Skin Manifestations of Internal Disease

10

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10.1 Introduction

As the largest organ in the body, the skin may reveal the first manifestations of internal disease. The astute clinician can often use dermatologic findings to diagnose an underlying systemic disease. This chapter outlines some of the most important skin manifestations of internal disease. Common yet clinically important systemic diseases will be reviewed, and their most notable skin findings will be delineated.

10.2 Hyperlipidemia

Hyperlipidemia is a well-known risk factor for coronary artery disease. Hyperlipidemia may be a primary disorder or secondary to another cause. Primary hyperlipidemia consists of dyslipidemia syndromes while secondary hyperlipidemia may be associated with endocrine disorders, renal disorders, chronic liver disease, medications, and pregnancy. Xanthomas and xanthelasmas are dermatologic manifestations indicative of a possible abnormality in lipid metabolism.

10.2.1 Xanthomas

Xanthomas appear as yellowish or pink papules, plaques, or nodules. Histologically, dermal accumulations of lipid-laden macrophages are characteristic. Eruptive xanthomas are small papules that appear suddenly on the buttocks, hands, or extensor surfaces, sometimes accompanied by pruritus or tenderness [1] (Fig. 10.1). They are associated with very high triglyceride levels and clear rapidly when serum lipid levels are lowered. They can also be secondary to uncontrolled diabetes. Patients with eruptive xanthomas are at risk of developing severe pancreatitis and should be appropriately managed with dietary and pharmacologic interventions such as statins to normalize serum lipid levels [2].

Tuberous xanthomas tend to be larger and deeper than eruptive xanthomas and evolve slowly. They appear on the knees, palms, or extensor surfaces of the body. The lesions are painless and due to cholesterol accumulation within the tissues. Tuberous xanthomas are associated with primary hyperlipoproteinemias with elevated cholesterol levels, such as familial hypercholesterolemia and familial dysbetalipoproteinemia. Tendinous xanthomas, which are similar lesions found in extensor tendons such as the Achilles tendon, may also be present in these patients. Treating the underlying

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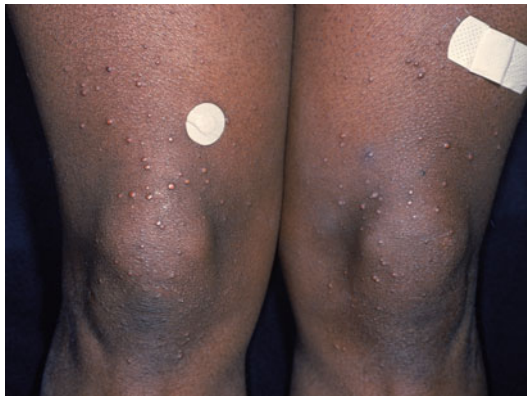

Fig. 10.1 Diffuse yellow papules and small plaques consistent with eruptive xanthomas. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

condition is essential in conjunction with dietary changes, exercise, and pharmacologic intervention. While eruptive xanthomas can resolve within weeks of initiating systemic medical treatment, and tuberous xanthomas can resolve after months of similar treatment, tendinous xanthomas may persist for years despite treatment and may even need surgical intervention to alleviate infrequent but obvious swelling which can rarely lead to chronic morbidity.

10.2.2 Xanthelasma

Xanthelasmas, also known as xanthelasma palpebrarum, are yellowish plaques that are most commonly found on the inner canthi. More common in women and older individuals, xanthelasmas are the most common of all xanthomas [3]. The lesions can be soft, semisolid, or calcified, and are characterized by a tendency to be symmetric, permanent, progressive, multiple, and coalescent [4]. They tend to grow slowly with time, and the diagnosis can often be made clinically. Histologically, the lesions are composed of foamy, lipid-laden histiocytes that tend to be located in the superficial dermis in perivascular and periadnexal locations.

Although roughly 50% of patients with xanthelasma have normal serum cholesterol levels, studies have shown that the presence of xanthelasma is a risk factor for mortality from atherosclerotic disease regardless of cholesterol level. It has also been reported that patients with xanthelasmas in the setting of normal levels of cholesterol and triglycerides may have elevated LDL and VLDL and decreased HDL. Therefore, xanthelasma should be considered a marker of dyslipidemia, and a full lipid profile should be considered to identify those with more subtle lipid abnormalities that are still associated with increased risk of cardiovascular disease. Familial hypercholesterolemia or familial dysbetalipoproteinemia should be considered especially in those patients who develop xanthelasma at a young age.

Xanthelasmas are not known to cause serious complications expect in rare instances in which the lesions become large and obstruct vision [5]. Although the classic method of treatment is surgical excision, surgical scarring can occur. This has led to investigations of other methods of treatment including trichloroacetic acid peeling, electrodessication, and laser therapy, all of which result in varying success [6]. Regardless of the mode of treatment, recurrence of xanthelasma is common, especially in cases of familial hyperlipoproteinemia where involvement of all four eyelids, or more than one recurrence, is common [7].

10.3 Kidney Disease

10.3.1 Half-and-Half Nails

Half-and-half nails (also known as Lindsay's nails) are associated with chronic renal failure. This nail finding is a result of nail bed edema and characterized by apparent leukonychia in the proximal half of the nail which fades upon application of pressure [8]. These nail changes are thought to be an occasional but very specific finding of chronic renal failure, and it is estimated that up to 40% of patients with renal insufficiency have the nail changes during the course of their disease [9]. It has been proposed that the distal dark color is caused by melanin deposition resulting from stimulation of nail matrix melanocytes by acidosis and uremia [10]. Others have proposed that changes in the nail bed rather than in the nail

produced the change, such as an increase in the number of capillaries and a thickening of the capillary walls in the nail bed [11].

10.3.2 Uremic Pruritus

While pruritus is infrequent in patients with acute renal failure, it is a common symptom in patients with chronic renal failure [12]. The pathogenesis of uremic pruritus is unknown, with various proposed mechanisms including nitric oxide, pruritogenic cytokines, and altered skin innervations secondary to neuropathy [13].

Before initiating treatment, a specific diagnosis should first be made as patients with chronic renal failure may experience pruritus secondary to other skin conditions such as infections or contact dermatitis from dialysis catheters. Secondary hyperparathyroidism due to chronic renal failure has also been associated with uremic pruritus (parathyroidectomy in dialysis patients with secondary hyperparathyroidism has been reported to decrease pruritus), though PTH itself does not seem to be pruritogenic. Thus, surgery should be considered for pruritus in association with secondary hyperparathyroidism. In cases without a specific cause, treatment includes optimizing dialysis, as well as the use of emollients and topical analgesics such as pramoxine. Ultraviolet light B therapy has also been shown to be effective.

10.3.3 Uremic Frost

Uremic frost is a rare dermatologi manifestation of severe azotemia which clinically manifests as characteristic white, crystalline, and friiable depostis arising in the head and neck area.. The lesions form as a result of the accumulation of urea and other nitrogenous waste products in sweat which then crystallize after evaporation [14]. Today, this dermatologic finding is rarely seen in developed countries due to the availability of hemodialysis [15]. Uremic frost should be differentiated from eczema, postinflammatory desquamation, and retention keratosis. A history of severe azotemia as well as the presence of characteristic lesions help to make the diagnosis. To verify the composition of the lesions, scrapings can be taken and diluted in normal saline, and then tested for elevated urea nitrogen levels.

10.4 Diabetes

10.4.1 Necrobiosis Lipoidica

Necrobiosis lipoidica is present in approximately 0.3% of patients with diabetes. It may be seen in both type I and type II diabetes with about two-thirds of cases occurring in type II [16]. Although not all patients with necrobiosis lipoidica have diabetes, studies have shown that majority of those without diabetes had abnormal glucose tolerance tests, subsequently developed diabetes, or had a strong family history of diabetes [17]. Most patients are females. The pathogenesis remains unknown. Proposed mechanisms include vascular abnormalities, collagen abnormalities, sweat gland and nerve disturbances, and abnormal leukocyte function.

Necrobiosis lipoidica initially presents as an oval violaceous patch, most often in the pretibial region. It slowly evolves into a larger lesion with an erythematous advancing border and central epidermal atrophy (Fig. 10.2). Subsequent ulceration is common. Histologically, the lesions demonstrate layers of interstitial granulomatous inflammation and fibrosis with multinucleated histiocytes involving the entire dermis. Diagnosis can often be made clinically.

At this time, there is no consistently effective treatment for necrobiosis lipoidica. Treatment options include corticosteroids, fibrinolytics, antiplatelet agents, and surgical treatments (i.e., excision and grafting). Diabetic glycemic control does not seem to result in the resolution of necrobiosis lipoidica.

10.4.2 Bullae Diabeticorum

Although most commonly seen in patients with long-standing diabetes, bullosis diabeticorum may also occur as the initial presentation of diabetes [18]. The lesions are characterized by

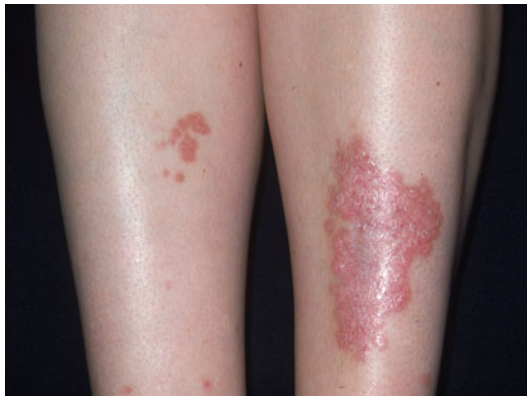

Fig. 10.2 Erythematous to violaceous atrophic plaques of the pretibial legs consistent with necrobiosis lipoidica. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

the rapid onset of tense, painless blisters on the feet, legs, or hands. They vary in size from 0.5 to 3 cm, can be unilateral or bilateral [19], and usually heal in 2–4 weeks [20]. The pathogenesis of bullosis diabeticorum is unknown. Proposed mechanisms include nephropathy, immune-mediated vasculitis, and disturbed metabolism of calcium, carbohydrates, or magnesium.

The diagnosis is made clinically as there is no specific diagnostic test for bullosis diabeticorum [21]. Histologically, subepidermal bullae are observed, and direct immunofluorescence is usually negative [22]. The differential diagnosis includes other blistering disorders such as bullous pemphigoid, porphyria cutanea tarda, pseudoporphyria, drug-induced bullous eruptions, and friction/burn blisters.

The goal of treatment is to prevent secondary infection and to allow the lesions to heal on their own [23]. While some clinicians suggest topical therapies are not necessary, others suggest aspirating the blisters to reduce discomfort and applying petroleum jelly or a topical antibiotic ointment to prevent secondary infection.

10.4.3 Acanthosis Nigricans

About 30–50% of patients with diabetes have acanthosis nigricans. Acanthosis nigricans is characterized by velvety, hyperpigmented plaques most commonly involving the axillae and/or neck creases, as well as other intertiginous areas such as the groin, and less frequently the flexural extremities, periorally, and periorbitally. High levels of circulating insulin promote increased liver production of insulin-like growth factor, which binds to epidermal growth factor receptors to produce thickening of the epidermis and hyperkeratosis [24]. These lesions are most often asymptomatic, but can be malodorous or painful. Histologically, acanthosis nigricans is characterized by hyperkeratosis, mild acanthosis, and papillomatosis. The hyperpigmentation results from thickness of the keratin-containing superficial epithelium rather than a change in melanocytes. Acanthosis nigricans is classified either as benign when it occurs in the context of insulin resistance, or as malignant when it is a paraneoplastic sign of an internal malignancy, most commonly gastric adenocarcinoma [25]. Thus, evaluation for an internal malignancy should be considered if patients with acanthosis nigricans are found not to have insulin resistance. Because obesity is an important cause of insulin resistance, weight control and dietary changes play an important role in therapy. Common pharmacologic therapies to improve insulin sensitivity such as metformin or long-term treatment with octreotide (a synthetic analog of somatostatin) to reduce insulin secretion and eventually reduce insulin binding to insulin-like growth factor may be helpful. Topical treatment includes retinoids, ammonium lactate, and calcipotriene.

10.5 Thyroid Disease

10.5.1 Graves' Disease

Graves' disease is an autoimmune hyperthyroidism caused by autoantibodies that bind to thyrotropin (also known as thyroid-stimulating hormone, TSH) receptors in the thyroid gland resulting in increased thyroid hormone synthesis. Pretibial myxedema is a specific sign of Graves' disease, but occurs in only 3–5% of patients with the disease [26]. It is characterized by indurated tan to brownish-red plaques over the pretibial areas (Fig. 10.3). Histologically, there is

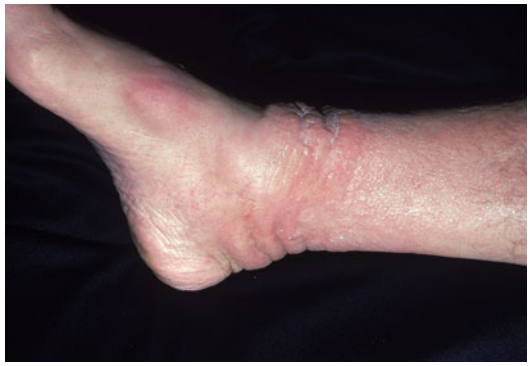

Fig. 10.3 Indurated waxy plaques of the pretibial leg in a patient with hyperthyroidism. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

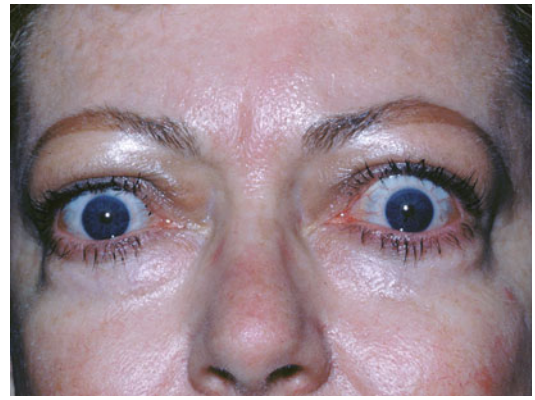

Fig. 10.4 Physical finding and eye changes seen in patients with Graves' disease. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

infiltration by mucopolysaccharides (mucinous ground substance), thought to be caused by stimulation of TSH receptors that are present in the pretibial connective tissue. Treating hyperthyroidism does not alter the presence of pretibial myxedema because treatment of Graves' disease treats hyperthyroidism rather than the underlying autoimmune disease [27].

Graves' ophthalmopathy (proptosis) may be the first sign of hyperthyroidism. Associated symptoms include photophobia, tearing, and sensation of a foreign material in the eye [28] (Fig. 10.4). It is thought to be caused by infiltration of retrobulbar tissues and extraocular muscles by mononuclear cells and mucopolysaccharides.

Dermatologic manifestations of hyperthyroidism may generally be characterized by warm, moist skin and separation of the nails from the nail bed (onycholysis). The nail changes are characterized by rapid growth, softening, and friability, and often reverse following successful therapy of hyperthyroidism. Hair caliber may be fine and thin; frank alopecia is also seen, though the severity of alopecia does not correlate with the severity of hyperthyroidism.

10.5.2 Hypothyroidism

Dermatologic manifestations of hypothyroidism include dry, scaly, and cold skin. Some patients may be severely xerotic and develop an acquired ichthyosis. The loss of the outer third of the eyebrows is considered a classic hair loss pattern for patients with hypothyroidism. Hair may be coarse and brittle, with slowed growth rate (increase in telogen hairs) [28]. In severe hypothyroidism, enlargement of the lips and tongue as well as diffuse thickened skin may be observed. The thickened skin, also called myxedema, differs from pretibial myxedema of Graves' disease; myxedema of hypothyroidism has a generalized distribution with smaller quantities of mucin. The skin of hypothyroid patients may appear yellow due to impaired hepatic conversion of carotene to vitamin A, resulting in excess deposition of serum carotene in the stratum corneum. There may be cutaneous pallor caused by both vasoconstriction and alteration of the fraction of incident light, which results from increased water and mucopolysaccharide content in the dermis [28]. About 90% of patients with hypothyroidism have some degree of nail changes. The nails are brittle, slow growing, and striated either longitudinally or horizontally. Onycholysis is more common in hyperthyroidism but has been reported in association with myxedema.

10.6 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Skin manifestations occur in approximately 25% of cases and may be

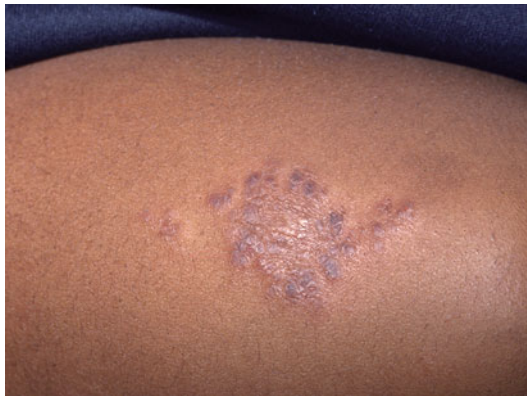

Fig. 10.5 Common nonspecific skin findings seen in Sarcoidosis. Note the annular pattern of lesions. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

the first sign of sarcoidosis. The lesions are classified as either specific or nonspecific, based on the presence or absence of non-caseating granulomas on histology, respectively.

The most common skin findings are small, smooth dermal papules of varying colors such as tan, red, violaceous, or brown (Fig. 10.5), though in African Americans, they may be hypopigmented. Lesions are most commonly located around eyelids, nasal alae, nasolabial folds, and neck [29]. The papules sometimes enlarge or coalesce to form annular lesions or plaques [30]. Uncommon but specific skin lesions of sarcoidosis include subcutaneous nodules, ulcerations, dystrophic nails, scarring alopecia, verrucous lesions, pustular lesions, and rarely erythroderma [29].

Lupus pernio is a distinct form of cutaneous sarcoidosis presenting as purplish plaques around the nose, ears, lips, fingers, and face [31]. The lesions appear insidiously and progress to result in scarring, fibrosis, and deformity. Lupus pernio is associated with the involvement of the upper respiratory tract, pulmonary fibrosis, as well as severe bony disease. Patients with lupus pernio often have persistent and progressive pulmonary manifestations [30].

Erythema nodosum is the most common nonspecific skin lesion of sarcoidosis. It is characterized by erythematous and tender subcutaneous nodules most often located in the pretibial areas. It is thought to be caused by a delayed hypersensitivity response, and studies have shown involvement of T-lymphocytes as well as reactive oxygen intermediates in producing the tissue damage and inflammation [32]. Erythema nodosum is typically associated with a subacute transient course of sarcoidosis. Löfgren's syndrome describes an acute form of sarcoidosis associated with erythema nodosum in the setting of asymptomatic bilateral hilar lymphadenopathy, uveitis, fever, and arthritis. It most often resolves without treatment. Erythema nodosum is usually self-limiting or improves with treatment of the underlying disorder. Symptomatic treatment to relieve the discomfort associated with the skin lesions can be achieved with salicylates or nonsteroidial anti-inflammatory drugs. Although the mechanism is unclear, potassium iodide (400–900 mg daily) has been reported to be beneficial in refractory cases.

Sarcoidosis is diagnosed by a combination of clinical, radiologic, histopathologic, and laboratory findings. In patients with asymptomatic bilateral hilar lymphadenopathy or Löfgren's syndrome, clinical presentation may be sufficient. Following diagnosis, patients should be thoroughly assessed to evaluate the extent of the disease.

Approximately 70% of cutaneous sarcoidosis resolve without treatment in 1–2 years. For mild disease, potent topical corticosteroids such as clobetasol or intralesional corticosteroids may be considered. For extensive cutaneous disease, prednisone is the drug of choice [33]. For refractory sarcoidosis, methotrexate is most commonly used as a nonglucocorticoid immunosuppressive agent. Other antimetabolites such as azathioprine and leflunomide are also used when patients fail or cannot tolerate methotrexate. Other options for patients who fail glucocorticoid treatments include antimalarial drugs with immunomodulating properties (e.g., chloroquine, hydroxychloroquine) and tumor necrosis factor alpha (TNFα) inhibitors (TNFα is thought to play a role in maintenance of granuloma formation in sarcoidosis by accelerating the inflammatory process).

10.7 Cushing's Syndrome

Cushing's syndrome refers to a state of excess glucocorticoids and has various dermatologic findings. Thinning and atrophy of the skin, easy bruising,

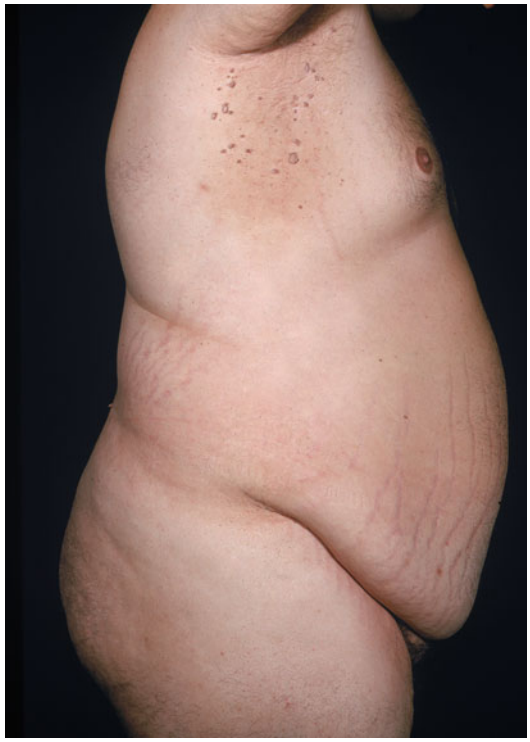

Fig. 10.6 Characteristic striae and body habitus of a patient with Cushing's syndrome. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

and inhibition of wound healing may be observed. A reduction in epidermal and dermal components of the skin leads to atrophy; there is decreased collagen synthesis, elastic fibers, and dermal mucopolysaccharides [34]. The epidermis is shiny and may show scaling [35]. High levels of glucocorticoids impair wound repair and cause easy damage to the skin with subsequent ulceration and infection. Additionally, increased vascular fragility results in petechiae and ecchymoses.

Large, violaceous striae may appear in areas of stretched skin such as the abdomen and buttocks (Fig. 10.6) due to weak dermal connective tissue and the failure of normal regenerative capacity of the skin [35]. The striae of Cushing's are increased in depth, breath, and intensity of color as compared to the striae of adolescence or pregnancy.

Excess deposits of fat in the clavicles, posterior neck (buffalo hump), cheeks (moon facies), and abdomen result in the characteristic body habitus. Patients with Cushing's syndrome can also develop steroid-induced acne characterized

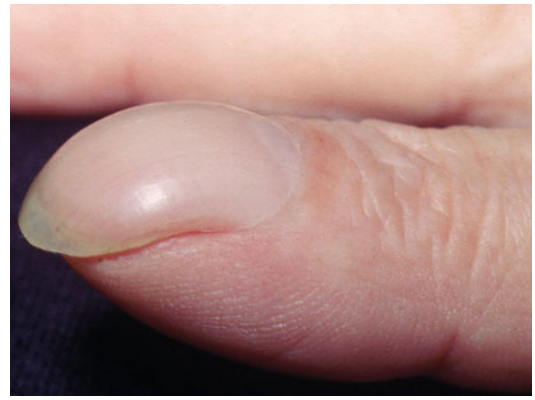

Fig. 10.7 Hyper-convexity of the nail consistent with clubbing. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

by erythematous papules and pustules uniform in their stage of development and without comedones. They spare the face and appear on the trunk, arms, and shoulders. Hypertrichosis is also common most often on the face. Hair tends to be laguno-like rather than true beard growth [35].

Hypercortisolism could be due to iatrogenic administration of glucocorticosteroids, pituitary or ectopic adrenocorticotropic hormone (ACTH) production, or adrenal tumors [35]. Although the most common cause is therapeutic administration of exogenous systemic glucocorticoids, it has been reported that the use of potent topical corticosteroids can induce similar skin changes [36]. Some suggest limiting the usage of potent topical glucocorticoids to 50 g/week in adults and 15 g/week in children to avoid such adverse reactions [36]. The skin changes caused by Cushing's syndrome are only partially reversible with treatment of the underlying disease.

10.8 Pulmonary Disease

Clubbing is characterized by increased convexity of the nail due to proliferation of the soft tissues in the distal phalanx (Fig. 10.7). The emergence angle of the nail becomes equal to or greater than 180° [37]. The nail plate enlarges in size. About 80% of nail clubbing is associated with respiratory diseases such as lung cancer, sarcoidosis, mesothelioma, empyema, cystic fibrosis, and interstitial lung disease.

Fig. 10.8 Absent lunulae, absent cuticles, thickening with curvature to the sides, and yellowing of nails in a patient with yellow nail syndrome. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

In the evaluation of clubbing, it is important to verify that the patient has true clubbing rather than pseudoclubbing, which involves only a single digit and is usually due to a subungual mass [37]. In those with true clubbing, a chest X-ray should be considered to rule out underlying pulmonary causes.

Hypertrophic osteoarthropathy is an important entity to consider when evaluating nail clubbing. It is a syndrome that consists of simple clubbing, peripheral neurovascular disease, acute bone pain, muscle weakness, joint pain, and hypertrophy of the extremities. The presence of these findings is associated with malignant tumors of the pulmonary system 90% of the time. The syndrome mostly affects males with a familial predisposition. Pamindronate may be considered in treating painful osteoarthropathy [38].

Yellow nail syndrome is also associated with pulmonary diseases such as tuberculosis, pulmonary malignancies, and asthma. The classic triad of yellow nail syndrome is lymphedema of the lower extremity, nail changes, and pleural effusion. The nail changes consist of absent lunulae and cuticles, nail thickening with lateral curvature, and yellowing (Fig. 10.8). The syndrome usually involves all 20 nails. Nail growth is slowed to less than 0.2 mm/week [39]. Total nail plate detachment may occur (secondary onycholysis), as well as colonization by Pseudomonas aeruginosa that may produce green-to-black discoloration of the nail plate. In patients with paraneoplastic yellow nail syndrome, the nails often return to normal when the underlying tumor is treated. The exact pathogenesis of the yellow nail syndrome remains unknown. One possible mechanism is a congenital abnormality of the lymphatic vessels, which explains the nail pathology characterized by ectatic lymphatics in the nail bed as well as matrix dermis [37].

10.9 Gastrointestinal

10.9.1 Pyoderma Gangrenosum

Pyoderma gangrenosum is a severe ulcerative skin condition that is associated with inflammatory bowel disease and chronic infectious hepatitis, as well as other non-gastrointestinal conditions such as rheumatoid arthritis, lupus erythematosus, and HIV infection. It is estimated that about 5% of patients with ulcerative colitis develop pyoderma gangrenosum. In some patients, pyoderma gangrenosum may develop years before the onset of inflammatory bowel disease.

The lesion begins as a small tender pustule, but eventually breaks down and forms an expanding ulcer. It can grow rapidly and extend to fat, fascia, and muscle. The ulcers can become very

large before healing with a thin and atrophic scar [40]. While not specific to pyoderma gangrenosum, patients may exhibit pathergy, a phenomenon where skin trauma or injury can trigger the development of skin ulcerations which may be resistant to healing. Pathergy may also lead to non-healing wounds at sites of surgical incisions. Facial pydoerma gangrenosum tends to be more superficial and less destructive.

The pathogenesis of pyoderma gangrenosum remains largely unknown. It is thought that abnormal neutrophil trafficking and immunologic dysfunction are involved. Pyoderma gangrenosum is a diagnosis of exclusion; culture for bacterial, viral, and fungal agents should be done. Therapy involves treating the associated disease and administration of systemic steroids (predinosolone 1–2 mg/kg daily with tapering as healing occurs) and other immunosuppressive agents such as cyclosporine. However, treatment is often recalcitrant when an underlying systemic condition cannot be identified and subsequently treated. More recently, the use of TNF-α inhibitors, specifically infliximab (5 mg/kg infusion at weeks 0, 2, and 6 and every 8 weeks after that), has also been shown to be effective in management of this difficult condition.

10.9.2 Pancreatic Panniculitis

Pancreatic panniculitis has been associated with both acute and chronic pancreatitis as well as pancreatic carcinoma, but overall is a rare associated finding in patients with pancreatitis. Pancreatitis results in the outpouring of digestive enzymes, such as pancreatic lipase, phospholipase, trypsin, and amylase, that may migrate into tissue to cause pancreatic panniculitis [41]. Tender, fluctuant, red subcutaneous nodules develop on the lower legs. Occasionally, the nodules rupture discharging a thick and oily liquid which may be a result of autodigestion of the subcutaneous fat by the pancreatic enzymes. Histologically, a mixed lobular and septal panniculitis with lipocyte necrosis ("ghost cells") and basophilic saponification may be seen. Prognosis depends on the underlying pancreatic disease, treatment of which may help to treat the skin lesions; the nodules may regress as the level of lipolytic pancreatic enzymes decreases.

10.9.3 Dermatitis Herpetiformis

Dermatitis herpetiformis, a cutaneous marker of gluten-sensitive enteropathy, is characterized by pruritic grouped papules and vesicles symmetrically distributed on the elbows, knees, scalp, buttocks, and extensor forearms [42]. Men are more often affected than women, and dermatitis herpetiformis usually first occurs at a young adult age. Gluten is the main adhesive substance of many grains, and gliadin is the most important sensitizing protein as well as the substrate for tissue glutaminase. Autoantibodies against tissue glutaminase also cross-react with epidermal transglutaminase leading to the formation of the cutaneous lesions. There is a strong HLA association with 90% of patients possessing HLA-DQ2.

The diagnosis can be made by histologic examination of an early blister and direct immunofluorescence of non-lesional skin in which IgA is seen in the dermal papillae. Suppressive therapy using dapsone is the mainstay of treatment. Dapsone is effective in rapidly clearing the rash, but relapse upon discontinuation of the medication is also rapid. Therapy should also include a gluten-free diet, which can be difficult, but essential in treating the underlying disease as well as dermatitis herpetiformis.

10.9.4 Hepatobiliary/Cirrhosis

10.9.4.1 Spider Angiomas

The cutaneous signs of liver disease generally correlate with the severity of the disease [43].

Cirrhosis distorts the normal liver anatomy causing decreased blood flow through the liver resulting in portal hypertension. Portal hypertension, in turn, results in ascites, peripheral edema, and varices. There is also impaired biochemical function; albumin as well as clotting factor synthesis are decreased. This results in purpura and ecchymoses.

Spider angiomas result from hyperestrinism, and develop in at least 75% of patients with cirrhosis. The lesion is characterized by centralized red macule or papule with outward vascular extensions resembling a spider web. The center is a coiled central arteriole, and the extensions are smaller vessels radiating outward. Spider angiomas are most often planar, but can enlarge to form hemangioma-like masses [43]. They are found on the face, neck, trunk, and upper extremities. The lesions are usually associated with chronic liver disease, but may be associated with pregnancy and oral contraceptives, as well. Thus, spider angiomas are not considered to be pathognomonic of liver disease.

10.9.5 Terry's Nails

Terry's nails occur in patients with liver disease, and are characterized by nails that turn opaque white except for the distal portion which remains pink in color. The discoloration stops suddenly at about 1–2 mm from the distal edge of the nail, leaving a reddish brown transverse band [44]. These nail findings are not specific to patients with cirrhosis, and may also be found in some normal women younger than 20 years of age. It is thought that hypoalbuminemia results in edema of the connective tissue in the distal nail bed, converting it into a loosely knit rather than highly compact collagenous structure. This change in turn stimulates the organization of the lunula producing a white color of the nail. Histologically, there are changes in vascularity, and specifically distal telangiectasias [44]. The recognition of Terry's nails may serve as an important clue to early diagnosis of hepatic disease.

10.10 Amyloidosis

Amyloidosis refers to a group of conditions characterized by the extracellular deposition of an abnormal protein [45]. While most of proteins in humans and other species are synthesized in an alpha-helical structure, amyloid protein is synthesized in a much less biodegradable beta-pleated sheet structure. There are many proteins that can be precursors for amyloid fibril deposition in the skin: light-chain monoclonal protein, beta-2 microglobulin, serum protein A, prealbumin, and keratin. Amyloidosis can be classified according to the type of amyloid protein deposition and clinical presentation.

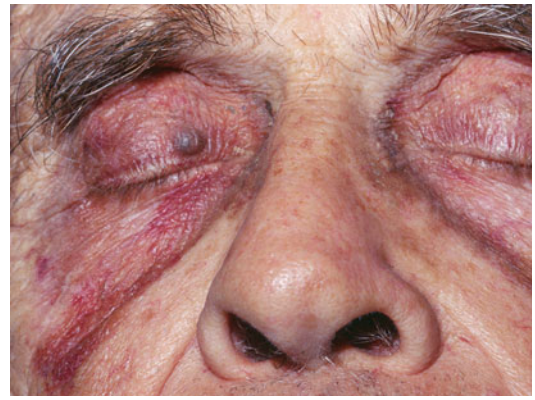

Fig. 10.9 Periorbital spontaneous purpura in a patient with systemic amyloidosis. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

About 30% of patients with primary or myeloma-related systemic amyloidosis have cutaneous manifestations. The dermatological signs of systemic amyloidosis can be helpful in diagnosis because these signs may be the only manifestations before systemic amyloidosis develops into a late-stage disease [46]. As amyloid infiltrates and weakens blood vessels, patients develop purpura, petechiae, or ecchymoses occurring spontaneously on skin folds (e.g., the eyelids, axillae, and anogenital area). "Pinch purpura" in which pinching the skin produces purpuric lesions may occur. Periorbital pupura may form following coughing or the valsalva maneuver (Fig. 10.9). When amyloid infiltrates travel to the dermis, subcutaneous nodules or plaques may form. The lesions appear hemorrhagic, though they may also appear smooth and waxy.

Lichen amyloidosis, the most common type of localized cutaneous amyloidosis, is characterized by tan to brown pruritic papules which may coalesce to form plaques [47]. The lesions most commonly form on the shins.

Various stains of a biopsied specimen can be used to diagnosis amyloidosis. Congo red, for

example, shows doubly refractive and apple green amyloid when examined in polarized light.

Although treatments are usually ineffective, topical corticosteroids could be tried as an antipruritic measure. PUVA or systemic retinoids may be considered as well. In macular amyloidosis, pruritic macular hyperpigmentation occurs in the interscapular area. Treatment is similar to lichen amyloidosis. Topical capsaicin once daily for long periods of time has helped some patients. Both lichen amyloidosis and macular amyloidosis are variants of primary localized cutaneous amyloidosis and occur most often in patients from Asia, the Middle East, and Central and South America.

10.11 Malignancy

10.11.1 Sister Mary Joseph's Nodule (Colon Cancer)

Sister Mary Joseph's nodule is a nodular umbilical metastatic tumor (Fig. 10.10). It was named after Sister Mary Joseph, the first surgical assistant to Dr. William Mayo and the superintendent of St. Mary's Hospital in Rochester, Minnesota, who noted the association between metastatic intraabdominal cancer and paraumbilical nodules [48]. Sister Mary Joseph's nodule is associated with cancers of the gastrointestinal tract and ovary. The most commonly associated malignancy is stomach (20%), followed by large bowel (14%), ovary (14%), and pancreatic tumors (11%). In about 20% of patients, the primary site cannot be identified.

In general, cutaneous metastasis is a poor prognostic sign and may signify widespread internal metastasis [49]. While the prognosis is dependent on the primary tumor, a study found that the average life expectancy after developing skin metastases was 3 months (Figs. 10.11 and 10.12).

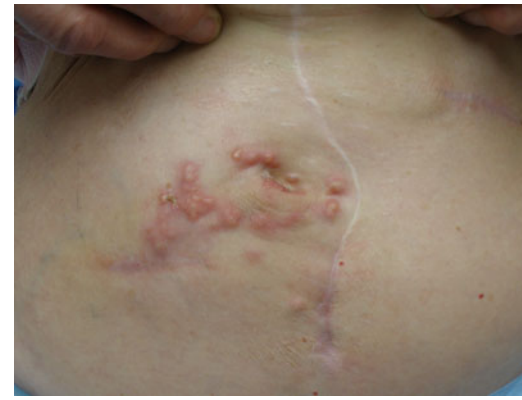

Fig. 10.10 Periumbical metastatic tumors consistent with a diagnosis of Sister Mary Joseph nodule. The diagnosis was made by an incisional biopsy. From the personal collection of Daniel Behroozan, M.D

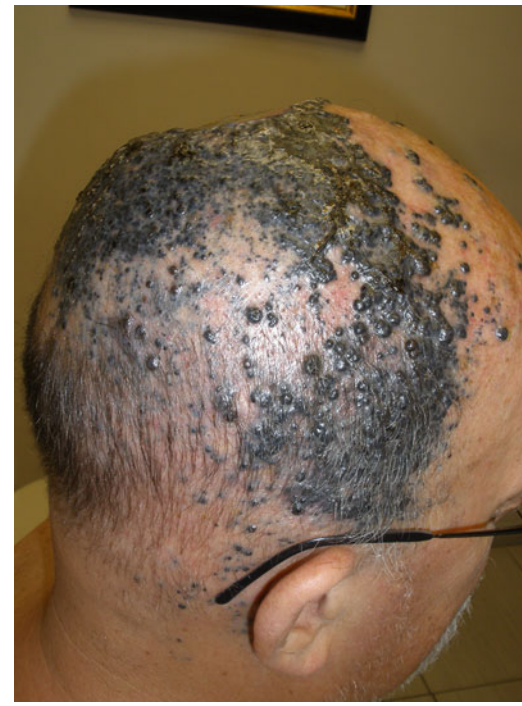

Fig. 10.11 Diffuse and disseminated blue nodules in two patients with metastatic melanoma. From the personal collection of Daniel Behroozan, M.D

10.11.2 Malignant Acanthosis Nigricans

Acanthosis nigricans (previously discussed under the diabetes section) is called malignant acanthosis nigricans when there is a sudden onset of widespread acanthosis nigricans with weight loss, suggesting an underlying malignancy [50]. About 60% of patients who develop malignant acanthosis nigricans have been found to have adenocarcinoma of the stomach, and most often

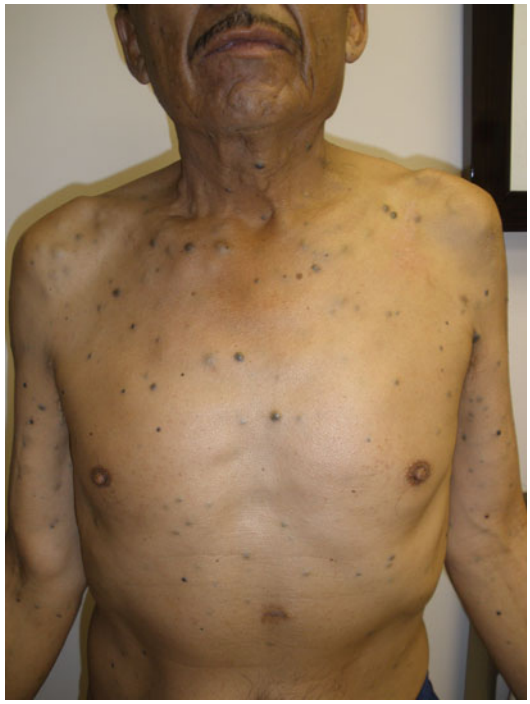

Fig. 10.12 Diffuse and disseminated blue nodules in two patients with metastatic melanoma. From the personal collection of Daniel Behroozan, M.D

are at an advanced stage of the disease. "Tripe palms," acanthosis nigricans of the palms, is characterized by a velvety furrowing of the palmar surfaces and is also often associated with internal malignancy. It is thought that acanthosis nigricans appears due to an epidermal growth factor that is secreted by the tumor. The evidence for this has been shown in some cases where successful resection of the adenocarcinoma results in regression of the acanthosis nigricans [50].

10.11.3 Sweet's Syndrome

Sweet's syndrome is commonly associated with hematopoietic malignancies including acute myelogenous leukemia (the most common), chronic myelogenous leukemia, lymphocytic leukemia, T- and B-cell lymphomas, and polycythemia [51]. No clinical or histopathologic differences exist between patients with and without associated malignancy. Sweet's syndrome most commonly occurs in women 30–60 years of age. It is characterized by skin lesions, fever, malaise, and leukocytosis. About 20% of patients have an associated hematopoietic malignancy. The classic cutaneous manifestation of Sweet's syndrome is sharply demarcated and painful plaque that often has papulovesicles and pustules on the surface. The plaques are present on the face, neck, upper trunk, and extremities. Lesions may be present in the oral mucous membrane and eyes as well. As in pyoderma gangrenosum, the phenomenon of pathergy (hypersensitivity reaction developing at the site of minor skin trauma) may be seen.

The laboratory abnormalities include leukocytosis (present in 60% of patients), elevated sedimentation rates, anemia, thrombocytopenia, and increased number of segmented neutrophils.

Sweet's syndrome responds well to systemic corticosteroids (e.g., prednisolone 60 mg daily tapered over two to four weeks), but recurs in about 25% of cases. Various alternatives such as potassium iodide, clofazimine, or colchicine may be considered in recurrent cases.

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