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Panniculitides of particular interest to the rheumatologist

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Abstract

The panniculitides remain as one of the most challenging areas for clinicians, as they comprise a heterogeneous group of inflammatory diseases involving the subcutaneous fat with potentially-shared clinical and histopathological features. Clinically, most panniculitides present as red edematous nodules or plaques. Therefore, in addition to a detailed clinical history, a large scalpel biopsy of a recent-stage lesion with adequate representation of the subcutaneous tissue is essential to specific diagnosis and appropriate clinical management. Herein we review the panniculitides of particular interest to the rheumatologist.

Keywords: Cutaneous polyarteritis nodosa, Erythema nodosum, Infective panniculitis, Lupus panniculitis, Panniculitis, Subcutaneous tissue, Vasculitis

Background

The panniculitides comprise a heterogeneous group of inflammatory diseases involving the subcutaneous fat. The basic unit of the subcutaneous fat is a cohesive collection of adipocytes called primary microlobule. An aggregation of primary microlobules, termed a secondary lobule, is surrounded by an easily discernible rim of connective tissue known as septum, which house the nerves, the lymphatic vessels, and the arteries and veins of the subcutis. Every adipocyte in the subcutaneous fat is encircled by a capillary [1].

This knowledge is crucial, once classification of the panniculitides is far too complex and often contradictory. From an academic point of view, in this review we have chosen to follow the three-step approach for histopathologic diagnosis of panniculitides. The first step is to classify them as mostly septal (Fig. 1) or lobular (Fig. 2) depending on where the inflammatory cell infiltrate is located. Secondly, is necessary to define if vasculitis is present or not. Finally, the third step is further characterizing the type of the inflammatory cell infiltrate and the presence and pattern of necrosis [2, 3]. Nevertheless, different stages in the evolution of diseases and categories that are not exclusive may lead clinicians to confusion. Therefore, after that initial classification, efforts should be made to look for the additional histopathological findings that may be considered as clues to reach specific diagnoses.

The purpose of this review is to present a comprehensive clinic pathologic overview of the panniculitides of particular interest to the rheumatologist.

Main text

Primarily-septal panniculitides

Primarily-septal panniculitides without vasculitis

Erythema nodosum Erythema nodosum (EN) is the most common clinical form of panniculitis. In children, up to the age of 12 years, the female-to-male ratio is approximately equal, whereas in adults it occurs three to six times more often in woman, usually in the second and third decades of life. EN typically manifest by the sudden onset of multiple painful inflammatory, cutaneous and subcutaneous red nodules, which may assume a deep bruised appearance as they fade, and coalescence-forming plaques. The most common location are the anterior and lateral surfaces of the lower limbs, although the extensor surfaces of the forearm, the thighs, and the trunk may also be affected (Fig. 3a). Systemic symptoms

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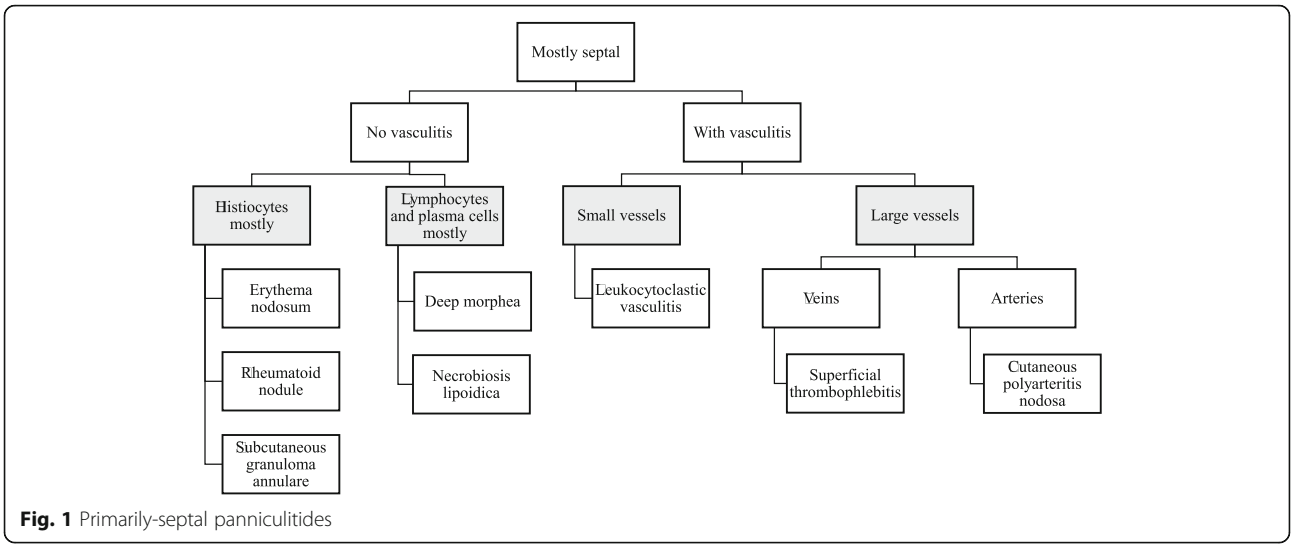

Fig. 1 Primarily-septal panniculitides

such as low-grade fever, fatigue, malaise, arthralgia, are present in more than 30% of the cases. The lesions never ulcerate and resolve spontaneously without leaving scars in approximately two to eight weeks [4, 5]. Currently, it is believed that EN migrans, subacute nodular migratory panniculitis, and chronic EN are clinical variants that may all be included within the spectrum of EN [6].

EN has been regarded a late type hypersensitivity reaction to several antigenic stimuli. The main etiologies are shown in Table 1 and may vary according to the geographic region. Streptococcal infection is a frequent cause of this panniculitis worldwide, especially in children; other potential infectious agents are represented by Epstein-Barr virus, Cytomegalovirus, *Yersinia spp.*, *Mycoplasma*, *Chlamydia*, *Histoplasma* and *Coccidioides*. Due to the elevated prevalence of tuberculosis in Brazil, *Mycobacterium tuberculosis* may be the most important factor in EN in our country. Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, "biological" therapeutic agents (adalimumab, infliximab, imatinib, BRAF inhibitors, and immune checkpoint modulators) [7], and antibiotics, besides a wide group of conditions, which include sarcoidosis, pregnancy, autoimmune disorders, malignancies (mostly Hodgkin's disease), and enteropathies

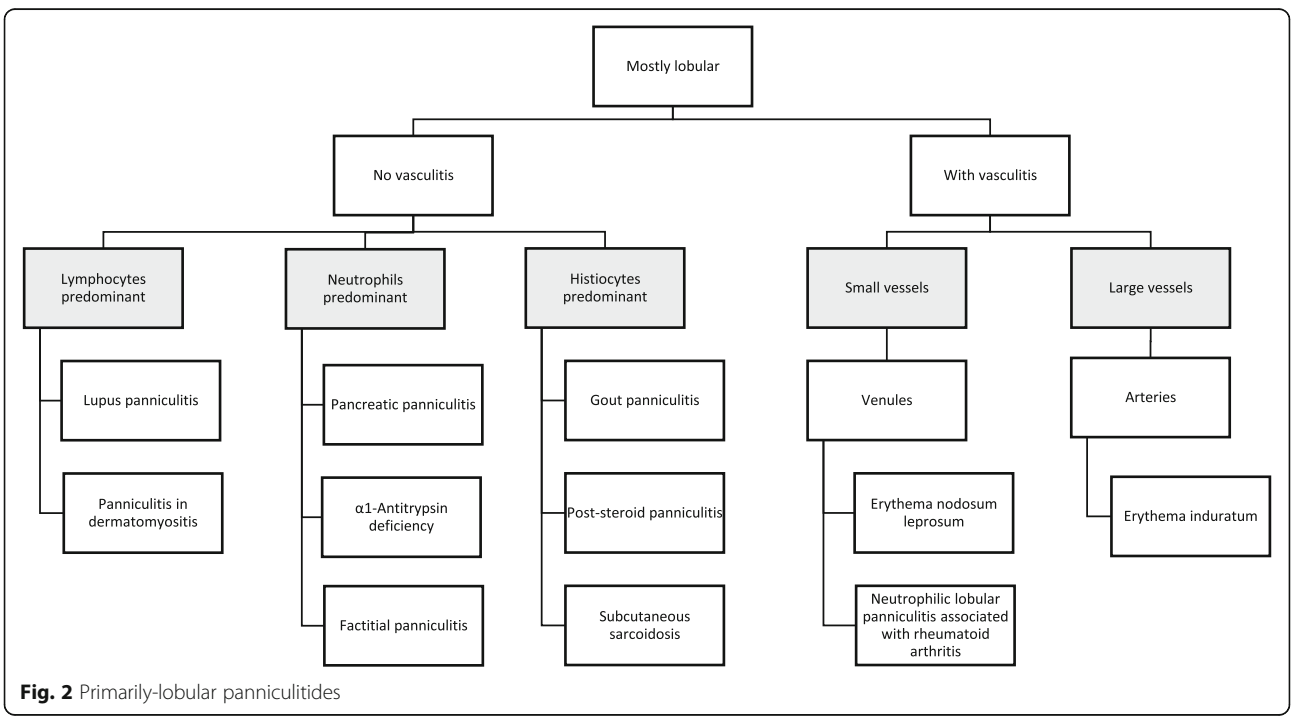

Fig. 2 Primarily-lobular panniculitides

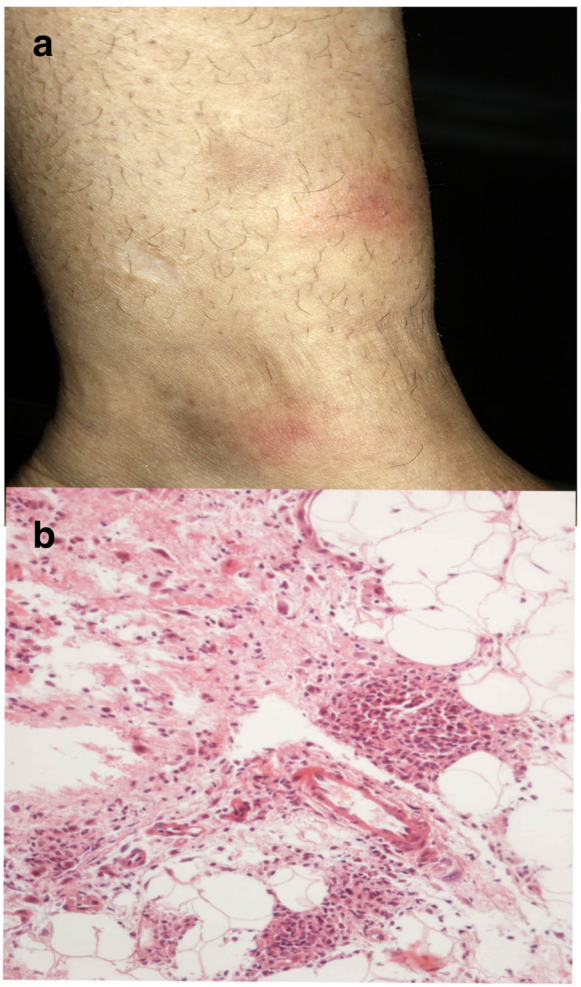

Fig. 3 Erythema nodosum. **a** Red nodules anterior on the anterior aspect of the lower limb. **b** Septal thickening with lymphohistiocytic infiltrate and formation of Miescher radial granulomas at the periphery of the subcutaneous fat lobule. H&E, 400x

(Crohn's disease and ulcerative colitis) can lead to secondary EN [8]. Meanwhile, nearly half of the cases are classified as having idiopathic EN [9, 10].

EN is the paradigm of predominantly septal panniculitides with no vasculitis, although hemorrhages within the small vessels may occur. The composition of the inflammatory infiltrate in the septa varies with the age of the lesion. In early lesions, sparse neutrophils are seen interstitially arranged and at the periphery of fat lobules, together with some foamy macrophages. Fully formed lesions are characterized by septal fibrosis, granulation tissue, lymphocytes and histiocytes, many of them multinucleated [2, 6]. Visualization of the so-called "Miescher radial granulomas", nodular aggregations of histiocytes and neutrophils radially surrounding small blood vessels, is quite characteristic in the histopathological evaluation (Fig. 3b) [4]. Fat lobules are reduced markedly in size.

In contrast, erythema nodosum leprosum (ENL) is an immune-mediated common complication of lepromatous leprosy, occurring in about 50% of these patients. The histology of ENL lesions shows an intense perivascular infiltrate of neutrophils throughout the dermis and subcutis in a lobular pattern often associated with vasculitis [11]. However, macrophage granuloma without neutrophil infiltration occur in up to 35% of the patients. Foamy histiocytes containing large numbers of acid-fast bacilli, known as Virchow cells, are frequently seen in ENL lesions, as they are in lepromatous leprosy [12].

Rheumatoid nodule Almost one-third of the patients with rheumatoid arthritis exhibit skin lesions related to the disease, 98.3% of which are rheumatoid nodules (RNs). RNs develop in patients with long-standing rheumatoid arthritis (RA) and a higher disease activity score compared to patients without skin lesions. Rheumatoid factor positivity is detected in 75% of them. These nodules are commonly located on the metacarpophalangeal and proximal interphalangeal joints, on the olecranon process, and on the

Table 1 Etiologic factors in erythema nodosum

Infections	Pancreatic carcinoma
Streptococcal infections	**Medications**
Mycobacterium tuberculosis	Estrogens/oral contraceptive pills
Gastroenteritis due to *Yersinia, Salmonella, and Campylobacter*	Penicillin
Deep fungal infections: Blastomycosis, Histoplasmosis, Coccidioidomycosis, Sporotrichosis, Aspergillosis	Minocycline
Chlamydia pneumoniae	Sulfonamides
Chlamydia trachomatis	Halogens (bromides, iodides)
Mycoplasma pneumoniae infections	Salicylates
Cat-scratch disease	Chlorothiazides
Syphilis	Phenytoin
Infectious mononucleosis	Thalidomide
Herpes simplex	**Underlying disease processes**
Cytomegalovirus infections	Sarcoidosis (Lofgren's syndrome)
Hepatitis B (infection or vaccine)	Crohn's disease
Hepatitis C infection	Ulcerative colitis
Epstein–Barr virus	Behçet's disease
Protozoal infections: Toxoplasmosis, Ancylostomiasis, Amebiasis, Giardiasis, Ascariasis	Sweet's syndrome
Malignancy	Reiter's syndrome
Hodgkin's lymphoma	Takayasu's arteritis
Acute myelogenous leukemia	**Hormonal states**
Carcinoid tumor	Pregnancy

Main categories of etiologic factors are in boldface

proximal ulna; less frequently the palms, the back of the hands and, in bedridden patients, the occiput and ischium are affected. RNs are often asymptomatic, persistent, firm, and moveable in subcutaneous planes, characteristics that make them distinguishable from RNs mimickers, mostly tenosynovitis and bursitis nodules, that are softer, compressible and painful in the majority of the cases [13–16].

RNs have a distinctive histological appearance, resultant of an immune-mediated granulomatous process involving the deeper dermis and extending into the septa of the subcutaneous fat. They exhibit a well-defined palisading of elongated histiocytes around central collagen degeneration, with an intensely eosinophilic accumulation of fibrin in the center of the granuloma. Extensive fibrosis is prominent in old lesions. Accelerated rheumatoid nodulosis, a phenomenon that has been observed not only in patients on methotrexate therapy, but also during treatment with azathioprine, leflunomide, infliximab, and etanercept reveals the same histopathological findings of RNs [16–18]. Histopathologic differential diagnosis is made with subcutaneous granuloma annulare and necrobiosis lipoidica.

Deep morphea Morphea, or localized scleroderma, is a rare fibrosing disorder of the skin resulting from inflammation and deposition of collagen-rich extracellular matrix [19]. When sclerotic changes extend beyond the dermis to involve the subcutaneous tissue, the fascia or the superficial muscle, we refer to deep variant of circumscribed morphea (previously known as subcutaneous morphea or *morphea profunda*). In contrast, when there is exclusive deep fascia involvement, classification as eosinophilic fasciitis or Shulman's syndrome is more appropriate [20]. Clinically, deep morphea appears in the form of indurated plaques or nodules, frequently located on the upper part of the trunk close to the midline and on the lower limbs (Fig. 4a). The overlying skin may feel hardened and adherent to the underlying tissues; however, acute inflammatory signs, such as edema and erythema, are rarely observed [21–23]. The presence of deep sclerosis, in some cases perineural, may account for the presence of pain [19].

Morphea and systemic sclerosis cannot be differentiated by histopathologic examination. In the early stages, deep morphea shows perivascular infiltration in the reticular dermis that is predominantly lymphoplasmacytic, although eosinophils are found in one-third of the specimens, with swollen endothelial cells and thickened collagen bundles (Fig. 4b) [23]. Late morphea is characterized by dense collagen sclerosis, which produces thickened septa and fat lobule obliteration. Lipomembranous changes can also be observed [20, 24]. On the other hand,

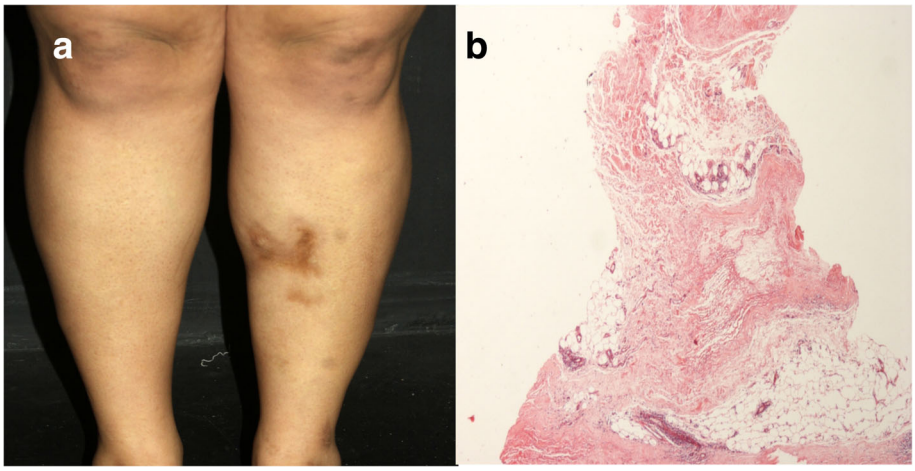

Fig. 4 Deep morphea. **a** Indurated plaque on the lower limb. **b** Thickening of the hypodermic septa by sclerotic collagen bundles, permeated by some lymphocytes and plasma cells, which extend to the periphery of the fat lobule. H&E, 100x

fibrous nodule formation in the setting of both systemic scleroderma and morphea consist histologically of mid dermal regions of fibrous tissue and inflammatory cells with increased mucin and decreased elastic fibers, indistinguishable from keloids [25].

Primarily-septal panniculitides with vasculitis

Cutaneous polyarteritis nodosa Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that predominantly targets small and medium-sized muscular arteries. In adult patients, it is more common in male sex and the median age at presentation is 33 (19–71) years. Both genders are equally affected in children and the median age at disease onset is 11 (2–16) years [26, 27]. The pathway(s) leading to necrotizing inflammation of the blood vessels have not yet been completely unraveled. Immunological mechanisms seem to play a relevant role in the pathogenesis of PAN. Most of the cases are idiopathic; nevertheless, several triggers have been identified. Hepatitis B virus infection (HBV) is the most common and it is well known that patients with HBV-related PAN have more severe disease, even though its occurrence has largely decreased due to widespread vaccination [27]. PAN can also be associated with malignancies and others infectious agents, such as group A β-hemolytic *Streptococcus* [28, 29].

The most common manifestations are palpable purpura and reddish-purple subcutaneous nodules mainly located on the lower limbs; nevertheless, they may also include livedo racemosa, 'punched out' necrotic ulcers, *atrophie blanche*, and ultimately gangrene of digits, especially in children (Fig. 5a). Cutaneous PAN (C-PAN), also known as cutaneous arteritis since the 2012 Revised International Chapel Hill Consensus Conference, is a special form of the disease restricted to the skin. Despite frequent relapses, cutaneous arteritis has a more benign course, milder constitutional symptoms and extra-cutaneous manifestations, which include arthritis, muscle pain and peripheral neuropathy, limited to the same area with overlying skin lesions [30, 31].

Skin biopsy is extremely useful for a definitive diagnosis. Cutaneous arteritis consists of a necrotizing vasculitis affecting small and medium-sized arteries within deep dermal or at the septa of the subcutaneous fat tissue. Fibrinoid degeneration involves all layers of the vascular wall, and internal elastic lamina disruption is detected (Fig. 5b). The histological changes can be divided into four stages (acute, subacute, reparative and healed), with a transition from a predominantly neutrophilic to lymphocytic infiltrate in the subacute and reparative stages. Then, vascular lumens become occluded by the fibrin thrombi with perivascular neovascularization in the healed stages [32, 33]. Direct immunofluorescence staining may show C3 and IgM deposits within vessels in the lesions [34]. Nodular vasculitis and thrombophlebitis are considered histopathologic differential diagnosis.

Primarily-lobular panniculitides

Primarily-lobular panniculitides without vasculitis

Gouty panniculitis Gouty panniculitis represents an extremely rare manifestation of gout, characterized by the deposition of monosodium urate crystals in the lobular hypodermis. The pathophysiology is currently poorly understood and serum uric acid level need not to be elevated to its development [35]. Gouty panniculitis may precede, appears concomitantly or years after the articular clinical expression of tophaceous gout. On physical examination, patients present with indurated, erythematous,

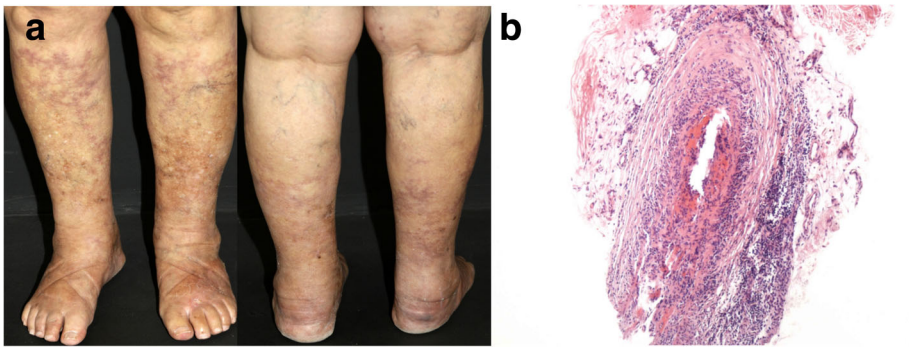

Fig. 5 Cutaneous polyarteritis nodosa. **a** Multiple infiltrated erythematous nodules mixed with livedo racemosa on the lower legs. **b** Vasculitis of medium-size-artery at the septa of the subcutaneous fat tissue. H&E, 200x

and irregular subcutaneous nodules or plaques, frequently painful, which can ulcerate and drain serous or opaque fluid. Lesions are located predominantly on the lower extremities, although they may be observed on upper extremities, torso, buttocks and scalp [36–38]. Skin biopsy reveals amorphous eosinophilic deposits in the deep dermis and subcutaneous tissue surrounded by a granulomatous reaction with macrophages and many multinucleated giant cells. Urate crystals causing lobular panniculitis show a needle-like shape and are doubly refractive under polarized light [39].

Post-steroid panniculitis This is a very rare panniculitis mostly described in childhood, but also in early adulthood, one to 10 days after cessation of systemic corticosteroid therapy. It has been suggested that a sudden decrease or withdrawal of high doses of corticosteroids either oral or intravenous may cause an increase in the ratio of saturated to unsaturated fatty acids, leading to crystal formation. The nodules tend to appear in those areas prone to accumulation of fat during steroid therapy such as the cheeks, jawline, arms and trunk, although it has also been reported on the legs. Usually there are no general symptoms [40, 41].

Characteristic histopathological findings consist of lobular panniculitis without vasculitis, with narrow strands needle-shaped clefts in radial arrangement within the cytoplasm of histiocytes, multinucleated giant cells, and the great majority of fat cells. The needle-shaped clefts represent negative images of crystals of triglycerides dissolved during tissue processing. These features are also seen in *sclerema neonatorum* and subcutaneous fat necrosis of the newborn. The lesions generally subside in weeks or months even without any treatment, leaving residual hyperpigmentation. If ulceration occurs in late stage, resuming steroid therapy may be indicated and then a slower and gradual decrease of the dose should be programmed [40, 41].

Lupus panniculitis Lupus panniculitis (LEP), also known as *lupus erythematosus profundus*, affects approximately 2% of the patients diagnosed with lupus erythematosus [42]. It can also appears concomitantly with discoid lupus erythematosus or subacute cutaneous lupus erythematosus (on the overlying skin or elsewhere), as well as an isolated phenomenon [43]. The development of LEP after an injury to the area, such as HPV vaccination, preceding trauma and injection site of adalimumab - a human monoclonal antibody to tumor necrosis factor (TNF)-α - has been previously described [44–47].

There is a predilection for the female sex. The mean age at diagnosis range from 28.5 to 32.9 years in different case series. In approximately two-thirds of the patients, the lesions are found on the head, mainly on the cheeks, and scalp. LEP involve predominantly the proximal part when affecting the limbs (Fig. 6a). The lateral aspect of the arms, the trunk, including the breasts, and the buttocks are commonly affected [43, 48, 49]. It presents clinically as deep subcutaneous nodules and erythematous to violaceous infiltrated plaques, which occasionally ulcerate and often resolve leaving depressed areas [42, 48]. A linear configuration of LEP has been sometimes reported, especially in children and adolescents [50]. Serologic abnormalities include antinuclear antibodies, usually at low titers, anti-double-stranded-DNA and anti-ENA-antibodies [51].

Histopathologic findings comprise a mostly lobular lymphoplasmacytic infiltrate, the presence of lymphoid follicles in the subcutaneous tissue, and hyaline fat necrosis (Fig. 6b). Epidermal and dermal changes typical of discoid lupus erythematosus, including epidermal atrophy, follicular plugging, vacuolar alteration, basement membrane thickening, and mucin deposition are observed in about one half to two-thirds of the patients in different case series. A positive lupus band test may be used to support a diagnosis of LEP. The predominant

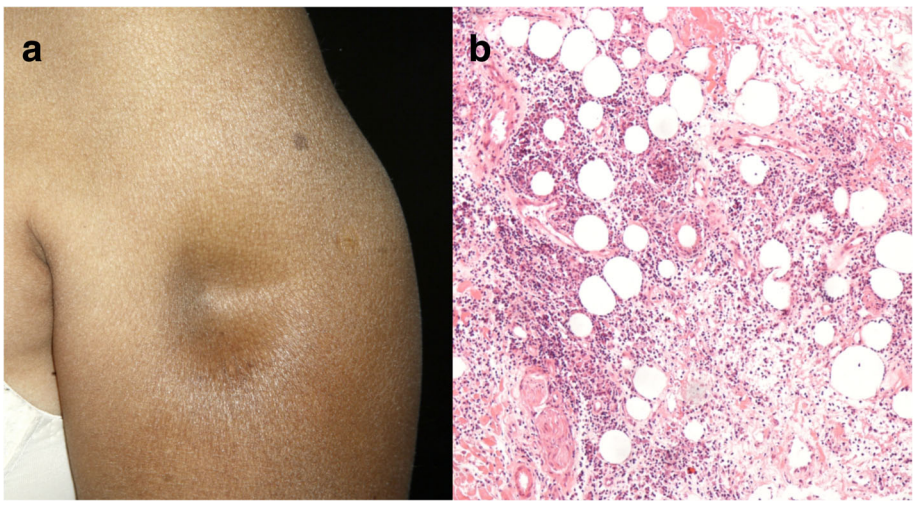

Fig. 6 Lupus panniculitis. **a** Depressed area involving the proximal part of the arm. **b** Extensive lobular infiltrate composed of lymphocytes. H&E, 200x

immune-deposit in direct immunofluorescence is IgM, and C3 and IgG are seen in half of the cases [43, 50].

The most troublesome differential diagnosis of LEP is subcutaneous panniculitis-like T-cell lymphoma, a subtype of non-Hodgkin lymphoma presenting with nodules, solitary or multiple, or deeply seated plaques mainly involving the legs, the arms and the trunk, that leave areas of lipoatrophy after regression. Systemic symptoms, such as fever, fatigue and weight loss are common. Although lymphoid nodules with germinal centers within fat cells are not pathognomonic of LEP, they are especially useful since their occurrence is not observed in cases of subcutaneous lymphoma, whilst rimming of fat lobules by lymphocytes and vascular invasion by atypical lymphocytes have been described in both entities. Immunohistochemistry is even more helpful in recognizing subcutaneous panniculitis-like T-cell lymphoma, revealing a cytotoxic T-cell phenotype consisting of CD3-positive, CD8-positive, CD4-negative lymphoid cells, coexpressing cytotoxic proteins granzyme B, TIA-1 and perforin [45, 49, 52]. Although rare, rheumatologists should be also aware of this malignancy, since there is one case report of subcutaneous panniculitis-like T-cell lymphoma in a patient receiving etanercept for rheumatoid arthritis [53].

Panniculitis in dermatomyositis Panniculitis is an usual finding in both juvenile and adult forms of dermatomyositis. It is characterized by a lobular infiltrate composed of lymphocytes and plasma cells. A certain degree of pseudomembranous changes, that refers to pseudocystic spaces lined with eosinophilic membranes in areas of fat necrosis, may be seen in a great number of panniculitides, besides those cases related to dermatomyositis, including: sclerosing panniculitis, LEP, *erythema induratum* (EI), necrobiosis lipoidica, traumatic panniculitis, pancreatic panniculitis and subcutaneous sarcoidosis. There are reports of overlying dermal-epidermal vacuolar change and increased mucin deposition in the panniculitis associated with dermatomyositis resembling LEP [54, 55].

Neutrophilic lobular panniculitis The term neutrophilic (lobular) panniculitis refers to histopathological findings shared by a variety of cutaneous and systemic disorders, which includes pustular panniculitis associated with RA, pancreatic panniculitis, α1-antitrypsin deficiency panniculitis, subcutaneous Sweet syndrome, and factitious panniculitis [56, 57]. The most common form of panniculitis occurring in the setting of RA is EN [13]. However, rare cases of neutrophilic lobular panniculitis have also been reported in these patients. Cutaneous eruption manifests as tender erythematous nodules on the lower legs in which eventual ulceration and discharge of purulent material allow clinical distinction from EN (Fig. 7a). Histopathology in neutrophilic panniculitis associated with RA shows fat necrosis and neutrophilic dust in the subcutaneous tissue with surrounding fibrosis (Fig. 7b) [58].

Vemurafenib and dabrafenib were recently approved for the treatment of patients with unresectable or metastatic melanoma harboring the BRAF V600E mutation. Several cases of BRAF inhibitors-induced panniculitis have been reported within 7 days to 16 months after starting the medication. Joint pain and fever were associated with tender subcutaneous nodules on the upper or lower limbs, mostly the thighs, in 44 and 31% of the patients, respectively [7]. Histopathological investigation

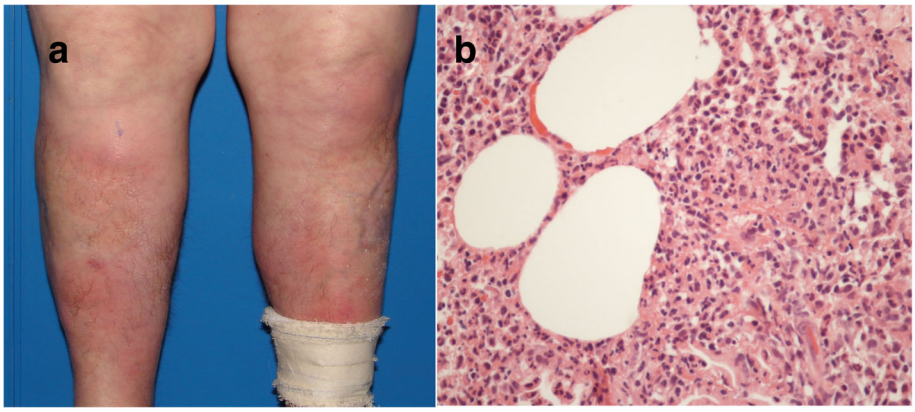

Fig. 7 Neutrophilic lobular panniculitis associated with rheumatoid arthritis. **a** Erythematous nodules on the anterior aspect of the legs. **b** Necrosis of adipocytes and intense infiltrate composed of neutrophils and histiocytes, in the lobules of the hypodermis**.** H&E, 400x

has shown mixed (both septal and lobular) panniculitis in some instances, but primarily lobular neutrophilic panniculitis usually predominates. Occasionally, small foci of fatty necrosis and some foamy macrophage are seen. Only in a few cases an inflammatory infiltrate surrounding blood vessel walls and focal erythrocyte extravasation were revealed, as did non-necrotizing granulomas. Spontaneous resolution despite drug maintenance is possible; however, low-dose topical or systemic steroids and nonsteroidal anti-inflammatory drugs may be used for symptomatic treatment [7, 59]. Similarly, panniculitis has been reported as a rare side effect of specific inhibitors of tyrosine kinase activity ibrutinib, with marked activity in several B-cell malignant neoplasms, and dasatinib, used to treat chronic myeloid leukemia in chronic, blastic or accelerated phase that is resistant or intolerant to imatinib mesylate [60, 61].

Primarily-lobular panniculitides with vasculitis

Erythema induratum Erythema induratum (EI) has a female predominance and typically affects patients with some degree of obesity and venous insufficiency of the lower extremities. The disease presents with relapsing episodes of painless violaceous nodules on the calves and shins, but also on the buttocks and lower trunk, mostly during the winter. Lesions have a tendency to central ulceration and resolve spontaneously within a few months, leaving post inflammatory hyperpigmentation and occasionally atrophic pigmented scars (Fig. 8a). There are no accompanying systemic symptoms [62, 63].

EI occurs as hypersensitive immune reaction to *Mycobacterium tuberculosis*. As others tuberculids, which include lichen scrofulosorum and papulonecrotic tuberculid, although extremely rarely EI can be induced by tuberculin skin test, as well as by Bacillus Calmette–Guérin vaccine even in children. Ziehl-Neelsen staining for acid-fast bacilli and mycobacterial culture usually result negative [64, 65]. However, there is one report in which *M. marinum* was isolated [66]. The most striking features of EI are strongly positive tuberculin purified protein derivative (PPD) with an induration greater than 20 mm and clearance of skin lesions with anti-tuberculosis therapy, which occurs within 1–6 months (mean, 2.1 months). Once diagnosis is suspected a skin biopsy should be obtained for histologic examination and polymerase chain reaction analysis for mycobacterial DNA [67].

Histopathological analysis reveals a predominant lobular panniculitis, with mild to moderate inflammation of the neighboring fibrous septa, which appear widened. At an early stage, the inflammatory infiltrate is mainly composed of neutrophils, with or without leukocytoclasis; whereas histiocytes and lipophages predominate in fully developed lesions. Some type of vascular damage is detected in 90% of the cases. The most common pattern identified is inflammation involving small venules of the center of the fat lobule; however, vasculitis involving large septal vessels can also be found, irrespectively of the stage of the lesion [68]. There are varying degrees of caseous and coagulative necrosis, and poorly developed granulomas (Fig. 8b) [69]. Although nowadays most authors use both terms indistinctly, nodular vasculitis usually refers to the nontuberculous variant of EI. There is one case report on a 28-year-old man who developed erythematous painful nodules on the lower legs, one year after starting etanercept for psoriasis. Physical examination and histologic manifestations were compatible to nodular vasculitis. Since the screening for infectious and auto-immune conditions was negative, the development of this panniculitis was attributed to TNF-α inhibitor treatment [70].

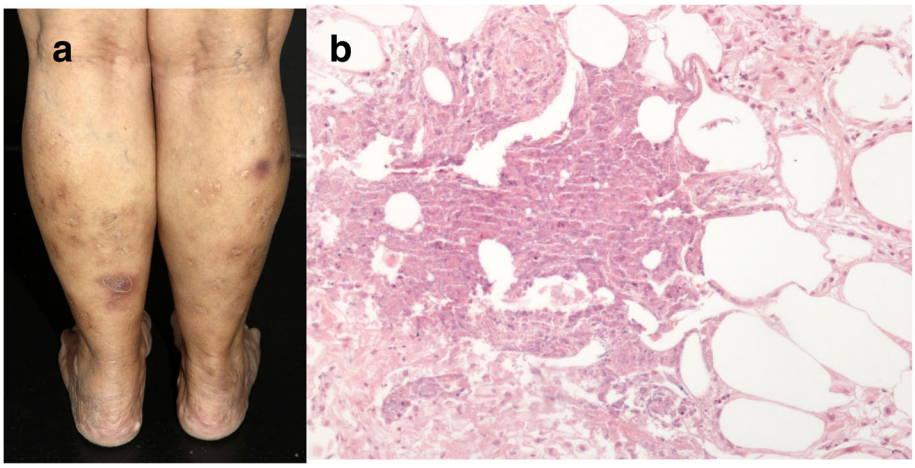

Fig. 8 Erythema induratum. **a** Erythematous nodules and atrophic scars in the legs. **b** Caseous necrosis in the lobules of the hypodermis. H&E, 400x

Panniculitis with crystals following etanercept injection According to Llamas-Velasco and Requena [71], panniculitis with lipid crystallization within adipocytes may be seen in several disorders, including crystal-storing histiocytosis, gouty panniculitis, post-steroid panniculitis, oxalosis and subcutaneous fungal infections by mucormycosis, zygomycosis or aspergillosis. These authors reported the first case of panniculitis with crystals induced by etanercept subcutaneous injection in a 62-year-old woman with severe psoriasis who developed an erythematous, slightly painful nodule on the skin of the anterior abdominal wall. The biopsy demonstrated a mostly lobular panniculitis with lymphocytic infiltrate, venulitis, as well as granulomas with foreign-body-type giant cells. Small radially arranged crystals surrounded by histiocytes were present at the interface between deep reticular dermis and subcutis. These crystals failed to stain with periodic acid-Schiff (PAS) and were slightly refractile under polarized light.

Mixed (septal and lobular) panniculitides

Infective panniculitis Infective panniculitis (IP) may occur as a primary infection by direct inoculation, as an extension from an underlying source of infection or secondarily via microbial hematogenous dissemination with subsequent infection of the subcutaneous tissue, induced by bacteria, mycobacteria, fungi, protozoa, or viruses. This type of panniculitis often manifests as multiple nodules predominantly found on the peripheral extremities, resembling EN (Fig. 9a). Other locations of involvement are possible such as the upper extremities, the gluteal region and the abdominal wall. However, the clinical picture can vary from infiltrated nodules with discharge or not to necrotizing ulcers depending on the organism involved, the route of infection, the host immune response, and the duration of the lesion at the time of biopsy [72, 73].

There are many bacterial etiologic agents of IP. The more common of these include *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas* spp., *Mycobacterium* spp. (most of the cases of mycobacterial panniculitis being caused by nontuberculous mycobacteria), *Actinomyces*, *Nocardia* spp., *Borrelia burgdorferi*, and *Klebsiella* spp. When it comes to fungal infections that involve the subcutaneous fat, they can be divided into two major types: (1) panniculitis in the setting of a disseminated fungal infection and (2) classical subcutaneous mycosis (with the most important being mycetoma, chromoblastomycosis, and sporotrichosis), introduced into the subcutaneous tissue from the environment via inoculation. Cytomegalovirus has been rarely reported as a causative agent; immunocompromised patients were particularly affected, as in most of these IP [72, 73]. Similarly, there has been sporadic reports on parasitic organisms (Leishmania spp.; *Trypanosoma cruzi*; and Gnathostoma spp.) causing panniculitis [74].

Diagnosis is quite challenging, not only because of a nonspecific clinical presentation, but also due to its histologic findings, which can be indistinguishable from several types of panniculitides. Bacterial IP should be strongly considered when extensive suppurative panniculitis with perivascular, lobular, or mixed septal-lobular neutrophil-dominated infiltrate is present, which often extends into the dermis (Fig. 9b) [58, 72]. IP caused by atypical mycobacteria or deep fungal infection shows suppurative granulomas within the lobule, which consist of collections of neutrophils surrounded by epithelioid histiocytes [39, 73]. Borreliosis have been documented to show a histological picture mimicking LEP and subcutaneous panniculitis-like T-cell lymphoma, with a dense

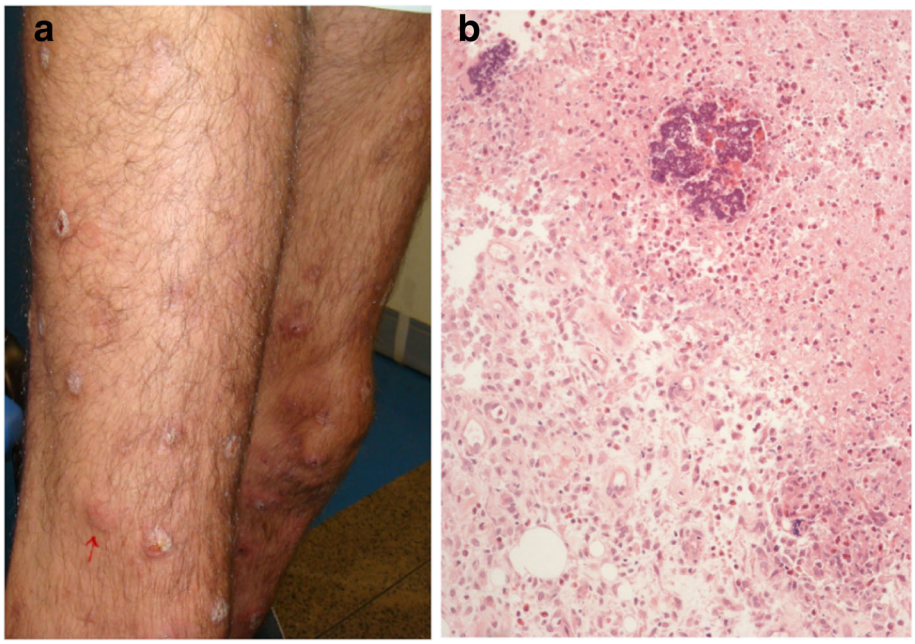

Fig. 9 Septic panniculitis in HIV positive male, caused by hematogenous dissemination. **a** Erythematous papules and ulcerated nodules on the lower limbs. **b** Basophilic areas corresponding to masses of microorganisms, with necrosis and infiltrate composed of neutrophils, eosinophils and histiocytes in the hypodermis. H&E, 200x

lymphocytic infiltrate of the subcutaneous tissue with scattered plasma cells [20]. Remarkably, besides typical cytomegalic inclusions localized predominantly within the endothelial cells of small vessels of the subcutaneous cellular tissue, skin biopsy of nodular lesions in panniculitis associated with cytomegalovirus infection may show septal involvement with abundant neutrophils, histiocytes, karyorrhexis and phagocytosis of cellular debris [75].

Regardless of the microorganism, vascular damage including necrotizing small vessel vasculitis involving arterioles and venules and/ or a thrombotic microangiopathy in the deep reticular dermis and subcutaneous fat (in secondary cutaneous infections) may be noteworthy [58, 76]. A high degree of clinical awareness is needed, since additional histological studies are necessary to identify the causative agent in many cases, including special stains (Gram, periodic acid-Schiff, Ziehl-Neelsen, methenamine-silver, anti–bacillus Calmette-Guerin antibody); cultures and molecular diagnostic techniques, like polymerase chain reaction PCR, especially in patients with preserved immune response [39, 72, 73].

Erythema nodosum-like lesions in Behçet's disease

EN-like lesions occur in 22.5 to 45.5% of the patients diagnosed with Behçet's disease (BD) [77, 78]. Nodular lesions are mostly present on the lower legs, but upper extremities may also be involved. They are histopathologically similar to those of conventional EN in approximately one-third of the cases, showing a mostly septal panniculitis pattern, and an inflammatory infiltrate composed of neutrophils and various numbers of lymphocytes and histiocytes in the thickened septa of the subcutis. However, biopsy specimens with features of a panniculitis lobular or mixed septal and lobular in pattern, with variable degrees of lymphohistiocytic and neutrophilic infiltration, and clear evidence of vasculitis are even more common to be found [79, 80].

Vessels involvement is usually extensive and not limited to the areas of severe inflammation. It can be both of the venulitis or of the phlebitis type. The latter characteristically simulates C-PAN, as in superficial thrombophlebitis, and therefore must be clarified based on the investigation of the internal elastic lamina fiber by specific staining, such as Verhoeff van Gieson. Although the subcutaneous muscular veins in the lower legs usually have a compact concentric smooth muscle pattern with a round lumen and intimal elastic fiber proliferation due to the persistent hydrostatic pressure mimicking the characteristic features of arteries, the elastic fibers in the muscular layer are distributed between the bundled smooth muscle in veins, whereas the elastic fibers are scantly distributed in the medial muscular layer in arteries [81]. A variable degree of fat necrosis is frequently observed [79, 80].

Conclusion

Inflammation of the subcutaneous tissue is a dynamic process that shows different histopathologic findings at

different stages of development. Even in the same stage of evolution, location and type of inflammation may vary among different cases of the same panniculitis; whereas similar histopathologic findings may be observed in panniculitides of different etiologies, for instance in superficial thrombophlebitis and C-PAN, or in EN and EI. In evaluating cases of panniculitidesis essential to know the associated changes outside the subcutis to establish a specific diagnosis.

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Authors' contributions
TCABM wrote the manuscript in consultation with GFST. GFST contributed to the writing of the manuscript. MSCG designed the tables and figures. IH provided histopathological images and aided in descripting histopathological findings of each panniculitis. PRC contributed to the design of the manuscript, provided clinical images and supervised the work. JFC conceived the idea of the manuscript and supervised the work. All authors read and approved the final manuscript.

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