

## Panniculitis. Part II. Mostly lobular panniculitis

Luis Requena, MD,<sup>a</sup> and Evaristo Sánchez Yus, MD<sup>b</sup> *Madrid, Spain*

The second part of our review of panniculitis summarizes the clinicopathologic features of the mostly lobular panniculitides. Erythema induratum of Bazin (nodular vasculitis) represents the most common variant of lobular panniculitis with vasculitis, although controversy persists about the nature of the involved vessels. Mostly lobular panniculitides without vasculitis comprise a series of disparate disorders. These include sclerosing panniculitis that results from chronic venous insufficiency of the lower extremities; panniculitis with calcification of the vessel walls such as calciphylaxis and oxalosis; and inflammatory diseases with crystals within the adipocytes such as sclerema neonatorum, subcutaneous fat necrosis of the newborn, and poststeroid panniculitis. Connective tissue diseases, such as systemic lupus erythematosus and dermatomyositis, pancreatic diseases, and  $\alpha_1$ -antitrypsin deficiency may also show a mostly lobular panniculitis with characteristic histopathologic features. Lobular panniculitis may also be an expression of infections, trauma, or factitial causes involving the subcutaneous fat. Lipoatrophy refers to a loss of subcutaneous fat due to a previous inflammatory process involving the subcutis, and it may be the late-stage lesion of several types of panniculitis. In contrast, lipodystrophy means an absence of subcutaneous fat with no evidence of inflammation and often the process is associated with endocrinologic, metabolic, or autoimmune diseases. Finally, cytophagic histiocytic panniculitis is the term that has been used to describe two different processes: one is inflammatory, a lobular panniculitis, and the other one is neoplastic, a subcutaneous T-cell lymphoma. The only common feature of these two different processes is the presence of cytophagocytosis in the lesions. (J Am Acad Dermatol 2001;45:325-61.)

**Learning objective:** At the completion of this learning activity, participants should be familiar with the pathogenesis, clinical manifestations, histopathologic findings, and treatment options for the most frequent variants of the lobular panniculitides.

### MOSTLY LOBULAR PANNICULITIS WITH VASCULITIS (Table I)

#### Erythema nodosum leprosum

Erythema nodosum leprosum presents with painful erythematous and violaceous nodules, mostly involving the extremities of patients with lepromatous leprosy. The onset of these nodules is accompanied by severe constitutional symptoms. The term *erythema nodosum leprosum* is inadequate because it may easily be confused with authentic erythema nodosum. Erythema nodosum leprosum is mostly an immune complex-mediated vasculitis involving the dermis. In some instances, however, the inflammatory process extends to the subcutaneous fat, involving the small

vessels of the fat lobule, which appear with fibrinoid necrosis of their walls and luminal thrombi.<sup>1,2</sup> Direct immunofluorescence studies reveal deposits of IgG and complement in the walls of the involved vessels.<sup>1</sup>

Erythema nodosum leprosum may be controlled by thalidomide in a dose of 400 mg taken at night.<sup>3</sup> When thalidomide is not available or is contraindicated, clofazimine in a dose of 300 mg daily and prednisone in an initial dose of 30 mg daily have been shown to be helpful, although the response to these drugs is not as dramatic as with thalidomide.

#### Lucio's phenomenon

Lucio's phenomenon is another variant of a leprosy reaction that appears in patients with the diffuse form of lepromatous leprosy. It consists of a necrotizing vasculitis, resulting in infarction that causes painful and hemorrhagic ulcers.<sup>4,5</sup> The bouts of cutaneous lesions are accompanied by severe systemic symptoms, and the process may be fatal.

Histopathologically, like erythema nodosum leprosum, Lucio's phenomenon is more a dermal inflammatory process than a panniculitis. Lesions

From Department of Dermatology, Fundación Jiménez Díaz, Universidad Autónoma,<sup>a</sup> and Department of Dermatology, Hospital Clínico San Carlos, Universidad Complutense.<sup>b</sup>

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**Table I.** Histopathologic classification of the mostly lobular panniculitides

<i>With vasculitis</i>	
Small vessels	
Venules	Erythema nodosum leprosum Lucio's phenomenon Neutrophilic lobular (pustular) panniculitis associated with rheumatoid arthritis
Large vessels	
Arteries	Erythema induratum of Bazin Crohn's disease
<i>No vasculitis</i>	
Few or no inflammatory cells	
Necrosis at the center of the lobule	Sclerosing panniculitis
With vascular calcification	Calciphylaxis Oxalosis Sclerema neonatorum
With needle-shaped crystals in adipocytes	
Lymphocytes predominant	
With superficial and deep perivascular dermal infiltrate	Cold panniculitis
With lymphoid follicles, plasma cells, and nuclear dust of lymphocytes	Lupus panniculitis (lupus erythematosus profundus)
With lymphocytes and plasma cells	Panniculitis in dermatomyositis
Neutrophils predominant	
Extensive fat necrosis with saponification of adipocytes	Pancreatic panniculitis
With neutrophils between collagen bundles of deep reticular dermis	$\alpha_1$ -Antitrypsin deficiency
With bacteria, fungi, or protozoa identifiable by specialized stains	Infective panniculitis
With foreign bodies	Factitial panniculitis
Histiocytes predominant (granulomatous)	
No crystals in adipocytes	Subcutaneous sarcoidosis Traumatic panniculitis Lipoatrophy Subcutaneous fat necrosis of the newborn Poststeroid panniculitis Gout panniculitis Crystal-storing histiocytosis Cytophagic histiocytic panniculitis Postirradiation pseudosclerodermatous panniculitis
With crystals in histiocytes or adipocytes	
With cytophagic histiocytes	
With sclerosis of the septa	

exhibit a necrotizing vasculitis of the small vessels in the upper and mid dermis that results in ulceration of the epidermis.<sup>5</sup> In addition to the vasculitis, there is a mild perivascular inflammatory infiltrate composed mostly of foamy histiocytes that contain numerous acid-fast bacilli.<sup>6</sup> Bacilli may also be demonstrated within the endothelial cells. Occasionally, the process extends deep into the subcutaneous fat, with small-vessel vasculitis in the fat lobules. Usually, cutaneous lesions of Lucio's phenomenon show an inflammatory infiltrate of lesser intensity than those of erythema nodosum leprosum.<sup>6</sup>

Thalidomide is also used in the treatment of Lucio's phenomenon,<sup>3</sup> although the severe recurrent ulceration due to deep subcutaneous vasculitis is often accompanied by systemic vasculitis, and this type of leprosy reaction may be fatal.

### **Neutrophilic lobular panniculitis associated with rheumatoid arthritis**

To our knowledge, there are only 4 reported cases of this unusual variant of panniculitis. It consists of a neutrophilic lobular panniculitis with vasculitis in patients with rheumatoid arthritis. This variant of panniculitis has been named *pustular* panniculitis,<sup>7-10</sup> which in our opinion is an inaccurate term because the lesions are not pustules but erythematous subcutaneous nodules. Neutrophilic lobular panniculitis with vasculitis is an uncommon variant of panniculitis in patients with rheumatoid arthritis because these patients present classic erythema nodosum as the most frequent form of panniculitis.

Clinically, the 4 described patients with this uncommon variant of panniculitis were middle-aged women with long-standing rheumatoid arthritis. The

cutaneous lesions appeared suddenly in the form of painful subcutaneous erythematous nodules on the posterior aspect of the lower legs.<sup>7-10</sup> In some of the patients, ulceration with discharge of liquefied fat occurred.

Histopathologic examination of the lesions showed a mostly lobular panniculitis, with severe necrosis of the adipocytes in the fat lobule and an inflammatory infiltrate composed of neutrophils, foamy histiocytes, and multinucleated giant cells. Small cystic spaces lined by amorphous eosinophilic material were seen in some cases as an early expression of lipomembranous or membranocystic panniculitis.<sup>10</sup> Focally, features suggestive of leukocytoclastic vasculitis such as nuclear dust and neutrophils in perivascular arrangement were seen, although no fibrin deposits in the vessel walls or unquestionable leukocytoclastic vasculitis could be demonstrated. One of these 4 patients with neutrophilic lobular panniculitis and rheumatoid arthritis also had leukocytoclastic vasculitis involving the blood vessels of the papillary dermis.<sup>8</sup>

Because only a few patients with this rare variant of panniculitis have been described, it is difficult to evaluate the response to different treatments. In one patient with neutrophilic lobular panniculitis and rheumatoid arthritis, a course of dapsone was initiated, but it was discontinued after 6 weeks because of a drop in the patient's hematocrit. Shortly after the dapsone was discontinued, the nodular eruption on the lower extremities resolved.<sup>10</sup>

### **Erythema induratum of Bazin (nodular vasculitis)**

Currently, the terms *erythema induratum of Bazin* and *nodular vasculitis* are used as synonyms by most authors to describe the most common form of lobular panniculitis with vasculitis. However, this has not always been the case. This form of panniculitis was described by Bazin<sup>11</sup> in 1861, as subcutaneous indurated erythematous plaques appearing mainly on the posterior aspects of the lower legs of middle-aged women. He classified the process as one of the "erythematous benign scrofulids," which also included rosacea and chilblains. Bazin used the term "scrofulids" as a descriptive term to refer to deep erythematous nodules, and it seems that he did not consider this panniculitis as a tuberculid. The link between tuberculosis and erythema induratum was emphasized later, around 1900, mostly by French dermatologists who included erythema induratum within the spectrum of the tuberculids.<sup>12</sup> Almost simultaneously, identical clinical cases with no evidence of tuberculosis were reported by English authors,<sup>13,14</sup> which led later to the development of Whitfield's concept of

erythema induratum as nontuberculous in origin.<sup>15</sup> In 1945, Montgomery, O'Leary, and Barker<sup>16</sup> in the United States proposed the term *nodular vasculitis* for Whitfield's erythema induratum and described its clinical and histopathologic features as different from those of erythema induratum of Bazin. Since then, most popular textbooks of dermatology describe erythema induratum of Bazin, erythema induratum of Whitfield, and nodular vasculitis as 3 different entities.<sup>17</sup> Still some current authors have proposed to keep the name erythema induratum of Bazin for those cases in which an etiologic relationship with tuberculosis is demonstrated and refer to the remainder of cases as nodular vasculitis. In recent years there seems to be a consensus considering erythema induratum of Bazin and nodular vasculitis as the same entity,<sup>18,19</sup> an opinion that we share. Like erythema nodosum, erythema induratum of Bazin (nodular vasculitis) is currently considered to be a reactive disorder related to several etiologic factors, one of which may be tuberculosis, especially in some geographic areas.<sup>20</sup> In our country, tuberculosis is by far the most important etiologic factor for erythema induratum of Bazin (nodular vasculitis), and recent polymerase chain reaction investigations have demonstrated *Mycobacterium tuberculosis* DNA in 77% of the cutaneous biopsy specimens of patients with this variant of panniculitis.<sup>21</sup> Although the frequency varies from some geographic areas to others, in many countries tuberculosis is still the main etiologic factor for erythema induratum of Bazin (nodular vasculitis).<sup>22-29</sup>

Typical erythema induratum of Bazin (nodular vasculitis) is a disease of middle-aged women in whom erythematous subcutaneous nodules and plaques appear on the posterior aspects of the lower legs (Fig 1). Erythrocyanosis, heavy column-like calves, erythema surrounding follicular pores, and cutis marmorata are frequently associated changes and may be predisposing factors. Although nonulcerated lesions may heal without scarring, often subcutaneous nodules become adherent to the skin surface and ulcerate. Healing of these ulcers is usually a slow process, resulting in atrophic scars that allow retrospective diagnosis in old residual cases. Erythema induratum of Bazin is more frequent in obese women with some degree of venous insufficiency of the lower extremities, and subcutaneous nodules with ulceration develop mostly during cold winter months. Lesions are usually tender but may be indolent or painful only on pressure. The course is protracted and recurrent episodes over years, even decades, are common. Individual lesions tend to involute, but new crops appear at irregular intervals. Patients with erythema induratum of Bazin (nodular vasculitis) are otherwise in good health.

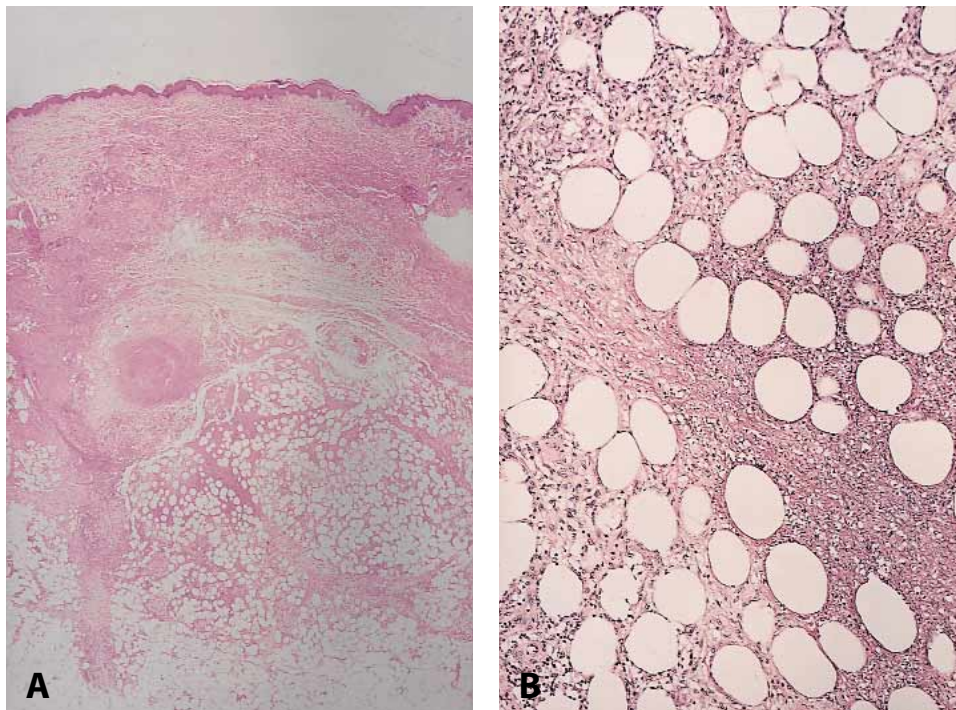


**Fig 1.** Erythema induratum of Bazin. Erythematous nodules, some of them ulcerated, on posterior aspect of the legs of a middle-aged woman.

Atypical forms of erythema induratum of Bazin (nodular vasculitis) are seen in men, with unilateral lesions, involving shins, thighs, or elsewhere.

From a histopathologic point of view, erythema induratum of Bazin (nodular vasculitis) is mostly a lobular panniculitis (Fig 2). At an early stage, the fat lobules are punctuated throughout by discrete collections of inflammatory cells, mostly neutrophils. There may be extensive necrosis of the adipocytes of the fat lobule. These necrotic adipocytes call for histiocytes that ingest lipid and become foamy. Epithelioid histiocytes, multinucleated giant cells, and lymphocytes contribute to the granulomatous appearance of the inflammatory infiltrate in fully developed lesions of erythema induratum of Bazin (nodular vasculitis). When intense vascular damage is present, extensive areas of caseous necrosis appear and the lesions show all the histopathologic attributes of tuberculosis. Caseous necrosis may extend to the overlying dermis and secondarily involve the epidermis with ulceration and discharge of liquefied necrotic fat.

Controversy persists in the literature about whether or not vasculitis is a histopathologic requirement to establish the diagnosis of erythema induratum of Bazin (nodular vasculitis). Even with vasculitis



**Fig 2.** Histopathologic features of erythema induratum of Bazin. **A**, Low-power view shows a mostly lobular panniculitis. Note involvement of large blood vessel of the upper subcutis. **B**, Higher magnification demonstrated necrosis of the adipocytes at the center of the fat lobule. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

accepted as a histopathologic criterion, there is no agreement about the nature of the involved vessel. Some investigators believe that the involved vessel in erythema induratum of Bazin (nodular vasculitis) is an artery,<sup>30,31</sup> whereas other authors favor a venous involvement,<sup>32</sup> and still others consider that both arteries and veins are involved.<sup>16,33-37</sup> In our experience, veins and venules are the primary affected vessels, whereas arteries are secondarily entrapped within large areas of caseous necrosis of the fat lobule.<sup>38</sup> In a recent series of patients with erythema induratum of Bazin (nodular vasculitis), the lesions were histopathologically classified into two types: focal panniculitis (type I) and diffuse panniculitis (type II). In type I erythema induratum of Bazin (nodular vasculitis) only one artery or a small blood vessel within the fat lobule was involved by neutrophilic vasculitis. In type II erythema induratum of Bazin (nodular vasculitis) several blood vessels of different sizes both in the septa and the fat lobule showed features of neutrophilic vasculitis. Necrosis of the adipocytes and inflammatory response were more intense in type II.<sup>39</sup> In our opinion, this classification is difficult to apply in a particular case and does not have any practical use. In our experience, some cases with all the stereotypical clinicopathologic features of erythema induratum of Bazin (nodular vasculitis), serial sections through the block of a subcutaneous nodule do not demonstrate findings of vasculitis. Therefore we do not consider vasculitis as a sine qua non criterion to establish the diagnosis of erythema induratum of Bazin (nodular vasculitis) when other characteristic findings are present.

In those cases in which there is a strong positive reaction in the Mantoux test<sup>40</sup> or *Mycobacterium tuberculosis* DNA is demonstrated in the cutaneous biopsy specimen by polymerase chain reaction techniques, a full course of 9 months of antituberculosis triple-agent therapy is recommended.<sup>40-47</sup> As with erythema nodosum, potassium iodide has been reported as effective and rapid treatment for erythema induratum of Bazin (nodular vasculitis).<sup>48,49</sup> Supporting bandages, bed rest, and treatment of the venous insufficiency of the lower extremities are also helpful. Nonsteroidal anti-inflammatory drugs may be used to alleviate painful ulcers.

### **Crohn's disease**

Crohn's disease involving the skin is usually characterized by abscesses, sinuses, and fistulas on the genital and perianal areas. These lesions are histopathologically characterized by noncaseating granulomas composed of epithelioid histiocytes and involving the full thickness of the dermis with a morphology very similar to that of the bowel disease.<sup>50,51</sup>

When lesions of Crohn's disease involve the lower extremities, they show a clinical appearance similar to erythema nodosum, but histopathologically they consist of noncaseating granulomas involving the septa of subcutaneous fat.<sup>52</sup> However, cases of authentic erythema nodosum, with Miescher's radial granulomas in the septa, have also been described in patients with Crohn's disease. In these cases the subcutaneous nodules are usually related to the activity of the bowel disease and regress when the bowel improves.<sup>53,54</sup> There are also reports of cutaneous polyarteritis nodosa in patients with Crohn's disease.<sup>55-61</sup>

However, the panniculitis included in this section is different from those previously mentioned. In some instances, patients with Crohn's disease present with a mostly lobular panniculitis characterized by noncaseating granulomas within the fat lobules and lymphocytic vasculitis involving the walls of medium-sized vessels at the junction of the dermis and the subcutaneous fat. This variant of lobular panniculitis is described, though not illustrated, in the second edition of the textbook *Histologic Diagnosis of Inflammatory Skin Diseases* by Ackerman et al.<sup>62</sup> We have been unable to find other references to this type of lobular panniculitis in Crohn's disease; therefore it seems to be very rare.

### **MOSTLY LOBULAR PANNICULITIS WITHOUT VASCULITIS**

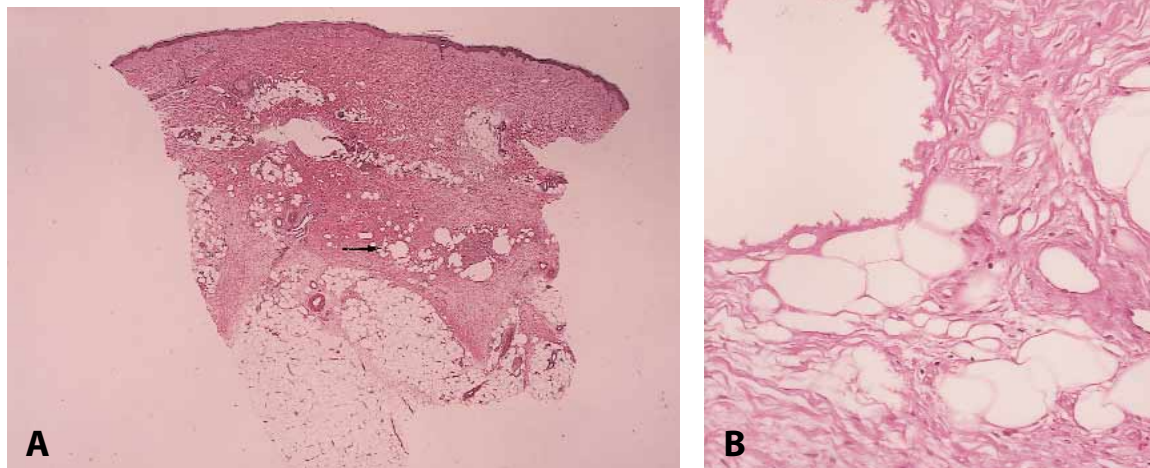
#### **Sclerosing panniculitis**

Jorizzo et al.<sup>63</sup> in 1991, proposed the term *sclerosing panniculitis* as the best name to describe a variant of panniculitis previously known by a variety of names, including hypodermatitis sclerodermiformis,<sup>64</sup> lipodermatosclerosis,<sup>65</sup> and lipomembranous change in chronic panniculitis.<sup>66</sup> The cutaneous lesions of this disorder consist of woodlike indurated plaques with erythema, edema, telangiectasia, and hyperpigmentation involving the lower legs with a stocking distribution. The condition is usually associated with chronic venous insufficiency, arterial ischemia, and previous episodes of thrombophlebitis. The involved area of the lower extremities resembles an inverted bottle, a deformity secondary to extensive deep fibrosis and sclerosis resulting in atrophy of the subcutaneous fat (Fig 3). In the original description, this process was thought to be an infectious disease related to unusual acid-fast bacteria,<sup>64</sup> but subsequent studies failed to identify any bacteria in the cultures of the lesions. Currently, venous insufficiency of the lower extremities is considered to be the main etiologic factor of sclerosing panniculitis. Venous insufficiency leads to sludging in the lobular capillaries, which results in ischemia and necrosis of the central portion of the fat lobule.<sup>63</sup>



**Fig 3.** Sclerosing panniculitis resulting in the so-called inverted bottle deformity of the lower leg.

Histopathologic findings in sclerosing panniculitis vary according to the evolution of the lesions. In any stage, changes of stasis dermatitis are present in the superficial dermis, with a proliferation of capillaries and venules in the papillary dermis, fibrosis, and abundant hemosiderin deposition. In the early stages of sclerosing panniculitis, there is sparse inflammatory infiltrate mostly composed of lymphocytes between the collagen bundles of the septa. There are also areas of ischemic necrosis at the center of the fat lobule, manifested as pale, small, anucleated adipocytes. Small lobular vessels appear congested and sometimes there are numerous extravasated erythrocytes, hemosiderin, and necrosis of endothelial cells within the areas of fat necrosis. In later stage lesions, the septa appear thickened and fibrotic, resulting in dramatic atrophy of the subcutaneous fat. The inflammatory infiltrate is composed of lymphocytes, histiocytes, and foamy macrophages. The periphery of the fat lobule often shows lipophagic granuloma with scattered lymphocytes and plasma cells. In late-stage lesions, septal sclerosis is the main histopathologic finding. The fat lobules become small because of lipophagic fat necrosis and there are fatty microcysts with foci of membranocystic changes (Fig 4). These consist of amorphous eosinophilic or amphophilic



**Fig 4.** Histopathologic features of sclerosing panniculitis. **A**, Scanning power shows thickened septa and cystic spaces in the fat lobules. Fat lobule is small and there are congested blood vessels (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates cystic spaces lined by eosinophilic corrugated membrane, early stage of the so-called lipomembranous or membranocystic change. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

material, sometimes with corrugated appearance, lining cystic spaces that result from fat necrosis.<sup>66</sup> Lipomembranous or membranocystic fat necrosis is a frequent finding in late-stage lesions of sclerosing panniculitis but is not exclusive to any type of panniculitis. It has been described in long-standing lesions of many variants of lobular panniculitis.<sup>66</sup>

Treatment of sclerosing panniculitis is difficult. In some cases, standard measurements for venous insufficiency of the lower extremities, including compression stockings, have been useful but not curative. Some authors have reported that the anabolic steroid stanozolol improves this condition rapidly and consistently.<sup>65</sup>

### Calciophylaxis

Calciophylaxis is an uncommon and poorly understood cutaneous process usually associated with chronic renal failure. Its main feature is the calcification of cutaneous vessel walls resulting in necrosis and ulceration. In 1962, Selye<sup>67</sup> described calciophylaxis from a pathogenic point of view as a purely experimental phenomenon observed in an animal model system. He postulated that two steps are required in calciophylaxis: (1) a systemic "sensitization" with one or several agents, such as parathyroid hormone, vitamin D, or a diet with high calcium and phosphorus contents. Nephrotoxic agents would increase the potential of these sensitizer agents.<sup>68</sup> (2) After a "critical period," there is exposure to the appropriate "challenging" agents, such as local trauma, iron salt and various other inorganic metal salts, glucocorticoids, albumin, egg white and yolk, polymixin, 5-hydroxytryptamine and other mast cell releasers, and radiopaque contrast media.<sup>69,70</sup>

In humans, calciophylaxis occurs almost exclusively in patients with end-stage chronic renal failure, although rarely patients with normal renal function have been reported.<sup>71</sup> Most of these patients have abnormalities in calcium-phosphorus metabolism, with elevated serum calcium and phosphorus levels, often in the context of the secondary hyperparathyroidism associated with renal failure. However, these tests are normal in some patients with calciophylaxis, supporting the idea that other factors are also involved in the pathogenesis of calciophylaxis. It seems that arterial hypertension and posthemodialysis metabolic alkalosis also predispose patients to calciophylaxis. Vascular calcification of calciophylaxis often persists despite the decrease of the calcium-phosphate products,<sup>72</sup> in contrast to the benign nodular calcification, that appears in patients with chronic renal failure and disappears with normalization of serum calcium and phosphate levels.<sup>73</sup> Functional abnormalities in

either protein C or protein S have been reported in several patients with calciophylaxis, which supports the idea that a preexisting hypercoagulable stage predisposes affected patients to calciophylaxis.<sup>74</sup> However, these proteins are normal in other patients.<sup>67,71</sup> Calciophylaxis has been also described in AIDS patients with renal failure.<sup>75</sup>

From a clinical point of view, cutaneous lesions of calciophylaxis usually appear in patients with end-stage renal disease undergoing hemodialysis or after kidney transplantation. Skin lesions consist of violaceous, mottled to reticulated patches and plaques resembling livedo reticularis (Fig 5). Occasionally bullae have been reported. Lesions evolve to necrotic, indurated plaques and nodules, resulting in large, deep, nonhealing ulcers associated with significant tenderness, ischemic digital pain, and, in some cases, gangrene of the digits, which necessitates amputation. The lesions exhibit bilateral symmetry, and distal parts of the extremities, thighs, and buttocks are the most frequently involved sites.<sup>72,73,76-81</sup> Less frequently the trunk and upper extremities are affected by cutaneous lesions of calciophylaxis. Necrosis of the penis secondary to calciophylaxis has also been described,<sup>69,82</sup> and we have recently seen an example of this.<sup>83</sup> Despite dramatic ulcers and necrosis, no internal organ failure is usually reported in patients with calciophylaxis.

Histopathologic features in cutaneous lesions of calciophylaxis are characteristic. They consist of calcium depositions in the walls of small- to medium-sized-diameter blood vessels of the reticular dermis and subcutaneous fat (Fig 6). These are associated with lobular fat necrosis, intralobular calcification, and inflammatory infiltrate of neutrophils, lymphocytes, and foamy histiocytes.<sup>73-85</sup> This histopathologic picture of ischemic necrosis, with infarction of the adipocytes within the lobule and congested capillaries, closely resembles the early changes seen in sclerosing panniculitis. In calciophylaxis, however, the calcification of the vessel walls and subsequent endovascular fibrosis is the cause of ischemia. Some patients with calciophylaxis, in addition to vascular calcification in the deeper dermis and subcutaneous fat, also show calcium deposition in the lower dermis and subcutaneous septa that appears to involve elastic tissue, similar to pseudoxanthoma elasticum.<sup>84</sup>

The prognosis in patients with calciophylaxis is poor, and a review of the literature reveals the mortality rate to be as high as 80%.<sup>68</sup> In some patients, parathyroidectomy with normalization of abnormal calcium and phosphorus serum levels stopped the progression of the disease.<sup>68</sup> In patients with chronic renal failure undergoing hemodialysis, a diet poor in calcium and phosphorus, binding agents, and low-



**Fig 5.** Calciphylaxis in patient with end-stage chronic renal failure. Violaceous plaques and necrosis on anterior aspect of the leg.

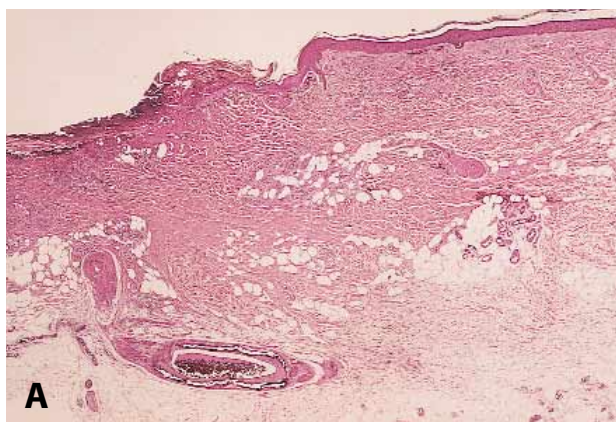
calcium hemodialysis is recommended.<sup>86</sup> In single case reports, improvement of cutaneous lesions of calciphylaxis has been reported after hyperbaric oxygen therapy<sup>87</sup> and with prednisone and subsequent cimetidine.<sup>88</sup> Unfortunately, most patients with calci-

phylaxis die of overwhelming infection and sepsis resulting from a compromised skin barrier in an immunosuppressed patient with chronic renal failure or after kidney transplantation.

### Oxalosis

Oxalosis is another rare crystalline deposit-associated panniculitis seen in relationship with renal failure. There are two forms of oxalosis, namely, primary or inherited oxalosis and secondary or acquired oxalosis. Primary oxalosis is an autosomal recessive inherited metabolic disease caused by enzymatic defects.<sup>89</sup> Primary oxalosis includes two different metabolic diseases, both with similar clinical manifestations, but with different basic enzymatic defects: type I primary oxalosis results from a deficiency of 2-hydroxy-3-oxoadipate carboxylase, whereas type II primary oxalosis is a deficiency of D-glyceric dehydrogenase.<sup>89</sup> Secondary oxalosis results from excessive oxalate or glycolic acid ingestion, ethylene glycol poisoning, intravenous glycerol or xylitol infusion, methoxyflurane anesthesia, pyridoxine deficiency, intestinal disease, ileal resection, and, in the setting of chronic renal failure, in hemodialysis.<sup>90,91</sup> Both primary and secondary oxalosis often lead to renal failure and death of the patient.

Cutaneous involvement is more frequent in secondary than in primary oxalosis. In secondary oxalosis the presence of miliary deposits of calcium oxalate on the palmar aspects of the fingers is characteristic.<sup>90,92</sup> This calcium deposition in the dermis calls for histiocytes and granulomatous inflammation appears in the dermis surrounding the crystals. In contrast, cutaneous lesions in primary oxalosis, when present,



**Fig 6.** Histopathologic features of calciphylaxis. **A**, Low-power view shows necrotic epidermis and lobular fat necrosis. Also shown is calcification of wall of large blood vessel of the subcutaneous fat. **B**, Higher magnification shows calcification of the blood vessel wall. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 40$ ; **B**,  $\times 200$ .)



consist of livedo reticularis and acral gangrene.<sup>89,93-97</sup> Biopsy findings of skin lesions of primary oxalosis show calcium deposition and oxalate crystals on the vessel walls, with a histopathologic picture quite similar to that of calciphylaxis.<sup>89,93-98</sup> Often the involved blood vessels show luminal thrombosis.

Treatment is different in primary and secondary oxalosis. In secondary oxalosis kidney transplantation is usually followed by significant improvement of the disease, but in primary oxalosis renal graft survival is limited because of recurrent oxalate deposition. If diagnosis is established before the onset of renal failure, treatment consists of large volume of fluid, alkalinization, and medications to minimize the oxalate formation, trying to maintain renal function as long as possible. When renal failure is established, kidney transplantation should be combined with hepatic transplantation to revert the underlying enzymatic deficiency.<sup>99</sup>

### **Sclerema neonatorum**

Sclerema neonatorum is rare because of the improvements in neonatal care. Most of the cases of this rare disorder have been described in low-weight premature newborns during the course of a wide variety of severe illnesses, particularly serious infections, congenital heart disease, and other major developmental defects. The affected infant is generally severely ill at the onset of sclerema neonatorum, and cutaneous lesions appear during the first days of life. These usually begin on the buttocks and thighs in the form of diffuse yellow-white woody induration of the skin and rapidly extend to involve large areas of the body, resulting in immobility of the extremities. The prognosis is poor and most infants affected with sclerema neonatorum die within a few days.<sup>100</sup> It has been postulated that the ratio of saturated to unsaturated fatty acids is relatively high in the adipose tissue of all neonates and that this ratio is even higher in infants with sclerema neonatorum, thereby predisposing premature and small-for-gestational age infants to this disease.<sup>101</sup>

From a histopathologic point of view, at first glance the cutaneous biopsy specimen shows little abnormality in the subcutaneous fat. Inflammatory infiltrate is sparse or even absent, and the process does not resemble a panniculitis. The sparse inflammatory infiltrate reflects the poor immunologic response of the severely ill infant. There is little evidence of fat necrosis, but the most characteristic feature of sclerema neonatorum is the presence of radially arranged, needle-shaped clefts in adipocytes, and, occasionally, in some of the few multinucleated giant cells present in the sparse inflammatory infiltrate.<sup>102</sup> Autopsy studies in

infants who died as a consequence of sclerema neonatorum have identified identical needle-shaped crystals in adipocytes of visceral fat.<sup>103,104</sup>

Treatment of sclerema neonatorum is primarily treatment of the underlying disease. Systemic corticosteroids are ineffective, but there is evidence that repeated exchange transfusions may reduce mortality.<sup>105</sup> Infants who survive an episode of sclerema neonatorum during the first week of life have normal-appearing skin with no calcifications or other long-term complications.

### **Cold panniculitis**

Cold panniculitis is also more frequent in infants after exposure to severe cold.<sup>106-108</sup> Cases of this variant of panniculitis have also been described in the cheeks of children sucking ice cubes, ice packs, or ice lollies (popsicles).<sup>109,110</sup> Cold panniculitis may also develop during cold months in the thighs or buttocks of women who ride horses wearing tight trousers that obstruct the blood supply to the subcutaneous fat (equestrian panniculitis).<sup>111,112</sup>

Clinically, the affected areas appear as indurated erythematous plaques with ill-defined margins. If the involved area is kept warm, the plaques slowly soften and resolve in some days without scarring.

Biopsy specimens of cold panniculitis show a mostly lobular panniculitis with an inflammatory infiltrate of lymphocytes and histiocytes in the fat lobules. There may also be marked edema in the papillary dermis as well as superficial and deep perivascular lymphocytic infiltrate in the dermis that extends to the subcutaneous septa. The histopathologic findings closely resemble those of perniosis.<sup>113</sup>

Cold panniculitis resolves if further exposure to cold is avoided. In horse-riding women with inadequate clothing, looser trousers should be recommended. Vasodilator drugs are not effective in preventing or treating cold panniculitis.

### **Lupus panniculitis (lupus erythematosus profundus)**

Lupus panniculitis is a chronic recurrent panniculitis that appears in approximately 1% to 3% of patients with cutaneous lupus erythematosus.<sup>114,115</sup> Lupus panniculitis is more frequent in women than in men, and the lesions have a predilection for the upper arms, shoulders, face, and buttocks, which are areas infrequently involved by other variants of panniculitis. Cases of lupus panniculitis involving the subcutaneous fat of the breast ("lupus mastitis"),<sup>116-118</sup> orbital,<sup>119,120</sup> and periparotid fat tissue<sup>121,122</sup> have also been recorded. Unusual forms of lupus panniculitis include lesions mimicking morphea,<sup>123</sup> linear arrangement of the lesions,<sup>124</sup> and the association of



**Fig 7.** Lupus erythematosus profundus. Shoulder and upper arms are the most frequently involved areas. Erythematous nodules correspond to active lesions, whereas areas of lipoatrophy indicate regressed lesions. Scar is due to previous biopsy at this site.

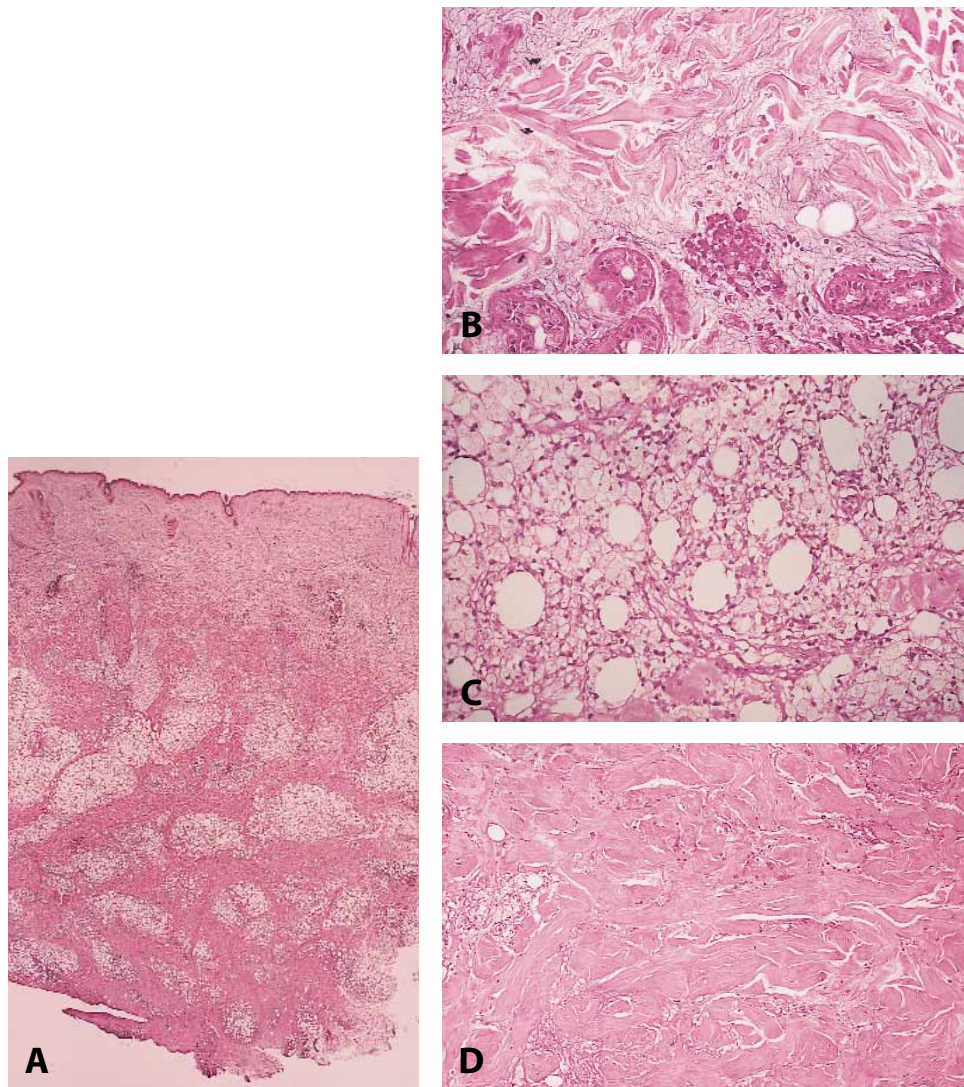
lupus panniculitis and neonatal lupus erythematosus.<sup>125</sup> Occasionally, subcutaneous nodules of lupus panniculitis are the only clinical manifestation of lupus erythematosus.<sup>126</sup> Trauma to subcutaneous fat seems to be a precipitating factor for lesions of lupus panniculitis. Some patients develop the lesions at the point of previous injections, and the aggravation of the process at the site in which a biopsy is taken or recurrence of the subcutaneous nodules along scars of previous excisions are distinctive clinical features of lupus panniculitis.<sup>127,128</sup>

Clinically, the lesions consist of deep situated subcutaneous nodules or plaques. The surface of the nodules may show classic features of discoid lupus erythematosus<sup>125</sup> or may appear as normal skin. When lesions of lupus panniculitis regress, they leave atrophy and swelling of the involved area. Persistent areas of lipoatrophy on the shoulders and upper arms are so characteristic that they allow a retrospective diagnosis of lupus panniculitis (Fig 7). Subcutaneous nodules of lupus panniculitis may precede, appear simultaneously, or develop after other extracutaneous manifestations of systemic lupus erythematosus,<sup>129</sup> but usually patients with lupus panniculitis have a mild disease course.

Histopathologic findings in lupus panniculitis are relatively characteristic. In more than half of the cases, there are epidermal and dermal changes of discoid lupus erythematosus. These include atrophy of the epidermis, vacuolar change at the dermoepidermal junction, thickened basement membrane, interstitial mucin between collagen bundles of the dermis, and superficial and deep perivascular inflammatory infiltrate of lymphocytes involving the dermis.<sup>128,129</sup> In the other half of the cases, the changes are confined to the subcutaneous fat, with no anomalies in the dermis or epidermis. There is a mostly lobular panniculitis with inflammatory infiltrate predominantly composed of lymphocytes (Fig 8). A characteristic feature, found in more than half of the patients, is the presence of lymphoid follicles.<sup>130</sup> Often, these lymphoid follicles show germinal centers and numerous plasma cells at the periphery that also extend interstitially between collagen bundles of the septa of the subcutis. Lymphoid follicles in the subcutaneous fat are quite characteristic of lupus panniculitis, but they are not exclusive because they have also been described in deep morphea, erythema nodosum, panniculitis associated with dermatomyositis, and erythema induratum of Bazin.<sup>131</sup> Necrosis of adipocytes is usually sparse or absent in lupus panniculitis. Sometimes, however, lymphocytes of the infiltrate show nuclear dust, an infrequent finding in other variants of lobular panniculitis, so that it has been proposed as a clue to the diagnosis of lupus panniculitis.<sup>132</sup> Collagen bundles of subcutaneous septa appear to be hyaline and sclerotic, and they also contain an interstitial inflammatory infiltrate of lymphocytes and plasma cells. Less constant features that have been described in cases of lupus panniculitis include lymphocytic vasculitis in the small blood vessels of the fat lobule, hyaline necrosis of the vessel walls, abundant mucin between collagen bundles, calcification, and numerous eosinophils in the inflammatory infiltrate.<sup>133</sup> As in other variants of lobular panniculitis, late-stage lesions of lupus panniculitis may show membranocystic changes.<sup>134,135</sup>

Immunofluorescence studies in lesions of lupus panniculitis have in most cases shown a linear deposition of IgM and C3 along the dermoepidermal junction.<sup>115,128</sup> Immunofluorescent deposits in the subcutaneous fat are more inconstant and difficult to accomplish technically. When a biopsy specimen of clinically typical lesions of lupus panniculitis does not show definitive findings, the positive lupus band test along the dermoepidermal junction supports a diagnosis of lupus panniculitis.<sup>127</sup>

Local treatment with potent corticosteroids under occlusion has been reported as being helpful



**Fig 8.** Histopathologic features of lupus erythematosus profundus. **A**, Scanning power shows lobular panniculitis with small fat lobules and thickened septa. **B**, Abundant mucin is seen between collagen bundles of the reticular dermis. **C**, Lobular panniculitis with lymphocytes and plasma cells among necrotic adipocytes. **D**, Sclerotic collagen bundles are seen in the thickened septa. (**A-D**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B-D**,  $\times 200$ .)

in lesions of lupus panniculitis,<sup>136</sup> but often a systemic course of corticosteroids<sup>116</sup> or hydroxychloroquine<sup>137</sup> is necessary. Dapsone has also been reported as effective in the management of lupus panniculitis.<sup>138</sup>

#### **Panniculitis in dermatomyositis**

Panniculitis is less frequent in dermatomyositis than in lupus erythematosus and scleroderma. In a series of 55 patients with dermatomyositis and cutaneous lesions, studied histopathologically, panniculitis was only demonstrated in 5 cases.<sup>139</sup> In some patients, lesions of panniculitis are present in association with other characteristic cutaneous lesions of dermato-

myositis,<sup>140</sup> whereas in other cases panniculitis is the only cutaneous manifestation of the disease.<sup>141</sup>

Histopathologic findings in lesions of panniculitis associated with dermatomyositis are quite similar to those of lupus panniculitis. There is a mostly lobular panniculitis with lymphocytes and plasma cells among the adipocytes. The collagen bundles of the septa show hyaline sclerosis, and there is progressive replacement of fat with fibrous tissue.<sup>127</sup> Additional histopathologic findings in lesions of panniculitis associated with dermatomyositis include thickening of the blood vessels of the fat lobule, neutrophilic vasculitis with fibrinoid necrosis or lymphocytic vasculitis involving the arterioles of the septa, and calci-

fication. Lymphoid follicles, with or without germinal center formation, have also been described in lesions of panniculitis in dermatomyositis,<sup>142</sup> but this finding is less frequent than in lesions of lupus panniculitis or deep morphea. As in lupus panniculitis, some lesions of panniculitis associated with dermatomyositis exhibit vacuolar change at the dermoepidermal junction.<sup>141-143</sup> Late-stage lesions may also show membranocystic change.<sup>144</sup>

Immunofluorescence studies have only been performed in 3 cases of panniculitis associated with dermatomyositis. The results were negative in one case.<sup>142</sup> Another case had deposits of IgM, C3, and fibrinogen in the blood vessel walls of the dermis, but not at the dermoepidermal junction.<sup>141</sup> The third case showed deposits of C3 at the basement membrane zone of the dermoepidermal junction and around the dermal blood vessels, but in the subcutaneous fat only deposits of fibrinogen were detected.<sup>142</sup> In general, patients with dermatomyositis and associated panniculitis seem to be a subgroup of patients with a good prognosis, with no higher incidence of malignancy, as is the case in other patients with dermatomyositis.<sup>145</sup> Only one patient with dermatomyositis and panniculitis had an associated rhabdomyosarcoma.<sup>146</sup>

More common than pure panniculitis in dermatomyositis is the panniculitis associated with calcification of the muscle and deep tissue. In these cases the fat lobules show lipophagic granuloma, calcification, and various degrees of acute and chronic inflammation.<sup>127</sup>

Lesions of panniculitis in patients with dermatomyositis respond to systemic treatment of dermatomyositis and the best response is with high-dose courses of corticosteroids.<sup>140,142</sup>

### **Pancreatic panniculitis**

Several pancreatic diseases have been associated with a characteristic variant of panniculitis, named pancreatic or enzymatic panniculitis. This variant appears in approximately 2% to 3% of all patients with pancreatic diseases.<sup>147</sup> It has mostly been described in association with acute and chronic pancreatitis,<sup>148-157</sup> but also in patients with pancreatic carcinoma, more frequently with acinar cell carcinoma type,<sup>158-162</sup> and less commonly with pancreatic islet cell carcinoma.<sup>163-165</sup> In some patients with pancreatic panniculitis the skin lesions were the presenting feature of the pancreatic disease.<sup>158,166</sup> Other less frequent pancreatic abnormalities that have been described in association with pancreatic panniculitis include pancreas divisum,<sup>167,168</sup> pancreatic pseudocysts,<sup>169-171</sup> vasculopancreatic fistulas,<sup>172</sup> and pancreatitis secondary to sulindac intake.<sup>173</sup> These cases are interpreted to be

the result of subclinical pancreatitis with no abdominal symptoms. In some patients, however, there is no demonstrable pancreatic disease, although high serum levels of pancreatic lipase of unknown origin were detected.<sup>174</sup> Recently a case of pancreatic panniculitis has been reported in association with primary HIV infection and a hemophagocytic syndrome.<sup>175</sup>

Clinically, cutaneous lesions of pancreatic panniculitis appear as erythematous subcutaneous nodules that spontaneously ulcerate and exude an oily brown material, which results from liquefaction necrosis of adipocytes (Fig 9). The distal parts of the lower extremities, around the ankles and knees, are the most frequent locations of these lesions,<sup>174</sup> although nodules of pancreatic fat necrosis have also been described in other areas including the thighs, buttocks, calves, arms, and abdominal skin. Cases of pancreatic panniculitis with a single subcutaneous nodule have been reported.<sup>176</sup> Usually, those cases associated with pancreatitis show resolution of the cutaneous lesions when the inflammatory episode of the pancreas regresses. In contrast, subcutaneous nodules of pancreatic panniculitis in patients with pancreatic carcinoma tend to be more chronic and persistent, with frequent recurrences, ulceration, and involvement of cutaneous areas beyond the lower extremities.<sup>177</sup> Often the onset of subcutaneous fat necrosis in pancreatic diseases is accompanied by acute arthritis that results from necrosis in periarticular fat tissue.<sup>151,154,177-182</sup> In rare instances pancreatic panniculitis is associated with necrosis of the abdominal fat,<sup>178</sup> bone marrow fat,<sup>163</sup> pleural effusions,<sup>158,166</sup> mesenteric thrombosis,<sup>166</sup> and leukemoid reaction and eosinophilia.<sup>174</sup> A patient with pancreatic panniculitis and pancreatic carcinoma developed a woodlike induration of the fingers as a consequence of an associated fasciitis.<sup>183</sup>

From a pathogenic point of view, it has been proposed that pancreatic enzymes, mostly lipase, that escape to the blood from the inflamed pancreas are responsible for the subcutaneous fat necrosis in enzymatic panniculitis.<sup>156,174</sup> The finding of pancreatic lipase in the areas of subcutaneous necrosis,<sup>174</sup> and the immunohistochemical demonstration with anti-lipase monoclonal antibodies of that enzyme within the necrotic adipocytes<sup>155</sup> support the pathogenic role of pancreatic lipase. However, pancreatic lipase must not be the only etiologic factor because there is a contrast between the relative frequency of pancreatitis with high serum levels of lipase and the fact that pancreatic panniculitis is a rare disorder.<sup>184</sup> Furthermore, *in vitro* investigations failed to reproduce pancreatic panniculitis when normal human subcutaneous fat was incubated with the serum of a patient with high levels of pancreatic lipase, trypsin, and amylase.<sup>156</sup> Well-docu-

mented examples of pancreatic panniculitis have been described in patients with normal serum levels of all pancreatic enzymes.<sup>185,186</sup>

From a histopathologic point of view, pancreatic panniculitis shows the characteristic features of a mostly lobular panniculitis with intense necrosis of the adipocytes.<sup>187</sup> Some authors have proposed that the earliest feature is a septal panniculitis that results from the enzymatic damage of the endothelial cells lining the blood vessels of the septa. These altered endothelial cells allow the crossing of pancreatic enzymes from the blood to fat lobules, resulting in necrosis of the adipocytes.<sup>188</sup> Regardless of the earliest features, fully developed lesions of pancreatic panniculitis show a characteristic coagulative necrosis of the adipocytes, which leads to ghost adipocytes. Ghost adipocytes are those that have lost their nuclei and show a finely granular and basophilic material within their cytoplasm because of calcification (Fig 10). Often, ghost adipocytes appear grouped in small clusters at the center of the fat lobule, whereas an inflammatory infiltrate of neutrophils is present at the periphery. Dystrophic calcification in ghost adipocytes results from hydrolytic action of pancreatic enzymes on fat followed by calcium deposition, a process known as saponification. In older lesions, fat necrosis and calcified ghost adipocytes are less evident and the fat lobule is replaced by granulomatous inflammatory infiltrate composed of foamy histiocytes and multinucleated giant cells.

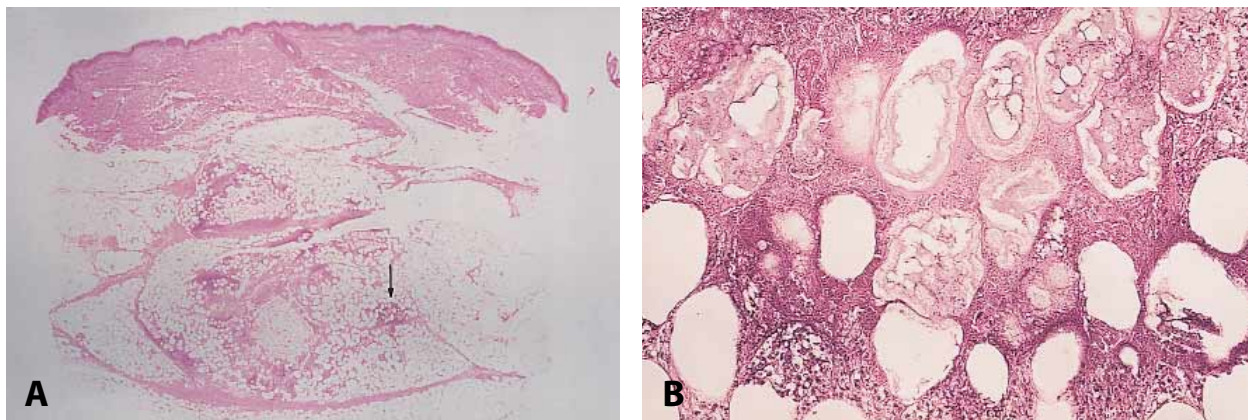
Treatment of pancreatic panniculitis is primarily directed to the underlying pancreatic disease. Sometimes, complete resolution of the symptoms occurs when the pancreatic anomaly is surgically corrected.<sup>152,167</sup>



**Fig 9.** Pancreatic panniculitis. Erythematous subcutaneous nodules that ulcerated and exuded oily yellow material.

#### **$\alpha_1$ -Antitrypsin-deficiency panniculitis**

Clinical manifestations of  $\alpha_1$ -antitrypsin deficiency ( $\alpha_1$ -protease inhibitor deficiency) only appear in homozygous patients. Currently, more than 33 allelic variants of this disorder are known. In every person, two of these alleles combine to determine the pheno-



**Fig 10.** Histopathologic findings in pancreatic panniculitis. **A**, Scanning power shows a mostly lobular panniculitis (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates necrotic adipocytes containing finely granular deposits of calcium (ghost adipocytes) surrounded by neutrophils. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 400$ .)

type of  $\alpha_1$ -antitrypsin. The most common allele associated with normal levels of  $\alpha_1$ -antitrypsin is M. Some alleles, such as S and Z, are associated with low levels of plasma  $\alpha_1$ -antitrypsin. A heterozygotic person with PiMS or PiMZ phenotype usually shows moderate deficiency of  $\alpha_1$ -antitrypsin, whereas homozygous patients with phenotype PiZZ have severe  $\alpha_1$ -antitrypsin deficiency with serious clinical manifestations, including emphysema, hepatitis, cirrhosis, vasculitis, angioedema, and panniculitis.<sup>189-191</sup> In these patients, the liver produces the proenzyme of  $\alpha_1$ -antitrypsin, but the proenzyme is not released.  $\alpha_1$ -Antitrypsin is a serine protease inhibitor that mostly inhibits trypsin activity, but is also a potent inhibitor of chemotrypsin, plasmin, thrombin, neutrophilic elastase, pancreatic elastase, serine proteases, collagenase, factor VIII, and kallikrein.<sup>192</sup> Therefore severe  $\alpha_1$ -antitrypsin deficiency is associated with variable clinical manifestations including disorders of blood coagulation and fibrinolysis, anomalies in the phagocytic mechanisms of the immune response, and abnormalities in activation of zymogens and the release of peptide hormones.<sup>193-199</sup>

From a dermatologic point of view, panniculitis is the most important clinical manifestation of  $\alpha_1$ -antitrypsin deficiency. Panniculitis may be the first sign of the disease, although lesions of subcutaneous fat necrosis usually appear when other clinical manifestations of the disorder have already developed. Cutaneous lesions of  $\alpha_1$ -antitrypsin deficiency panniculitis consist of subcutaneous nodules mostly located on the lower extremities, but other areas of the skin, such as the arms, trunk, and face, are often also involved.<sup>189,200-221</sup> The earliest lesions resemble cellulitis and show a tendency to ulcerate and exudate oily material that represents necrotic adipocytes. When lesions resolve, they leave atrophic scars (Fig 11). Occasionally, lesions of  $\alpha_1$ -antitrypsin deficiency panniculitis appear on areas of previous trauma or on scars of previous cryosurgery.<sup>221</sup> The association of  $\alpha_1$ -antitrypsin deficiency panniculitis and Marshall's syndrome has been described and consists of Sweet's syndrome leading to acquired cutis laxa. This association supports the notion that Marshall's syndrome represents part of the clinical spectrum of  $\alpha_1$ -antitrypsin deficiency.<sup>222</sup>  $\alpha_1$ -Antitrypsin deficiency equally affects both sexes, and it may affect children<sup>217</sup>; however, subcutaneous fat necrosis due to  $\alpha_1$ -antitrypsin deficiency develops most commonly during adult life.<sup>212</sup>

Biopsy specimens of cutaneous lesions of  $\alpha_1$ -antitrypsin deficiency panniculitis show severe necrosis of the fat lobules. A histopathologic feature that has been proposed by some authors<sup>219</sup> as a specific clue to early lesions of  $\alpha_1$ -antitrypsin deficiency panniculitis is the splaying of neutrophils between collagen bundles of

the reticular dermis (Fig 12). Another histopathologic feature considered to be characteristic of  $\alpha_1$ -antitrypsin deficiency is the focality of the lesions, appearing as large areas of normal fat adjacent to necrotic adipocytes containing many neutrophils and histiocytes.<sup>211</sup> Occasionally, the intense inflammatory infiltrate of neutrophils causes collagenolysis and degeneration of elastic tissue with destruction of the septa of the subcutis and then necrotic fat lobules appear to be "floating" and surrounded by neutrophils.<sup>212</sup> Vasculitis, except for that resulting from areas of necrosis, is usually not seen in biopsy specimens from patients with  $\alpha_1$ -antitrypsin deficiency panniculitis. In late-stage lesions, neutrophils and necrotic adipocytes are less evident, and the fat lobules appear to be occupied by lymphocytes, foamy histiocytes, and variable degrees of fibrosis.<sup>210,214</sup>

Trauma and surgical debridements are frequent precipitating factors of panniculitis in patients with  $\alpha_1$ -antitrypsin deficiency and they should be avoided, if possible. Dapsone has proved to be an effective treatment in cases of panniculitis due to  $\alpha_1$ -antitrypsin deficiency.<sup>210,215,223,224</sup> In homozygous patients with severe forms of the disease, presenting with severe emphysema and liver failure, the only therapeutic possibility is supplemental infusion of exogenous  $\alpha_1$ -protease inhibitor concentrate, in an intravenous dose of 60 mg/kg per week, or liver transplantation.<sup>225,226</sup> At present, the production of  $\alpha_1$ -antitrypsin by genetic engineering is being investigated.<sup>227,228</sup>

### Infective panniculitis

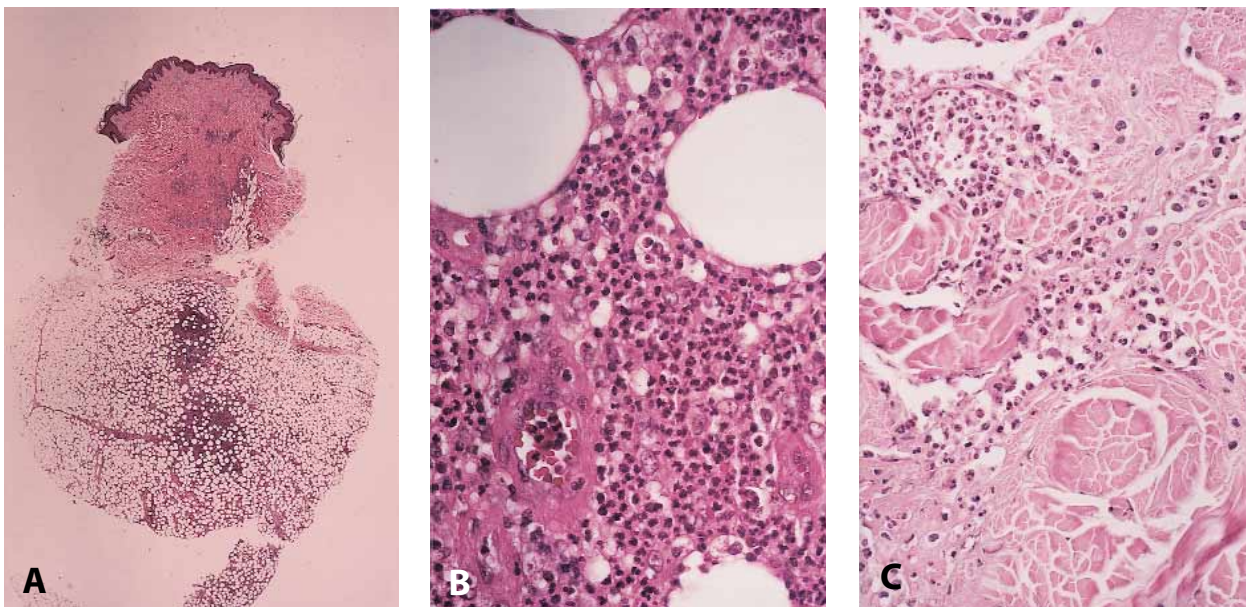
Several bacteria or fungi may cause lobular panniculitis as the main clinical manifestation. These infective panniculitides include infections of the subcutaneous fat caused by *Streptococcus pyogenes*,<sup>229</sup> *Staphylococcus aureus*,<sup>229</sup> *Pseudomonas* spp,<sup>229,230</sup> *Klebsiella*,<sup>229</sup> *Nocardia* spp,<sup>229</sup> atypical mycobacteria,<sup>231-234</sup> *Mycobacterium tuberculosis*,<sup>235</sup> *Candida* spp,<sup>229,236</sup> *Fusarium* spp,<sup>229</sup> *Histoplasma capsulatum*,<sup>237,238</sup> *Cryptococcus neoformans*,<sup>31</sup> *Actinomyces israelii*,<sup>31</sup> *Sporothrix schenckii*,<sup>31</sup> *Aspergillus fumigatus*<sup>239</sup> (Fig 13), and chromomycosis.<sup>31</sup> Most of these infective panniculitides occur in immunosuppressed patients.

The evaluation of patients with neutrophilic lobular panniculitis should include cultures of the biopsy specimen. Infective panniculitis caused by atypical mycobacteria show suppurative granulomas within the lobule, which consist of collections of neutrophils surrounded by epithelioid histiocytes.<sup>234</sup> Immunocompromised patients with these cutaneous infections can present with either primary or secondary skin lesions. Primary cutaneous infections arise either from direct physical inoculation or at the

site of an occlusive dressing of an indwelling catheter. Secondary cutaneous infections develop from either direct extension, to the chest wall in pulmonary infections, or from hematogenous dissemination. As a consequence of the different routes of dissemination, there are several histopathologic differences. In primary cutaneous infections, the epicenter of the inflammation is the superficial dermis, and thrombosed vessels do not contain intravascular organisms. In contrast, in secondary cutaneous infections, the epicenter of inflammation is more deeply seated and involves only the deep reticular dermis and subcutaneous fat. The blood vessels are thrombosed and dilated with masses of organisms expanding their lumens.<sup>239</sup> In other words, infective panniculitis usually results from hematogenous dissemination; the respiratory tract is the most common portal of entry. In immunosuppressed patients, microorganisms are numerous and they may be identified in tissue sections with the routine hematoxylin-eosin stain (Fig 14) or with special stains (eg, Gram, periodic acid-Schiff, Ziehl-Neelsen). Because anti-BCG immunostaining shows cross-reactivity with many bacteria and fungi as well as high sensitivity and minimal background staining, it has been proposed as the best screening tool for detection of bacterial and fungal microorganisms in paraffin-embedded skin specimens.<sup>240</sup> In patients with preserved immune response, the microorganisms are



**Fig 11.** Atrophic scars and lipoatrophy secondary to resolved lesions of panniculitis in patient with severe  $\alpha_1$ -antitrypsin deficiency.



**Fig 12.** Histopathologic features of  $\alpha_1$ -antitrypsin deficiency panniculitis. **A**, Scanning power shows a mostly lobular panniculitis. **B**, Aggregations of neutrophils within the fat lobule. **C**, Neutrophils interstitially arranged between collagen bundles of the deep reticular dermis. (A-C, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 400$ ; **C**,  $\times 200$ .)



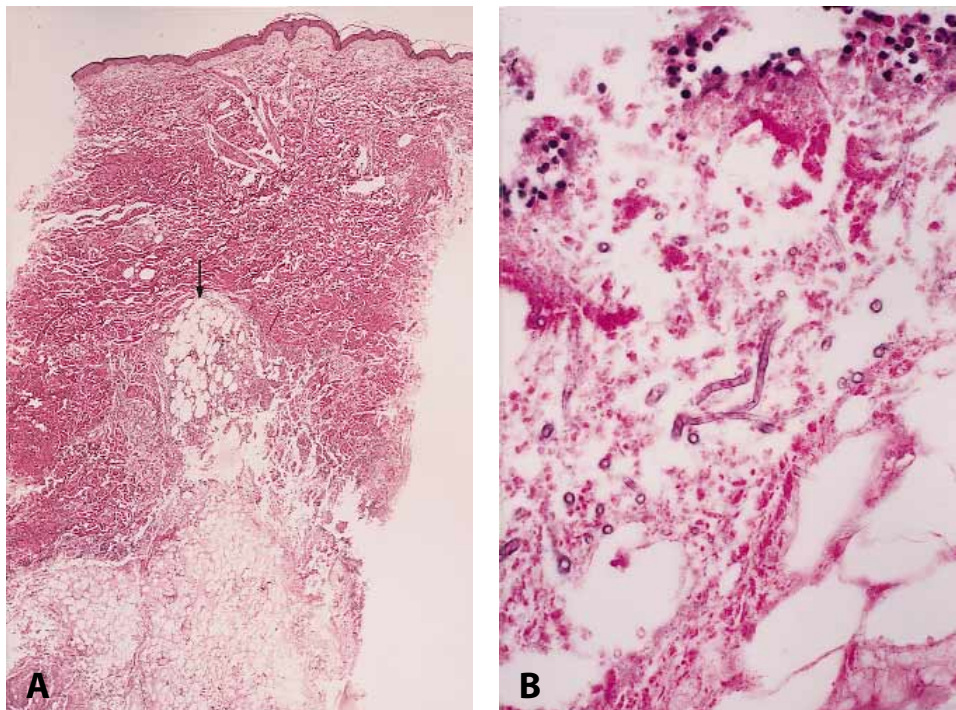
**Fig 13.** Infective panniculitis by *Aspergillus fumigatus* in diabetic patient. Erythematous subcutaneous nodules, some of them ulcerated, on the leg.

sparse and often they cannot be identified with special stains; thus the diagnosis must be established by a positive culture of the lesion or serologic studies.

Treatment of infective panniculitis requires systemic administration of antibiotics, which should be selected according to susceptibility tests.

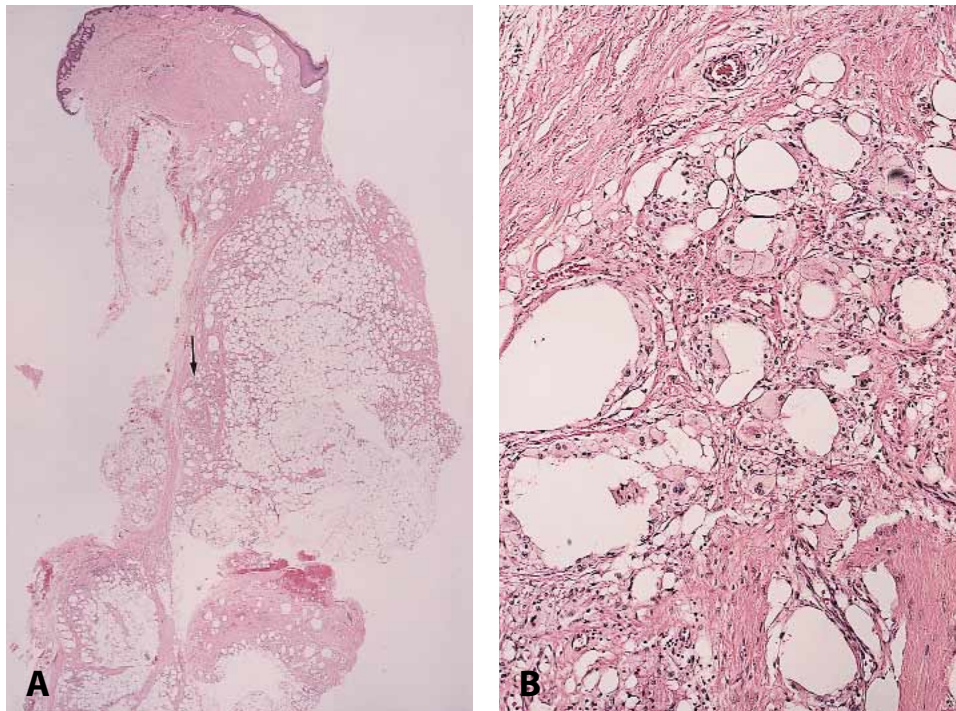
#### **Factitial panniculitis**

Some patients inject themselves with the most disparate substances within the subcutaneous fat, thereby causing panniculitis. Other times panniculitis results from the subcutaneous implantation of different materials for cosmetic or therapeutic reasons. These self-inflicted or iatrogenic panniculitides include those caused by some drugs injected in the subcutaneous fat such as povidone,<sup>241</sup> meperidine,<sup>242</sup> pentazocine,<sup>243,244</sup> and vitamin K<sub>1</sub>,<sup>245</sup> or substances used to augment the size of breasts or genitalia or to correct facial wrinkles or other contour abnormalities such as paraffin,<sup>246-251</sup> silicone,<sup>252-254</sup> PMMA-microspheres (Artecoll),<sup>255</sup> or polymethylsiloxane (Bioplastique).<sup>255</sup> Psychiatric patients with personality aberrations have been reported with self-inflicted panniculitis due to subcutaneous injections of the most unsuspected substances including acids, alkalis, mustard, milk, microbiologically contaminated material, urine, and feces.



**Fig 14.** Histopathologic features of panniculitis by *Aspergillus fumigatus*. **A**, Scanning power shows a mostly lobular panniculitis (arrow indicates area enlarged in **B**). **B**, Higher magnification demonstrates neutrophils and hyphal elements of *A fumigatus* within the fat lobule. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 400$ .)





**Fig 15.** Histopathologic features of paraffinoma. **A**, Scanning power shows a mostly lobular panniculitis (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates cystic spaces within the fat lobule surrounded by foamy histiocytes. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

Histopathologically, factitial panniculitis usually shows a pattern of a mostly lobular panniculitis, with an inflammatory infiltrate predominantly composed of neutrophils in early lesions and a more granulomatous infiltrate in late-stage lesions. Sometimes polarization of the slide can identify the refractile foreign material causing the panniculitis. However, some histopathologic findings may be helpful in identifying the nature of the foreign material. For example, in cases of povidone panniculitis stained with hematoxylin-eosin, povidone appears as blue-gray foamy deposits within the cytoplasm of large, distended macrophages that replace the fat lobule.<sup>241</sup> Povidone stains intensely with Congo red and chlorazol-fast pink and variably with periodic acid-Schiff.<sup>241</sup> Lesions of panniculitis secondary to subcutaneous injections of pentazocine show marked sclerosis of the dermis and the septa of subcutaneous fat, with necrotic adipocytes, lipophagic granuloma, and thrombi in the lumina of the small blood vessels of the fat lobule.<sup>244</sup> Subcutaneous injections of vitamin K<sub>1</sub> induce sclerosis of the collagen bundles of the subcutaneous septa and an inflammatory infiltrate of lymphocytes and plasma cells closely resembling the histopathologic features of deep morphea.<sup>245</sup> Paraffinoma develops after injections of mineral oil into tissues, resulting in

a histopathologic picture that has been named sclerosing lipogranuloma. Sclerosing lipogranuloma consists of multiple “Swiss-cheese-like” pseudocystic spaces replacing the fat lobules (Fig 15). These are surrounded by fibrosis and an inflammatory infiltrate composed of foamy histiocytes and multinucleated giant cells.<sup>246,247</sup> Silicone injections used for cosmetic reasons may produce granulomatous reaction in some patients. This is histopathologically characterized by foamy histiocytes containing multiple vacuoles in their cytoplasm and multinucleated giant cells surrounding polygonal translucent angulated foreign bodies, which represent impurities in the silicone.<sup>253</sup> Bioplastique granulomas present with irregularly shaped cystic spaces of varying size containing jagged, translucent, nonbirefringent foreign bodies surrounded by multinucleated giant cells.<sup>255</sup> Artecoll granulomas show numerous round vacuoles nearly identical in size and shape enclosing round and sharply circumscribed, translucent, nonbirefringent foreign bodies surrounded by sclerotic stroma.<sup>255</sup>

Patients with self-inflicted factitial panniculitis are mentally disturbed and psychiatric treatment is usually required. A case of factitial panniculitis mimicking pyoderma gangrenosum has been reported as a manifestation of Münchausen syndrome.<sup>256</sup> In



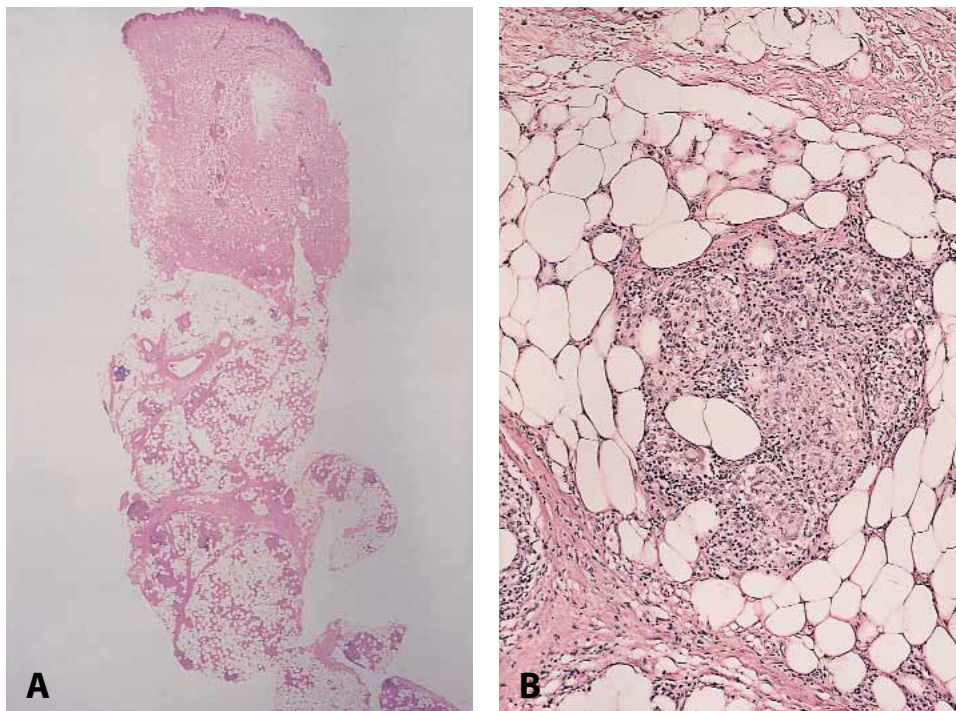
**Fig 16.** Subcutaneous sarcoidosis. Erythematous nodule on the knee.

patients with panniculitis secondary to materials used for breast augmentation or correction of cosmetic defects, the implanted material should be removed.

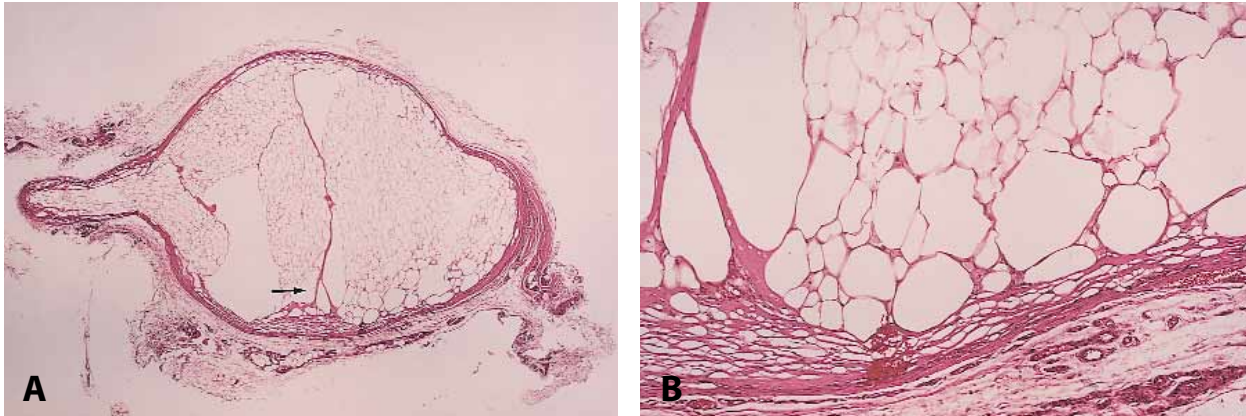
### Subcutaneous sarcoidosis

Sometimes specific lesions of sarcoidosis are seen involving the subcutaneous fat. Clinically the lesions consist of subcutaneous nodules on the lower extremities (Fig 16) with no signs of inflammation on the skin surface.<sup>257-260</sup> These are different from the lesions of erythema nodosum that frequently appear in patients with sarcoidosis and that are clinically and histopathologically indistinguishable from lesions of erythema nodosum associated with other disorders.

Histopathologically, these specific subcutaneous nodules of sarcoidosis show small noncaseating granulomas involving fat lobules (Fig 17) with few lymphocytes at the periphery (“naked” granulomas).<sup>257</sup> Sometimes calcification develops on these sarcoidal granulomas,<sup>261</sup> and in some cases small areas of necrosis may appear at their center, raising the differential diagnosis with tuberculosis.<sup>262</sup> This variant of panniculitis does not result from a deep extension into the subcutaneous fat from a dermal



**Fig 17.** Histopathologic features of subcutaneous sarcoidosis. **A**, Scanning power shows several discrete collections of inflammatory cells scattered within the fat lobules. Note sparing of the dermis. **B**, Higher magnification demonstrates that each collection of inflammatory cells consisted of small noncaseating granuloma within the fat lobule. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)



**Fig 18.** Histopathologic features of late stage lesions of traumatic panniculitis. This lesion corresponds to the so-called nodular cystic fat necrosis or mobile encapsulated lipoma. **A**, Scanning power shows encapsulated and well-circumscribed lesion with no inflammatory infiltrate (*arrow* indicates area enlarged in **B**). **B**, At periphery of the lesion necrotic adipocytes appear as anucleated fat cells. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

sarcoidosis, and subcutaneous sarcoidosis is an inflammatory disorder exclusively involving the subcutaneous fat. Sometimes there is also an accompanying superficial and deep perivascular inflammatory infiltrate of lymphocytes in the dermis.

Treatment of subcutaneous sarcoidosis is the same as that for sarcoidosis in general, and systemic corticosteroids have been shown to be the most effective therapy.

### Traumatic panniculitis

Traumatic panniculitis may result from accidental blunt trauma in several areas of the skin. Traumatic panniculitis is especially frequent in women with large breasts, in which the excessive breast weight favors the trauma of the mammary subcutaneous fat. Clinically, lesions of mammary traumatic panniculitis appear as indurated nodules deeply situated on the breast tissue that are covered by normal skin or, occasionally, the skin surface shows an “orange peel” appearance, raising the differential diagnosis of breast cancer.<sup>263,264</sup> Lesions of traumatic panniculitis involving the breasts usually resolve, leaving areas of lipoatrophy. Another frequent location for lesions of traumatic panniculitis is the shin, where erythematous tender subcutaneous nodules appear after minor trauma. Traumatic factitial panniculitis has also been described as a self-inflicted panniculitis due to blunt trauma on the forearm and dorsum of the hand (*l'œdème bleu*).<sup>265</sup> Less common variants of traumatic panniculitis include lesions in children involving the face,<sup>266</sup> and panniculitis lesions on points of cupping or places where acupuncture tech-

niques have been performed for relief of pain.<sup>267</sup> The process known as lipoatrophia semicircularis may also be considered a variant of traumatic panniculitis. This presents as semicircular bandlike atrophy of the subcutaneous fat that involves half of the circumference of the anterolateral aspects of the thighs of women who repeatedly knock their thighs against a desk or chair because of their working habits.<sup>268</sup> Another lesion that may be considered to be a residual stage of traumatic panniculitis is the so-called nodular-cystic fat necrosis, also named mobile encapsulated lipoma and encapsulated fat necrosis. The process consists of well-demarcated movable nodules that appear in the subcutis of lower limbs, elbows, or hips after trauma.<sup>269-274</sup>

Histopathologically, subcutaneous nodules of traumatic fat necrosis show cystic spaces of variable size and shape within fat lobules, as a consequence of confluent necrosis of the fat cells, surrounded by variable degrees of fibrosis and hemorrhage. At the periphery of the cystic spaces, foamy histiocytes and lymphocytes are usually present. In late-stage lesions hemosiderin may be abundant both extracellularly and within the cytoplasm of the macrophages. Histopathologic features of traumatic panniculitis are often seen in the re-excision specimens of cutaneous and subcutaneous tumors, as a consequence of the trauma caused by the original surgical procedure.<sup>275</sup> The so-called *mobile encapsulated lipomas* are lesions totally or nearly totally encapsulated by thin, fibrous tissue that contain well-preserved adipocytes with no evidence of inflammatory infiltrate. At the periphery of the lesions, necrotic

adipocytes in the form of anucleated fat cells (Fig 18) are usually seen.<sup>274</sup> The process seems to be related to trauma, rapid vascular insufficiency, and subsequent fibrous capsule formation. As in other forms of residual lobular panniculitis, membranocystic or lipomembranous changes have been also described in lesions of mobile encapsulated lipoma.<sup>276</sup> At first glance, mobile encapsulated lipoma closely resembles lipoma, but close scrutiny reveals the absence of nuclei in well-preserved but necrotic adipocytes at the periphery of the lesion.<sup>274</sup>

### Lipoatrophy

Atrophy of the subcutaneous fat may result from two different processes from a pathogenic point of view: lipoatrophy and lipodystrophy. Lipoatrophy refers specifically to a loss of subcutaneous fat due to a previous inflammatory process involving the subcutis. In contrast, lipodystrophy means an absence of subcutaneous fat with no evidence of inflammation. Lipodystrophy may be congenital or acquired and clinical variants include total, partial, and localized forms of lipodystrophy.<sup>127,277</sup> It has been suggested that the so-called lipedema, characterized by the abnormal deposition of subcutaneous fat in the legs associated with edema, is a type of lipodystrophy.<sup>278</sup>

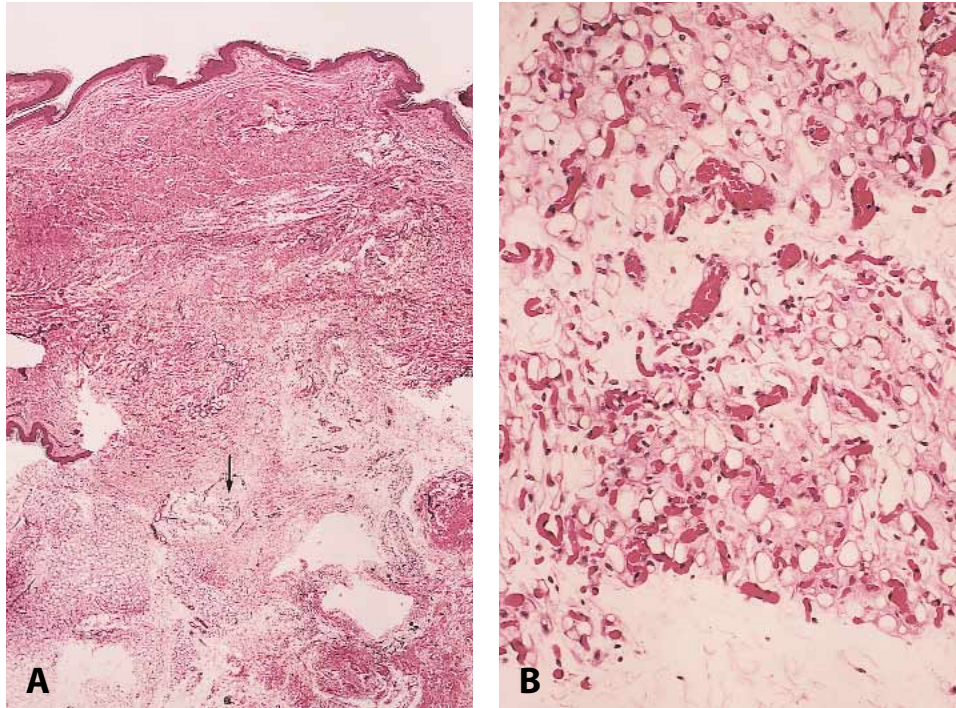
Localized lipoatrophy has received different names according to its clinical appearance and location, including annular lipoatrophy,<sup>279</sup> abdominal lipoatrophy,<sup>280</sup> semicircular lipoatrophy,<sup>281</sup> and postinjection localized lipoatrophy.<sup>282,283</sup> Lesions of localized lipoatrophy have been described as residual lesions of different types of panniculitis,<sup>127,284-287</sup> as well as at the points of injection of different drugs including antibiotics,<sup>288</sup> corticosteroids,<sup>283,288-291</sup> insulin,<sup>292-296</sup> vasopressin,<sup>297</sup> and human growth hormone.<sup>298</sup> Localized lipoatrophy secondary to pressure and compression by tight-fitting clothes has been described near the ankles,<sup>299-301</sup> on the thighs,<sup>268,281,302</sup> over the sacrum,<sup>303</sup> on abdominal skin,<sup>280,304-308</sup> and on the extremities.<sup>309,310</sup>

In contrast, fully developed lesions of lipodystrophy show total absence of subcutaneous tissue with no evidence of inflammation, although some authors have postulated an early inflammatory stage in lipodystrophy lesions.<sup>311-313</sup> Total lipodystrophy consists of a complete congenital or acquired loss of subcutaneous tissue involving all body surfaces. Acquired total lipodystrophy is usually associated with hepatomegaly, hyperglycemia, hyperlipemia, hypermetabolism, and other endocrinologic and metabolic disorders.<sup>127</sup> Partial lipodystrophy usually begins on the face and is manifested by a symmetric loss of facial fat with or without atrophy of the subcutaneous fat of the arms and upper trunk. This

process is named cephalothoracibrachial lipodystrophy.<sup>314</sup> However, there are forms of partial lipodystrophy sparing the face,<sup>315</sup> unilateral variants of facial lipodystrophy<sup>316</sup> (some of them related to *Borrelia burgdorferi* infections<sup>317</sup>), and localized lipodystrophy involving only the subcutaneous fat of the abdominal wall<sup>318</sup> or the neck.<sup>319</sup> Some patients with partial lipodystrophy present associated immunologic anomalies or autoimmune diseases, including low levels of complement,<sup>127,320</sup> membranoproliferative glomerulonephritis,<sup>320,321</sup> systemic lupus erythematosus,<sup>322</sup> scleroderma,<sup>323</sup> dermatomyositis,<sup>324,325</sup> sicca syndrome,<sup>326</sup> Sjögren's syndrome,<sup>327</sup> high titers of thyroid autoantibodies,<sup>328</sup> and recurrent infections.<sup>127</sup>

From a histopathologic point of view, lipoatrophy is a residual process of several inflammatory conditions involving the subcutaneous fat lobules. In most cases the histopathologic findings are those of lipophagic granuloma surrounding a small fat lobule, with perilobular fibrosis. In those cases of lipoatrophy secondary to subcutaneous injections of corticosteroids, two different histopathologic patterns have been described.<sup>288</sup> Both patterns are characterized by the small size of the lobules and by the atrophy of the reduced number of adipocytes. The first pattern consists of faintly acidophilic or albuminous small adipocytes that are retracted from the surrounding connective tissue of the septa. These changes are more prominent at the periphery of otherwise histologically normal fat lobules, suggesting that this is an early alteration of the lipoatrophic process. The general configuration of the fat lobule and the smallness of the adipocytes resemble those features of embryonic fat. Inflammatory cells are sparse and blood vessels appear prominent, congestive, and dilated. The second histopathologic pattern seen in lesions of lipoatrophy secondary to subcutaneous injections of corticosteroids is characterized by small atrophic fat cells surrounded by a prominent vasculature (Fig 19). The smallness of the fat lobule and adipocytes, the relative absence of inflammation, and the proliferation of small blood vessels give an angiomatous appearance to the fat lobule.

In fully developed lesions of lipodystrophy there is an absence of subcutaneous fat with deposition of new collagen and with no evidence of inflammation. However, some authors have described an early inflammatory stage in lesions of lipodystrophy, with lymphocytes<sup>311-313</sup> and vascular involvement<sup>284,328</sup> in the fat lobule. Recently, two histopathologic variants of lipodystrophy have been proposed.<sup>329</sup> In the first type, there are prominent involutinal changes in the fat lobule, with small adipocytes and intervening hyaline or myxoid con-



**Fig 19.** Histopathologic features of lipoatrophy secondary to subcutaneous injections of corticosteroids. **A**, Low-power view showed small fat lobules (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates small adipocytes and prominent capillary proliferation, resembling embryonic fat. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

nective tissue and proliferation of small blood vessels. The second type is the inflammatory type because lymphocytes, foamy histiocytes, and plasma cells appear within the small fat lobules with normal-appearing adipocytes and vasculature. Usually, cases of lipodystrophy with the second histopathologic pattern show multiple areas of localized lipodystrophy and direct immunofluorescence studies demonstrate immunoreactants in the blood vessel walls or in the basement membrane zone of the dermoepidermal junction. It is uncertain, however, whether or not these two patterns represent two different stages of a single process.

Treatment of localized lipoatrophy secondary to lesions of panniculitis is disappointing. Some improvement has been reported with oral and topical corticosteroids,<sup>277</sup> but it is questionable whether the effect is due to corticosteroids or to spontaneous improvement of the lesions with time. In some cases in which residual lipoatrophy led to important cosmetic deformity, improvement was achieved with reconstructive surgery.<sup>285</sup> Lipodystrophy also shows poor response to treatment. In localized forms, the lesions tend to recede over time, restoring some of the lost subcutaneous tissue.

### Subcutaneous fat necrosis of the newborn

Subcutaneous fat necrosis of the newborn is a rare variant of lobular panniculitis that appears in newborns during the first days of life.<sup>330,331</sup> Clinically, the lesions consist of indurated plaques or subcutaneous nodules with a predilection for the buttocks (Fig 20), shoulders, cheeks, and thighs.<sup>332-334</sup> Often, infants affected by subcutaneous fat necrosis of the newborn have hypercalcemia of unknown significance.<sup>335-345</sup> Other etiologic factors that have been postulated in relationship with subcutaneous fat necrosis of the newborn include obstetric trauma<sup>330,331</sup> and induced hypothermia for cardiac surgery.<sup>346-348</sup> Rare examples of subcutaneous fat necrosis of the newborn have been described after prostaglandin E administration,<sup>344</sup> in newborn infants with brown fat deficiency,<sup>349</sup> in infants with serum abnormalities of lipids and lipoproteins,<sup>350</sup> in newborns from mothers who used cocaine during pregnancy,<sup>351</sup> as a consequence of the intrapartum administration of calcium channel blockers,<sup>352</sup> and in association with thrombocytopenia.<sup>353</sup> The newborn has a relatively large body surface in comparison with weight and a greater ratio of saturated to unsaturated fatty acids than in adult fat, and these



**Fig 20.** Subcutaneous fat necrosis of the newborn. Indurated plaques on the buttocks of a newborn.

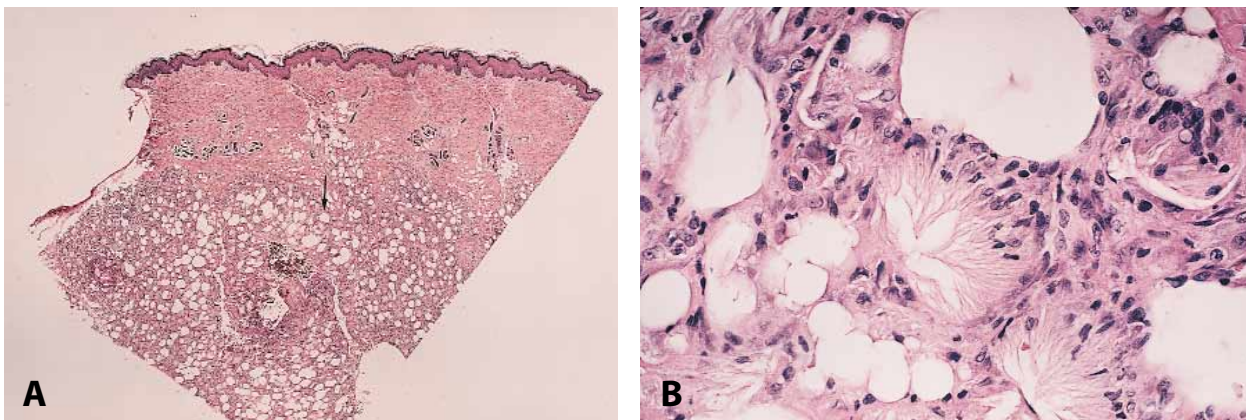
two factors favor the release of hydrolases that induce breakdown of unsaturated fatty acids caused by minor trauma.<sup>330</sup> Usually, cutaneous lesions of subcutaneous fat necrosis of the newborn develop during the first days of life, although cases with congenital and ulcerated lesions that were already present at delivery have also been described.<sup>354</sup> In an example of subcutaneous fat necrosis of the newborn, the cutaneous lesions appeared simultaneously with an episode of acute pancreatitis.<sup>355</sup> There is a report describing lesions of sclerema neonatorum and subcutaneous fat necrosis of the newborn in the same patient,<sup>356</sup> but usually these two variants of panniculitis of the newborn appear in infants with completely different clinical situations.

Histopathologically, most of the cases of subcutaneous fat necrosis of the newborn show characteristic findings. They consist of a mostly lobular panniculitis,

with a dense inflammatory infiltrate composed of lymphocytes, histiocytes, lipophages, multinucleated giant cells, and sometimes eosinophils interspersed among the adipocytes of the fat lobule. Many adipocytes are replaced by cells with finely eosinophilic granular cytoplasm that contain narrow needle-shaped clefts radially arranged (Fig 21). These needle-shaped clefts represent crystals of triglycerides of the adipocytes. Some of these clefts may also be seen within the cytoplasm of multinucleated giant cells.<sup>330,357-359</sup> The needle-shaped crystals in radial fashion within the cytoplasm of adipocytes and histiocytes are quite characteristic of subcutaneous fat necrosis of the newborn. They are not exclusive, however, because they have also been described in lesions of sclerema neonatorum and post-steroid panniculitis. Furthermore, in some cases of stereotypical examples of subcutaneous fat necrosis of the newborn, serial sections through the block did not demonstrate these clefts.<sup>346</sup> In late-stage lesions there is septal fibrosis and areas of calcification may appear within the fat lobule.

Histopathologic differential diagnosis with lesions of sclerema neonatorum is straightforward because lesions of subcutaneous fat necrosis of the newborn show a dense inflammatory infiltrate of histiocytes and lymphocytes in the fat lobules. In lesions of sclerema neonatorum, the inflammatory infiltrate is characteristically lacking.<sup>360</sup>

In contrast to sclerema neonatorum, infants with subcutaneous fat necrosis of the newborn have an excellent prognosis and the subcutaneous plaques and nodules spontaneously regress in a few days with no sequelae. Recently, etidronate, a diphosphonate, has been proposed as effective treatment for the associated hypercalcemia that frequently



**Fig 21.** Histopathologic features of subcutaneous fat necrosis of the newborn. **A**, Scanning power shows a mostly lobular panniculitis (arrow indicates area enlarged in **B**). **B**, Higher magnification demonstrated narrow needle-shaped clefts radially arranged and surrounded by histiocytes. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

appears in infants with subcutaneous fat necrosis of the newborn.<sup>361</sup>

### Poststeroid panniculitis

Poststeroid panniculitis is another rare variant of mostly lobular panniculitis that has been reported in children who were receiving high doses of systemic corticosteroids and in whom the doses were decreased quickly or steroid therapy was suddenly withdrawn. The reasons why these infants received high doses of systemic corticosteroids were variable, including rheumatic fever, leukemia, nephrotic syndrome, and cerebral edema.<sup>362-370</sup>

Clinically, cutaneous lesions of poststeroid panniculitis consist of erythematous subcutaneous nodules that appear 1 to 10 days after cessation of high doses of systemic corticosteroids. Because the lesions develop mostly in those areas in which steroids induced the greatest accumulation of fat, subcutaneous nodules of poststeroid panniculitis appear mostly on the cheeks.

Histopathologically, lesions of poststeroid panniculitis show features similar to those of subcutaneous fat necrosis of the newborn. They consist of a mostly lobular panniculitis with an inflammatory infiltrate of foamy histiocytes and lymphocytes involving the fat lobules. Often, narrow strands of needle-shaped clefts are evident within the cytoplasm of some histiocytes,<sup>370</sup> although usually they are not as numerous as in subcutaneous fat necrosis of the newborn.

Lesions of poststeroid panniculitis gradually resolve during some weeks with no long-standing complications, except when ulceration occurs, leaving atrophic scars on the cheeks of the infant. If the diagnosis is established in early stages, readministration of high doses of systemic corticosteroid is indicated and then a slower and gradual decrease of the dose should be programmed.

### Gout panniculitis

Patients with hyperuricemia may show urate crystal deposition in the fat lobule of the subcutis. As in tophus, urate crystals causing lobular panniculitis show a needle-like shape, have a tendency to form sheaves, and are doubly refractile under polarized light. Surrounding the urate crystals of the fat lobule is a granulomatous reaction with macrophages and many multinucleated giant cells.<sup>371,372</sup>

### Crystal-storing histiocytosis

Crystal-storing histiocytosis is a rare disease in which aggregations of histiocytes containing crystalline deposits of immunoglobulins are seen in the subcutaneous fat. Crystal-storing histiocytosis appear-

ing as a lobular panniculitis has been described in a patient with lymphoblastic lymphoma.<sup>373</sup>

### Cytophagic histiocytic panniculitis

Two different processes are included under the term *cytophagic histiocytic panniculitis*; one is an authentic panniculitis, namely cytophagic histiocytic panniculitis, whereas the other one is a lymphoma with clinical appearance of panniculitis. The preferred term for the latter is subcutaneous "panniculitic" lymphoma. This is a high-grade aggressive lymphoma, nearly always with cytotoxic T-cell immunophenotype.<sup>374</sup> These two processes differ from the etiologic, clinical, histopathologic, and biologic behavioral aspects.

Cytophagic histiocytic panniculitis was first described as a distinct entity by Winkelmann and Bowie<sup>375</sup> in 1980. They proposed the following histopathologic criteria: a mostly lobular panniculitis with inflammatory infiltrate in the fat lobules composed of histiocytes and mature T lymphocytes, and with cytophagocytosis that results from macrophages that contain intact or fragmented erythrocytes, leukocytes, or lymphocytes within their cytoplasm, which produce the so-called "bean-bag" cells. In our review of the literature, we have found approximately 40 well-documented cases of cytophagic histiocytic panniculitis.<sup>374-404</sup> An additional case considered to be sinus histiocytosis and massive lymphadenopathy (Rosai-Dorfman disease) showed lesions of lobular panniculitis with cytophagocytosis on the lower extremities and most likely represents an additional example of cytophagic histiocytic panniculitis.<sup>405</sup>

Patients with cytophagic histiocytic panniculitis have a prolonged clinical course of the disease that lasts years and usually ends in a terminal state characterized by fever, hepatosplenomegaly, and pancytopenia secondary to hemocytophagocytosis involving the bone marrow.\* However, there are also well-documented examples of cytophagic histiocytic panniculitis with a benign clinical behavior, even after a long follow-up period ranging from 7 months to 28 years.† Genotypic studies on the lymphoid cells involving the subcutaneous fat lobule did not demonstrate monoclonality in either early disease or in the terminal phase,<sup>374</sup> and no evidence of latent or active Epstein-Barr virus (EBV) infection as determined by in situ hybridization or serologic studies has been found in these cases.<sup>374</sup> Most of the patients with cytophagic histiocytic panniculitis show favorable response to immunosuppressive therapy with prednisone<sup>389,391,395,404</sup> or cyclosporine.<sup>388,395,397,401</sup>

\*References 376, 377, 379-381, 384, 385, 390, 392, 393, 403.

†References 383, 386-388, 391, 394-399, 401, 402, 404, 405.

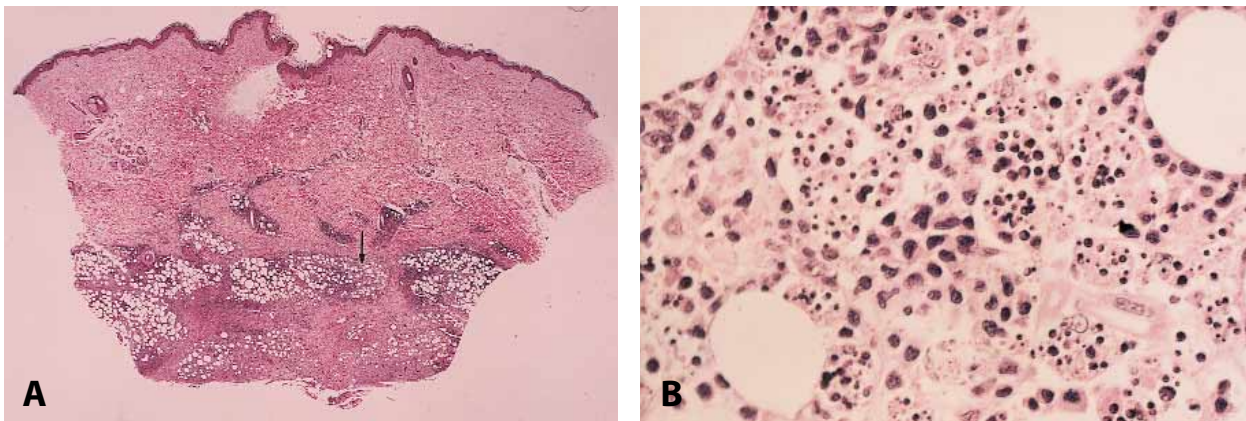


**Fig 22.** Subcutaneous T-cell lymphoma. Erythematous plaques and nodules on anterior aspect of the legs.

In contrast, subcutaneous “panniculitic” lymphoma is not a panniculitis, but a malignant neoplastic proliferation of T lymphocytes that involves the subcutaneous fat lobules, resulting in cutaneous

lesions with the clinical appearance of panniculitis (Fig 22). Histopathologically, neoplastic lymphocytes involving the fat lobule show marked atypia, with large and hyperchromatic nuclei, karyorrhexis, and frequent atypical mitotic figures. Often atypical lymphocytes form a ring surrounding necrotic adipocytes (Fig 23). There are also histiocytes showing cytophagocytosis that involve not only the subcutaneous fat, but also the bone marrow. Most of the patients with subcutaneous “panniculitic” lymphoma have a short clinical course with early death despite aggressive treatment with chemotherapy or radiotherapy, or both. Approximately 40 cases of subcutaneous “panniculitic” lymphoma have been described in the literature.<sup>374,406-426</sup> Immunohistochemical studies have demonstrated that atypical lymphoid cells have a cytotoxic T-cell phenotype. Most of the neoplastic lymphocytes express CD3, CD8, and cytotoxic granular proteins (TIA-1 and perforin) and lack expression of CD4.<sup>409,411,417-420</sup> In rare instances, subcutaneous “panniculitic” lymphoma showing a B-cell immunophenotype of the neoplastic lymphocytes has been described.<sup>427-430</sup> All but one case<sup>416</sup> of subcutaneous “panniculitic” lymphoma in which evidence of latent or active EBV infection has been investigated by serology, in situ hybridization, or PCR techniques yielded positive results.<sup>374,410,422,423,427</sup> Those cases of subcutaneous “panniculitic” lymphoma in which genotypic studies have been performed showed monoclonality of the atypical lymphocytes involving the fat lobule.<sup>409,410,413-416,422</sup>

In summary, cytophagic histiocytic panniculitis and subcutaneous “panniculitic” lymphoma are two



**Fig 23.** Histopathologic features of subcutaneous T-cell lymphoma. **A**, At scanning magnification lesion appears as a mostly lobular panniculitis (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates atypical lymphocytes, some of them forming ring around necrotic adipocytes (upper right corner) and large macrophages with cytophagocytosis, so-called “bean-bag cells.” (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 400$ .)



different pathologic processes, that is, the former is a lobular panniculitis and the latter is a malignant lymphoma. These two different diseases have in common a histopathologic finding, namely, the presence of cytophagocytosis in the subcutaneous fat that may also extend to the bone marrow. Patients with cytophagic histiocytic panniculitis have no evidence of latent or active EBV infection and show a prolonged clinical course, whereas patients with subcutaneous “panniculitic” lymphoma have serologic and/or genotypic evidence of EBV infection and the lymphoproliferative process shows an aggressive biologic behavior with early death.

The patients recently described by Ruiz-Maldonado et al<sup>431</sup> with “edematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential” probably represent examples of subcutaneous “panniculitic” lymphoma in children, and 3 of the 4 cases in which in situ hybridization investigation for EBV infection has been performed showed positive results.<sup>432</sup>

#### **Postirradiation pseudosclerodermatous panniculitis**

Winkelmann et al<sup>433</sup> recently described 4 cases of women with breast cancer that was treated by radical mastectomy and radiotherapy. These patients developed indurated erythematous plaques on the irradiated skin 1 to 6 months after radiotherapy. Histopathologic study showed hyalin collagen bundles in the dermis and subcutaneous septa and an inflammatory infiltrate of lymphocytes and plasma cells involving the fat lobules. In some areas, lipophagic granuloma was seen at the periphery of the fat lobule. The authors named these lesions “postirradiation pseudosclerodermatous panniculitis.”

### **DISORDERS ERRONEOUSLY CONSIDERED AS SPECIFIC VARIANTS OF PANNICULITIS (Table II)**

#### **Weber-Christian disease**

Weber-Christian disease is the term that has been classically used to refer to cases of mostly lobular panniculitis without vasculitis and systemic manifestations including fever and involvement of visceral fat tissue. Additional terms such as *idiopathic nodular panniculitis*, *nodular panniculitis*, and *relapsing febrile nonsuppurative nodular panniculitis* have been used as synonyms for Weber-Christian disease. The first cases of Weber-Christian disease as a distinct entity were described at the end of the 19th century and the beginning of the 20th century,<sup>434-436</sup> and similar cases appeared in the literature shortly afterward.<sup>437-444</sup> However, many cases originally considered as examples of Weber-Christian disease were

**Table II.** Disorders erroneously considered as specific variants of panniculitis

- 
- Weber-Christian disease
  - Rothmann-Makai disease
  - Lipomembranous or membranocystic panniculitis
  - Eosinophilic panniculitis
- 

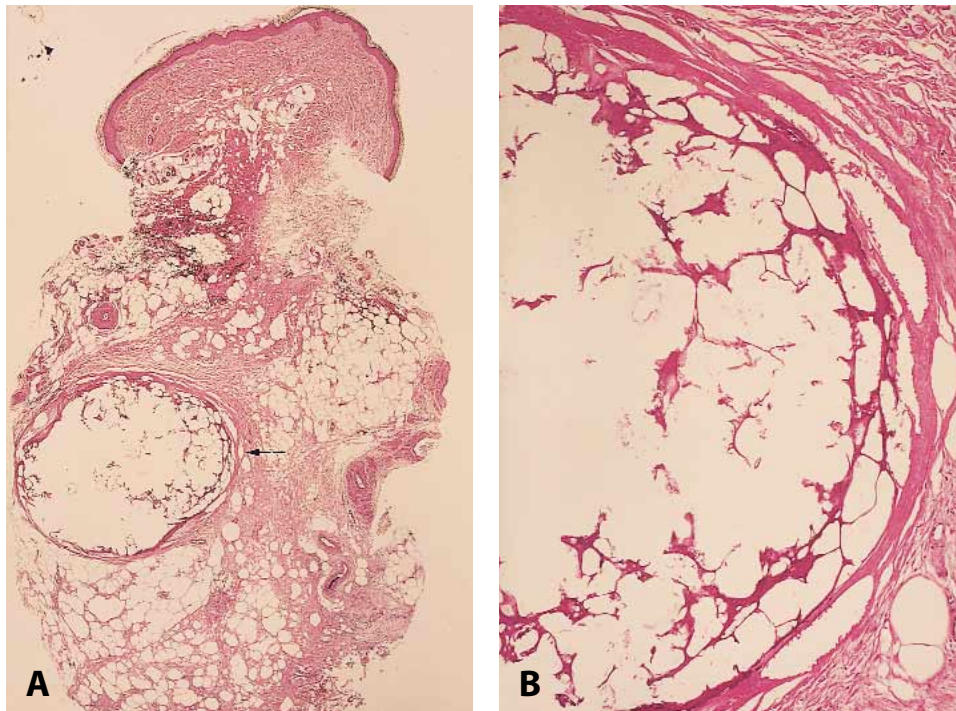
later reclassified when other variants of lobular panniculitis, including erythema induratum of Bazin (nodular vasculitis), pancreatic panniculitis, and  $\alpha_1$ -antitrypsin deficiency panniculitis, were separated as specific diseases. Currently many cases of lobular panniculitis may be attributed to specific causes, and, although some textbooks of dermatology<sup>445,446</sup> and dermatopathology<sup>37,447</sup> still include a section dedicated to Weber-Christian disease, most authors believe that Weber-Christian disease should no longer be considered a distinctive entity.<sup>445-447</sup> An interesting recent report on this topic is that of White and Winkelmann,<sup>448</sup> who reviewed the clinical and histopathologic features of 30 cases of panniculitis previously diagnosed as Weber-Christian disease at the Mayo Clinic. A review of the biopsy specimens of these 30 patients led to the conclusion that 12 cases were actually examples of erythema nodosum, 6 cases corresponded to superficial thrombophlebitis, 5 cases were reclassified as factitial panniculitis, 3 cases were traumatic panniculitis, 1 case was cytophagic histiocytic panniculitis, 1 case turned out to be subcutaneous “panniculitic” lymphoma, and 1 case resulted from subcutaneous involvement by leukemia. The authors concluded that the term *Weber-Christian disease* should be abandoned as a diagnosis for cases of lobular panniculitis because now a more specific diagnosis may be rendered in most cases. We agree with them.

#### **Rothmann-Makai disease**

Rothmann-Makai disease was the term used in the past to describe cases of relapsing nodular panniculitis similar to that of Weber-Christian disease, but with no fever or other systemic manifestations.<sup>449,450</sup> Rothmann-Makai disease is also an obsolete term that is no longer used.

#### **Lipomembranous or membranocystic panniculitis**

Lipomembranous panniculitis was first described by Nasu, Tukahara, and Terayama<sup>451</sup> in 1973 as “membranous lipodystrophy.” The authors considered the process as a specific and hereditary form of lobular panniculitis associated with anomalies of the long bones and neuropsychiatric manifestations.



**Fig 24.** Histopathologic features of so-called lipomembranous or membranocystic panniculitis. **A**, Scanning power shows cystic structure in the fat lobule (*arrow* indicates area enlarged in **B**). **B**, Higher magnification demonstrates that eosinophilic membrane lined the cystic space with reticulated projections into the cystic cavity. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 200$ .)

However, cases with identical histopathologic findings were described shortly afterwards in late-stage lesions of several variants of lobular panniculitis; thus the term *lipomembranous* or *membranocystic fat necrosis* was proposed to refer these histopathologic features in different types of panniculitis. These findings consist of cystic spaces in the fat lobule that result from necrosis of the adipocytes. The cystic spaces are lined with a homogeneous eosinophilic membrane with convoluted projections into the cystic cavity (Fig 24). These intracystic papillary projections stain brightly with periodic acid–Schiff and Sudan black and are resistant to diastase.<sup>452–454</sup> A case of lipomembranous fat necrosis showing myspherulosis, which consists of small bag structures containing tingible bodies that represent degenerated erythrocytes by lipids from adipocytes, has been recently described.<sup>455</sup>

Lipomembranous fat necrosis seems to be especially frequent in late-stage lesions of sclerosing panniculitis,<sup>63</sup> although identical histopathologic findings have also been described in lesions of neutrophilic lobular panniculitis associated with rheumatoid arthritis,<sup>10</sup> erythema nodosum,<sup>135</sup> deep morphea,<sup>452</sup> lupus panniculitis,<sup>134</sup> traumatic panni-

culitis,<sup>266</sup> panniculitis associated with dermatomyositis,<sup>142,456</sup> subcutaneous “panniculitic” lymphoma,<sup>457</sup> septal<sup>458</sup> and lobular<sup>459</sup> panniculitis associated with Behçet’s syndrome, arterial ischemia<sup>460</sup> and venous insufficiency<sup>63,65,66,461</sup> of the lower extremities, and diabetic microangiopathy.<sup>462,463</sup> Some authors distinguish between a primary lipomembranous panniculitis, when only the cystic structures are seen in the fat lobules, and secondary lipomembranous panniculitis when additional histopathologic features of a more specific variant of lobular panniculitis are present.<sup>276,453,454</sup> Probably, those cases considered to be primary lipomembranous panniculitis represent late-stage lesions of different types of lobular panniculitis and therefore are also examples of secondary lipomembranous panniculitis in which no other more specific histopathologic findings may be identified. In our opinion, the so-called lipomembranous or membranocystic panniculitis is a histopathologic pattern, but not a specific variant of panniculitis.

#### **Eosinophilic panniculitis**

Eosinophilic panniculitis is the term used to refer to those cases of septal or lobular panniculitis in

which eosinophils predominate in the inflammatory infiltrate. Eosinophilic panniculitis is also a histopathologic pattern rather than a distinct entity. It has been described in several types of panniculitis and other inflammatory disorders involving the skin, including erythema nodosum, deep insect bites, narcotic dependency with injection granuloma, asthma, atopic dermatitis, psychiatric diseases, thyroid diseases, parotitis, glomerulonephritis, sarcoidosis, bacterial infections, infestation with the parasites *Gnathostoma* and *Toxocara canis*, leukocytoclastic vasculitis, systemic vasculitis, Well's syndrome, lupus panniculitis, deep morphea, Sjögren's syndrome, T- or B-cell lymphoma, leukemia, and solid neoplasms.<sup>133,464-470</sup> This wide spectrum of disparate disorders indicates that eosinophilic panniculitis is a nonspecific reactive process, and the presence of eosinophils in the subcutaneous fat should be followed by pertinent clinical and laboratory investigations to rule out an associated systemic process.<sup>468</sup>

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## Answers to CME examination

Identification No. 801-109

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Questions 1-30, Requena L, Sánchez Yus E. *J Am Acad Dermatol* 2001;45:325-61.

- |       |       |
|-------|-------|
| 1. b  |       |
| 2. b  | 17. a |
| 3. e  | 18. e |
| 4. d  | 19. c |
| 5. c  | 20. b |
| 6. e  | 21. c |
| 7. e  | 22. b |
| 8. c  | 23. d |
| 9. b  | 24. e |
| 10. e | 25. e |
| 11. e | 26. e |
| 12. e | 27. d |
| 13. a | 28. e |
| 14. e | 29. b |
| 15. d | 30. e |
| 16. e |       |

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Answer sheets are bound into the Journal for US, Canadian, and life members. Request additional answer sheets from American Academy of Dermatology, Member Services Department, PO Box 4014, Schaumburg, IL 60168-4014. Phone 847-330-0230; E-mail: tsmith@aad.org

## CME examination

Identification No. 801-109

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Requena L, Sánchez Yus E. *J Am Acad Dermatol* 2001;45:325-61.

*Directions for questions 1-30: Give single best response.*

- The most effective treatment for patients with erythema nodosum leprosum is
  - dapsone
  - thalidomide
  - clofazimine
  - corticosteroids
  - none of the above
- Which of the following statements regarding neutrophilic lobular panniculitis associated with rheumatoid arthritis is correct?
  - It is a rare variant of panniculitis only described in men with rheumatoid arthritis.
  - The lesions consist of subcutaneous nodules on the lower extremities with tendency to ulceration.
  - The nodules of the panniculitis appear in early stages of rheumatoid arthritis.
  - Vasculitis has not been described in lesions of neutrophilic lobular panniculitis associated with rheumatoid arthritis.
  - It is more frequent than erythema nodosum in patients with rheumatoid arthritis.
- Each of the following features has been described in cutaneous lesions of erythema induratum of Bazin *except*
  - erythrocyanosis
  - heavy column-like calves
  - erythema surrounding follicular openings
  - cutis marmorata
  - hyperkeratotic lesions
- Each of the following statements is true in erythema induratum of Bazin *except*
  - it is a disease mostly of middle-aged women
  - the posterior aspects of the lower legs are the most frequently involved areas
  - subcutaneous lesions often heal with atrophy and scarring
  - ulceration of the lesions develops mostly during warm summer months
  - the course of the disease is protracted with frequent recurrences
- Each of the following statements is true in lesions of erythema induratum of Bazin *except*
  - DNA of *Mycobacterium tuberculosis* has been demonstrated by polymerase chain reaction in the lesions
  - the lesions consist of a mostly lobular panniculitis with vasculitis
  - Ziehl-Neelsen stain often demonstrates *M tuberculosis* in the lesions
  - caseous necrosis is seen in the fat lobule when intense vascular damage is present
  - involvement of veins and arteries has been described in lesions of erythema induratum of Bazin
- From a histopathologic point of view, each of the following statements is true in erythema induratum of Bazin *except*
  - in early lesions, neutrophils are seen punctuated throughout the fat lobule
  - it is a mostly lobular panniculitis
  - fully developed lesions show extensive necrosis of the adipocytes of the fat lobule
  - fully developed lesions show tuberculoid granulomas in the fat lobule
  - vasculitis is always seen in biopsy specimens of erythema induratum of Bazin
- Each of the following therapies has been shown to be effective for erythema induratum of Bazin *except*
  - tuberculostatic drugs
  - potassium iodide
  - supporting bandages
  - nonsteroidal anti-inflammatory drugs
  - intense physical activity
- Each of the following statements is true in Crohn's disease *except*
  - the histopathologic features of cutaneous lesions are similar to those of the bowel lesions

- b. the clinical appearance of the lesions of Crohn's disease involving the lower extremities is similar to that of erythema nodosum
  - c. the histopathologic features of the subcutaneous lesions of Crohn's disease consist of tuberculous granulomas with central caseous necrosis
  - d. subcutaneous nodules of Crohn's disease usually appear when there is active bowel disease
  - e. subcutaneous nodules of Crohn's disease regress when the bowel disease improves
9. Which of the following mechanisms seems to be the most important pathogenic factor in sclerosing panniculitis?
- a. Acid-fast bacteria
  - b. Chronic venous insufficiency of the lower extremities
  - c. Vasculitis involving blood vessels of the septa of the subcutaneous fat
  - d. Vasculitis involving small blood vessels of the fat lobule
  - e. Sclerosis of the collagen bundles of the septa of the subcutaneous fat
10. Each of the following histopathologic features has been described in lesions of sclerosing panniculitis *except*
- a. changes of stasis dermatitis in the superficial dermis
  - b. ischemic necrosis at the center of the fat lobule
  - c. congested small blood vessels of the fat lobule
  - d. lipophagic granuloma at the periphery of the fat lobule
  - e. Miescher's radial granuloma in the septa of subcutaneous fat
11. Regarding calciphylaxis,
- a. it usually appears in patients with end-stage chronic renal failure
  - b. most patients have normal serum levels of calcium and phosphorus
  - c. most patients have secondary hyperparathyroidism
  - d. necrosis of the penis has been described in patients
  - e. *a, c, and d*
12. In the treatment of primary oxalosis
- a. kidney transplantation is usually followed by permanent improvement of the disease
  - b. kidney transplantation must be performed even with normal renal function
  - c. large volumes of fluid, alkalinization, and medications to minimize the oxalate formation are helpful to retain renal function as long as possible
  - d. kidney transplantation should be combined with hepatic transplantation to revert the underlying enzymatic defect
  - e. *c and d* are correct
13. In infants with sclerema neonatorum
- a. the prognosis is usually poor
  - b. cutaneous lesions do not appear until the second month of life
  - c. histopathologic examination of lesions shows intense inflammatory infiltrate of histiocytes surrounding needle-shaped clefts in the adipocytes
  - d. the fat lobule shows intense necrosis of the adipocytes
  - e. all of the above
14. Lupus panniculitis
- a. appears in approximately 1% to 3% of patients with cutaneous lupus erythematosus
  - b. is more frequent in women than in men
  - c. lesions have predilection for the upper arms, shoulders, face, and buttocks
  - d. may involve the subcutaneous fat of the breast
  - e. all of the above
15. Lymphoid follicles in the subcutaneous fat have been described in each of the following variants of panniculitis *except*
- a. lupus panniculitis
  - b. deep morphea
  - c. panniculitis associated with dermatomyositis
  - d. panniculitis associated with pancreatic disease
  - e. erythema nodosum
16. From a histopathologic point of view, lupus panniculitis
- a. is a mostly lobular panniculitis
  - b. lesions show epidermal and dermal changes of discoid lupus erythematosus in 50% of cases
  - c. frequently shows lymphoid follicles in the subcutaneous fat
  - d. specimens demonstrate a sclerotic appearance of collagen bundles of the subcutaneous septa
  - e. all of the above
17. Each of the following therapies has been demonstrated to be effective for lupus panniculitis *except*
- a. potassium iodide
  - b. topical potent corticosteroids under occlusion
  - c. systemic course of corticosteroids
  - d. hydroxychloroquine
  - e. dapsone
18. Which of the following pancreatic diseases has been associated with pancreatic panniculitis?
- a. Acute pancreatitis
  - b. Chronic pancreatitis
  - c. Pancreatic carcinoma
  - d. Pancreatic pseudocyst
  - e. All of the above
19. Each of the following abnormalities has been described in patients with pancreatic panniculitis *except*
- a. arthritis
  - b. pleural effusions
  - c. thrombocytopenia
  - d. leukemoid reaction
  - e. eosinophilia
20. From a histopathologic point of view, each of the following features has been described in lesions of pancreatic panniculitis *except*
- a. a mostly lobular panniculitis

- b. vasculitis involving small blood vessels of the fat lobule
  - c. intense necrosis of the adipocytes of the fat lobule
  - d. ghost adipocytes that result from coagulative necrosis of the adipocytes and subsequent calcification
  - e. in mature lesions, neutrophils at periphery of the fat lobule
21. Each of the following statements is true in panniculitis associated with  $\alpha_1$ -antitrypsin deficiency *except*
- a. lesions of panniculitis only appear in homozygous patients
  - b. lesions of panniculitis occasionally appear on areas of previous trauma
  - c. lesions of panniculitis show no tendency to ulceration
  - d. lesions of panniculitis may be seen in children and adults
  - e. lesions of panniculitis are mostly located on the lower extremities
22. Each of the following therapies has been reported as being effective for panniculitis associated with  $\alpha_1$ -antitrypsin deficiency *except*
- a. dapsone
  - b. surgical debridement
  - c. supplemental infusions of exogenous  $\alpha_1$ -antitrypsin
  - d. liver transplantation
  - e. none of the above
23. Each of the following microorganisms has been described as a cause of infective panniculitis *except*
- a. *Staphylococcus aureus*
  - b. *Klebsiella*
  - c. *Nocardia* spp
  - d. *Borrelia burgdorferi*
  - e. *Mycobacterium tuberculosis*
24. A biopsy specimen showing lobular panniculitis with the fat lobule replaced by round vacuoles nearly identical in size and shape enclosing round and sharply circumscribed translucent foreign bodies surrounded by sclerotic stroma is due to subcutaneous injection of
- a. povidone
  - b. paraffin
  - c. silicone
  - d. Bioplastique
  - e. Artecoll
25. Each of the following statements is true in subcutaneous sarcoidosis *except*
- a. lesions consist of subcutaneous nodules on the lower extremities
  - b. histopathologically, subcutaneous sarcoidosis is a mostly lobular panniculitis
  - c. histopathologically, subcutaneous nodules of sarcoidosis show small noncaseating granulomas in the fat lobule
  - d. calcification occasionally develops in the granulomas of subcutaneous sarcoidosis
  - e. lesions of subcutaneous sarcoidosis show a tendency to ulceration
26. Infants with subcutaneous fat necrosis of the newborn
- a. usually have a good prognosis
  - b. often have hypercalcemia of unknown origin
  - c. may have mothers who used cocaine during pregnancy
  - d. *a* and *b*
  - e. *a*, *b*, and *c*
27. Each of the following statements is true for subcutaneous fat necrosis of the newborn *except*
- a. it has been described after hypothermia for cardiac surgery
  - b. it has been described after obstetric trauma
  - c. it has been described as being associated with thrombocytopenia
  - d. it has been described in infants with cystic fibrosis of the pancreas
  - e. it has been described as a consequence of intrapartum administration of calcium channel blockers
28. Needle-shaped clefts within the adipocytes have been described in
- a. erythema nodosum
  - b. sclerema neonatorum
  - c. subcutaneous fat necrosis of the newborn
  - d. poststeroid panniculitis
  - e. *b*, *c*, and *d*
29. Patients with subcutaneous "panniculitic" lymphoma
- a. usually have a good prognosis
  - b. usually have evidence of latent or active Epstein-Barr virus infection
  - c. usually have expression of B-cell immunophenotype in neoplastic lymphocytes
  - d. mostly show a favorable response to therapy with prednisone or cyclosporine
  - e. all of the above
30. Lipomembranous fat necrosis
- a. is a specific variant of panniculitis
  - b. is a histopathologic finding in late-stage lesions of different types of panniculitis
  - c. is a hereditary form of lobular panniculitis
  - d. is especially frequent in lesions of sclerosing panniculitis
  - e. *b* and *d*