

Multiple painful skin lesions on the legs

Hassab El-Naby H, MD, El-Khalawany M, MD

Department of Dermatology, Al-Azhar University, Cairo, Egypt

CLINICAL FINDINGS

A 58 year old female patient presented with painful skin lesions on the lower limbs for two months duration. The condition started with gradual onset on the left leg and rapidly progressed to involve both lower limbs. The patient was treated initially by topical steroids and systemic antibiotics for 10 days without any improvement. The patient had a history of diabetes mellitus for 11 years and hypertension for 9 years. There was past history of similar condition 8 years back. There was no family history of similar condition.

Skin examination showed multiple bilateral, asymmetrical ulcers and atrophic plaques, distributed mainly on the anterior and medial aspects of both legs and also extended onto the ankles (Fig. 1). The lesions were tender and had irregular shapes. The edges were erythematous and purpuric and in some lesions there was reticulate pigmentation (Fig. 2). Old lesions were covered with



Fig. 1 An atrophic plaque close to the ankle with central crust formation and scarring.

crust while some lesions healed with scarring. Post inflammatory hyper and hypo pigmentation was evident in some lesions (Fig. 3). General examination revealed elevated blood pressure, while routine investigations showed elevated blood glucose level. Examination of inguinal lymph nodes showed no abnormal findings.



Fig. 2 Multiple ulcers on the legs with erythematous borders and reticulate pigmentation on the edges.



Fig. 3 Old lesions show scarring, hyper and hypo pigmentation.

What is your clinical differential diagnosis?

Allergic cutaneous vasculitis, erythema induratum of Bazin (nodular vasculitis), polyarteritis nodosa, livedo vasculopathy and superficial thrombophlebitis.

Correspondence: Dr. Hassab El-Naby H, Department of Dermatology, Al-Azhar University, Cairo, Egypt

PATHOLOGICAL FINDINGS

A skin biopsy was performed from a newly erupted lesion (punch 6 mm). Histological examination showed a superficial and deep perivascular inflammatory infiltrate formed of lymphocytes, histiocytes and neutrophils (Fig. 4). The lower dermis showed abnormal histological findings in the medium sized arteries in the form of fibrin deposition in the wall, prominent neutrophilic infiltrate within and surrounding the blood vessel, marked leukocytoclasia and nuclear dust formation (Fig. 5). The epidermis showed mild acanthosis while the papillary dermis showed increased number of small-sized blood vessels.

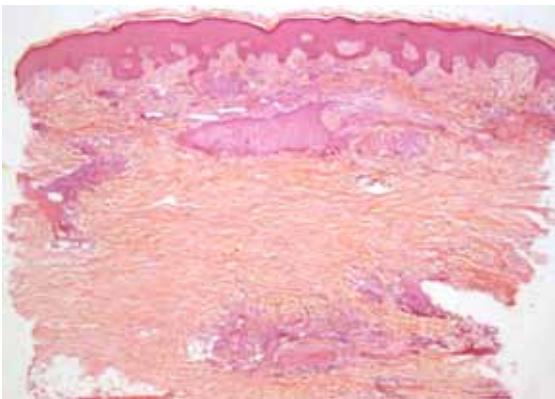


Fig. 4 Scanning power showed superficial and deep perivascular mixed inflammatory infiltrate.

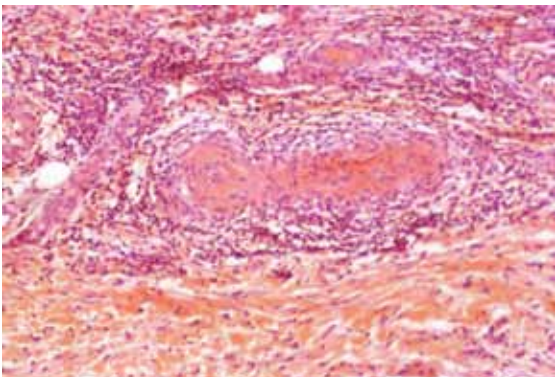


Fig. 5 A high power field shows fibrin deposition of medium sized artery with leukocytoclasia and neutrophilic infiltrate.

DIAGNOSIS

Cutaneous polyarteritis nodosa (CPAN).

COMMENT

Cutaneous polyarteritis nodosa (CPAN) is an uncommon and rare form of cutaneous vasculitis. It involves small and medium sized arteries of the dermis and subcutaneous tissue. The precise etiology of CPAN remains unknown, but immune complex mediated disease plays a role in etiopathogenesis. There is high prevalence of IgM antiphosphatidylserine – prothrombin complex among patients with CPAN. These immunoglobulins are presumed to activate the classical complement pathway to cause CPAN.¹

Several infectious and noninfectious conditions have been associated both with initiation and relapse of the disease. The noninfectious conditions associated with CPAN are connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis), Wegener's granulomatosis and Churg-Strauss syndrome. The streptococcal infection has been commonly implicated in addition to other infectious agents such as parvovirus B19, mycobacterium, hepatitis B and C viruses.²

Skin lesions are observed in 25%–60% of patients with polyarteritis nodosa (PN) and include subcutaneous nodules, livedo reticularis, ulcers and gangrene. PN is known as a systemic vasculitis, and discussion has been made on the association between skin and systemic lesions, i.e., whether a pathological condition in which vasculitis is limited to the skin is present or not, and, if present, how it is diagnosed and what its prognosis is?³

CPAN frequently affects females aged ≥ 40 years, with peaking at 50–59 years of age (male: female ratio = 2:3). The skin manifestations of CPAN as well as PN include nodules (mostly subcutaneous), livedo reticularis, ulcers, and gangrene. Purpura, papules, atrophie blanche, and edema have also been reported. Other findings include petechiae, cutaneous necrosis, auto amputations, and local extracutaneous manifestations like arthral-

gia, myalgia, constitutional symptoms (such as fever, malaise) and peripheral neuropathy (mononeuropathy and mononeuritis multiplex).⁴

The diagnosis of CPAN is based on clinical features of isolated skin involvement and confirmed by histopathological findings. A deep incisional biopsy, including subcutaneous tissue, is necessary for the accurate diagnosis of the disease. The characteristic pathologic feature is a leukocytoclastic vasculitis in the small to medium sized arterioles of the deep dermis or subcutis, with or without associated fibrinoid necrosis. Both CPAN and systemic PAN share the same histopathologic features of necrotizing arteritis of small and medium sized vessels.⁵

As the histological stage classification of PN, Arkin's classification is widely used in the world. Stages I (degenerative stage) and II (inflammatory stage) are vascular inflammation stages in which edema and/or fibrinoid degeneration of the media and intima occur, and the infiltration of inflammatory cells, mainly neutrophils, eosinophils, lymphocytes, and plasma cells, is observed. Fibrinoid degeneration involves all layers of the vascular wall, and the internal elastic lamina is disrupted.⁶ Patients with mild CPAN often show improvement after rest of the legs and the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or systemic steroids. Systemic immunosuppressant administration can be considered in patients with intractable CPAN who do not respond to other treatment methods.⁷ Treatment methods that improve circulation (anticoagulants, thrombolytic agents, anti-platelet drugs, vasodilators) are also attempted, and can be actively considered in patients showing markedly impaired circulation due to ulcers or gangrene. In treatment-resistant cases, colchicine and dapsone could be used, but their definite effectiveness has not been reported.⁸

Immunosuppressive agents such as cyclophos-

phamide, azathioprine, or methotrexate, can be used in cases unresponsive to steroid therapy.⁹ Antibiotics are used in cases of antecedent streptococcal throat infections. In cases resistant to systemic steroids and immunosuppressive therapy, studies have shown that intravenous immunoglobulin can be successfully used.¹⁰

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The clinicopathological challenges of CPAN

Diagnosis	Clinical	Pathological
Allergic cutaneous vasculitis	<ul style="list-style-type: none"> • Often asymptomatic, but itching, burning, or pain may occur • Palpable purpura is the most common manifestation • Skin sores mostly located on the legs, buttocks, or trunk • Urticarial lesions may last longer than 24 hours and are more likely to resolve with residual pigmentation or ecchymosis • Open sores with dead tissue (necrotic ulcers) may complicate intense purpura 	<ul style="list-style-type: none"> • Presence of vascular and perivascular infiltration of polymorphonuclear leukocytes • Formation of nuclear dust (leukocytoclasia) • Extravasation of erythrocytes • Fibrinoid necrosis of the vessel walls
Erythema induratum (nodular vasculitis)	<ul style="list-style-type: none"> • Female predominance (aged 20-30 years) • Lower extremities are the most common sites • History of tuberculosis occurs in about 50% of patients • Crops of small, tender, erythematous nodules • Lesions may ulcerate with bluish borders • These irregular and shallow ulceration can result in permanent scarring and hyperpigmentation 	<ul style="list-style-type: none"> • Mixed septal and lobular granulomatous panniculitis with neutrophilic vasculitis • Caseation-like necrosis may also be seen • Vasculitis is not always identified and is not a requisite for the diagnosis • Presence of both septal granulomatous inflammation and lobular granulomatous inflammation
Livedo vasculopathy	<ul style="list-style-type: none"> • Common among females (average 45 years) • The initial findings are typically painful purpuric macules or papules on the ankles • Livedo appearance, skin ulcerations, and purpuric lesions on the lower extremities • Mostly bilateral • Atrophie blanche is common 	<ul style="list-style-type: none"> • Moderately dense, superficial and deep perivascular infiltrate of lymphocytes • Sparse neutrophils in the upper dermis • Fibrin in the walls of venules, in particular in the upper dermis • Thrombi occluding the lumen of venules in the upper dermis • Fibrin in the wall and thrombi in the lumen of the same venules in one or more venules • Large numbers of extravasated red blood cells in the upper part of the dermis • Edema of the papillary dermis • Spongiosis and ballooning sometimes resulting in intraepidermal vesiculation • Epidermal necrosis (sometimes)
Superficial thrombophlebitis	<ul style="list-style-type: none"> • Can occur spontaneously, especially in the lower extremities (the greater saphenous vein) • Presents as redness and tenderness along the course of the vein • Usually accompanied by swelling • Bleeding also can occur, this may turn to brownish pigmentation over the vein as the inflammation resolves • Thrombophlebitis in a varicose vein develops as a tender, hard knot and is frequently surrounded by erythema 	<ul style="list-style-type: none"> • Inflammatory reaction in the vein wall and thrombus in the lumen of the vein. • The reaction is localized mainly to the deep dermal medium-sized veins • Perivascular and intravascular inflammatory cells, mostly lymphocytes and histiocytes • Neutrophils may be prominent • Thrombus inside the lumen may be seen