Skin manifestations in vasculitis and erythema nodosum

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ABSTRACT

Cutaneous lesions are frequent in medium-sized and small vessel systemic vasculitides. The classic cutaneous manifestation of vasculitis is palpable purpura; however the clinical manifestations greatly depend on the size of the vessels affected. They usually do not affect prognosis but relapsing or intractable forms have been described. When skin manifestations are only one of the clinical signs of vasculitis, treatment with corticosteroids and, when indicated, an immunosuppressant, is mandatory, which usually leads to the rapid disappearance of cutaneous lesions. Conversely, when skin lesions are isolated, the diagnosis can be more challenging, but initial treatment may be less aggressive, e.g., dapsone or colchicine, reserving corticosteroids only for those patients in whom the former are ineffective. Erythema nodosum (EN) is the most frequent septal panniculitis. In general it is characterized by the sudden eruption of one or more erythematous and tender nodules or plaques located mainly over the extensor sides of lower extremities. EN resolves with complete "restitutio ad integrum" of the skin in 3-6 weeks. Relapses are uncommon but in patients with idiophatic, streptococcal or EN associated with other upper respiratory tract infections they are more frequent. The main treatment of EN is that of the underlying associated conditions, if demonstrated. Aspirin and other NSAIDs in full doses are often sufficient.

Introduction

Vasculitides are multiple organ and/or system diseases characterized by inflammation of blood vessel walls and classified according to the type of vessels affected. Medium-sized vessel vasculitides include Kawasaki disease, which primarily affects children, and polyarteritis nodosa (PAN), whereas the 3 main small vessel vasculitides are Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA). Dermatologic manifestations are frequent in patients with systemic vasculitides, but may also be induced by drugs or infections. The classic manifestation of cutaneous small vessel vasculitis is palpable purpura; however the clinical manifestation greatly depend on the size of the vessels affected. Leukocytoclastic vasculitis is a pathologic description used to describe inflammation of postcapillary venules and is clinically more correctly termed cutaneous small vessel vasculitis (CSVV). Erythema nodosum (EN) is the most frequent septal panniculitis. In general it is characterized by the sudden eruption of one or more erythematous and tender nodules or plaques located mainly over the extensor sides of lower extremities.

Systemic vasculitides

Polyarteritis nodosa

Skin lesions have been reported in 25-60% of PAN patients (1). They are usually associated with other PAN-related symptoms. Notably, systemic PAN may develop later in a few patients, after a period varying from 1 to 20 years after the first cutaneous signs (2). The spectrum of PAN can range from chronic cutaneous to acute systemic PAN.

Theoretically, cutaneous or subcutaneous nodules are the hallmark of PAN skin manifestations. They measure 5-15 mm in diameter, are mainly located in the lower legs, and may occur in clusters along the superficial arteries. However, the most common cutaneous finding is palpable purpura, corresponding to subcutaneous small vessel vasculitis, in association with medium-sized vessel involvement. Lesions usually begin as tiny red macules, which later become papules and plaques, ranging from a few millimeters to several centimeters in diameter. Livedo reticularis is less frequent and appears as a reddish blue mottling of the skin in a 'fishnet' reticular pattern, which may

precede, follow or occur concomitantly with the onset of nodules. Local rupture of superficial arteries may lead to cutaneous hematoma or ecchymosis. Painful ulcerations may develop, resulting from the coalescence of nodules. Peripheral embolization of thrombi may cause infarction of the extremities. Other manifestations have been reported, such as urticaria, transient erythema, superficial phlebitis, Raynaud's phenomenon and splinter hemorrhages. Pustular vasculitis is less frequent and usually results from secondary infection of necrotic lesions.

Churg-Strauss syndrome

Cutaneous lesions have been observed in 40-75% of CSS patients (3). They are rarely (6%) the presenting symptom (4).

Palpable purpura, often necrotic, on the legs and feet is the most frequent cutaneous manifestation, seen in half the patients with skin involvement. Cutaneous nodules (1/3 of the patients) or papules, sometimes with an urticarial appearance, are also very common, localized on the lower limbs or on the extensor side of the elbows, fingers, scalp and/or breasts. Various other skin lesions have been reported: maculopapules resembling erythema multiforme, ulcerations, livedo reticularis, patchy and migratory urticarial rashes, nailfold infarctions, deep pannicular vasculitis and facial edema (4).

Histologically, the inflammatory infiltrate in purpuric lesions may be rich in eosinophils (3), while nodules may correspond to granulomatous vasculitis, necrotizing vasculitis of arterioles in the deep dermis or the subcutis, or to extravascular granulomas. However, histology is often disappointing, since typical and/or eosinophilic granulomas are detected in less than half of CSS patients with skin lesions.

Wegener's granulomatosis

Skin lesions occur in 10-50% of the patients (5, 6). They may be present at disease onset in about 10% of the patients and, exceptionally as the presenting symptom (7).

Palpable purpura on legs and feet is the most frequent cutaneous manifestation. Necrotic papules on the extensor surfaces of the limbs are less frequent but more suggestive. Occasionally, they can resemble erythema elevatum diutinum and may be associated with IgA paraproteinemia. Nodules are frequent, mainly on the limbs. Extensive and painful cutaneous ulcerations may precede by several weeks to several years other systemic manifestations. Ulcers are sometimes described as 'pyoderma gangrenosum-like lesions', especially when occurring after even minor trauma to painful nodules. In contrast to PAN, livedo reticularis is unusual in WG.

Histologically, purpuric papules correspond to leukocytoclastic vasculitis of small vessels; necrotic and purpuric lesions can be a consequence of necrotizing vasculitis of superficial and/or deep dermal and subcutaneous vessels. Nodules coincide with necrotizing or granulomatous vasculitis of medium-sized arterioles, or to extravascular granulomas (8).

Microscopic polyangiitis

Skin manifestations have been reported in 30-60% of patients (1). However, the real frequency of skin lesions in MPA has probably been underestimated, because MPA had not yet been separated from PAN in most early populations studied.

Maculopapular purpuric lesions of the lower limbs are the most frequent skin manifestations. Other lesions have been described, e.g., mouth ulcers, vesicles, necrosis, ulcerations, nodules, splinter hemorrhages, livedo, hand and/or finger erythema, and facial edema. Leukocytoclastic vasculitis of the small vessels of the dermis is usually observed. Sometimes, arterioles or smaller vessels of the deep dermis and subcutis are also involved, thereby explaining the nodular appearance of some skin lesions.

Histopathology. Skin biopsies often show some abnormalities, but not specific to any of the primary systemic necrotizing vasculitides. Nevertheless, they are important to exclude other diagnoses. Palpable purpura and papular lesions, like urticaria, usually correspond to leukocytoclastic or lymphocytic vasculitis of the small vessels of the dermis, while nodules are preferentially associated with vasculitis of arterioles or small vessels at the junction of the dermis and subcutis or in the subcutis. Necrosis may develop when small or larger vessels or both are involved.

Treatment. General measures, like wearing elastic support stockings, combined with local treatments of ulcers and/or gangrene, are the same as those applied for non-vasculitic skin ulcerations. Dapsone and colchicine can occasionally help control some relapsing cutaneous manifestations (9), and antihistamines may be useful for urticarial vasculitic manifestations.

The combination of corticosteroids (CS) and immunosuppressants should be prescribed to patients with severe forms of classical PAN, MPA or CSS, i.e. when kidney, heart, gastrointestinal tract and/or central nervous system is/are involved. When such factors of poor prognosis are absent, CS can be given alone. Conversely, for WG, the combination of CS and cyclophosphamide is mandatory, followed by maintenance therapy with azathioprine, methotrexate or mycophenolate mofetil. Alternative treatments, like intravenous immunoglobulins, plasma exchange, monoclonal anti-CD20 antibodies or anti-TNFα antibodies, can be administered for relapses or patients whose disease does not respond to conventional regimens (10).

Cutaneous small vessel vasculitis including urticarial vasculitis

Vasculitis refers to inflammation and necrosis of blood vessels, whether they are arteries, veins or both. It can be local or systemic, and may be primary or secondary to another disease process. The classic cutaneous manifestation of vasculitis is palpable purpura; however the clinical manifestation greatly depend on the size of the vessel affected. Leukocytoclastic vasculitis is a pathologic description used to describe inflammation of postcapillary venules and is clinically more correctly termed cutaneous small vessel vasculitis (CSVV). The histopathologic pattern is that of a leukocytoclastic vasculitis — angiocentric, segmental inflammation with nuclear dust, endothelial cell swel-

ling and fibrinoid necrosis of blood vessel walls (11,12).

CSVV occurs equally in both sexes and at all ages (12). It is estimated that 10% of affected patients are children (13, 14). Prevalence numbers remain uncertain however given the lack of consensus on a classification schema.

Most of the etiologic factors identified have been incriminated by association rather than by direct demonstration (15). Lynch (14) proposed that the frequency of viral or bacterial infections is probably underestimated. In up to 50-60% of patients no cause is identifiable (15). CSVV has been reported in association with numerous coexistent diseases. These include collagen vascular disease, inflammatory bowel disease, HIV/AIDS and malignancy (12,14,16).

The pathogenesis of vasculitis is a complex subject, not least because there are likely to be many different pathogeneses reflecting the many different causes. Mackel *et al*. (17,18) described circulating immune complexes in a large percentage of patients with CSVV. Factors that play a part in the pathogenesis of vasculitis include antigen-antibody related mechanisms (including autoantibodies and immune complex disease), inflammatory cells, complement, cytokines, genetic influences and the fibrinolytic system (19).

The typical primary skin lesion of CSVV is palpable purpura with lesions ranging in size from 1 mm to several centimeters. The lesions arise as a simultaneous 'crop', resulting from the exposure to an inciting stimulus. Usually macular in the early stages, they may progress to wide array of lesions including, papules, nodules, vesicles, plaques, bullae or pustules. Secondary findings include ulceration, necrosis and post-inflammatory hyperpigmentation. Other cutaneous findings include livedo reticularis, edema, and urticaria. Lesions most commonly occur on dependent areas, such as ankles and lower legs, or other areas prone to stasis (11).

Although normally asymptomatic, local symptoms may include pruritus, pain, or burning. Complaints of systemic symptoms, including fever, arthralgias, myalgias, anorexia, or gastrointestinal pain should raise the suspicion that a cutaneous vasculitis may be associated with a systemic vasculitis.

A thorough history and physical examination is required for the correct diagnosis of CSVV. This should include screening tests for infections, connective tissue disease, medication usage and cancer. Laboratory screening test are always required both to confirm the diagnosis and to determine the etiology and possible extent of systemic disease. Vasculitides with systemic manifestations must be ruled out, as CSVV is diagnosed by exclusion. The necessary laboratory evaluations include histopathologic and occasionally immunofluorescent microscopic studies, blood tests and urinalysis (12, 14-16). Treatment of CSVV is sometimes unnecessary as the disease is usually self-limiting. When possible, identification and removal of causative agents (eg, infection, drug, chemicals, food) should be accomplished. Removal of an inciting agent is occasionally followed by rapid resolution of the lesions and no other treatment is indicated; otherwise local and systemic therapies are recommended (12, 14, 16).

Local therapies are aimed at improving lower extremity circulation and relieve symptomatic complaints. Topical treatment (corticosteroid creams, calcineurin inhibitors, and antibiotic ointments) may be helpful in some patients; however there is no data to support their use (19). Gradient support stockings may also be useful as stasis changes often times compound the issue (12).

Systemic treatment is advised for patients with CSVV with significant systemic manifestations or those with significant cutaneous ulceration; however almost no double-blind, placebo-controlled prospective trials exist (15).

Urticarial vasculitis (UV) is a chronic disorder consisting of episodic urticarial lesions lasting greater than 24 hours that histologically manifest features of leukocytoclastic vasculitis. UV can be thought of as a subtype of CSVV. Two type of UV have been described: UV associated with hypocomplementemia and normocomplementemic UV.

No single treatment is effective for all cases of UV, however the majority of patients respond to systemic corticosteroids. Hydroxychloroquine sulfate, colchicine, dapsone, NSAIDs or pentoxifylline may be useful as steroids sparing agents (20). For control of angioedema and urticaria-like lesions, patients may also benefit from antihistamines.

Henoch-Schonlein purpura

The International Consensus Conference on Nomenclature of Systemic Vasculitides has defined Henoch-Schönlein purpura as "a vasculitis with IgA-dominant immune deposits affecting small vessels and typically involving skin, gut, and glomeruli and associated with arthralgias or arthritis" (21). Henoch Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are considered nowadays as related diseases since they have been described in identical twins and bear identical pathological and biological abnormalities. In children, the annual incidence varies between 10 and 20/100,000 children (23, 24) and decreases to about one /million in adults (25). As none of epidemiological studies performed in children used the presence of IgA in tissue for diagnosis, it is possible that reported results are overestimated.

Tissue lesions are characterized by predominant IgA1 deposits often encountered in association with factors of the alternative pathway. Histologically, cutaneous HSP is a leukocytoklastic form of vasculitis, with vessel wall necrosis and perivascular accumulation of inflammatory cells, mostly polymorphonuclear leukocytes and mononuclear cells, surrounding the capillaries and post-capillary venules of the dermis (26). The classification of pathologic glomerular changes in HSPN is based on endocapillary and extracapillary inflammation of the glomerulus (27) and bears strong similarity to glomerular lesions observed in systemic vasculitis. Glomeruli show crescents in more than 50% of patients (27). Evolution to chronic renal failure is more frequently seen when extensive crescent formation is found.

Multiple IgA abnormalities have been described in HSP: increased plasma levels, mainly involving polymeric IgA1, abnormally glycosylated IgA1,

increased IgA synthesis, circulating IgA1 containing immune and non immune complexes. Abnormally glycosylated IgA1 is possibly less cleared by the hepatocyte receptor for asialoglycoproteins than normal IgA1. This might favour the accumulation of IgA1 complexes in blood and their deposition in tissue. A synthesis stimulation of abnormally glycosylated IgA1 might result from an increased penetration of antigens inside of the organism resulting from a lack of specific mucosal IgA production as in IgAN. Indeed, de Fijter *et al*. (28) have shown in IgAN an impairment of the specific IgA1 response in mucosae and blood after intranasal immunization with cholera toxin subunit B as a novel antigen in adult patients with IgAN.

A history of a recent or simultaneous infection is reported in 1/3 to 2/3 of cases according to the studies (29). Although any of the four major components of the syndrome (rash, joint pain, abdominal symptoms, and renal disease) may be present before the other, it is rare for the renal disease to do so (29). Skin involvement is per definition present. The characteristic sites of the rash are the external aspects of the limbs, the buttocks and occasionally the face. The eruption begins as a crop of erythematous macules, some of which may resolve in the early stages but most of which become papular, urticarial and purpuric. Generally, lesions resolve in a few days but relapses are possible. The renal involvement conditions the general prognosis. The incidence of renal involvement varies considerably among the different reports (20-100%) (30). The proportion of HSPN as cause of ESRF in adults is minimal (29) whereas it can reach up to 5.1% in children (31). In selected series, HSPN leads to chronic renal failure in up to 20% of children 20 years after the diagnosis (32). The risk of chronic renal failure is related to the initial clinical presentation (32). Chronic renal failure will be encountered in less than 5% when clinical signs at presentation are hematuria and/or minimal proteinuria, 15% when proteinuria is heavy but not nephrotic or in case of acute nephritic syndrome, 40% in case of nephrotic syndrome and more than 50% when nephritic and nephrotic syndromes are associated.

Gastro-intestinal symptoms occur in 50 to 90% of patients (29). Abdominal pain is the most common symptom. Gastro-intestinal bleeding or positive occult blood is reported in up to 40% of patients in some series (30). Intussusception, bowel perforation and hypovolemic shock have been exceptionnaly reported.

Joint pain occurs in 2/3 of cases, and is the presenting symptom in one-quarter (29). The arthralgia varies from mild to moderately severe. Swelling accompanies usually the pain but not always. The large joints, especially the ankles and knees, are principally affected. Diffuse swelling of the dorsum of hands and feet is often observed. Affected joints are never permanently damaged. Testicular, intracerebral, cardiac and pulmonary involvements have been described in a few patients (29). Usefulness of therapy for HSPN is not easy to assess. Even if the severity of clinical signs and histological lesions are often related with the development of chronic renal failure, it is not a constant finding. Moreover, even an apparent complete healing may be followed by chronic renal insufficiency after decades. Finally, the small number of patients with bad prognosis (those with nephrotic syndrome, or a combination of nephrotic and nephritic syndrome) do not allow prospective randomized studies in which some patients should not be treated. Therefore, it is not astonishing that there is no strong evidence that any form of treatment alters the course of HSPN. Older studies report no beneficial effects in patients with already established nephritis. Likewise, no or few preventing effects of prednisone on the development of nephritis have been found. More recent studies are however more encouraging mainly when methylprednisolone pulses, associated or not, with other immunosuppressive drugs are given. Therefore, in his decision to treat, the pediatric nephrologist must overweight the possible beneficial effect of treatment versus possible complications of immunosuppression.

Mixed cryoglobulenimia

The term cryoglobulinemia refers to the presence in the serum of one or more immunoglobulins, which precipitate at temperatures below 37°C and redissolve on re-warming (33-35). Cryoglobulinemia is classified according to Ig composition into three main subgroups; cryoglobulinemia type I is composed by a single monoclonal Ig; type II and III mixed cryoglobulinemia (MC) are immune complexes including polyclonal IgGs, the autoantigens, and mono- or polyclonal IgMs, respectively. Cryoglobulinemia type I, usually a paraprotein, is mainly found in patients with overt lymphoid neoplasias, (33-35). Type II and III MC can be associated with well-known infectious, immunological or neoplastic diseases (33, 32); while the so-called 'essential' MC represents a distinct clinical syndrome, which can be classified among systemic vasculitides (33-35). Besides the presence of serum mixed cryoglobulins, the 'essential' MC is characterized by a typical clinical triad – purpura, arthralgias, and weakness – and frequent multiple organ involvement (23, 24). The prevalence of MC presents great geographic heterogeneity, being more common in Southern Europe than in Northern Europe or Northern America. The clinical MC syndrome affects prevalently the female gender, while the disease onset varies between 4th and 6th decade (33).

Etiopathogenesis. Since 1990, an increasing number of epidemiological studies suggested an important role for HCV in the pathogenesis of MC (34-36). HCV seropositivity in MC varies from 70% to 100% of individuals in different patient populations. The pathogenic role of HCV infection in MC syndrome has been definitely demonstrated by a large body of clinico-epidemiological and laboratory investigations (34-36).

The large diffusion of HCV infection world-wide contrasts with the geographical heterogeneity observed in the prevalence of HCV-related MC, suggesting a role for particular HCV genotypes, unknown environmental and/or genetic co-factors (25). The histopathological hallmark of MC is the leukocy-

toclastic vasculitis of small-sized vessels, including arterioles, capillaries, and venules, secondary to the vessel deposition of circulating immune-complexes, mainly the cryoglobulins, and complement (33-36).

The consequence of vasculitis is the ischemic organ damage responsible for typical clinical manifestations of MC syndrome: skin purpura and ulcers, peripheral neuropathy, glomerulonephritis, lung alveolitis, endocrine disorders, and diffuse vasculitis (33-38).

Both epidemiological and clinico-pathological observations suggest that MC is the result of a multifactorial and multistep pathogenetic process (33-36). The immune-complex-mediated vasculitis is the result of this complex process, while B-lymphocyte expansion (34, 38) may represent the remote disorder responsible for autoantibodies and immune-complex production and in some instances for malignant lymphomas complicating the MC syndrome.

Clinical manifestations. Skin manifestations are the most frequent symptoms of the MC (33-38). Orthostatic purpura represents the typical manifestation of MC; after repeated episodes of purpura two-third of patients showed characteristic, often confluent areas of ochreous coloration on the legs. Besides the vasculitic mechanism, various co-factors, in particular chronic venous insufficiency, physical stress, such as prolonged standing, and/or muggy weather may trigger orthostatic purpura. Moreover, the disease may be responsible for severe skin ulcers of the legs and malleolar areas, present in 20-30% of patients and usually resistent to treatments. Other cutaneous manifestations such as diffuse urticaria vasculitis or bollous dermatitis are seldom recorded.

Other symptoms are arthralgias (clinically overt polyarthritis is quite rare), sicca syndrome, peripheral neuropathy, chronic hepatitis, renal involvement, usually membranoproliferative glomerulonephritis type I, and widespread vasculitis (28). Interstitial lung involvement has been anecdotally observed in HCV-positive patients with or without MC syndrome (35, 37).

Some endocrine gland disorders can be observed in a significantly higher number of MC patients compared with age- and sex-matched controls; in particular, diabetes mellitus type II, thyroid, and gonadal dysfunction (35, 38-41). B-cell lymphomas represent the most frequent neoplastic complication of MC (33, 35, 37, 38). Other neoplastic complications of MC are hepatocellular carcinoma and papillary thyroid cancer. In this light, the MC can be regarded as a pre-neoplastic disorder (35, 38).

Diagnosis. Since there are not diagnostic criteria for MC, the clinical syndrome may be correctly classified on the basis of clinical (purpura, weakness, arthralgias, and/or visceral organ involvement), pathological (leukocytoclastic vasculitis) and laboratory (mixed cryoglobulins, low C4) findings (35,38). The MC syndrome represents the result of a multistep process; a single manifestation (skin vasculitis, hepatitis, nephritis, peripheral neuropathy, etc.) is often the only apparent or clinically predominant feature, so that a correct diagnosis might be delayed or overlooked entirely (35, 38).

Because of its clinical polymorphism MC syndrome may overlap with a variety of immunological and neoplastic diseases; namely, other systemic vasculitides, Sjögren's syndrome, autoimmune hepatitis, and B-cell lymphoproliferative disorders.

Treatment. The therapeutic approach of MC syndrome is particularly challenging because of the complex etiopathogenesis of the disease. A correct therapeutic approach to HCV-related MC must deal with three conflicting conditions: HCV infection, autoimmune, and lymphoproliferative alterations. Considering the cascade of events leading from HCV infection to overt MC syndrome we can treat the disease at three different levels by means of etiological (antiviral), pathogenetic (immunosuppressors), and symptomatic (steroids, plasmapheresis, etc.) treatments (35, 38, 42).

In all MC patients, the following therapeutic guidelines should be taken into account: the treatment have to be tailored for the single patient, according to the severity of clinical symptoms (35, 38, 40); during the asymptomatic phases of the disease, patients usually do not need any treatment, even in the presence of high levels of cryocrit; some symptoms such as arthralgias and palpable purpura are particularly sensitive to the smallest variations of daily steroid dosage (1-2 mg); combined peg-interferon/ribavirin may represent the choice treatment in patients with moderate-severe MC manifestations, especially those with active hepatitis; finally, severe, life-threatening vasculitic manifestations must be promptly treated with a combined therapy (35, 38, 42) with plasma exchange, high dosage of steroids, and immunosuppressors (cyclophosphamide, rituximab). A careful clinical monitoring of the disease is mandatory in all cases, with particular attention to neoplastic complications.

Erythema nodosum

Erythema nodosum (EN) is the most frequent septal panniculitis. In general it is characterized by the sudden eruption of one or more erythematous and tender nodules or plaques located mainly over the extensor sides of lower extremities.

Skin lesions have a tendency to a spontaneous remission in several days or weeks without ulcerations. Scarring and atrophy are uncommon, but in the sites of a pre-existing nodule an area of iperpigmented skin is often seen.

It may be idiopathic or triggered by several diseases: infections, sarcoidosis, autoimmune diseases, intestinal bowel disease (IBD) and malignancies being the most frequently associated (43). The disorder occurs most commonly in women in the second to fourth decades of life and the frequency in man is between 1/3 and 1/6 of that seen in women, but before puberty no difference between the sexes can be detected. In England the prevalence is about 2.4 per 1000 population per year (44). The hospital incidences of new cases varies from 0.38% of all patients seen in a Department of Internal Medicine (Spain) to 0.5% in Departments of Dermatology (England).

Clinical features. The pattern is characteristic and consists of an abrupt onset of tender, erythematous warm nodules or plaques often symmetrical. They are

variable in diameter (1-5 cm or more) and may merge into a larger one. Extensor areas such as shins and the anterior side of foot and ankles are commonly affected; skin is raised and tender if the nodule is of recent onset; its color changes with time from bright red to livid or purplish bruise. In few weeks it evolves towards a yellow/greenish appearance or an iperpigmented normal skin, with absence of skin ulceration. General signs or symptoms like joint pain, fever, fatigue, malaise, headache, abdominal pain, diarrhea and vomiting may accompany an acute onset or recurrence of the disease.

Four clinical variant of EN have been described (1): EN migrans (similar to classic EN but often unilateral and with only one or few lesions), subacute nodular migratory panniculitis (characterized by marked thickening of the septa of subcutaneous fat), chronic EN (a mild degree of thickening of the septa and inflammatory infiltrate), and children EN (shorter duration, frequent fever, sometimes skin lesions developing only in palms and soles) (45).

Etiology. In 37-60% of the reported series (46) its etiology remains uncertain (so-called idiopathic EN). The etiologic factors include infections (tubercolosis (TB), leprosy, streptococcal disorders, other upper respiratory tract infections), drugs, malignancies, sarcoidosis, IBD (especially Crohn disease), autoimmune diseases (systemic lupus erythemathosus (SLE), vasculitis), other diseases (Behçet disease (BD), Sweet's syndrome, acne fulminans) and pregnancy.

EN is considered a septal panniculitis without vasculitis. Subcutaneous fat is thickened and infiltrated by inflammatory cells invading the periseptal areas. A perivascular inflammatory infiltrate of lymphocytes is commonly seen in the involved deep and superficial dermis. The inflammatory infiltrate of the septa is different in early (the thickening is due to edema, hemorrhage and neutrophils) and late lesions (it is due to fibrosis, periseptal granulation tissue, lymphocytes and multinucleated giant cells).

A relative specific aspect is represented by the *Miescher's radial granulomas* (47) in which small histiocytes (transforming with time into multinucleated giant cells) surround central clefts of variable shape. The *absence of vasculitis* is the other histopatologic marker of EN. Only rarely a necrotizing small vessel vasculitis with fibrinoid wall necrosis has been observed in the septa. Despite the diffuse fibrosis, the lesions do not induce atrophy or scarring of the involved areas (43).

EN is considered an antigen induced disease with a hypersensitivity response. The triggering factors are numerous and the disorder may be considered a cutaneous aspecific reactive process because the skin has only few responses to the different agents involved. The skin reaction probably is provoked by the local formation and deposition of immune complexes in connective tissue septa,venules and subcutaneous fat (48). Moreover some histologic features suggest that an important role may also be played by the type IV delayed hypersensitivity reaction.

Laboratory and other diagnostic tests. A complete history of the patient including previous diseases, drugs, travels, hobbies, familiarity and allergies must be always collected. Each patient must undergo a complete evaluation of serum and urine biochemistry including antistreptolysin O (ASO) titre, acute phase reactants, angiotensin converting enzyme (ACE), throat culture, intradermal tuberculin test and chest X-ray (49). An elevated erythrocyte sedimentation rate (ESR) is common when the eruption is active and may correlate with the number of skin lesions. ASO titre may be high and in doubtful cases may be indicated a serological investigation for those infectious agents more common in the living area of the patients (45).

Lofgren's syndrome, an acute clinical pattern of benign sarcoidosis generally improving in few weeks, is particularly common in pregnant females or in puerperium (50).

Differential diagnosis. *Erythema induratum of Bazin* (EIB). The nodules are persistent, may ulcerate and the healing is with an athropic scar. The histopathology is different, because EIB is a lobular and not a septal panniculitis; the course of EIB is generally chronic and not acute as in EN (51). *Superficial thrombophlebitis*, located at the medial or lateral side of the lower legs. *Cutaneous polyarteritis nodosa* with livedo of the involved area and frequent skin ulceration. *Subcutaneous sarcoidosis* with granulomatous involvement of the fat lobules and not septa (52-54). *EN leprosum* consists in an immunocomplex deposition process of the dermis of patient with lepromatous leprosy; these nodules, however, are associated with necrotic, pustular or hemorrhagic lesions and may involve the face. *Traumatic plantar urticaria*, consisting in tender nodules developing in children after physical activity. *Cutaneous B-cell lymphoma* is histopatologically different because atypical lymphocytes with hyperchromatic nuclei and mitotic figures in septa, fat lobule and blood vessels lumina are often observed (55).

Prognosis and treatment. EN resolves with complete *restitutio ad integrum* of the skin in 3 - 6 weeks. Relapses are uncommon but they are more frequent in patients with idiopathic, streptococcal or EN associated with other upper respiratory tract infections (46). Severe complications are extremely uncommom (retrobulbar optical nerve neuritis or serious concomitant skin lesions). The main treatment of EN is that of the underlying associated conditions, if demonstrated. Aspirin and other NSAIDs in full doses are often sufficient, together with bed rest (43). Some patients have a good response to potassium iodide (400 - 900 mg daily); obviously it cannot be used in pregnancy or thyroid disorders (56). If systemic corticosteroids are indicated, an underlying infection should be ruled out. In general 40 mg of prednisone per day induces the resolution of the nodules in few days. (43). Other drugs less commonly used include intralesional injection of triamcinolone acetonide, colchicine 1-2 mg daily, hydroxychloroquine 200 mg twice a day, dapsone 100 mg daily and thalidomide 100-200 mg daily.

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