Chronic ulcerative Cutaneous Vasculitis of the legs Clinical and histopathological study

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Summary:

Background*:* Cutaneous small vessel vasculitis characterized by necrosis and inflammation of upper dermal blood vessels. It presents with ulcers and systemic manifestations after extensive acute onset. Many patients have a form of cutaneous vasculitis that presents with chronic painful ulcerations & purpuras involving the ankles without systemic manifestations, with some similarity in clinical presentation to livedoid vasculopathy.

Patients and Methods: Thirteen patients were seen in the Department of Dermatology and Venereology, Baghdad Teaching Hospital, for a period extending from January 2004 to March 2005. They were evaluated clinically, histopathologically and other laboratory studies. In addition, evaluation of the clinical response to prednisolone 0.5mg/kg/day and azathioprine150mg/day was done.

Results: Thirteen patients were included in this study; eight females and five males, with male to female ratio of 1:1.6. Their ages ranged between 26-66 years with a mean ±SD of 42 ± 13.8 years. The duration of the disease ranged from 0.5 – 18 years with a mean ±SD of 38 ± 59.2 months.The clinical examination revealed multiple oval punched out ulcers, with an indurated base, and surrounded by a zone of erythema; affecting mainly the ankles and dorsa of feet. Histopathological evaluation showed upper dermal vessels' wall necrosis, fibrinoid deposition, obliteration of the lumen, extravasation of red blood cells, endothelial cells swelling with perivascular and vascular wall infiltration mainly by mononuclear cells.The treatment was started with prednisolone & azathioprine. The ulcers healed completely with residual hyperpigmentation - hypopigmentation, atrophy and scars within 10-15 weeks

Conclusions: Chronic ulcerative cutaneous vasculitis is often a neglected and misdiagnosed variant of vasulitis. Histologically it has vascuiltic features, and clinically looks like livedoid vasculopathy.

Key words: cutaneous vasculitis, clinical, histopathological

Introduction:

Cutaneous small vessel vasculitis is characterized by necrosis and inflammation of upper dermal blood vessels and can present with persistent ulcers and systemic manifestations after extensive acute onset. Many patients have a certain form of cutaneous vasculitis that presented with chronic painful ulcerations & purpuras involving always the ankles and the legs without systemic manifestations, with some similarity in clinical presentation to livedoid vasculopathy.(1,2)

The etiology of vasculitis is attributed to hypersensitivity to various antigens like drugs, chemical, microorganisms and endogenous antigens with formation of circulating immune complexes that are deposited in the vessels walls, this will activate compliment that is chemotactic for neutrophils. This result in vascular wall damage and extravasation of red blood cells (3). This study was designed to shed a light on chronic ulcerative cutaneous vasculitis regarding its clinical, histopathological and management aspects and to find differentiating points between it and livedoid vasculopathy which has similar clinical picture.

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Patients &Methods:

Thirteen patients with chronic ulcerative cutaneous vasculitis involving the legs (the cases diagnosed according to the criteria mentioned below) were seen in the Department of Dermatology and Venereology, Baghdad Teaching Hospital, Medical City for a period extending from January 2004 to March 2005. A detailed history was taken regarding the age, gender, the onset and duration of complaint, constitutional symptoms, and previous treatment and the response to it. History of associated systemic involvement including pain and swelling of the joints, abdominal pain, vomiting, hematemesis, bleeding per rectum or malena, loin pain, dysuria were recorded. Also a history of any possible

precipitating factor like upper respiratory tract infection, tuberculosis, drugs, alcohol, diabetes mellitus and hypertension. Patients with connective tissue disorders, Behcet's disease or malignancy were excluded.

The weight and height of patients were recorded and body mass index was calculated.Examination of ulcers regarding the site, size, shape, margin, base, floor and number. In addition the skin surrounding the ulcer to see signs of inflammation, pigmentation, varicose veins and scars. Distal arterial leg pulses, capillary refilling time were also examined in all patients. The vasculitis was diagnosed according to the American college of Rheumatology classification criteria: (3) Age more than 16 years, medications that may have precipitated event, palpable purpura, cutaneous eruption and positive biopsy results. Three criteria give the diagnosis.

Laboratory tests were performed for each patient including:-Hematological tests: hemoglobin, white blood cells and platelet counts, and ESR. These were performed every 2 weeks for 3 months and monthly thereafter. Serum glutamic-pyruvic transaminase, alkaline phosphatase and total serum bilirubin were performed at each visit.

Blood urea and serum creatinine were performed before starting treatment.

General urine examination, General stool examination and chest X-ray.Blood sugar for diabetic and hypertensive patients were repeated at each visit.

A deep incisional skin biopsy was taken from each patient.The second part of the study was performed to evaluate the clinical response to prednisolone 0.5mg/kg/day and azathioprine 2mg/kg/day (not more than 150mg/day). The patient response to treatment was assessed every two weeks for three months and monthly later on. Remission was considered as satisfactory when there were reduction of the ulcer size, edema, tenderness, oozing and erythema, no development of new lesions and growth of granulation tissue at the floor of ulcers, reduction of pain and decrease erythrocyte sedimentation rate. Photographs were taken before and after treatment until complete healing.

Patients were advised to stop smoking and alcohol intake, and to rest with elevation of legs above the level of heart few hours at frequent intervals per day. Proper management for infections was advised.

On remission tapering of treatment was done as following: Prednisolone was reduced by 5mg every 2week. After steroid was stopped, azathioprine was tapered by 50mg every month.

Results:

Thirteen patients were included in this study, five males and eight females (male to female ratio of 1:1.6), their ages ranged between 26-66 years (mean ±SD of 42 ± 13.8 years). The duration of the illness at the 1st visit was ranged from 6 months-216 months, with a mean ±SD of 38±59.2 months. Two patients (15%) had persistent lesions, while 11 patients (85%) had chronic active disease, with appearance of new lesions. Associated medical and social factors were shown in (Table-1).Body mass index of patients shown in (Table- 2)

On examination, most ulcers were oval-round, punched out, with indurated base and margins, tender and surrounded by a zone of erythema about 1cm wide. The ulcers size ranged from 0.5-5 cm in greater diameter. This description fits all patients (Figure-1A). Oozing from the ulcers at the time of presentation was observed in 4 patients (31%), while the ulcers were dry in 9 patients (69%). All patients complained of pain at their ulcers.

The sites of ulcers were, around the ankles in 10 (77%), dorsal feet 8(62%), shins 7(54%) and calves 1(8%) patients.

Secondary skin manifestations were white atrophic scars in 5 patients (38%), dyspigmentation in 5 patients (38.5%) and pitting leg edema in 6 patients (46%). All patients had positive distal arterial pulses, normal capillary refilling time and normal neurological examination. No patient had varicose veins.

Investigations: Hematological tests: Hemoglobin of 12gm\dl was observed in 3 male patients (23%) and less than 11.5gm\dl in 5 female patients (39%) . ESR was more than 30 mm ⁄ hour in 8 patients (62%). Platelet and WBCs counts were normal**.**

General urine examination*:* positive red blood cell cast in the urine were seen in 2 patients (15%).

General stool examination was negative results in all patients.

Liver and renal function tests were normal at time of presentation and during follow-up. For diabetic and hypertensive patients; blood sugar and serum cholesterol were under control at presentaton and on follow up. Histopathological evaluation reveals the picture of cutaneous vasculitis in all patients. Table -3 and Figure-1C

The treatment was started with prednisolone 0.5mg/kg/day combined with azathioprine 150mg/day in three divided doses. The response to treatment started within 2-11 weeks with a mean ± SD of 3.8±2.7 weeks (Figure-1B) in 12 patients, while in one alcoholic patient, treatment failed to produce any response within 6 weeks, but on stopping alcohol intake, healing started within 4 weeks..

Ulcers healed completely in 10 patients (77%) with residual hyperpigmentation – hypopigmentation. After that tapering of treatment was commenced. Two patients (15%) needed longer time of treatment. One patient had heart failure and old healed pulmonary TB was stopped the treatment, because of unwanted side effects.

The duration of treatment ranged from 7.5-13 months with mean ±SD of 9.5±1.8 months. ESR level: returned to normal after therapy.

The following complications of treatment were noted, weight gain was seen in 2 patients (15%), acniform eruption in 1 patient (8%), mild hypertension in 1 patient (8%) and avascular necrosis of head of right femure in 1 patient (8%)

was reported (The patient was already on systemic steroids at time of presentation).

Table (1): Frequency of associated (medical and social) factors

Associated factors	No. of patients	Percentage
Body Mass Index>25kg\m^2	10	77%
Hypertension	4	31%
Smoking	4	31%
Diabetes mellitus	2	15%
Sinusitis	2	15%
Heart failure	1	8%
Bronchitis	1	8%
Old healed Pulmonary tuberculosis	1	8%
Alcoholism	1	8%

Table (2) :Body mass index (BMI) of patients

	BMI <24.9 (Normal)	BMI 25-29.9 (Overweight)	BMI > 30 (Obese)	total
Number of patients	3	7	3	13
Values of BMI	24, 21, 22	28, 26, 28, 28, 27, 29, 29	35, 33, 30	
percentage	23.07	53.84	23.07	100%

Table (3): Frequency of histopathological findings

Histopathological finding	No. of patients	percentage
Atrophic epidermis	4	31%
Basal cell layer liquefactive degeneration	2	15%
Upper dermal vessels wall necrosis:- Severe Mild	 7 6	 54% 46%
Periappendegeal infiltration	3	23%
Perivascular and vessels wall cellular infiltration:- *Mononuclear cells *Neutrophils	 13 5	 100% 38.5%
Extravasations of RBCs	13	100%
Swelling of endothelial cells	13	100%
Dermal edema	13	100%

Discussion:

Cutaneous vasculitis is a relatively common disease. However few patients were referred to have a certain form of chronic cutaneous ulcerative vasculitis that attracted little attention. The present study shows that the primary lesions started as several red tender papules affecting mainly the ankles, dorsum of feet and sometimes the calves. This led us to diagnose vasculitis. The features were similar to that reported in literature about cutaneous small vessel vasculitis (3, 4).The papules then change into highly painful multiple ulcers. The striking histopathological findings in this study were mononuclear cells are always present in the infiltration. About 38.5% of cases who had less than one year ulcer duration had mixed infiltration by neutrophils and mononuclear cells. The explanation for this may be the mononuclear cells are more common in chronic lesions (5). In addition, we found that 15% of cases had basal liquefactive degeneration which was not mentioned before in cutaneous vasculitis.

This variety of chronic ulcerative vasculitis seems to be different from the leukocytoclastic vasculitis (LCV) by the followings:Patients with LCV present with acute prodromal symptoms (fever, malaise, myalgia, joint pain and gastrointestinal symptoms) (3). This was not seen in the present study and the mean duration of illness at presentation was 38 months. Therefore, chronic ulcerative vasculitis is chronic from the start, LCV can affects the lower legs, back of trunk and the hands and arms (3) ; while in chronic ulcerative vasculitis only the ankles and lower legs were affected,The lesions in LCV last for 1-4 weeks, and could persist for months or years with associated systemic disease like the kidneys, nervous system, gastointestinal tract, lung, joints (3). The present study showed that the duration of the disease was longer than 6 months and can reach to 18 years, but without systemic involvement apart from arthralgia in one case and the presence of casts in urine in 15% of patients that might indicate a subclinical renal involvement, and the histopathological findings of the present study showed infiltration of the vessels wall and perivascular area by mononuclear cells. This was different from LCV, which characterized mainly by leukocytes infiltration and leukocytoclasia.

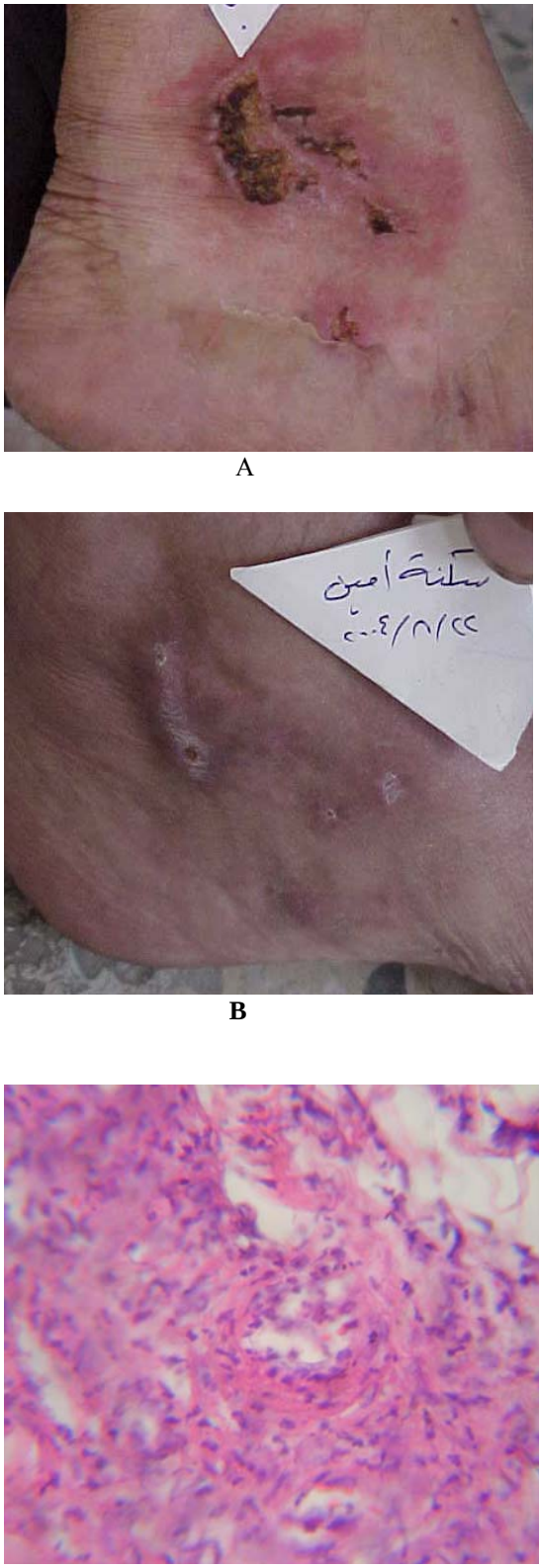
Overweight and obesity were present in 77% of cases. This could increase hydrodynamic pressure and result in sluggish flow that lead to localization of the autoantibody complexes in the vessels of the lower legs (6).

There is a great similarity between the cases in the present work of chronic ulcerative cutaneous vasculitis and livedoid vasculopathy. Especially the sites of involvement of ulcers in the ankles and the lower legs; chronic disease process; unknown etiology and the resultant scar, white atrophy and dyspigmentation (7). However, in the present report a number of differentiating characteristics were found. They are listed in (Table-4). The response to the treatment with prednisolone and azathioprine started in 2-11 weeks. Complete healing was achieved in 10-15 weeks with residual hyperpigmentation, hypopigmentation, atrophy and scars.

In conclusion, chronic ulcerative cutaneous vasculitis could be regarded as a variant of chronic vasulitis and should be differentiated from livedoid vasculopathy as both of them share many clinical features.

	Chronic cutaneous vasculitis	Livedoid vasculopathy (LV)
Age	Ranged from 26-66 years old. With 54% of cases younger than 40 years.	Greater than 40 years old.(8)
Gender	Male to female ratio = 1:1.6. no seasonal variations.	Predominantly female, mainly at summer season (summer ulcer).(9)
Pathogenesis	Small vessel vasculitis, circulating Immune complexes and circulating cytokines.[10, 11]	Thrombo-occlusive process of small and medium sized dermal vessels.(7,10)
Etiology	Obesity, alcoholic, upper respiratory tract infection, pulmonary tuberculosis, some patients had hypertension or diabetes on medications.	May be associated with hypercoagulable state, venous or arterial peripheral vascular disease (varicose veins, atherosclerosis, SLE).(7)
Clinical features	Tender red papules that became crusted ulcers within few weeks. *Sites: ankles, dorsum of feet, and calves. *All ulcers painful, surrounded by a zone of erythema *About 2\3 of cases had anemia with ESR≥30mm\hour.	*Primary lesions were petechiae which become atrophic centrally, then develope to ulcers, surrounded by telangectasia.(11, 9) *Sites: Feet or ankles, with rare involvement of dorsum of hands. *The ulcers slightly painful and is not surrounded by erythema.(11, 9) *The anemia &elevated ESR is not reported in literatures
Histopathology.	Necrosis of vessels wall of upper dermis. Perivascular and vessels wall infiltrate mainly by mononuclear cells, neutrophils in (38.5%). Endothelial cells swelling. Extravasations of RBCs. Epidermis (liquefactive degeneration in 15% of cases).	Capillary dilatation of mid and lower dermis without necrosis of vessels wall. Mild infiltration of vessels wall only by lymphocytes. Endothelial cells proliferation without swelling. RBCs extravasations in lesser extent. (No liquefactive degeneration). (7, 9)
Treatment	Prednisolone + azathioprine.	Anticoagulant, pentoxifylline or nifedipine. (7)

Table (4) Showing comparison between chronic ulcerative cutaneous vasculitis and livedoid vasculopathy.



A

B

C

Figure- 1: A 34 year's old female with 2 years history of chronic ulcerative cutaneous vasculitis. (A) Before treatment. (B) After 8weeks of follow

up. (C) Histopathology shows infiltration mainly by neutrophils.

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