, and Spain that link PCT with an underlying HCV infection showed a global prevalence of 71% in sporadic PCT.[82] No large studies on patients in the United States have been published, but preliminary reports[83,84] suggest that HCV infection is common in these persons as well.

Cribier et al.[82] found a 58% prevalence of HCV infection in a series of 12 patients with sporadic PCT. The young age at onset of PCT suggests that HCV is a major triggering factor of PCT. No correlation was found between the severity of the viral infection and presence of PCT symptoms, which suggests an indirect role of HCV. The mechanism of action of HCV in PCT is unknown. The proposed hypotheses are that decreased activity or presence of inhibitor of uroporphyrinogen decarboxylase produced by damaged liver cell or an excess of hepatocellular iron in the liver accounts for the development of PCT. In a study of 34 patients with sporadic PCT, antibodies against HCV were detected in 91% and against HBV in 41%.[85]

Because HCV and HBV infections are common in patients with PCT and these patients may be asymptomatic for liver disease and only 50% have abnormal liver function tests, it is strongly suggested that screening for HCV and HBV infections should be done in all patients with PCT.[83]

Pseudoporphyria is a condition that clinically mimics PCT with bullae and increased skin fragility in exposed areas, principally the dorsum of the hands. Bullae may heal with scarring and milia formation. The histologic, immunofluorescence findings and ultrastructural features are identical to those found in PCT. In contrast to PCT, hypertrichosis, hyperpigmentation, and sclerodermoid skin changes are usually absent. There is no abnormality of porphyrin metabolism in pseudoporphyria.

Pseudoporphyria occurs in patients undergoing prolonged hemodialysis[86,87] and less often in those undergoing peritoneal dialysis.[88] In a series of 180 patients who were receiving hemodialysis therapy, 28 patients (16%) showed a PCT-like eruption. Normal porphyrin levels in urine, plasma, and stool were found. However, in a few patients receiving hemodialysis therapy for chronic renal failure, true PCT may coexist.[89,90] In patients with pseudoporphyria, urinalysis may not be representative of porphyrin metabolism, and the plasma and fecal porphyrins should be measured for correct diagnosis.[87,91]

Pseudoporphyria may occur after intake of certain medications such as tetracyclines, furosemide, nalidixic acid, dapsone, pyridoxin, and naproxen.[91,92] It has also been reported after exposure to a large dose of UVA.[93]

Erythropoietic protoporphyria. Erythropoietic protoporphyria (EPP) is an autosomal dominant disorder of ferrochelatase activity in the terminal step of heme synthesis. It does not display neural manifestations. Symptoms develop in early childhood and often consist of acute burning erythema and edema of the skin with sun exposure. Linear crusted lesions occur on the face and hands and heal with scarring. Protoporphyrin cholelithiasis and mild liver disease can occur.[71] Severe hepatic disease has been reported in a small percentage of patients. Rarely, liver disease may lead to acute liver failure.[94]

Laboratory evaluations reveal normal urinary porphyrins because of the insolubility of protoporphyrins in water.[71] Elevations of protoporphyrin are present in erythrocytes, plasma, and occasionally feces. Coproporphyrins may also be present in feces and erythrocytes.

Histology

The histologic findings are similar in all six types of porphyria with skin lesions. Epidermal hyperkeratosis, hypergranulosis, acanthosis, as well as peculiar, elongated, segmented eosinophilic structures in the roof of PCT and EPP bullae called "caterpillar bodies" may be seen. These structures are composed of basement membrane material (type IV collagen and laminin) that likely become incorporated into the blister roof after reepithelialization of the blister.[95] Cell-poor subepidermal bullae (Fig. 11) are formed from cleavage within the lamina lucida. The mechanism of lesion formation remains unclear. Both the epidermal basement membrane and upper dermal blood vessels contain homogeneous, eosinophilic

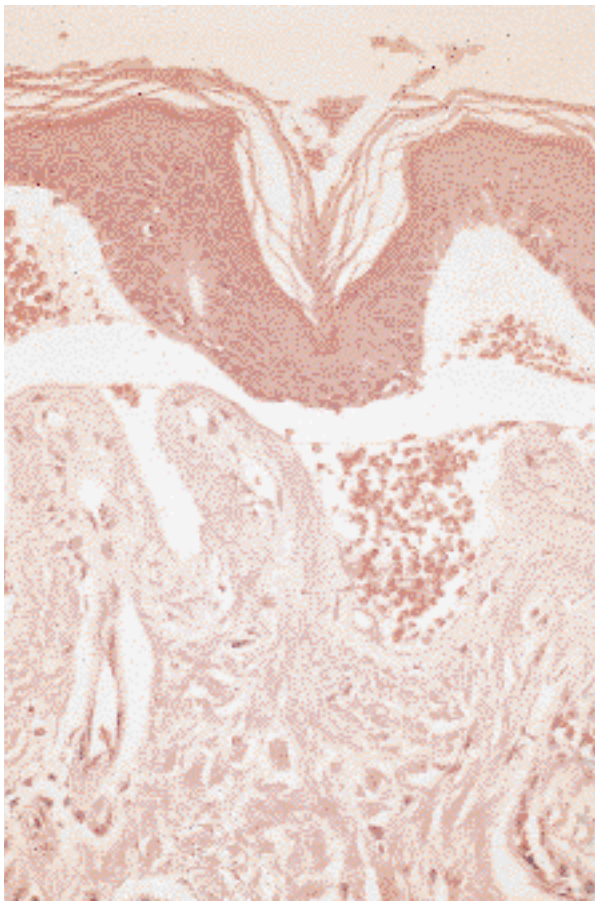

Fig. 11. Cell-poor subepidermal bulla with prominent festooning in a case of PCT. (Hematoxylin-eosin stain; original magnification ×66.)

deposits of PAS-positive (Fig. 12), diastase-resistant material on light microscopy.[96] It is the dermal vessel changes that seem to play the dominant role in bullae formation in PCT; the basement membrane zone (BMZ) changes are milder and are nonspecific findings seen in other bullous dermatoses. The cleavage may result from proteases released from damaged vessel endothelial cells, with interleukin-1 and interleukin-2 serving as inflammatory mediators.[97] The possible role of autoantibodies has also been raised.[97] The inflammatory mediators may cause lamina lucida separation with resultant bullae formation and may be the trigger for basal lamina reduplication.[97]

Acid mucopolysaccharides and lipids can be demonstrated in the BMZ and perivascular eosinophilic deposits. In severe lesions, as seen in EPP, these perivascular mantles may be seen in the deeper dermis and around eccrine glands.

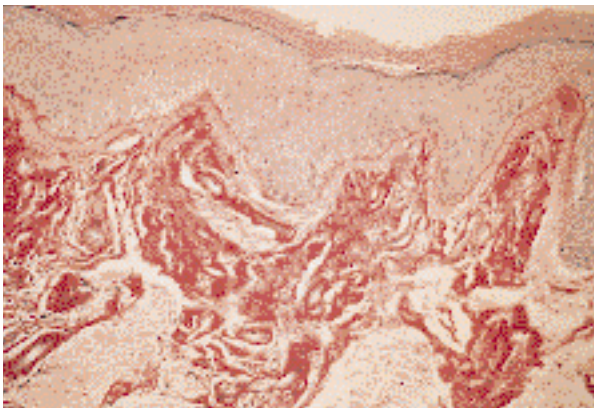

Fig. 12. Erythropoietic protoporphyria shows marked papillary dermal and perivascular deposition of eosinophilic material. (Periodic acid-Schiff stain; original magnification ×45.)

Ultrastructurally, these hyaline-like deposits consist of concentric basement membrane multiplications. Peripheral to this is an unlayered, amorphous, and filamentous mantle containing type IV collagen and possibly reticulum fibers; the exact composition, however, is unknown.[98]

Tissue amyloid P component, a glycoprotein identical to SAP, has been identified in perivascular deposits of EPP.[98]

On direct immunofluorescence (DIF) staining, immunoglobulins, especially IgG (Fig. 13), complement, and fibrin deposits are present in vessel walls and at the BMZ.[99] These probably represent deposition of circulating proteins rather than a primary immunologic event. These DIF findings are found in almost all active lesions and in approximately one half of uninvolved skin of patients with active disease.[99] The changes are chronic and probably irreversible, despite clinical and biochemical remission.[100] It is the presence of both vascular and BMZ fluorescence that distinguishes the porphyrias from other bullous diseases such as epidermolysis bullosa acquisita and pemphigoid, which often show only BMZ fluorescence.[96]

Dermal sclerosis can be seen in both sun-exposed and protected skin. The mechanism is likely direct phototoxicity induced by porphyrins.[101] Uroporphyrin I has been shown to induce collagen synthesis in vivo without UV light and may explain sclerosis in nonexposed skin in PCT.[101] Infiltration of the vessel walls and epidermal basement membrane with hyaline-like material imparts rigidity to the papillary dermis and

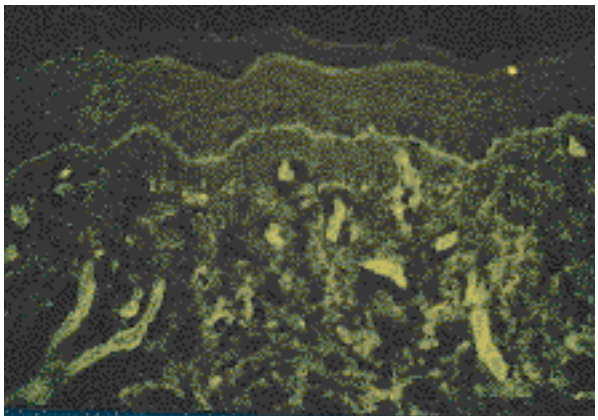

Fig. 13. DIF reveals linear staining of IgG at the dermoepidermal junction and around blood vessels in PCT. C3 was also positive in this case. (DIF; original magnification ×50.)

results in the festooning seen histopathologically. These findings can distinguish sclerotic lesions of PCT from morphea.[102] Fluorescent cytoid bodies staining with anti-IgM can also be seen in various porphyrias, as well as a mild perivascular mononuclear infiltrate in the papillary dermis.[96]

A recently described rapid screen for patients suspected of having porphyria involves serum fluorescent spectrophotometry analysis.[103] After the patient's plasma is exposed to an excitation wave length of 400 to 410 nm, the fluorescent emission peak can be observed. The emission peak for PCT, CEP, AIP, and HCP is 619 nm (Fig. 14). The emission peaks for EPP and VP are 634 and 626 nm, respectively.

Treatment

Treatment options for CEP are limited to symptomatic measures, sun avoidance, and when indicated, transfusions and splenectomy. Bone marrow transplantation has also been reported in severe cases.[104]

Treatment of AIP includes glucose loading and supportive measures including pain control and antipsychotic phenothiazines. Although hematin infusions provide negative feedback to the ALA synthase enzyme and have been shown to produce remissions,[105] it remains an investigational drug for use in acute attacks only.[106] Cimetidine and luteinizing hormone–releasing hormone may also be of some benefit.[105]

Treatment of HCP and VP is the same as that for both AIP and PCT.

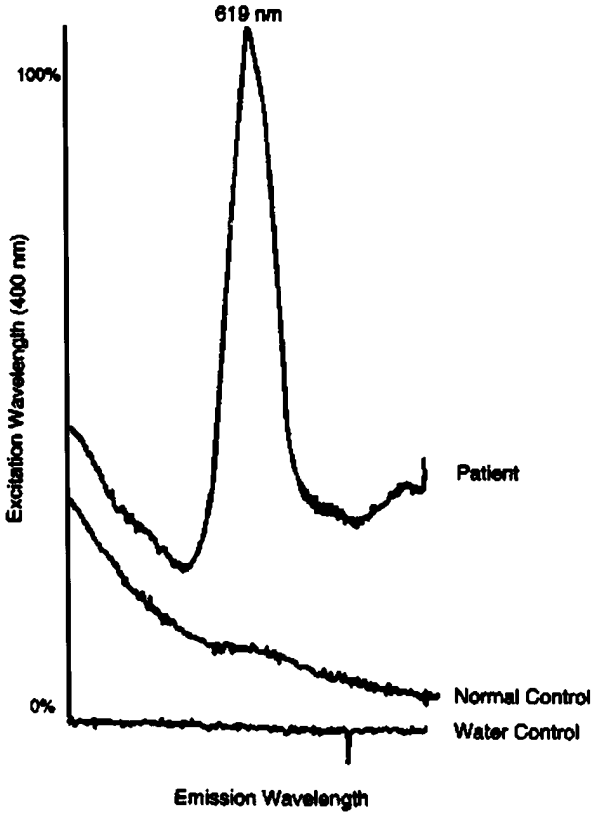

Fig. 14. Serum fluorescent spectrophotometry reveals emission peak of 619 nm in a patient with PCT. (From Walsh DS, Beard JS, James WD. JAMA 1994;272:1580-1. Copyright 1994, American Medical Association.)

Treatment of PCT includes phlebotomy of 500 ml once or twice a week until the hemoglobin falls to 10 to 11 g/dL. Chloroquine in low[70,71] or high doses[107] is also used to solubilize hepatic porphyrins, which can then be rapidly excreted in the urine.[106] Low-dose antimalarial therapy consists of chloroquine phosphate 125 to 250 mg twice a week or hydroxychloroquine 100 to 200 mg twice a week for 8 to 18 months.[70,71] Liver functions should be checked before and 1 week after therapy. Liver functions and urinary porphyrins are then checked biweekly; the medication should be continued until the excretion of urinary uroporphyrin is less than 100 μg per 24 hours.[71] High-dose hydroxychloroquine (250 mg three times a day for 3 days) may induce a more rapid remission but is often associated with a hepatotoxic reaction.[107] Other treatments including cholestyramine, vitamin E, and urine alkalization have shown less benefit.[106]

Treatment of EPP primarily includes sun avoidance and beta carotene, a free radical scavenger.

Hematin,[71] transfusion,[108] terfenadine,[108] and pyridoxine[71] treatment have also been reported. Liver transplatation may be required in severe liver disease leading to hyperbilirubinemia and acute liver failure.[94]

COLLOID MILIUM

Colloid milium is characterized by deposition of amorphous material in the dermis. It is typically classified in three clinical types: adult colloid milium (ACM), juvenile colloid milium (JCM), and nodular colloid degeneration. A fourth variant, pigmented colloid milium associated with hydroquinone use,[109] is also seen.

Pathogenesis

The pathogenesis of ACM remains unclear. On the basis of ultrastructural[110] and immunohistochemical studies,[111] the prevailing opinion on the origin of the colloid involves elastic fibers undergoing actinic degeneration. The possibility that actinically damaged fibroblasts produce the colloid has not been ruled out, however,[111] and may provide a link between sun exposure and ACM.[110,111]

Amino acid studies of ACM have revealed high levels of sulfur-containing amino acids and the absence of hydroxyproline and hydroxylysine,[113] which argues against an origin from collagen. The colloid contains many sugar residues consistent with elastic microfibrils.[110] Indirect immunofluorescence revealed SAP in colloid deposits.[111] This substance in found in both normal and abnormal elastic fibers,[110] which shows that the origin of the colloid may be elastic microfibrils.

Ultrastructurally,[110,111] the colloid appears as a medium electron-dense amorphous material with delicate, short, wavy, branching filaments 1.5 to 2.0 nm in diameter. The filaments are much shorter and smaller than amyloid filaments, which are 6 to 10 nm straight filaments. The colloid is consistent with degenerated elastin, with transitional stages noted between actinic elastoid and colloid. Electron-dense layers have been found to aggregate and concentrate in the center of involved elastic fibers; as these layers increased in size, they lost electron density and formed granulofibrillar colloid material.[110]

Both histologically and ultrastructurally, the lesions of JCM consist of an amyloid-like substance originating from degenerated epidermal keratinocytes.[114] Ultrastructural studies[114,115] of JCM reveal colloid deposits within the epidermis and dermis. Within the epidermis, it is located both intracellularly and extracellularly, as larger deposits. Degenerated organelles and desmosomes can be seen within the masses; the earliest change appears to be clumping and degeneration of the tonofilaments. Later, they appear as wavy bundles and whorls. Basement membrane damage is variable.[114,115]

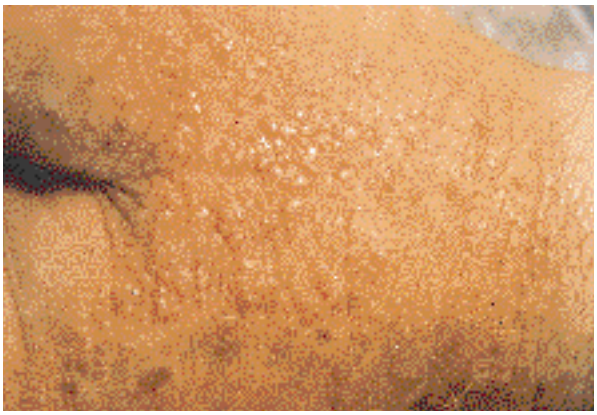

Fig. 15. ACM: discrete, translucent papules on the dorsum of the hand. (From the files of Walter Reed Army Medical Center [WRAMC].)

Ultrastructurally, the colloid in nodular colloid degeneration appears similar to that seen in ACM,[8] an amorphous deposit with randomly arranged short, wavy filaments. The fissures are lined by fibroblasts.[116]

Clinical features

ACM is the most common form of the disease, occurring in fair-skinned middle-aged patients in actinically damaged skin.[117] The lesions are small (1 to 5 mm), discrete, amber, translucent papules (Fig. 15), often located on the face, neck, ears, and dorsal hands. The underlying skin may be thickened and furrowed.[118] A gelatinous material can often be expressed after puncture of the lesions.[117,118]

The incidence of the disease remains unknown. The ratio of men to women is reported to be 4:1.[119] Long-term sun exposure and exposure to petroleum derivatives[109] have been linked to the onset of ACM. A recent report[117] describes a patient with a 7-year history of UVA exposure, in whom facial ACM developed. Two cases of unilateral left upper-extremity ACM were reported in taxi drivers

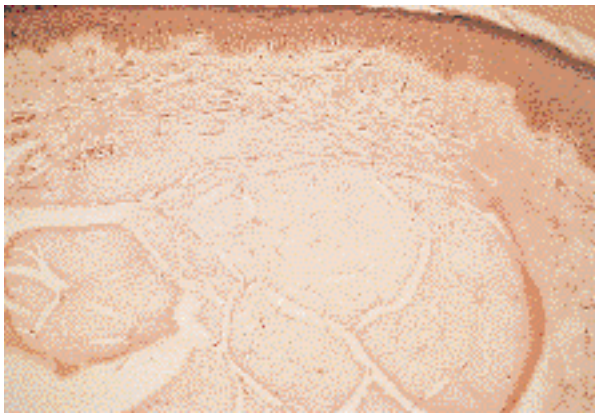

Fig. 16. ACM: Homogeneous, pink, fissured masses in the papillary dermis. (Hematoxylin-eosin stain; original magnification ×25.)

with left-sided sun exposure.[120] An unusual clinical presentation involved a patient with ACM and multiple myeloma.[121] The lesions were distributed primarily on the peribuccal mucosa, lips and scalp, sparing the dorsal hands. Trauma-induced purpura[122] of lesions was noted in an adult, as well as JCM, presumably from perivascular deposition of colloid with resultant vascular fragility.

JCM[114,115] is a rare, familial form of the disease with onset before puberty. The lesions are clinically indistinguishable from ACM but can occur in normal skin.[115] More commonly, however, they follow a severe sunburn or excess sun exposure[114,115] and occur on the face. The cause is unclear but may involve a hereditary predisposition to sun-induced keratinocyte damage,[114] with a possible autosomal recessive mode of inheritance.

Nodular colloid degeneration, or paracolloid of the skin,[116] is a single or multiple yellow-brown nodules up to 5 cm in size, primarily on the face and occasionally on the trunk or scalp. They may be telangiectatic with a slightly "lumpy" surface. Sun exposure is not believed to play a role because in some patients the lesions are restricted to the chest.[121] Pruritus may be a feature.[123]

An interesting variant[123] was reported with clinical and histologic features of both colloid milium and amyloidosis with ultrastructural evidence of amyloidosis as well.

Pigmented colloid milium is a disorder associated with exogenous ochronosis secondary to hydroquinone use.[109] It is associated with colloid milium production resembling caviar-like papules darker than the patient's normal skin. Between the milia, atrophy may be present. The distribution is similar to that of uncomplicated exogenous ochronosis in sun-exposed areas of the face. The cause remains unknown. Ultrastructurally, pigmented colloid milia were identical to ACM.[109]

Histology

The histologic composition of ACM reveals homogenous, pale-pink, fissured masses (Fig. 16) within the papillary dermis.[8] Spindle-shaped fibroblasts may be seen within the lines of fissuring of the colloid and dispersed throughout the deposit.[117] Solar elastosis is generally present. A narrow grenz zone separates the colloid from the overlying epidermis and often contains elastic fibers.[110] The epidermis may be atrophic.[117] Dilated blood vessels may also be present.[121]

Histologic examination[114,115] of JCM with hematoxylin-and-eosin staining reveals subepidermal, eosinophilic, fissured colloid masses abutting the epidermis without a grenz zone. Colloid-like material appears to be developing in basal keratinocytes, some of which appear crescentic, with vacuolization and "dropping off" into the dermis. Colloid-like material can also be seen in the upper hair follicles. Apoptotic, eosinophilic keratinocytes suggestive of colloid bodies surround the lesion. Histiocytes, melanophages, and mast cells have been noted within the colloid islands. Increased blood vessels may also be seen within the reticular dermis.[8] Rete ridges may be elongated at the periphery of the lesion.

On routine hematoxylin-and-eosin staining of nodular colloid degeneration,[8] the epidermis appears flattened. The eosinophilic homogeneous colloid mass fills almost the entire dermis and reveals clefting. Fibroblasts are present within the colloid, and dilated vessels can also be seen. No inflammation is present.[116]

The colloid in all three types stains positive with PAS both before and after diastase digestion[117] and negative with alcian blue at pH 2.5. Congo Red stain is positive and shows green birefringence, but the reaction is sometimes weak. This stain is negative in JCM. Variable staining patterns are reported with methyl violet and crystal violet.[117,122,124] It does not stain with pagoda red and other cotton dyes.[125] The colloid can be stained immunohistochemically for amyloid P protein, and it stains negative with antikeratin anti-

body.[117] JCM, in contrast, stains positively with antikeratin antibodies[114,115] usually at the periphery, further supporting the epidermal origin of the JCM. Direct immunofluorescence reveals "trapping" of immunoglobulins and complement.[8]

The major histologic differential diagnosis is lichen amyloidosis.[126] The deposits in ACM are much larger and associated with solar elastosis and epidermal atrophy, rather than hyperplasia, as seen in lichen amyloidosis. Because of the histochemical similarity, EM is used commonly for differentiation.[127]

Treatment

Treatment of colloid milium is limited. Dermabrasion[119] was reported to be effective on the dorsum of the hands without functional loss. Sunscreens are also recommended.[114,119] Systemic ascorbic acid and exfoliative agents have been tried.[119]

LIPOID PROTEINOSIS

Lipoid proteinosis, also referred to as hyalinosis cutis et mucosae or Urbach-Wiethe disease (UWD), was first described in 1929 by Urbach, a dermatologist, and Wiethe, an otolaryngologist.[128] It is a rare autosomal recessive deposition disorder in which masses of hyaline-like material are deposited in the skin, mucous membranes, brain, and other internal organs.[129] Most patients are of European descent, including South African descendants of German or Dutch immigrants.[130] The deposits are primarily found in the walls of small blood vessels and lying freely in the papillary dermis. Ultrastructurally, reduplication of the basement membrane of vessels and occasionally the dermoepidermal junction is seen.

Pathogenesis

Ultrastructural studies reveal that two separate substances are present in the eosinophilic hyaline seen in lesions of UWD (ie, true hyaline of fibroblast origin and reduplicated basement membranes produced by multiple cells).[131] One study revealed peculiar cytoplasmic inclusions in lesional fibroblasts and cytoplasmic vacuolization, suggesting the possibility of a lysosomal storage disease.[132] The inclusions contained granular, electron-dense structures, the nature of which remains unknown. They do not occur in normal skin. Biochemical studies suggest high levels of carbohydrates within the inclusions, again supporting the possibility of a lysosomal storage disease, although no recent data are available to confirm this.

The hyaline deposits in the papillary dermis and around vessels may contain increased amounts of an uncharacterized noncollagenous glycoprotein[131] secreted by fibroblasts. Studies of gene expression in cultured fibroblasts from patients with UWD have been performed with molecular hybridization with various procollagen complementary DNA probes.[133] Abnormal expression of procollagen genes was observed with a decreased type I/III procollagen mRNA ratio.[133] This was primarily caused by decreased type I procollagen mRNA levels. It is possible that other collagen genes are over expressed in this disorder.[134] Although a markedly reduced proliferative capacity of fibroblasts has been reported,[133] it remains unclear whether the primary underlying disorder is an abnormality of collagen metabolism.[135]

The mantles of eosinophilic hyaline-like material seen on hematoxylin and eosin staining around skin appendages are shown electron-microscopically to be reduplications of the basement membranes. Indirect immunofluorescence microscopy reveals strong staining of the layers for both type IV collagen and laminin.[131,136] Minimal reduplication is seen at the epidermal basement membrane. Between the "onion-skin" layers, fine collagen fibrils in an amorphous granular matrix are seen[131,134] with streaming of fine deposits of electron dense material from the layers into the surrounding connective tissue. Multiplication of the basal lamina is, however, a nonspecific finding seen in a variety of disorders,[134] although not to the degree seen in UWD. Increases in type V collagen have also been reported with endothelial basement-membrane thickening.[135]

Biochemical and histochemical studies of the deposits reveal neutral mucopolysaccharides with hyaluronic acid, neutral fat, tryptophan, and free cholesterol.[137] The PAS-positive material corresponds to glycoproteins, possible noncollagenous protein, and neutral polysaccharides. Hyaluronic acid may be found in small amounts in the deposits.[138] The deposits do not contain glycogen.[139]

Lipid production by lesional fibroblasts have been shown to be normal in cell cultures,[140] arguing against the disease being considered a lipoidosis. Although small lipid granules in the deposits

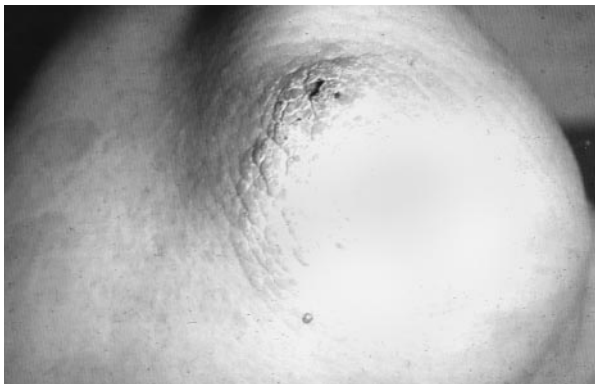

Fig. 17. Verrucous, hyperkeratotic papules on the elbow in lipoid proteinosis.

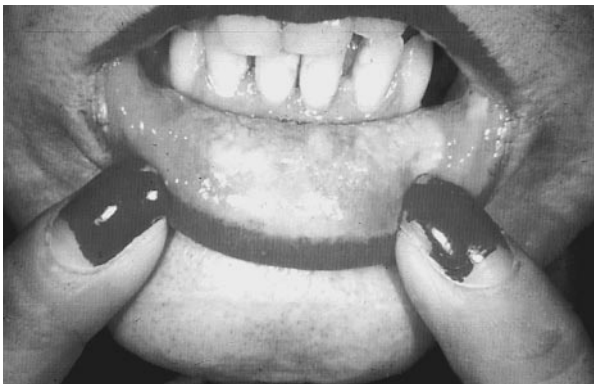

Fig. 18. Mucosal "pebbling" of lower lip as seen in lipoid proteinosis. (From the files of Walter Reed Army Medical Center [WRAMC].)

stain with lipid stains, the exact nature of the lipid substance remains uncharacterized.[139] Neutral fat is most commonly found, but overall fat staining of lesions is highly variable, even within the same patient.[137] Free cholesterol may be seen; no evidence of lipofuscin-like pigment exists.[128] It appears that the presence of lipids in the lesion is a secondary phenomenon and not involved in the pathogenesis of the disease.

The pathogenesis of UWD is still unknown. Many theories have been proposed. The structural changes may represent a secondary attempt at repair, rather than a primary degenerative process.[139] Vascular fragility or release of a toxic substance from vessel walls and sweat glands has been proposed, although normal capillaries are often present in the deposits. Fluoroscopy also fails to show increased vascular permeability.[139] The disease may involve a hypersensitivity to physiologic trauma, thermal damage, or lysosomal fragility.[139] Simple collagen and elastic tissue degeneration do not explain the presence of tryptophan nor the cerebral lesions.[141]

Clinical features

The earliest clinical manifestation is hoarseness or a weak cry in infancy. The hoarseness remains throughout life.[130] Skin lesions usually appear during the first 2 years of life and occur in two overlapping stages. The first, lasting until the late teens, consists of pustules, bullae, and hemorrhagic crusts of the skin, mouth, and throat. The skin lesions resolve with "ice-pick" acneiform scarring,[142] predominantly on the face and distal extremities. This early inflammatory stage has not been well characterized histologically, although the scar reveals hyaline-like deposits on biopsy. In the second stage, deposits increase in the dermis, and the skin becomes thickened, yellowed, and waxy. Papules, plaques, and nodules occur primarily on the face but also in the axillae and on the scrotum[139,143] and may eventually coalesce, resulting in a generalized infiltration. Verrucous lesions may occur on the extensor surfaces, especially the elbows (Fig. 17) and hands after frictional trauma.[3] A generalized hyperkeratosis of the skin may also occur.

Infiltration of the posterior tongue and frenulum may result in impaired gustation,[128] speech impediments,[144] and limited mobility to the extent that the tongue is fixed to the floor of the mouth.[145] The tongue is often firm and woody.[139] Other mucosal lesions include pebbling of the lip mucosa (Fig. 18), induration of the lip mucosa in early childhood, progressing to granular lesions[144] and pitting[139] later on. The gingiva,[146] uvula, and soft palate may be involved. Lesions may also be found in the pharynx, epiglottis, aryepiglottic folds, and vocal cords producing hoarseness, dysphagia,[147] and occasionally respiratory insufficiency. Patchy alopecia and diffuse hair loss have been reported.[134,145] Dental anomalies[144] include hypoplasia or aplasia of the upper incisors, premolars, or molars. Other oral findings include tongue ulceration, vesicular glossitis, and transient lip and tongue swelling. Beaded papules on the palpebral margins (moniliform blepharosis) are a characteristic finding (Fig. 19).

A unique and pathognomonic finding in UWD

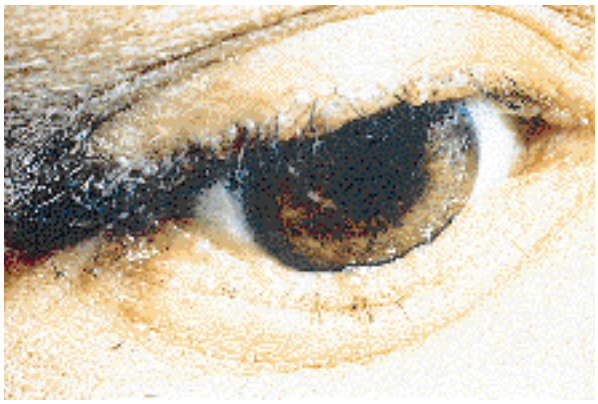

Fig. 19. Beaded papules on palpebral margins of eyelid (moniliform blepharosis) in lipoid proteinosis. (From the files of Walter Reed Army Medical Center [WRAMC].)

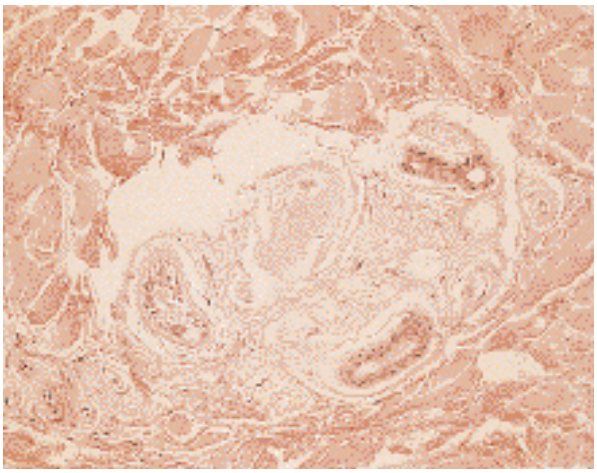

Fig. 20. Hyaline mantles surrounding and replacing eccrine glands in the dermis in lipoid proteinosis. (Hematoxylin-eosin stain; original magnification ×25.)

is bilateral, intracranial, sickle-shaped calcifications within the temporal lobe. Neurologic manifestations are common and include psychomotor and grand mal seizures, memory loss, and rage attacks.[147] Schizophrenic behavior may also occur. Computed tomography may be helpful in the diagnosis and follow-up of these patients.[148] Histologically, the calcified area reveals haphazardly arranged calcified blood vessels proliferating around large calcified masses with surrounding dense gliosis.[145] One case revealed areas of actual bone formation in a calcified mass. Grossly normal brain tissue also showed calcified vessels occluded with fibrin and surrounded by small zones of infarction.[145] Multiple other organ systems may be affected in UWD, although few result in significant clinical symptoms.[129]

The disease runs a stable or slowly progressive course[139,149] and is compatible with a normal life expectancy.[139] Infant mortality rates may be higher than average, possibly from respiratory insufficiency.[139] Adults are also at some increased risk of laryngeal obstruction, at times requiring tracheostomy. Fluctuations in the course of the disease have been noted.[139]

The clinical differential diagnosis of UWD includes xanthomatosis, extracellular cholesterolosis, amyloidosis, colloid millium, papular mucinosis, and myxedema.

There is no consistent laboratory abnormality in UWD except, possibly, an elevated erythrocyte sedimentation rate.[139] This elevation is presumably caused by increased α- and β-globulins[139,150]; the significance of this remains unclear, however. Inconsistent findings in serum lipids and lipoproteins have been found, and elevated total lipids have been reported only rarely.[151] Bone marrow biopsy specimens have been reported as normal,[152,153] as well as chromosomal studies in one patient.[134] Calcium levels have not been consistently documented. Therefore it is difficult to determine the role of abnormal calcium metabolism in UWD and, in particular, the cerebral calcifications.[139] Urine testing has revealed no known alteration typical of UWD.[139]

Histology

Hematoxylin-and-eosin staining of early lesions reveals pale pink, hyaline-like thickening of the papillary dermal capillaries.[138] Later lesions reveal hyperkeratosis, occasionally papillomatosis, and a thickened dermis in which diffuse thick bundles of pink hyaline deposits are seen oriented perpendicular to the dermoepidermal junction in diffuse pattern.[138] The lower dermis reveals smaller scattered deposits of hyaline. Hyaline mantles can be seen surrounding or replacing eccrine glands (Fig. 20).[8,138] Deposits can also surround hair follicles, sebaceous glands, and, rarely, arrector pili muscles.[138] In advanced cases, the perineurium of upper dermal nerves may also be hyalinized.[139]

The hyaline stains strongly with PAS and is diatase resistant, indicating that neutral mucopolysaccharides are present. Alcian blue staining and hyaluronidase treatment reveal the presence of

hyaluronic acid.[8] Although fat stains give inconsistent results, neutral fat is commonly present in small droplets, predominantly around blood vessels. It stains with Sudan III or Oil Red O. Free cholesterol is also found in the deposits.[8] Only rarely do the deposits stain with Congo Red or other amyloid stains. Dermal connective tissue changes involve decreased collagen and elastic fibers within the hyaline masses, with collagen fibers entering the deposits from the periphery.[138] Fibroblasts may also be seen, but xanthoma cells are absent.[139] Lesions are not present in the subcutaneous fat.

Histologically, UWD must be differentiated from EPP, in which the hyalinization is milder and more focal.[138] Amyloidosis can usually be distinguished histologically, but overlap may occur. Diabetic microangiopathy may show an identical histologic picture to UWD.[139] Colloid milium does not show the striking perivascular distribution of deposits seen in UWD.

Treatment

There is no known cure for UWD. Anecdotal reports of treatment successes are difficult to evaluate because of the fluctuating course of the disease.[139] One report of clinical and histologic regression after dermabrasion was of interest.[154] Oral DMSO has also been reported to be effective.[155] Surgical resection of plaques on vocal cords may improve hoarseness.[137] Supportive treatment, especially anticonvulsants, should be considered.

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