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Skin Disorders in Association with Monoclonal Gammopathies

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Abstract: Monoclonal gammopathy represents a condition characterized by clonal proliferation and accumulation of immunoglobulin producing B-cells. A variety of skin disorders are associated with an increased level of monoclonal immunoglobulin proteins. These skin disorders can be divided into two groups. The first group represents a direct consequence of plasma cell proliferation. The colonization of the plasma cell clone in the dermis expressed as a deposition of proteins related to the M component belongs to this group for which the pathogenesis is well identified, as is the case for example with AL amyloidosis and cryoglobulins. The second group represents skin disorders such as scleromyxedema and Schnitzler syndrome that are highly associated with an M component, or diseases such as pyoderma gangrenosum and leukocytoclastic vasculitis that are more weakly associated with increased levels of monoclonal immunoglobulins. In some other dermatoses such as pemphigus, bullous pemphigoid, epidermolysis bullosa aquisita, Sézary syndrome, lymphomatoid papulosis, urticaria pigmentosa, and acquired ichthyosis, only presumptions exist regarding associations with monoclonal gammopathies. In this the pathogenesis, therapy and prognosis of the most relevant dermatoses shall be described in order of their degree of association with monoclonal gammopathies, which shall also be discussed.

Introduction

Monoclonal gammopathies represent a spectrum of diseases characterized by clonal proliferation and accumulation of immunoglobulin-producing cells derived from the B-cell lineage. Five major classes of immunoglobulins exist that are synthesized by normal plasma cells (IgG, IgM, IgA, IgE, IgD). Normally, immunoglobulin production is heterogeneous polyclonal, with each plasma cell clone secreting only one heavy chain (γ, μ, α, δ, or ε) and one light chain (κ or λ) during its life span. Dysfunctional clonal plasma cells produce one type of immunoglobulin, or in some instances only the κ or λ light chain molecules. Disproportionate proliferation of one clone results in a corresponding serum increase of its secreted molecular product, the monoclonal immunoglobulin protein (M component). The M component is readily detected as a sharp symmetric spike (M spike) with α_2, β, or γ mobility on electrophoresis of serum or urine. Immunofixation or immunoelectrophoresis is required to identify the heavy and light chain class of the protein. The magnitude of the M spike is related to the number of cells producing the M component (Alexanian et al. 1999, Kyle 1999, Barosi et al. 2004). Monoclonal gammopathy of unknown significance (MGUS) represents a common manifestation of multiple disorders and normal variants. MGUS occurs in 1 percent of healthy people over the age of 50 and in 3 percent of people over the age of 70. In about 80 percent of cases, the abnormal protein does not cause any clinical symptoms (Varterasian 1995, Herrinton 1996, Brigden 1999). However, over time, 25 percent of people will experience an increase in the amount of abnormal protein in their blood, which may progress to a B-cell malignancy or multiple myeloma (MM) (Bergsagel 1995). MGUS might be associated with a variety of diseases (Table 1). The M component is not only present in plasma cell disorders such as MM, Waldenstrom's macroglobulinemia (WM), and various rare heavy chain diseases (Table 2). M components are also detectable in other lymphoid and non-lymphoid neoplasm's such as acute myeloid leukemia (AML), breast and colon cancer and even in a variety of non-neoplastic conditions such as liver cirrhosis, sarcoidosis and rheumatoid arthritis (Alexanian et al. 1999, Kyle and Greipp 1998) (Table 1 and 2).

Monoclonal Gammopathies and Skin Disorders

A variety of skin disorders have been reported to be associated with an increased level of monoclonal immunoglobulin proteins in the serum. They can be divided into two main groups. The first group represents disorders that are a direct consequence of the usually malignant process. They result from plasma cell proliferation and consecutively high levels of monoclonal immunoglobulins in the serum. As such they can also be further subdivided. On the one hand, there is a direct infiltration of proliferative plasma cells into the skin, especially in malignant conditions such as MM and WM (Dimopoulos et al. 2000). On the other, there are disorders related to the deposition of proteins associated with the M component, as is seen for example with AL amyloidosis and cryoglobulins (Mussini et al. 1993, Daoud et al. 1999, Siami and Siami 1999, Piette 1986). The second main group represents skin disorders in which an M component is detectable. There are diseases highly associated with an M component such as scleromyxedema and Schnitzler syndrome. Other disorders such as pyoderma gangrenosum occur in some malignant and inflammatory

Table 1. Monoclonal gammopathies and associated diseases (Duggan and Schattner 1986, Alexanian et al. 1999, Kyle and Greipp 1998).

Category	Associations	Examples
MGUS	Associated with plasma cell dyscrasias	Progression to multiple myeloma and other plasma cell dyscrasias in 25 % after 2 decades
	Associated with other lymphoid and non-lymphoreticular neoplasms	Carcinomas of the breast, gastrointestinal tract, kidney, Hodgkin's lymphomas, chronic myeloic leukemia
	Associated with chronic inflammatory diseases	Rheumatoid arthritis, sarcoidosis, tuberculosis, osteomyelitis, pernicious anemia, etc.
	Asymptomatic and non-progressive	Age-related incidence, occurs in apparently healthy persons (majority)
	Transient plasma cell dyscrasias	Virus infections, heart surgery, drug hypersensitivity
Malignant plasma cell dyscrasias	Symptomatic and progressive	Multiple myeloma, Waldenstrom`s macroglobulinemia, heavy chain disease, AL amyloidosis

Table 2. Diagnostic criteria for multiple myeloma, myeloma variants and MGUS. Multiple myeloma: I+b, I+c, I+d, II+b, II+c, II+d, III+a, III+c, III+d, a+b+c, a+b+d. MGUS: presence of a serum M-protein value less than 3 g/dL, fewer than 15% plasma cells in the bone marrow, no or only small amounts of Bence-Jones protein in the urine, absence of lytic bone lesions, no related anemia, hypercalcemia, or renal failure (Barosi et al. 2004, Kyle and Rajkumar 2004).

Major criteria

I	Plasmacytoma in tissue biopsy
II	Bone marrow with more than 30% plasma cells
III	Monoclonal globulin spike in serum protein electrophoresis, with an immunoglobulin G (IgG) peak of greater than 3.5 g/dL or an immunoglobulin A (IgA) peak of greater than 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) greater than 1 g/24 h

Minor criteria

a	Bone marrow with 10-30% plasma cells
b	Monoclonal globulin spike present but less than category III
c	Lytic bone lesions
d	Residual normal immunoglobulin M (IgM) level of less than 50 mg/dL, IgA level of less than 100 mg/dL, or IgG level of less than 600 mg/dL

Table 3. Skin disorders in monoclonal gammopathies; a classification depending on the degree of association (Daoud et al. 1999).

Group I: direct correlation

Cutaneous plasmacytoma
Hyperviscosity syndrome
Cryoglobulinemia
Amyloidosis
POEMS syndrome

Group IIa: high association

Scleromyxedema, lichen myxedematosus, papular mucinosis
Scleredema
Plane xanthomas
Necrobiotic xanthogranuloma
Schnitzler syndrome
Erythema elevatum diutinum
Subcorneal pustular dermatosis

Group IIb: low association

Pyoderma gangrenosum
Sweet syndrome
Leukocytoclastic vasculitis

Group III: association sporadically reported

Pemphigus
Bullous pemphigoid
Epidermolysis bullosa aquisita
Sézary syndrome
Lymphomatoid papulosis
Acquired ichthyosis
Urticaria pigmentosa
Reticular erythematous mucinosis
Xanthoma disseminatum
Lupus erythematosus

conditions, but the association is much weaker. The pathophysiological pathway and the relevance of the M component in the second disease group are still unclear. Epidemiological studies are warranted to assess the relevance of dermatoses occurring with an M-component. Because of immunological aspects and growth factors, further examinations are required to understand whether a dermatosis represents a paraneoplastic disorder of a malignant plasma cell process or whether the M-component is a parameter arising from the dermatological disorder. In a large number of other dermatoses including pemphigus, bullous pemphigoid, epidermolysis bullosa aquisita, Sézary syndrome and lymphomatoid papulosis, an association with MGUS is merely presumed. Table 3 summarizes the most relevant skin disorders in MGUS, classified according to the degree of association. Pruritus, purpura, infections due to decreased immunoglobulin production and a variety of drug reactions represent other dermatologic manifestations of monoclonal gammopathies (Daoud et al. 1999, Piette 1986).

Group I: Direct Correlation

Cutaneous Plasmacytoma

Cutaneous plasmacytoma (CP) of the skin presents as non-tender, smooth, cutaneous or subcutaneous nodules of 1-5 cm in diameter. The lesions are flesh or plum-colored with a tendency to become crusted or ulcerated. They are mostly distributed on the extremities, trunk, and face. Frequently, skin lesions present as secondary CP in the setting of MM. Lesions may develop as a direct expansion of underlying bone lesions or they present as metastatic foci. Primary cutaneous plasmacytomas with no evidence of involvement of other tissues are exceedingly rare. Histologically, both the dermis and the subcutaneous tissues are infiltrated by plasma cells that vary in maturity. The so-called cutaneous plasmacytosis is based on monoclonality with the presence of only kappa or lambda light chains. Immunoglobulins produced may be of any type, but IgA appears to be frequently found (Daoud et al. 1999, Collet et al. 1991). Therapy for CP in the setting of MM includes chemotherapy and local radiation therapy. Surgical excision has a role in lesions restricted to the skin, which are unresponsive to radiation therapy.

Hyperviscosity Syndrome

Hyperviscosity syndrome (HS) is caused by a significant increase in whole blood viscosity, which may result from increased cellular blood elements, such as in myeloproliferative disorders, or from a large amount (>3 g/dL) of monoclonal proteins, mostly of the IgM type. Clinically, HS may present as mucous membrane bleeding, retinopathy, cardiac failure, and neurological disturbances. If HS is present together with cryoglobulins, Raynaud's syndrome might be observed. Blood viscosity must increase by at least 4-fold for clinical symptoms to appear. A bleeding tendency can also be explained by the presence of clotting factor antibodies and/or platelet dysfunction because of surface coating by immunoglobulins (Siami and Siami 1999, Kumar et al. 2003).

Cryoglobulinemia

Cryoglobulins are serum immunoglobulins complexed with other immunoglobulins or proteins that reversibly precipitate in cold temperatures. Cryoglobulinemia is associated with a range of clinical findings, including purpura in parts of the body exposed to cold temperatures, Raynaud's syndrome, acral hemorrhagic necrosis, arthralgia, neurological manifestations, and glomerulonephritis. The classification of cryoglobulinemia follows the initial description by Brouet et al. in 1974 and is based on the immunoglobulin involved. Type I cryoglobulins are monoclonal immunoglobulins (Mussini et al. 1993), usually IgG or IgM. Type II cryoglobulins are mixed cryoglobulins with a monoclonal and a polyclonal component. Type II cryoglobulins can be associated either with B-cell malignancies or with autoimmune disorders (Siami and Siami 1999, Cuellar et al. 1995, Bulfoni 1995, Dammacco and Sansonno 1997). Type III cryoglobulins are polyclonal immunoglobulins that form a cryoprecipitate with polyclonal IgG or a non-immunoglobulin serum component. Patients with this type of cryoglobulin are affected by an autoimmune process or infection. After serum is separated, it is stored at 4 °C. After approximately 24 hours, cryoprecipitates may be observed. The severity of symptoms reflects the serum concentration and the temperature at which cryoglobulins precipitate. Purpura is the most typical clinical presentation of cryoglobulinemia. Cold sensitivity is present in fewer than 50% of patients with cryoglobulinemia. Type I cryoglobulins are typically associated with Raynaud's syndrome, acrocyanosis, retinal hemorrhage, and arterial thrombosis. Type II and III cryoglobulins are associated with arthralgias and vascular purpura. Treatment of cryoglobulinemia is based on the severity of clinical presentation. Mild cutaneous symptoms may only call for avoidance of exposure to cold temperatures. NSAID can alleviate more bothersome dermatologic and articular manifestations. Renal involvement may require corticosteroids and/or cytotoxic agents. Plasmapheresis has been used in progressive refractory disease, but it needs to be combined with cytotoxic agents to avoid postpheresis rebound (Iwasaki and Kakishita 1995).

Amyloidosis

Amyloidosis consists of a group of disorders in which amyloid fibrils are extracellularly deposited in internal organs and skin. Amyloid fibers in x-ray diffraction studies demonstrate a beta-pleated structure, unlike that of most human proteins. The proteins serving as precursors for fibrils can be either light chain monoclonal proteins or serum protein A. This distinction serves as a basis for classification into amyloid light chain amyloidosis (AL) and serum protein A amyloidosis (AA). AA-type amyloidosis is usually associated with a chronic inflammatory process, such as rheumatoid arthritis, chronic osteomyelitis, tuberculosis, or leprosy. Although the deposition of amyloid in the skin is common in AA, it rarely leads to clinically apparent skin lesions. AL-type amyloidosis is associated with MM, MGUS and WM (Wong 1990). It common-

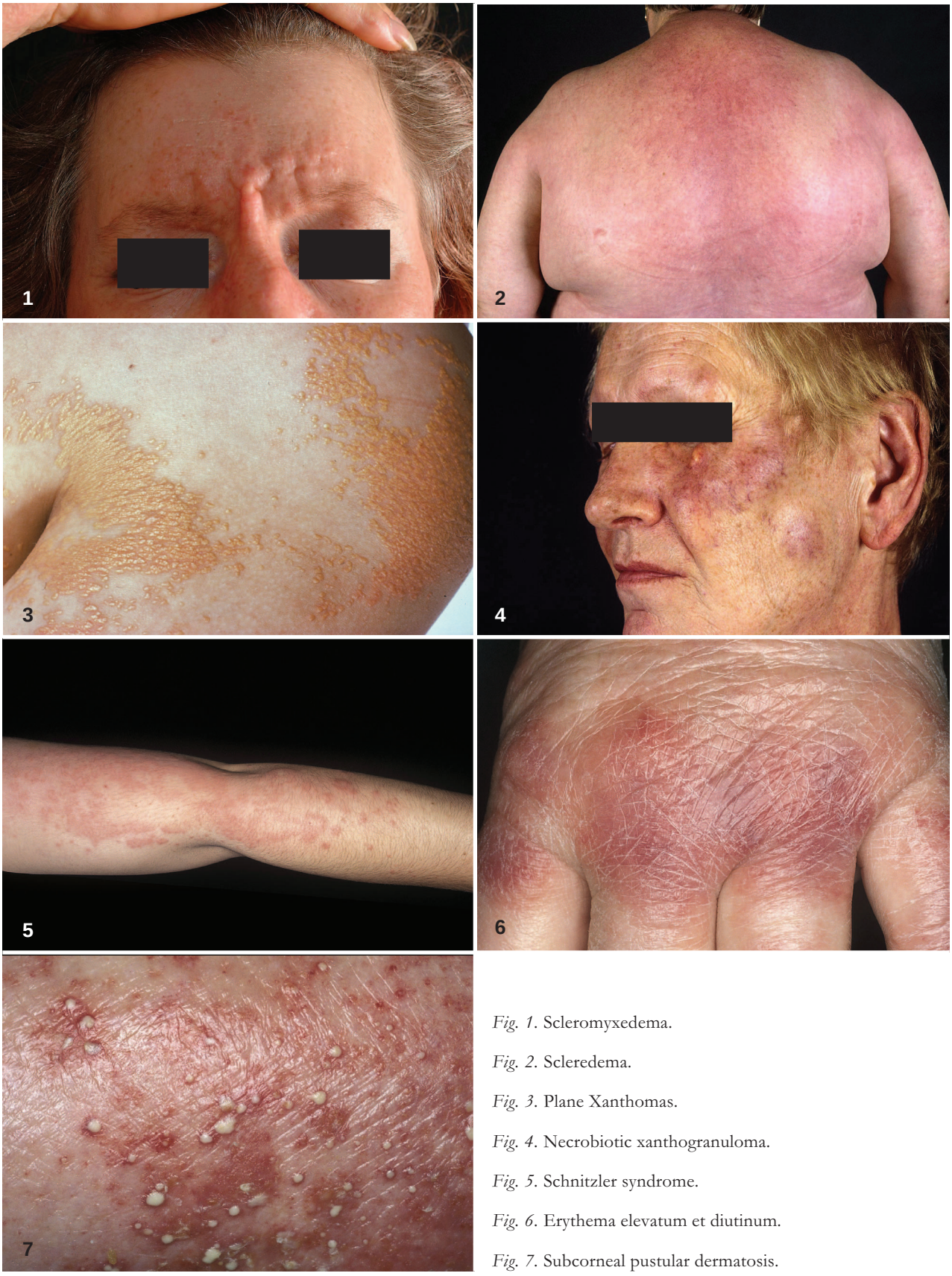

Fig. 1. Scleromyxedema.

Fig. 2. Scleredema.

Fig. 3. Plane Xanthomas.

Fig. 4. Necrobiotic xanthogranuloma.

Fig. 5. Schnitzler syndrome.

Fig. 6. Erythema elevatum et diutinum.

Fig. 7. Subcorneal pustular dermatosis.

ly affects the skin, with a reported incidence of 21 - 40%. The most characteristic features are non-pruritic, non-tender, shiny, waxy papules, commonly located on the eyelids. However, lesions can also be present in the skin folds, the retroauricular folds, the anogenital region, or the oral mucosa. Purpura is the type of lesion encountered most often because of the frequent deposition of amyloid in blood vessel walls, resulting

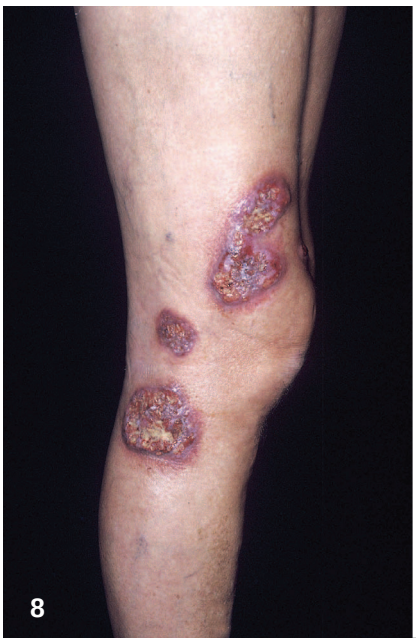

Fig. 8. Pyoderma gangrenosum.

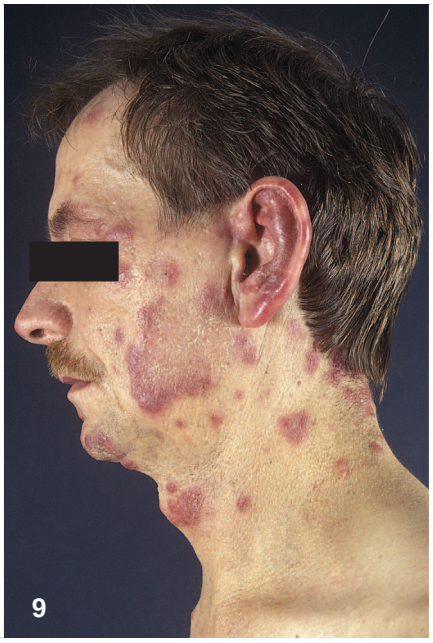

Fig. 9. Sweet syndrome.

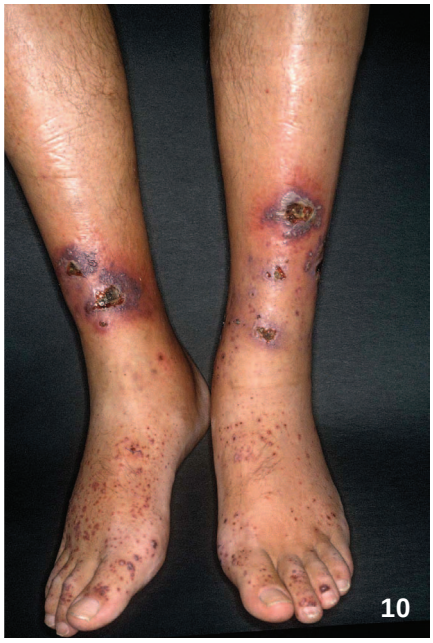

Fig. 10. Leukocytoclastic vasculitis.

in extreme fragility of the skin vessels. The deposition of amyloid in the blood vessel walls is also responsible for pinch purpura, which is frequently found on the eyelids of patients with AL-type amyloidosis (Wong 1990). AL amyloid deposition is also responsible for peripheral neuropathy, carpal tunnel syndrome and orthostatic hypotension. Approximately 10% of patients with AL amyloidosis develop macroglossia, which can produce dysphonia and dysphagia (Christiaens et al. 1999). Another manifestation of oral amyloidosis may be xerostomia, resulting from salivary gland infiltration by amyloid. Primary cutaneous amyloidosis does not appear to be related to systemic disease. The papular type, often referred to as lichen amyloidosis, presents with extremely pruritic, hyperkeratotic, brownish papules. These papules are most commonly the size of a pinhead, but they can reach 6-8 mm in diameter and usually occur on the shins. Macular amyloidosis is probably a variant of lichen amyloidosis, presenting as pruritic, oval, grayish brown macules on the lower extremities or back. Definitive diagnosis of systemic amyloidosis requires the confirmation of amyloid deposits in the tissue. The most commonly suggested sites include the rectum and the tongue. However, several reports recently published state that a skin biopsy is a sensitive, safer, and less complicated procedure (Lee et al. 1998). Evaluation of the patient with biopsy-proven cutaneous amyloid deposition depends on the clinical scenario. Vessel wall infiltration and epidermal atrophy in a biopsy sample obtained from a patient with waxy eyelid nodules should raise suspicion of an AL-type amyloidosis (Lee et al. 1998), and a search for underlying MM or WM is warranted. If all clinical and pathologic features appear to suggest lichen amyloidosis, no further search is necessary and local measures should be undertaken. Effective therapy for AL- and AA-type amyloidosis is not yet available, with treatment being symptomatic most of the time.

POEMS Syndrome

Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS syndrome) was described as a separate pathologic entity in Japan based on a series of 102 patients. However, since 1968 a number of cases have also been reported in the United States (Takatsuki 1994). Of the originally reported patients, 75% had a serum and occasionally an urinary monoclonal spike, and in 95% of these patients the monoclonal protein had a lambda light chain restriction (Soubrier et al. 1994, Costa et al. 1990). In the Japanese series, men were affected twice as often as women, with a mean age of 46 years. Polyneuropathy was present in all patients and was usually sensorimotor. Organomegaly usually manifested itself as hepatomegaly (82%), lymphadenopathy (65%), and splenomegaly (39%). Endocrinopathy presented as impotence (78%) and gynecomastia (68%) in men as well as amenorrhea (68%) in women (Cuellar et al. 1995). Other reported endocrine abnormalities included glucose intolerance, hyperthyroidism, hyperprolactinemia, and adrenal insufficiency. In contrast to MM, no anemia, no renal insufficiency, and only rare cases of hypercalcemia were reported. Bone marrow infiltration by plasma cells was unusual. Patients reported bony lesions, but unlike those in MM, these lesions were mostly osteosclerotic. Skin changes are commonly observed in patients with POEMS syndrome, with 93 - 98% having diffuse hyperpigmentation and 92% having peripheral edema. Ascites and pleural effusions were occasionally reported. Hypertrichosis, digital clubbing, white fingernails, sicca syndrome, and Raynaud's syndrome have also been described (Goldstein and Bandyopadhyay 2004, Lagueny et al. 2004).

Group IIa: High Association

Scleromyxedema, Lichen Myxedematosus, Papular Mucinosis

The terms lichen myxedematosus (LM), papular mucinosis (PM), and scleromyxedema (SM) are used interchangeably to describe the same disorder. A spectrum of disease appears to exist, with the more localized, less severe forms, which are generally called LM or PM, and the more sclerotic, diffuse form, which is referred to as SM. LM is a rare skin disorder characterized by fibroblast proliferation and mucin deposition in the dermis without any thyroid disease. The etiology is unknown. However, LM is commonly associated with plasma cell dyscrasia (Dinneen and Dicken 1995). The basic defect is hypothesized to be a fibroblast disorder that causes the increased mucin deposition in the skin. Most patients have a monoclonal paraprotein band, usually of the IgG type. The association between this paraprotein and mucin deposition is not clear, and the protein does not directly stimulate fibroblast proliferation. Most individuals with LM are aged 30-70 years. LM is usually a chronic disease (Dinneen and Dicken 1995). Although a majority of patients have MGUS, they rarely have associated MM. However, when MM is present, the patient generally has a poor prognosis. Patients with cardiac or pulmonary involvement also have poor prognoses. In LM or PM, the primary lesion is a 2-4 mm dome-shaped and flesh-coloured or erythematous papule. Regarding the distribution, lesions may coalesce into grouped lichenoid papules and are found on the dorsal hands, face, or extensor surfaces of the arms and legs. Papules often have a striking pattern of parallel ridges. In patients with the generalized lichenoid form, facial ridges and facial folds may be distorted. This condition is called leonine faces. Patients with leonine faces may have difficulty opening the mouth. In SM the primary lesions may involve widespread erythematous, indurated skin resembling scleroderma, and diffuse tightness of the skin (Fig. 1). The range of motion of the face, fingers, and extremities is decreased. Systemic manifestations include restrictive and obstructive pulmonary dysfunction, cardiovascular abnormalities, and polyarthritis. Obstructive and restrictive lung disease is often manifested by dyspnea on exertion. Gastrointestinal symptoms, most commonly dysphagia, are related to esophageal aperistalsis. Severe proximal muscle weakness, polyarthritis, and symptoms resembling those of organic brain disease might appear. Inflammatory myopathy is also reported. Ophthalmologic symptoms include ectropion and corneal opacities. Cardiovascular abnormalities occur in 10% of cases. Lesions feature large depositions of mucin in the dermis. Numerous plump stellate fibroblasts develop throughout the dermis. The mucin stains with periodic acid-Schiff and Alcian blue at pH 2.5, and it metachromatically stains with toluidine blue at pH 3.0. It has been identified as hyaluronic acid, a non-sulfated acid mucopolysaccharide. Treatment of LM is difficult and often ineffective. Many therapeutic approaches have been reported including retinoids, orthovoltage radiation, electron beams, corticosteroids, PUVA, plasmapheresis, extracorporeal photophoresis, dermabrasion, and carbon dioxide laser excision (Durani et al. 2001, Harris et al. 1979, Dinneen and Dickson 1995, Lister RK et al. 2000). For LM, the prognosis is a chronic course with little tendency for spontaneous resolution. SM usually has a poorer prognosis. Typical causes of death include complications from systemic therapeutic agents such as melphalan or systemic disease such as cardiovascular involvement.

Scleredema

Scleredema is an uncommon condition of unknown etiology. It is characterized by a non-pitting induration of the skin with occasional erythema (Fig. 2). Scleredema can be categorized into 3 clinical subgroups, each having a different history, course, and prognosis. Group 1 accounts for most cases. Patients in group 1 have a history of preceding febrile illness, particularly an upper respiratory tract streptococcal infection (Cron and Swetter 1994). The onset of skin lesions is rapid and usually clears within 6 months to 2 years. The duration is not affected by the use of antibiotics. Most pediatric patients fall into this group. Patients in groups 2 and 3 generally have no prior history of febrile illness. The onset of skin lesions in these patients is insidious. Patients in group 2 may have no prior history of medical problems, but they appear to be at a certain risk of developing MGUS or MM (Hodak et al. 1988). Patients in group 3 have a prior history of diabetes mellitus, usually with an adult onset and insulin dependent, and they tend to have an unremitting course. Although regarded as a benign, self-limited skin disease, scleredema may be persistent and involve the viscera. Rarely, it may result in death. The term scleredema is a misnomer because neither sclerosis nor edema is found upon microscopic examination. Histological findings of scleredema include a thickened dermis with deposition of mucin between thickened collagen bundles (Ulmer et al. 1998). Fibroblast cultures of affected skin have shown increased procollagen synthesis. Likewise, serum from patients with scleredema has been shown to stimulate collagen production in normal skin fibroblasts. The morbidity of skin changes in scleredema depends on the area of the body involved. Involvement of the skin over the joints may cause a limited range of motion. Scleredema on the face can result in difficulties in opening the eyes and mouth. Although rare, extensive truncal involvement may cause restrictive lung disease. The tongue may be involved in scleredema, resulting in dysarthria and difficulty with mastication and tongue protrusion. Other organs that may be affected in scleredema include the skeletal muscles, ocular muscles, pharynx, liver, parotid glands, pleurae, peritoneum, and spleen. Initial skin changes in scleredema usually occur on the face, neck, and upper part of the back. Affected skin may be flesh-coloured, erythematous, or hyperpigmented. Hands and feet are typically spared. No therapy is consistently effective for scleredema. A number of therapies, including systemic steroids, cyclosporine, methotrexate, PUVA, penicillamine, electron beam, and glycemic control with prostaglandin E1 have been tried with varying degrees of success (Bowen et al.

2003, Pujol et al. 1995). Patients with long-standing scleredema should be periodically monitored using the results of electrophoresis to detect the development of paraproteinemia or MM. Blood dyscrasias may occur several years after the onset of scleredema. Although the course of scleredema is unpredictable, patients in groups 2 and 3 typically have a slowly progressive or unremitting course over many years (Ulmer et al. 1998).

Plane Xanthomas

Plane xanthomas (PX) are mostly yellow-coloured macules and rarely form elevated lesions (Fig. 3). They can occur at any site. Involvement of the palmar creases is characteristic for type III dysbetalipoproteinemia. They can also be associated with secondary hyperlipidemias, especially in cholestasis. Generalized PX can cover large areas of the face, the neck, and the thorax, and the flexures can also be involved. They may be associated with hyperlipidemia, particularly hypertriglyceridemia (Hidalgo Calleja et al. 1993). IgG gammopathy is most common in PX, however, the role of paraproteins in the initiation of PX is still unknown (Daoud et al. 1999).

Necrobiotic Xanthogranuloma

Necrobiotic xanthogranuloma (NX) is a rare destructive cutaneous and subcutaneous disorder that most frequently involves the face, especially the periorbital region (Fig. 4). Twelve years after the original description, Mehregan and Winkelmann 1992 reported on 32 cases from their own patient circle and 16 from the literature. Since then, other cases have occasionally been reported. MGUS is common in NX. IgG-kappa was found in 23 cases and IgG-lambda in nine cases, while cryoglobulins have also been reported (Roth et al. 2002). Bone marrow examination usually shows plasma cell proliferation and, rarely, true myeloma. The clinical feature is a xanthogranuloma with focal necrosis, presenting as multiple large, sometimes ulcerated, red to yellow granulomatous nodules. Histologically, these xanthomatous lesions are different from xanthomata typically associated with primary hyperlipoproteinemia. The anticipated Touton-type foamy macrophages are present, but in addition there is collagen necrosis, which is not generally seen in other xanthomata. The clinical course is chronic and often progressive. Low-dose chlorambucil treatment is safe and effective, but individual patients have responded to treatment with corticosteroids, melphalan, local radiation, and plasma exchange (Machado et al. 2001).

Schnitzler Syndrome

Schnitzler syndrome (SS), first reported in 1974, is characterized by chronic, non-pruritic urticaria in association with recurrent fever, bone pain, and monoclonal IgM gammopathy at a concentration that is usually less than 10 g/dL (Fig. 5). Deposition of the IgM paraprotein, leading to formation of immune complexes and activation of the complement cascade, might be responsible for cutaneous manifestations. Another proposed mechanism involves the uncontrolled activation of interleukin-10. Most patients with SS have a benign course. Approximately 10 - 15% of patients eventually develop a lymphoplasmacytic malignancy, such as WM, lymphoplasmacytoid lymphoma, or IgM myeloma. Patients with SS present a chronic, recurrent, urticarial eruption that is classically non-pruritic. Rarely, mild pruritus may occur. Skin eruption is usually the first symptom to occur, primarily affecting the trunk and the extremities, sparing the palms, the soles, and the face. Approximately 75% of patients experience recurrent fevers in association with urticarial eruptions. Each febrile episode usually resolves within a few hours, however, fever can persist for up to 24 - 48 hours. Concurrent with fever, patients may complain of relapsing arthralgias (60%), bone pain (50%), and myalgias. The bone pain typically involves the tibia, the femur, the ileum, and the vertebral columns, but other sites can also be affected. Fatigue and weight loss is present in a high percentage of patients. The pathogenesis of SS is still unclear. In 1980, using anti-idiotype antibodies, Olsen et al. demonstrated that IgM monoclonal antibodies reacted with epidermal antigens. Saurat et al. in 1991 found that the monoclonal IgM targeted 50-kd, 31-kd, and 17-kd proteins within epidermal extracts. These findings suggest that IgM deposits may be involved in the pathogenesis of SS, perhaps via formation of immune complexes and activation of the complement system.

IL-10 is a known mediator of inflammation, and its injection into the skin causes persistent erythema. In 1991, Saurat et al. found that the serum from 6 out of 9 patients with SS contained polyclonal IgG–type autoantibodies directed against IL-10. These autoantibodies have been shown to prolong the half-life of IL-10, to change its tissue distribution, and to enhance its effects. As such, this increase in IL-10 activity could account for the symptoms of urticaria and fever found in SS. All cases of SS are associated with an IgM monoclonal gammopathy, which is demonstrated by serum immunoelectrophoresis. Most cases are of the IgM-kappa isotype. In 51% of cases, serum protein electrophoresis may not detect the IgM gammopathy because levels can be very low. Both low serum complement levels and low serum C1 inhibitor levels are seen in nearly 10% of patients. Cryoglobulin, antinuclear antibody, and rheumatoid factor test results are positive in a small percentage, 3%, 7%, and 7%, respectively. Abnormal lymphoid proliferation is present in 10% of bone marrow biopsy samples and 10% of lymph node biopsy samples (de Castro et al. 1996). A recent review of the pathology of SS showed that the histopathological findings were not consistent. Features in some included a superficial dermal and perivascular infiltrate of polymorphonuclear cells, mostly neutrophils, suggestive of neutrophilic urticaria. A small percentage demonstrated a superficial perivascular mononuclear infiltrate suggestive of chronic urticaria and lymphocytic inflammation. Vessels were intact, and dilatation of dermal lymphatics with mild superficial edema was present. Rare cases show fibrin deposition, extravasation of erythrocytes, or leukocytoclastic vasculitis. Deposits of IgM and complement in the upper dermis and/or at the dermoepidermal junction were seen in 45% of cases. IgM deposits were rarely found within

vessel walls (de Castro et al. 1996). The urticarial eruption of SS is typically resistant to treatment. Nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, and immunosuppressive agents have been reported to provide variable relief from symptoms of bone pain and arthralgias. However, no treatment is consistently effective. Skin and extracutaneous manifestations respond poorly to H1 and H2 antihistamines. Colchicine and dapsone have been tried with variable success. Chloroquine, chlorambucil, cyclophosphamide, azathioprine, plasmapheresis, and high-dose intravenous immunoglobulin usually have a poor response.

Prednisone, at doses of approximately 50 mg/d, is often effective in controlling cutaneous eruptions. Relapses are common in attempts to taper the dose of prednisone. NSAID have proved to be of some benefit for bone pain and fever but not for the urticaria. Often, a combination of low-dose prednisone and an NSAID, with or without another immunosuppressive agent, may be needed to control symptoms (Lipsker 2002).

Erythema Elevatum et Diutinum

Erythema elevatum et diutinum (EED) is a rare type of leukocytoclastic vasculitis characterized by red, purple, brown, or yellow papules, plaques, and nodules (Fig. 6). Lesions are usually distributed on the extensor surfaces of the body. The pathophysiology of EED still remains uncertain. According to Gibson and Su, lesions are caused by the deposition of immune complexes in small blood vessels inducing an inflammatory cascade with consecutive damage to the vessels (Gibson and Su 1995). This repetitive damage causes fibrosis and the appearance of cholesterol crystals and myelin figures. Direct immunofluorescence shows deposits of complement as well as IgG, IgM, IgA, and fibrin around the damaged vessels. Although first described in 1888, the largest study of EED was published in 1992 and included only 13 patients. Patients usually present with persistent, firm lesions on the extensor surfaces of their skin, especially over the joints (Yiannias et al. 1992). Lesions mostly consist of nodules and oval plaques. However, on rare occasions, blisters and ulcers may appear. The colour of the lesions progresses over time from yellow or pinkish to red, purple, or brown. They can be completely asymptomatic, painful, or cause a sensation of burning or itching. The general health of the patient may be otherwise good, although a history of arthralgia is often found in EED. Disorders that have been associated with EED include recurrent bacterial infections, viral infections such as hepatitis B or HIV, and rheumatologic disease (Sachdev et al. 2002). In recent years, several reports, including the two largest clinical studies completed on EED, have suggested hematologic diseases as the most common associated factor (Gibson and El-Azhary 2000). Direct immunofluorescence study results demonstrated changes consistent with vasculitis, including deposits of complement, immunoglobulins (IgG, IgA, IgM), and fibrin (Wayte et al. 1995). Yiannias et al. advocate routine immunoelectrophoresis testing for patients with EED. The growing number of studies showing that MGUS might play a causal role in EED supports the use of this technique. A skin biopsy is the most useful examination for diagnosing EED. No specific histological finding can be used to single out the diagnosis of EED from other leukocytoclastic diseases. However, the simultaneous presence of several histological findings can help distinguish this disease from others. Early lesions show vasculitis in small vessels of the upper and mid dermis. Furthermore, a perivascular infiltrate consisting of mainly polymorphonuclear neutrophils, fragmented nuclei, and to a lesser extent macrophages, lymphocytes, and eosinophils is present throughout the dermis. The epidermis can be affected and show signs of edema, acanthosis, and even necrosis. Granulation tissue and fibrosis in the dermis characterize older lesions. Toxic hyaline is less apparent, but extracellular cholesterol (EC) deposits may be observed in the fibrotic tissue. This has been termed EC and was thought at first to have a different etiology to EED (Sachdev et al. 2002). Today, EC is known to be a manifestation of EED. Furthermore, the use of the term extracellular cholesterosis tends to be restricted, since it is now believed that the main lipid deposits are intracellular and that they are formed from cholesterol esters produced by damaged tissue. Several studies and clinical experience have shown a good response to dapsone, whereas systemic steroids have not been found to be effective generally. Sulfapyridine has similar effects to dapsone. Intermittent plasma exchange was shown to control IgA paraproteinemia in association with EED. The IgA levels responded to intermittent plasma exchange treatment followed by consolidative doses of cyclophosphamide. This treatment might be promising for severe EED that cannot be controlled by dapsone. EED is a chronic disease that usually evolves over a 5- to 10-year period, at which point it may resolve. Lesions tend not to leave scars, but areas of hyperpigmentation or hypopigmentation might occur (Gibson and el-Azhary 2000).

Subcorneal Pustular Dermatosis

Subcorneal pustular dermatosis (SPD) is a rare, benign, chronic relapsing pustular eruption of unknown etiology (Fig. 7). This condition characteristically affects the flexural sites of the trunk. SPD has commonly been reported in middle-aged and elderly women. Sneddon and Wilkinson first described it as a separate entity in 1956 (Sneddon and Wilkinson 1979, Sneddon 1977). The exact pathophysiology remains unknown. Subcorneal accumulation of neutrophils suggests the presence of potent chemoattractants in the upper part of the epidermis. Neutrophil chemoattractants, such as interleukin-8, leukotriene B4, and complement fragments have been found at increased levels in scale extracts compared with controls. A possible etiologic pathogen has not been identified. Patients typically present with a chronic relapsing, pustular, erythematous eruption that affects the trunk, particularly the axillae, the groin, and the submammary region. The rash can cause irritation, but this is not a prominent feature. Systemic and toxic symptoms are not a feature, although skin lesions can become secondarily infected. A background history of MGUS, MM, pyoder-

ma gangrenosum, inflammatory bowel disease, or rheumatoid arthritis may be present (Bolcskei et al. 1992). The association of paraproteinemia with SPD is well recognized. Most reports include the presence of IgA MGUS of either the kappa or the lambda light chain type, but IgG gammopathies are also recognized (Takata et al. 1994, Atukorala et al. 1993). A recent series showed that 4 of 10 patients showed a detectable paraprotein level. Serum protein electrophoresis should be repeated at appropriate intervals because paraproteinemia has developed as late as 27 years after presentation. Additionally, lymphoproliferative disease, in particular MM, is known to develop in 17% of patients who have had MGUS for over 10 years (Stone and Lyckholm 1996). A skeletal survey and bone marrow aspiration should be undertaken if MM is suspected, particularly since this is a recognized association (Bolcskei et al. 1992). The hallmark sign is a subcorneal pustule that is filled with neutrophils and occasional eosinophils. This finding is not pathognomonic and it may be found in a number of other conditions, including pustular psoriasis, acute generalized exanthematous pustulosis, pemphigus foliaceus, bacterial impetigo, and dermatophytosis (Hensley and Caughman 2000). However, pustules are exclusively subcorneal, and they classically sit on top of a relatively undisturbed epidermis with minimal spongiosis. This feature differs from pustular psoriasis where the pustule indents and disrupts the epidermis with spongiform changes, and it may be associated with spongiform pustules of Kogoj or Munro microabscesses visible elsewhere in the epidermis. In SPD, neutrophils may be seen migrating up through the epidermis with minimal associated spongiosis. The underlying dermis shows a perivascular infiltrate of neutrophils and, occasionally, monocytes and eosinophils (Vignon-Pennamen and Wallach 1995). Acantholysis is not a prominent feature, although minor degrees may be seen in older lesions. Direct and indirect immunofluorescence results are typically negative, but repeated investigation at suitable intervals is recommended to detect late-onset intercellular IgA staining within the epidermis, which is referred to as IgA pemphigus or intercellular IgA dermatosis. The relationship between SPD and IgA pemphigus is still being elucidated, but a subgroup referred to as SPD type IgA pemphigus is clinically indistinguishable from classic SPD (Vaccaro et al. 1999). SPD responds to dapsone, but the response is not necessarily complete (Roger et al. 1990). Sulfapyridine and sulfamethoxypyridazine can be used as alternatives, but they are regarded as being less effective. Oral corticosteroids are usually ineffective but they have successfully been used in combination with dapsone. Etretinate, and more recently acitretin, have been reported as therapeutic alternatives. Narrowband (TL-01) UV-B, broadband UV-B, psoralen ultraviolet A (PUVA), and re-PUVA have all been reported as being of value in controlling SPD, but relapse may rapidly occur, necessitating maintenance therapy or repeated courses (Todd et al. 1991). Combination chemotherapy for underlying MM has been associated with clinical improvement. Other therapeutic modalities anecdotally recommended include colchicine, ketoconazole, and minocycline.

Group IIb: Low Association

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an inflammatory skin disease that occurs in association with systemic disorders in 50 - 80% of cases. Its most common association is ulcerative colitis (Callen 1998). Approximately 1% of cases of PG occur in association with hematologic disorders, including MM and other monoclonal gammopathies. IgA gammopathy is most commonly observed in patients with PG (Kohl et al. 1991, Mijuskovic et al. 2004). PG is characterized by painful nodules or pustules, which open to form enlarging ulcers with tender raised borders that are frequently vesicular or bullous (Fig. 8). Lesions are most often solitary, but if multiple they may coalesce. They are usually distributed on the lower extremities, although they can also appear on the trunk, the abdomen, and rarely the head and neck (Callen 1998). Systemic symptoms of fatigue and fever may accompany skin lesions. The pathogenesis of PG is unclear, and aberrations of cellular immunity and neutrophilic function have been discussed. Histopathological findings are non-specific and include ulceration and necrosis of the epidermis and dermis, chronic inflammatory cells in the centre of the lesions, and a dense infiltration of neutrophils at the margins. The diagnosis is strictly clinical. Lesions are typically sterile, unless secondary infection occurs. PG should be differentiated from bacterial cellulites, herpes simplex virus infection, atypical mycobacterial infection, and deep fungal mycoses. Excluding an infection is critical before treatment is instituted (Callen 1998). Corticosteroids remain the treatment of choice. In patients with underlying hematological malignancies, topical treatment is generally ineffective. Systemic doses of up to 60-80 mg daily may be administered. Intravenous pulse methylprednisolone remains an option in refractory cases. Regression of PG upon treatment of the underlying disease has been reported. Other systemic treatments include dapsone, sulfasalazine, and clofazimine. Of importance, immunosuppressive agents such as 6-mercaptopurine, azathioprine, cyclosporine, chlorambucil, and cyclophosphamide alone or in combination with steroids have been reported (Burruss et al. 1996, Powell et al. 1996, August and Wells 1974). The optimal sequence of therapy including both chemotherapy and PG treatment should be tailored to the patient. On the one hand, extensive loss of skin integrity causes patients with PG to be more prone to sepsis at the time of chemotherapy-induced neutropenia. On the other, immunosuppression with steroids remains an issue (Callen 1998).

Sweet Syndrome

In 1964, Robert Sweet described a syndrome involving an acute onset of febrile neutrophilic dermatosis. It is manifested by fever, neutrophilia, and erythematous plaques or nodules that respond to steroid therapy (von den Driesch 1994). Skin lesions most commonly involve the upper extremities and face and begin as tender erythematous plaques or nodules (Fig. 9). They

may evolve into vesicles, bullae, or pustules. Extracutaneous manifestations are not infrequent and commonly affect the eyes, lungs, liver, kidneys, and bones. Laboratory features include neutrophilia, anemia, and an elevated erythrocyte sedimentation rate (von den Driesch 1994). The diagnosis is based on clinical presentation and characteristic findings at skin biopsy (Su and Liu 1986). Histological evaluation reveals a neutrophilic infiltrate in the dermis, without evidence of infection, vasculitis, or malignant cells (Bourke et al. 1997). Clinical syndromes can mimic several other entities and differential diagnoses including erythema multiforme and cellulitis. Patients are often initially treated for an infectious process before the proper diagnosis is realized. In cases associated with malignancy, SS typically appears shortly before or coincident with the diagnosis. Lesions may wax and wane, but they typically persist until therapy is administered. Symptoms resolve with systemic steroids and/or successful cancer-directed therapy. Naproxen, colchicine, indomethacin and potassium iodide have been used in alternative approaches (Jeanfils et al. 1997, Maillard et al. 1999, von den Driesch 1994). Recurrent disease is reported and may be a result of an underlying malignancy. SS is associated with an underlying neoplasia in 20% of cases. Approximately 80% of these cases involve hematological malignancies including acute myeloid leukemia and MGUS (Nocente et al. 2002, Bourke et al. 1997). However, non-malignant conditions, including certain drug exposures, autoimmune diseases, and infections have been linked to SS. The exact mechanism for the development of SS is unclear, and several theories have been proposed, including abnormalities in neutrophil chemotaxis, autoantibodies directed against neutrophils, and alteration in cytokine levels including interleukin-6 and granulocyte colony-stimulating factor. The use of subcutaneous G-CSF injections has been implicated as the inciting event in several cases of SS (Arbetter et al. 1999). Although this syndrome is often linked to acute myeloid leukemia as a paraneoplastic process, skin lesions do not directly involve malignant cells. Abnormalities in cytokine production or response in the presence of leukemia are believed to underlie the neutrophilic invasion of the dermis (Reuss-Borst et al. 1993). On the other hand, dermal infiltration with leukemic cells is a separate entity referred to as leukemia cutis.

Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis (LV) is a histopathologic term commonly used to denote a small-vessel vasculitis (Fig. 10). Many possible causes exist for this condition, but a cause is not found in as many as 50% of patients. The disorder may be localized to the skin, or it may manifest in other organs. The internal organs most commonly affected include the gastrointestinal tract or the kidneys. Joints are also commonly affected. The prognosis is good when no internal involvement is present. In the past, circulating immune complexes were believed to cause LV (Lotti et al. 1998). Although immune complexes are involved in the pathogenesis of LV, other autoantibodies cause disease manifestations, such as antineutrophil cytoplasmic antibody (ANCA), other inflammatory mediators, and local factors that involve the endothelial cells and other adhesion molecules. The exact mechanisms remain to be elucidated. Patients with LV may complain of itching, burning sensation, and pain. Vasculitis of the skin may also occur in the absence of any systemic disease. Retiform lesions were associated with IgA related immune complex disease in one study. However, this result has not been validated in subsequent studies (Claudy 1998). Palpable purpura is most frequently observed on the legs, but any surface can be involved. Purpuric lesions are sometimes barely palpable. Urticarial lesions are of a different character than routine urticaria, tending to be of longer duration and tending to resolve with some residual pigmentation or ecchymosis. The picture of LV is a pattern that can occur in any vasculitic syndrome but may also occur in non-vasculitic diseases such as neutrophilic dermatoses, at the base of a biopsy sample of a leg ulceration, or in some insect bite reactions. A skin biopsy sample reveals the presence of vascular and perivascular infiltration of polymorphonuclear leukocytes with formation of fragmented nuclei, extravasation of erythrocytes, and fibrinoid necrosis of the vessel walls. This process is dynamic, a biopsy sample of a lesion too early or too late in its development may not reveal these findings. Between one third and one half of cutaneous vasculitis cases are idiopathic, the remainder have a variety of causes. Antibiotics are the most common drugs that can cause LV, particularly beta-lactams. NSAID and diuretics also frequently cause LV. However, almost all drugs are potential causes. Various infections can be associated with LV. Upper respiratory tract infections and viral hepatitis is most often implicated. Hepatitis C is a regularly recognized cause of LV, probably through the presence of cryoglobulins. Collagen vascular diseases account for 10-15% of cases of LV. Inflammatory bowel disease, ulcerative colitis, or Crohn colitis, even Sjörgren syndrome and other autoimmune disorders may be associated with cutaneous vasculitis (Claudy 1998). The presence of vasculitis often denotes active disease and possibly a poorer prognosis. Malignancy accounts for less than 1% of cases of cutaneous vasculitis. Lymphoproliferative diseases are common, but any type of tumor at any site may be related to LV. Out of 135 patients with LV, only one had MM. Cryoglobulinemia, infectious and medication hypersensitivity may also be relevant in the development of LV in patients with MM. Up to now no study has proven the incidence of LV in MGUS. Although LA is a rare manifestation of plasma cell dyscrasias, serum protein electrophoresis is useful for identifying a MGUS amongst patients without otherwise identified disease (Bayer-Garner and Smoller 2003). Serological studies including antinuclear antibody, ANCA, rheumatoid factor, complement levels, cryoglobulins, and hepatitis C antibody should also be obtained (Kaufmann et al. 2003).

Group III: Association Sporadically Reported

Numerous skin diseases have been reported in patients with MGUS. Nevertheless, it can be presumed

that the presence of MGUS in such cases tends to be coincidental since an underlying pathogenic mechanism is absent. Furthermore, larger collectives of these dermatoses have not been able to confirm any hypothesized association. Table 3 summarizes the most relevant skin diseases that have been sporadically reported in patients with MGUS.

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