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The rash with painful and erythematous nodules

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Abstract Erythematous painful cutaneous nodular lesions are associated with a host of disorders that may erupt acutely as a generalized or localized dermatitis or be associated with chronic and/or recurrent illnesses. This review discusses such disorders presenting with painful nodular lesions and attempts to provide a systematic approach to their clinical diagnosis.

Introduction and classification

Many dermatoses present with painful and erythematous nodular lesions, either localized or generalized. An appropriate clinical diagnosis is essential for further appropriate workup to confirm the diagnosis and for timely management. Disorders presenting with painful inflamed erythematous nodules generally reflect a deep dermal or subcutaneous pathology. Panniculitides, vasculitides, and dermal infiltrative disorders commonly account for such clinical presentation (Table 1). The clinical diagnostic approach can be based on the mode of onset, distribution, and spread of the lesions as depicted in Figures 1 to 5. Certain accompanying clinical findings help to support the clinical diagnosis and to carry out relevant laboratory tests (Table 2).

Acute onset generalized painful nodules

Erythema nodosum leprosum

Erythema nodosum leprosum (ENL) is a prominent cutaneous manifestation of type 2 lepra reaction occurring in borderline lepromatous or lepromatous leprosy. As opposed to erythema nodosum (see Erythema nodosum section), ENL is generalized in distribution and characterized by evanescent, erythematous, tender nodules occurring in crops (Figure 6). They favor the extensors of the arm and medial aspect of thigh and typically spare the preexisting leprosy lesions. It is a multisystem disease and is accompanied by constitutional clinical manifestations. Laboratory evaluation reveals neutrophilic leukocytosis such elevated markers of inflammation-as C-reactive protein, and erythrocyte sedimentation rate. Histopathologically, ENL is characterized by septal panniculitis.[1] Some patients may also have a chronic recurrent form of the disease.

Sweet's syndrome

Sweet's syndrome (acute febrile neutrophilic dermatosis) is an acute febrile neutrophilic dermatoses associated with infection, drugs, malignancies, and autoimmune disorders. Clinically, it is characterized by the acute onset of erythematous tender plaques and nodules favoring the head and neck region and proximal aspects of the extremities that may extend beyond, involving the trunk and legs (Figure 7). A diagnostic pointer can be the characteristic "pseudovesicular" appearance of the lesions due to marked dermal edema. Fever,

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Table 1 Disorders presenting with painful inflamed nodules

Disorder	Conditions
Panniculitides	Erythema nodosum
	Erythema nodosum leprosum
	Sclerosing panniculitis
	Pancreatic panniculitis
	Cytophagic histiocytic panniculitis
	$Alfa_1$-antitrypsin deficiency
Vasculitides	Nodular vasculitis
	Cutaneous polyarteritis nodosa
Neutrophilic dermatoses	Behçet's disease
	Sweet's syndrome
Neoplastic	Cutaneous metastases
Vasculopathic	Superficial thrombophlebitis
	Calciphylaxis
Infective	Chronic meningococcemia
	Pseudomonas hot foot syndrome
Others	Idiopathic palmoplantar hidradenitis
	Accelerated rheumatoid nodulosis

marked neutrophilic leukocytosis, arthralgia, conjunctivitis, episcleritis, and systemic features of neutrophilic alveolitis; multifocal sterile osteomyelitis; and acute renal failure may develop. The histology is characterized by marked dermal edema and diffuse nodular and perivascular neutrophilic infiltrate in the dermis.[2]

Cytophagic histiocytic panniculitis

Cytophagic histiocytic panniculitis is a rare multisystem disorder characterized by recurrent widespread acute onset of inflammatory subcutaneous nodules occurring in recurrent crops associated with fever, arthritis, hepatosplenomegaly, anemia, and pancytopenia. The nodular lesions later break down to form ulcers, discharging oily material. The disease is considered a specific cutaneous manifestation of the hemophagocytic syndrome, wherein there is a widespread phagocytically active histiocytic proliferation throughout the reticuloendothelial system. The histiocytic proliferation may also be secondary to various infections, malignancies, or autoimmune disorders. Many of the cases represent subcutaneous panniculitis-like T-cell lymphoma. The specific histologic feature is the proliferation of histocytes in the subcutis that are phagocytically active and are seen to have engulfed blood cells and nuclear fragments (bean bag histiocytes).[3]

$Alfa_1$-antitrypsin deficiency panniculitis

$Alfa_1$-antitrypsin is a serine protease inhibitor involved in the regulation of various proteases involved in tissue destruction. It is also known to be involved in regulating various proinflammatory cellular and immunological phenomena. Patients with severe deficiency of the enzyme are prone for ulcerating

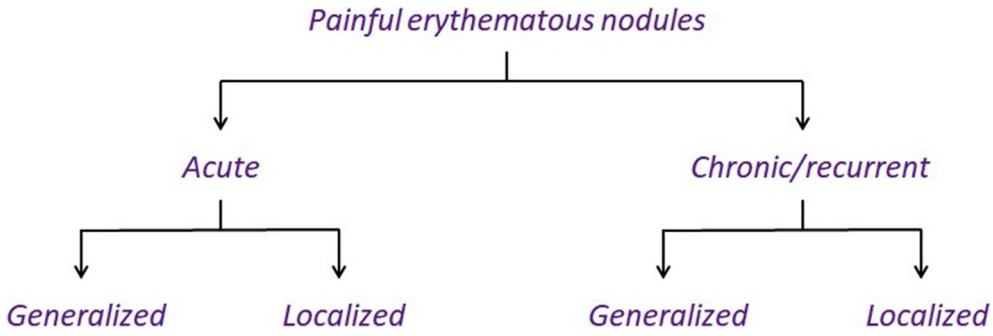

Fig. 1 Painful erythematous nodules.

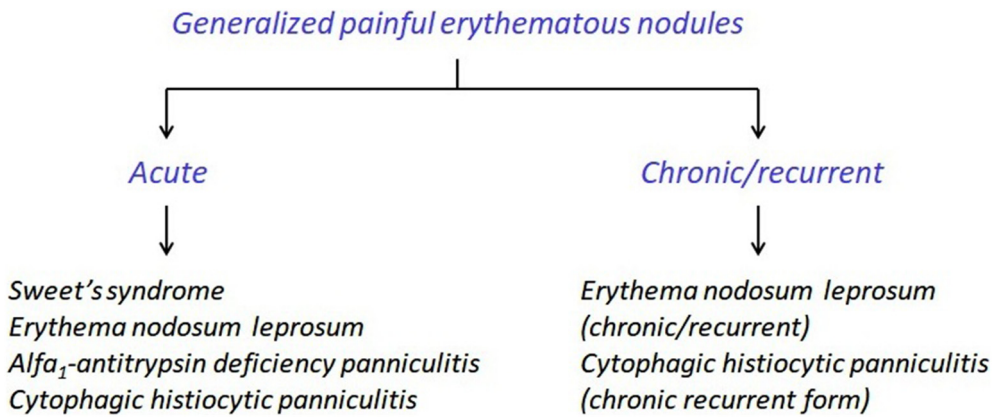

Fig. 2 Generalized painful nodules.

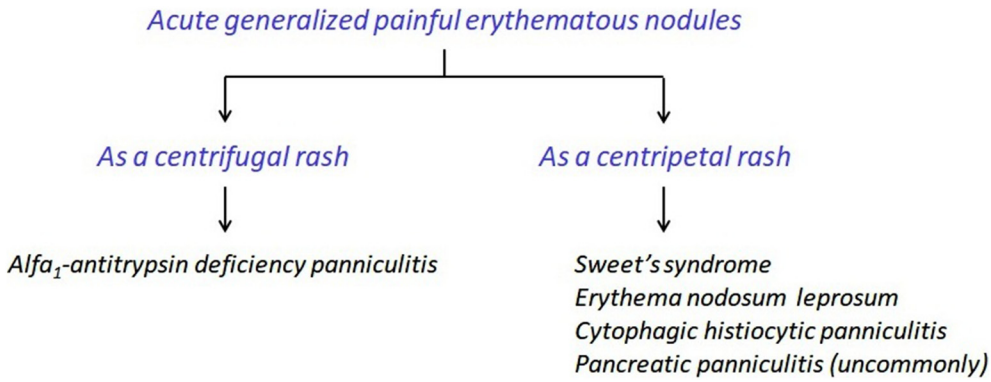

Fig. 3 Generalized erythematous painful nodules.

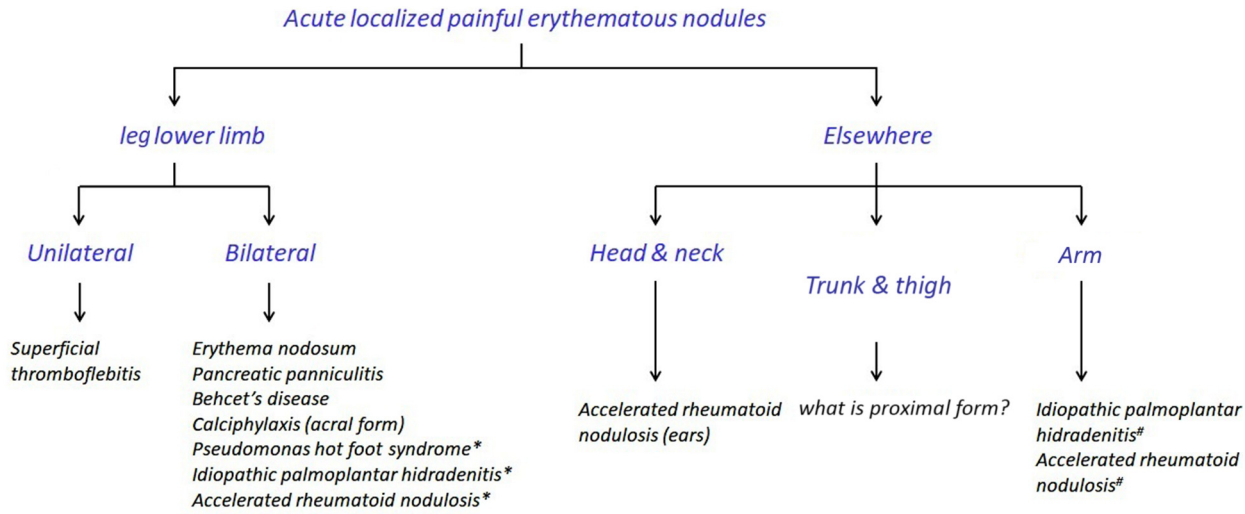

Fig. 4 Acute localized erythematous painful nodules.

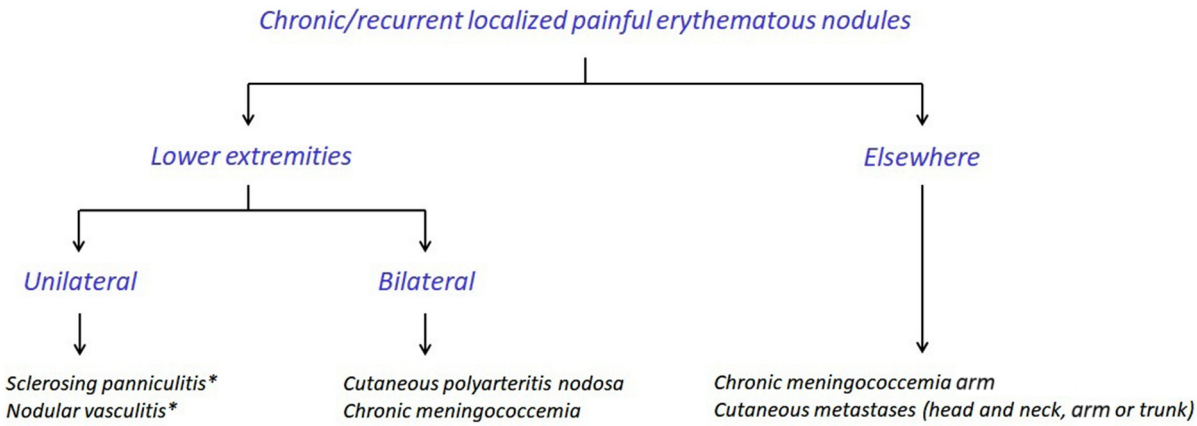

Fig. 5 Chronic and recurrent localized erythematous painful nodules.

Table 2 Clinical pointers to the diagnosis of dermatitis presenting as painful inflamed nodules

Disorder	Conditions	Clinical diagnostic pointers
Panniculitides	Erythema nodosum	Limited to lower extremities commonly or may be generalized with constitutional clinical manifestations
	Erythema nodosum leprosum	Generalized evanescent lesions occurring in crops with constitutional clinical manifestations. Evidence of leprosy in the background
	Sclerosing panniculitis	Painful nodules with a background of clinical changes due to chronic venous insufficiency
	Pancreatic panniculitis	Crops of painful erythematous nodules with constitutional clinical manifestations that rupture to discharge cheesy or oily material
	Cytophagic histiocytic panniculitis	
	$Alfa_1$-antitrypsin deficiency panniculitis	
Vasculitides	Cutaneous polyarteritis nodosa	Other clinical evidence of vasculitis-like palpable purpura, livedo reticularis, and punched-out ulcers
Neutrophilic dermatoses	Behçet's disease	Characteristic oral and genital aphthae and other cutaneous lesions of Behçet's disease with arthralgia/arthritis
	Sweet's syndrome	Constitutional clinical manifestations, typical "pseudovesicle" appearance of the lesions
Vasculopathic	Superficial thrombophlebitis	Inflammatory edema of the leg, tenderness, and prominent cordlike thickening of superficial veins accompanying the nodules
	Calciphylaxis	Frequent in the setting or chronic renal failure on dialysis. Nodules progressing to form characteristic stellate ulcers with surrounding noninflammatory retiform purpura
Infective	Chronic meningococcemia	Remitting and relapsing episodes of fever with arthritis, splenomegaly, and polymorphic skin lesions
	Pseudomonas hot foot syndrome	Common in children typically with a history of swimming in pools. Associated with mild constitutional clinical manifestations
Neoplastic	Cutaneous metastases	Sudden or gradual onset of lesions in the setting of an underlying internal malignancy. Cutaneous metastases are generally asymptomatic, but on occasions they may be painful and tender. Some of the malignancies metastatize to specific cutaneous sites
Others	Idiopathic palmoplantar hidradenitis	Common in children, acute-onset lesions, self-limiting lesions predominantly on the soles
	Accelerated rheumatoid nodulosis	Typical in the setting of treatment with methotrexate. As opposed to the painless subcutaneous nodules of the disease, these are painful

neutrophilic panniculitis in addition to disorders of liver, lung, and kidney. Lesions appear as tender erythematous nodules that eventually break open to form indolent ulcers discharging oily or cheesy material that heal with scarring. Involvement of the trunk (Figure 8) and proximal extremities is a clue, and the lesions may later extend beyond. Fever, pleural effusion, and pulmonary embolization may be accompanied in severe cases. The histology is characterized by acute neutrophilic lobular panniculitis with destruction of fat lobules.[3]

Acute-onset localized painful nodules

Erythema nodosum

Erythema nodosum is an acute inflammatory nodular eruption occurring as a reactive phenomenon in association with various infections (eg, tuberculosis), autoimmune diseases (eg, inflammatory bowel disease), and drugs (eg, sulfonamides). It is characterized by acute bilaterally symmetrical erythematous and painful nodules typically involving the pretibial areas of the leg (Figure 9). They are associated with constitutional clinical manifestations such as fever, malaise, headache, and gastrointestinal complaints. Erythema nodosum is histologically characterized by as septal panniculitis. A chronic form of the disease is also described but is quite rare.[4]

Pancreatic panniculitis

Pancreatic or enzymatic panniculitis is a form of subcutaneous fat necrosis associated with a variety of pancreatic disorders mediated by pancreatic lipase, amylase, and tryptase. Multiple tender erythematous subcutaneous nodules develop predominantly on the legs, which may uncommonly spread centripetally to involve the proximal areas of the thighs, arms, chest, and abdomen. Similar to other panniculitides, the nodules rupture to form ulcers discharging oily material. Pancreatic panniculitis precedes the systemic clinical manifestations of pancreatic disease by 1 to 7 months, and when associated with pancreatic carcinoma, it usually indicates an advanced metastatic stage. Systemic features may include fever, polyarthritis, and pleural effusion. Subcutaneous nodules associated with polyarthritis and eosinophilia (Schmid's triad) are indicative of a poor prognosis.[5,6]

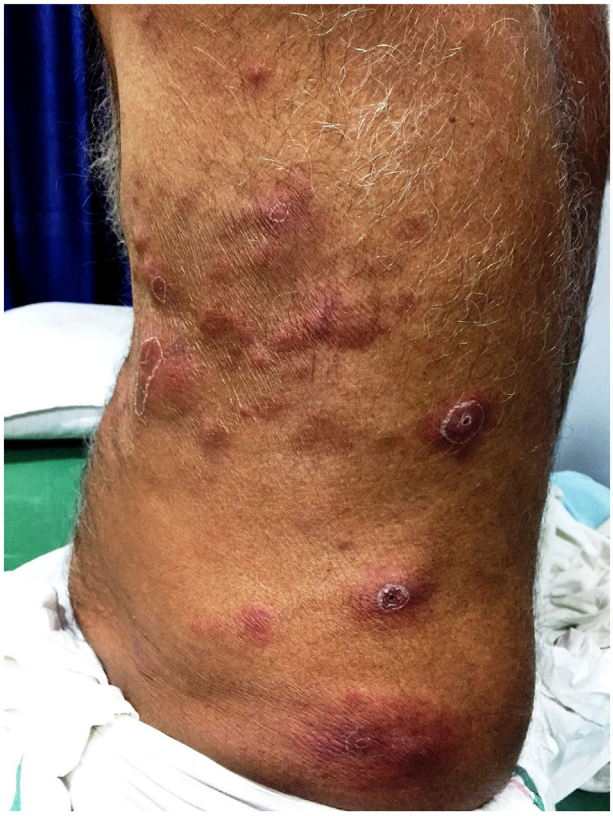

Fig. 6 Erythematous tender nodules on the trunk in a patient with lepromatous leprosy.

Behçet's disease

Erythema nodosum–like lesions presenting as acute painful erythematous nodules on the legs can occur in Behçet's disease, especially in women. They may also involve the buttocks and are difficult to distinguish histologically from typical erythema nodosum. In addition, typical erythema nodosum may also be associated with Behçet's disease.[7]

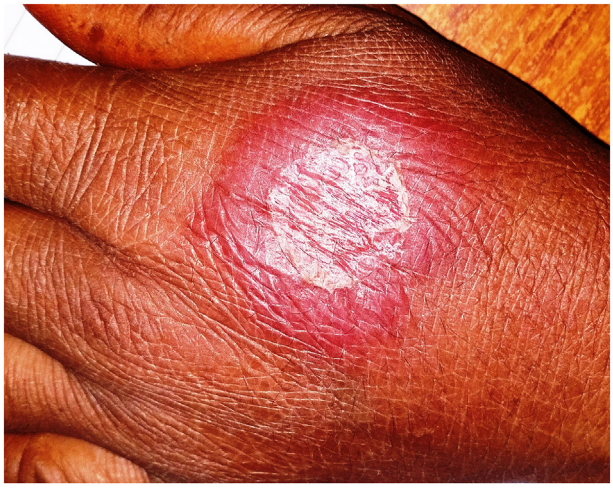

Fig. 7 Erythematous nodule with scaling on the dorsum of the hand in a woman with Sweet's syndrome.

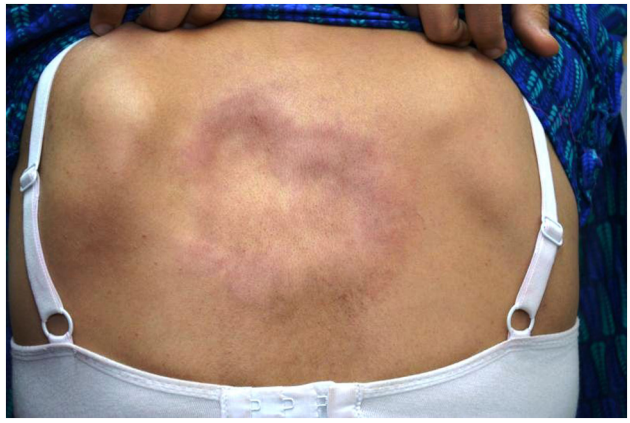

Fig. 8 Resolving erythematous nodules on the back of a woman with alfa$_1$-antitrypsin deficiency panniculitis. (Image courtesy: Sharad Mutalik, MD, Pune, India.)

Superficial thrombophlebitis

Superficial thrombophlebitis is clinically characterized by acutely inflamed and swollen extremity, associated with multiple tender nodules in a linear configuration (along the course

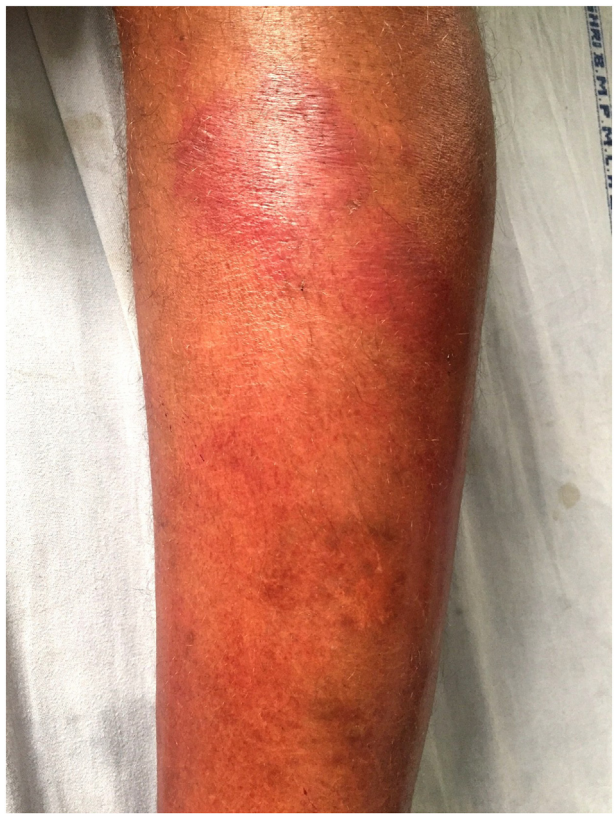

Fig. 9 Typical erythematous tender nodules of erythema nodosum involving the pretibial area.

of the vein). Dilated collaterals and diffuse erythema around the nodules are also present. Frequently, the great saphenous vein is involved. Superficial thrombophlebitis is an underreported condition, and the risk factors are similar to those with deep venous thrombosis (most commonly immobilization, obesity, pregnancy, trauma, underlying malignancy, or hypercoagulable states, and a history of superficial or deep venous thrombosis). It is prudent to look for accompanying deep vein thrombosis, as superficial thrombophlebitis may coexist with deep vein thrombosis and may also represent a risk factor.[8]

Calciphylaxis

Calciphylaxis (calcific uremic arteriolopathy) is an uncommon disorder with high mortality, seen most often in the setting of end-stage renal disease associated with secondary hyperparathyroidism. It often affects middle-aged women, with a greater frequency in the presence of comorbidities such as diabetes, hypothyroidism, obesity, liver disorders, and malignancies. Patients without renal failure and with normal calcium-phosphate product have also been described. The lower portions of the legs are commonly involved (distal form). Involvement of areas with high subcutaneous fat, such as proximal areas of the thighs, buttocks, and abdomen, appear to carry a worse prognosis. Initial lesions appear as fixed livedo (racemose type) overlying indurated plaques or nodules that eventually transform into stellate purpuric lesions that breakdown to form deep ulcers with violaceous margins and a black eschar. Exquisite pain and tenderness disproportionate to the clinical manifestations are the hallmark features.[9,10]

Pseudomonas hot foot syndrome

Pseudomonas hot foot syndrome is primarily a disease of childhood that is characterized by sudden development of very painful and tender papules and nodules with edema over the plantar surface of the feet. Exposure to swimming pool water contaminated with *Pseudomonas aeruginosa* is frequently implicated. Mild systemic clinical manifestations may accompany the rash and resolve spontaneously within a week or two with only symptomatic management. Perivascular and perieccrine neutrophilic infiltrate and occasional dermal microabscesses are typical histologic features.[11]

Idiopathic palmoplantar hidradenitis

Idiopathic palmoplantar hidradenitis is another benign self-limiting disease seen in children, characterized by the sudden onset of painful erythematous nodules on the soles and less commonly on the palms. Trauma or vigorous physical activity is implicated in the pathogenesis, and the disease is histologically characterized by a neutrophilic infiltrate involving the ductal and secretory components of the eccrine glands and formation of microabscesses. This disorder, in contrast to neutrophilic eccrine hidradenitis, is seen in healthy children. Neutrophilic eccrine hidradenitis is a disease of adults, typically in the setting of chemotherapy and often occurring on the abdomen, ears, and face.[12]

Accelerated rheumatoid nodules

Painless subcutaneous nodules are characteristic extraarticular manifestations of rheumatoid arthritis usually associated with elevated titers of rheumatoid factor and presence of other autoantibodies, and generally reflect a greater inflammatory process. Sudden onset or worsening of nodules in rheumatoid arthritis is commonly associated with methotrexate therapy. It is also described with other drugs, such as azathioprine, leflunomide, and immunobiologics, including tocilizumab and antitumor necrosis factor agents. These lesions typically suddenly develop and are often painful and typically favor the hands, feet, and ears. Lesions generally regress with discontinuation of methotrexate and may recur with reinitiation.[13,14]

Chronic/recurrent localized painful nodules

Nodular vasculitis

Nodular vasculitis or erythema induratum is a disorder characterized by an indolent eruption of painful erythematous nodules involving the calves, which may rupture and ulcerate to heal with atrophic scars. Women are more commonly affected. It was initially described in association with tuberculosis, but not always; hence, nodular vasculitis has been classified into two predominant types—erythema induratum of Bazin, which is associated with tuberculosis, and the Whitfield type, which is not associated with tuberculosis and may be seen with a host of autoimmune, infectious, and neoplastic disorders. Histologically, nodular vasculitis is characterized by a lobular panniculitis with vasculitis.[13]

Sclerosing panniculitis

Sclerosing panniculitis (lipomembranous panniculitis) is a common form of chronic panniculitis frequently in the setting of long-standing chronic venous hypertension on the legs of middle-aged, frequently obese, women. Initial manifestations of sclerosing panniculitis are characterized by multiple painful, indurated erythematous nodules, resembling erythema nodosum, either unilaterally or bilaterally. Features of long-standing venous hypertension, such as varicosities, venous ulcers, and stasis dermatitis, may be seen on the affected leg. The lesions evolve into diffuse sclerotic thickening of the entire leg with hyperpigmentation (lipodermatosclerosis), giving an "inverted champagne bottle" appearance. The histotopathology in early stages is characterized by ischemic necrosis of fat lobules with septal lymphocytic infiltrate. As the lesion advances, there is progressive sclerosis of the interlobular septae and lipomembranous changes characterized by thickened,

undulating membranes, derived from degenerated lipocyte membranes and forming cystic and papillary configurations.[6]

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa is a form of polyarteritis nodosa that is common in children and associated frequently with streptococcal infections, being limited to the skin with minimal and mild constitutional clinical manifestations. Clinically, it is characterized by painful subcutaneous nodules involving the legs that are associated with other features of vasculitis such as livedo reticularis and punched-out ulcers. The disease is benign but runs a chronic and relapsing course. About half of the patients with systemic polyarteritis nodosa exhibit cutaneous manifestations described above, but the painful nodules are more frequently seen with the cutaneous form of the disease.[15,16]

Chronic meningococcemia

Chronic meningococcemia is a rare disorder, characterized by recurrent fever, without meningitis, lasting for 2 to 7 days, and associated with arthralgia and arthritis, splenomegaly, and a polymorphous eruption, characterized by petechiae, purpura, and painful subcutaneous nodules, frequently involving the legs and less frequently the arms and trunk. With treatment, the disease remits with clearance of the bacteremia only to recur in 1 to 4 days.[17,18]

Cutaneous metastases

Cutaneous metastases from systemic malignancies generally indicate an advanced stage and poor prognosis. Classically, these lesions are known for being asymptomatic and painless, with some of the malignancies showing preference for specific cutaneous sites. In certain instances, however, the lesions resemble inflammatory cutaneous lesions characterized by chronic, painful erythematous nodules. Adenocarcinoma of the esophagus and colon, renal transitional cell carcinoma, and chondrosarcoma have been reported to produce painful cutaneous metastases commonly involving the extremities and scalp.[19]

Conclusions

An in-depth clinical knowledge of such conditions, presenting as painful erythematous cutaneous nodules, is essential not only for their clinical diagnosis but also for differentiation from other disorders with similar presentation. A systematic algorithmic approach to such presentations, together with awareness of the symptomatology, etiopathology, and associations, will assist in making a more precise diagnosis and providing appropriate management.

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