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HISTOPATHOLOGIC STUDY OF CLINICAL TYPES OF PYODERMA GANGRENOSUM

REPORT OF 9 CASES WITH A SHORT REVIEW OF THE LITERATURE

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ABSTRACT

Pyoderma gangrenosum (PG) is an ulcerative skin condition of uncertain aetiology. This paper reports nine cases seen in two years at the Hamad General Hospital, Doha, State of Qatar. .The clinical presentations varied and are described as pustular, ulcerative, bullous and superficial granulomatous or vegetative PG. The diagnosis was confirmed by histopathology; some being repeatedly biopsied. The most distinctive histopathologic features are summarised. Some aspects of PG are pointed out concerning its epidemiology, clinical picture, diagnosis, associated systemic conditions, aetiology and management.

Introduction :

Pyoderma gangrenosum (PG) is an ulcerating skin condition[1]. Its diagnosis depends mainly on its clinical picture which may show considerable variation. PG often presents as a pustule in 80% of patients and the pustule may be single or multiple[2]. The pustule ulcerates in its center and spreads peripherally fairly rapidly in the course of a few days and adjacent lesions coallesce to form a serpiginous ulcer with a well defined border. The ulcers are either superficial or vegetating or deep. The ulcer has a necrotic base and a ragged undermined edge, painful, tender and sometimes associated with malaise and low grade fever. The course of the disease is usually prolonged over weeks or months before healing. Clinical improvement is usually preceded by cessation of pain[2]. The lesions heal with atrophic cribriform scar associated with hypo or hyper pigmentation and the disease may recur over months or years[2].

The primary lesion in PG occurs spontaneously [3] or occurs at site of trauma in 30-40% of cases[2,4,5] exhibiting a form of positive pathergy. The diagnosis of PG is essentially clinical although there is considerable variation in the clinical picture which can take several forms; ulcerative, pustular, bullous or vegetative possibly depending upon the associated disease and also producing different histological manifestations.[6]

PG affects a wide age range, with more female patients than males[7]. The average age of onset is 40 years although a small proportion of cases has been reported in infants and children[8], the youngest being only 3 weeks old[9] and four of 46 other children being less than one year old[10].

This paper presents nine cases of PG that have been seen at Hamad General Hospital (HGH) over a recent period of two years, together with the histopathological findings and a discussion of the possible implications.

Patients and Methods

Nine cases of pyoderma gangrenosum diagnosed at Hamad Medical Corporation between May 1994 and June 1996 are reported. Clinical details including variants of the disease, associated or underlying conditions, laboratory investigations and response to treatment are described. Light microscopic findings of 19 skin biopsies are described on formalin-fixed, paraffin-embedded 4 micron sections stained with Hematoxyline and Eosin and a number of special stains. Immunofluorescent stainings for Ig G, IgA, Ig M, C3, C1q and fibrin were performed on frozen sections or on formalin-fixed paraffin-embedded sections or on both in nine biopsies from six of the cases.

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Results:

A. Clinical

The patients, their nationalities,ages, sex, associated systemic diseases, variant of PG and result of treatment are summarised in Table 1. Main features are described in the following case reports :

Case 1: Egyptian male, 52 y.o.,first showed pustules on the right leg in 1984. These healed after twelve months but recurred more extensively in 1986 and were treated with a steroid cream. In 1987 papulonodular rashes developed on the right leg, buttock and right upper arm. Vegetative PG was diagnosed. No systemic disease was associated. The lesions recurred persistently despite treatment with Terracortril ointment. In 1994, he presented with a large pigmented scar on the right leg with three superficial crusted ulcers in the margin. The lesions cleared after treatment with a single injection of triamcinolone acetonide 40 mg I.M. and oral minocycline 100 mg twice daily for five weeks. This patient has been followed for two years and about four times a year he receives minocycline 100 mgm twice daily and prednisolone 5 mg once daily for one week when the pustules reappear (Fig. 1: a, b, c, d, e).

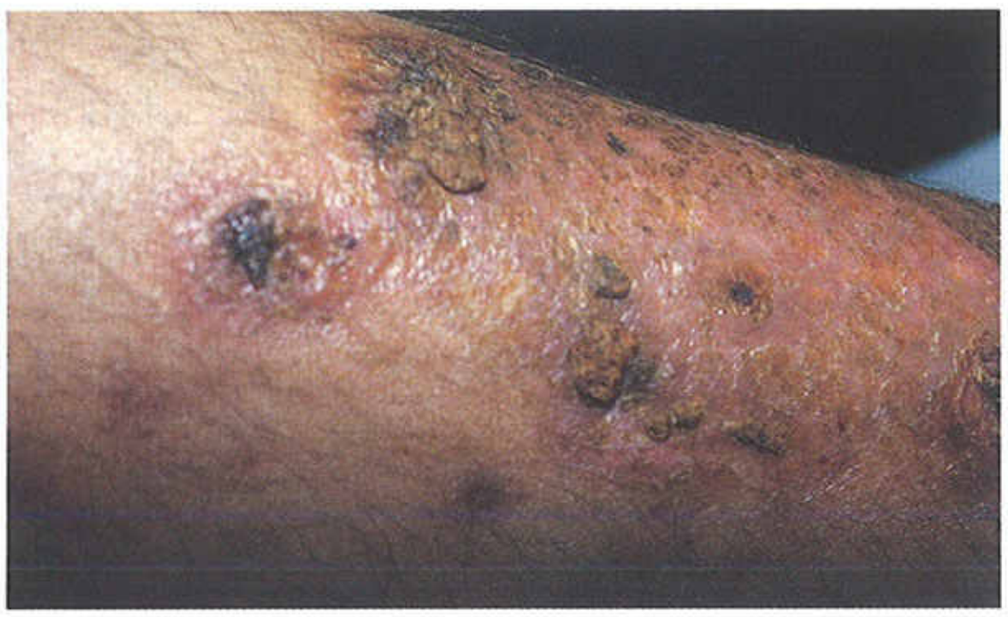


Fig. PG-1: a - Vegetating PG of right leg.

Fig. PG-1: b - A pustule around a hair follicle and lymphocytic vasculitis in the periphery

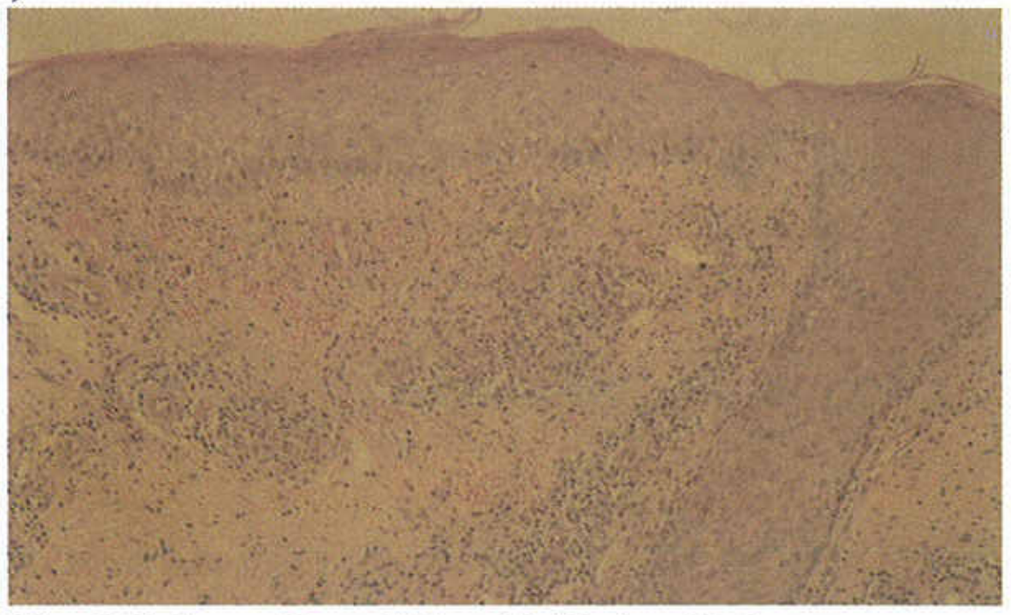


Fig. PG-1: c - Vasculitis with fibrinoid changes

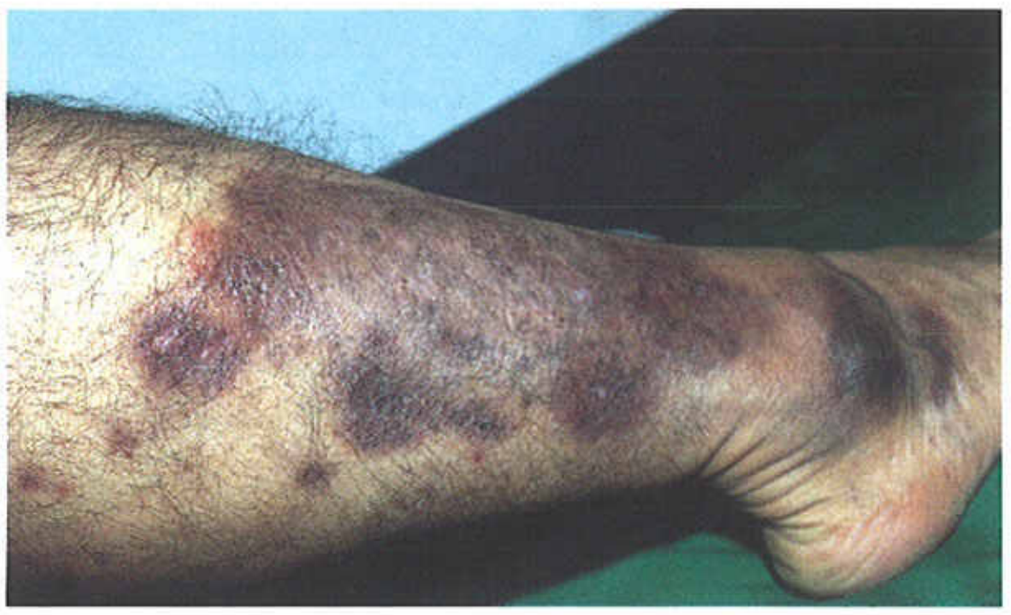


Fig. PG-1: d - PG after cure

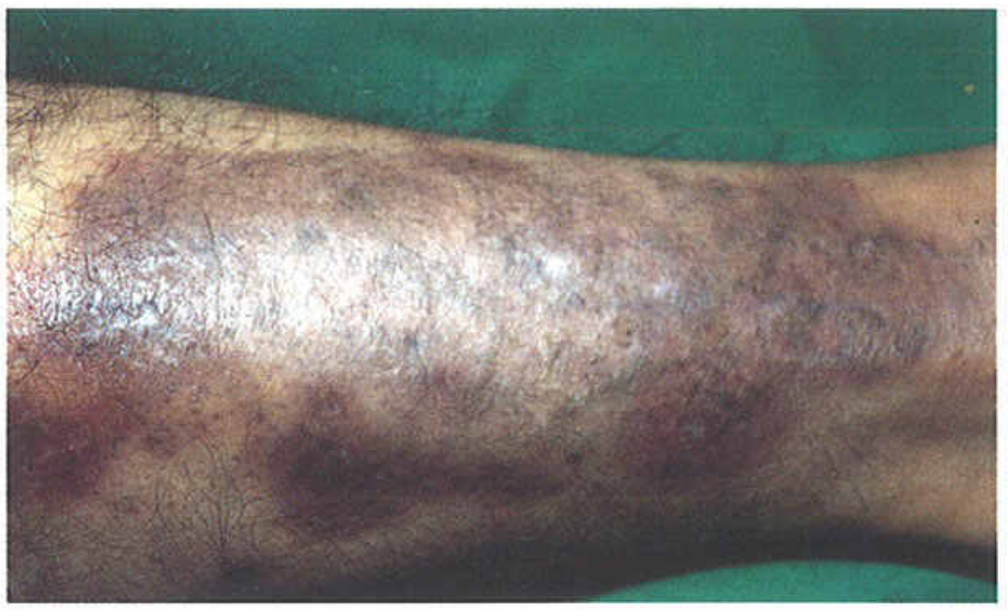


Fig. PG-1: e - PG with scarring and pigmentation

Case 2 British male, 42 y.o., hospitalised in late 1994 with a purulent ulcerated dorsum of the right foot. He had a perianal fistula and was being treated with Mesalazine for Crohn's disease of nine yearsduration. Ulcerative PG was diagnosed.. The patient was discharged cured of PG following debridement and a split thickness skin graft (Fig. 2: a, b, c, d).

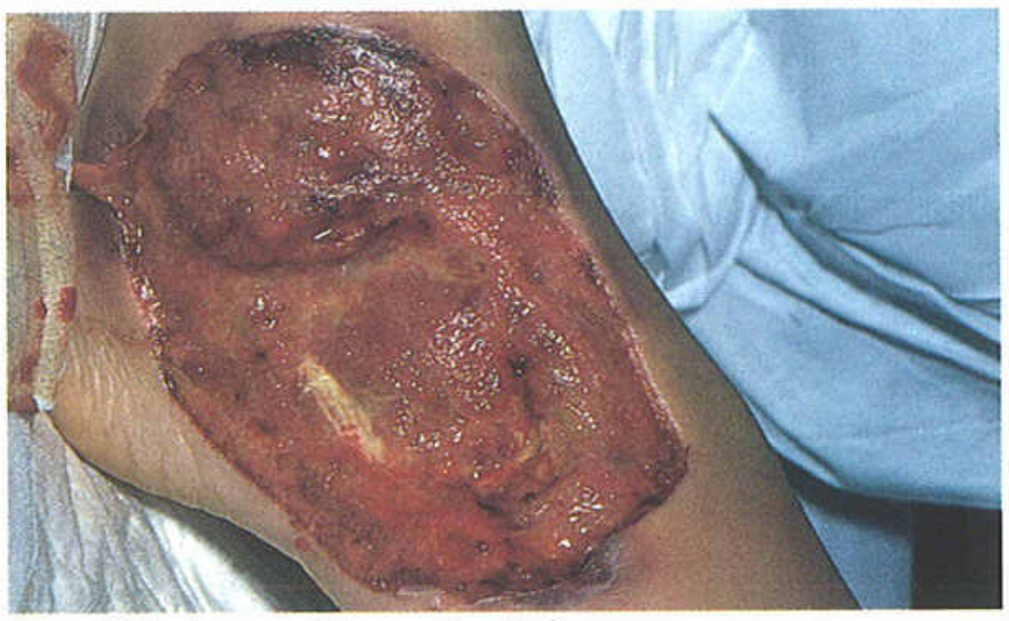


Fig. PG - 2: a - Ulcerative PG

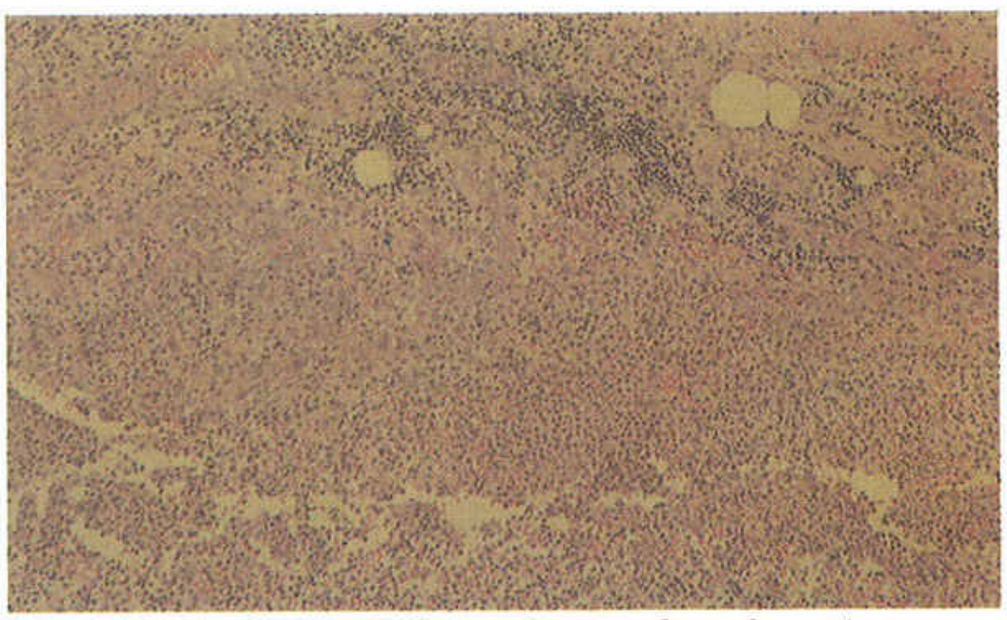


Fig. PG - 2: b - Pustule on the top, lymphocytic vasculitis in the deeper and more perpheral layers

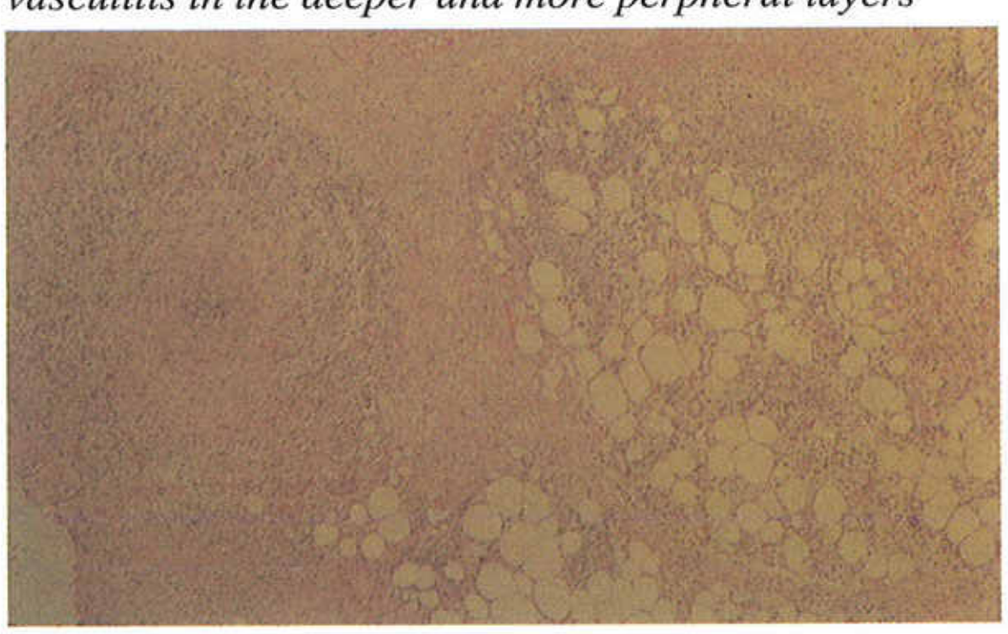


Fig. PG - 2: c - Panniculitis- Note almost total obliteration of the lumen in a large vessel

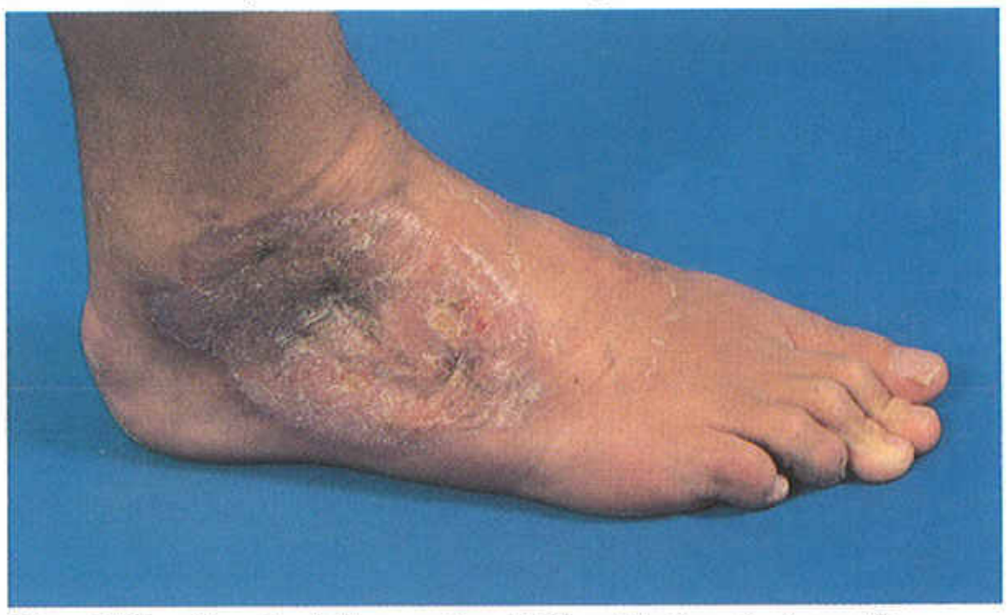


Fig. PG - 2: d - Ulcerative PG with healed graft

Case 3. Qatari male, 31 y.o. admitted in late 1994 with fever, swollen and tender knee, ankle, wrist and elbow joints and a diagnosis of migratory polyarthritis with rheumatic fever and erythema nodosum or Sweet's syndrome Extensive radiological and laboratory investigations were normal except for abnormal liver function tests (high alkaline phosphatase, SGPT and SGOT) and a leuco-erythroblastic reaction secondary to inflammation with a reactive thrombocytosis. Seven days later the patient developed ulcerated haemorrhagic bullae on both legs and bullous PG or Sweet's syndrome was diagnosed. The diagnosis of PG was confirmed by histopathology. Following a single injection of triamcinolone acetonide 40 mg I.M. and two days of treatment with prednisolone 25 mgm twice daily and minocycline 100 mg twice daily the fever subsided and two days later the prednisolone was reduced to 25 mgm once daily. The ulcers were dressed with 5% benzoyl peroxide and had healed completely ten days later (Fig. 3: a, b, c, d, e, f, g, h).

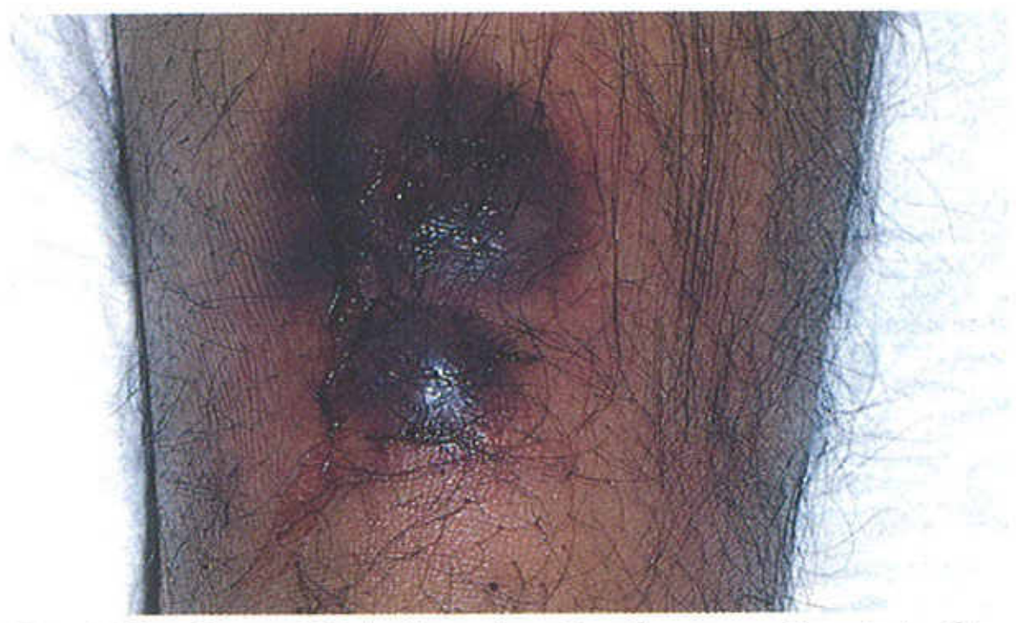


Fig. PG - 3: a - Right leg showing haemorrhagic bullae

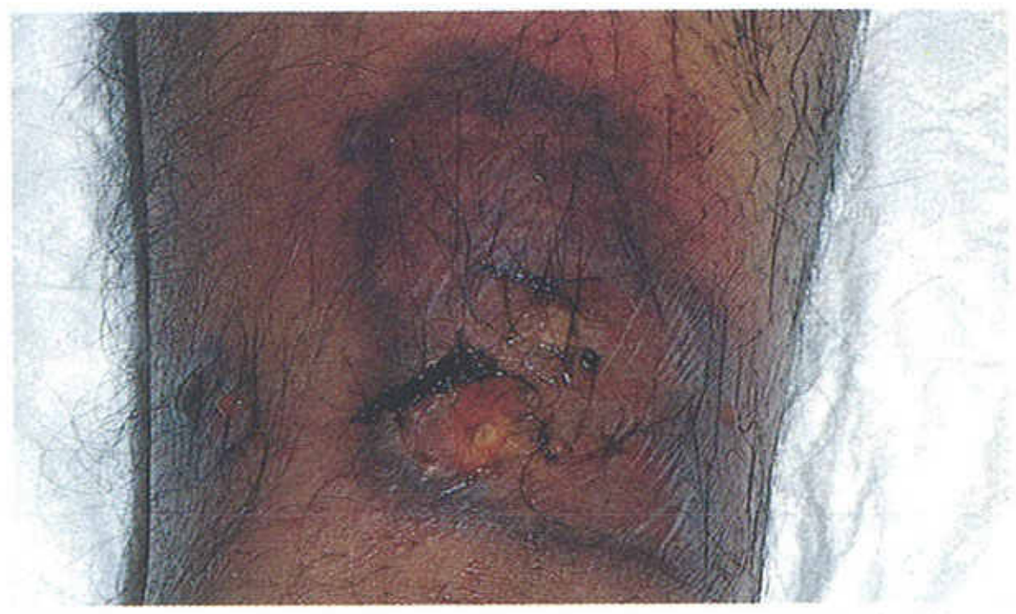


Fig. PG - 3: b - Left leg showing haemorragic bullae

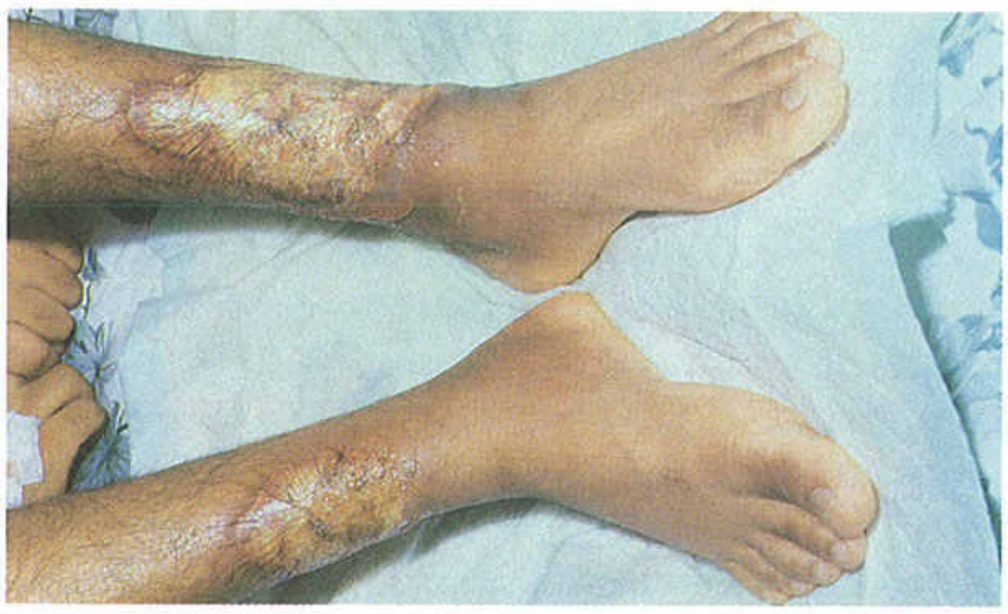


Fig. PG - 3: c - Both legs showing superficial ulceration

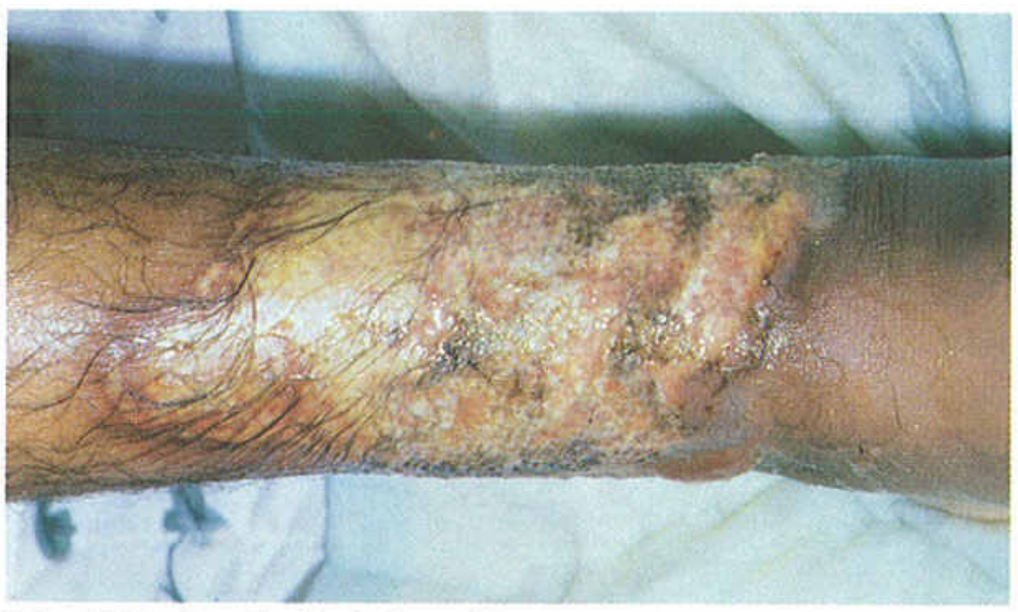


Fig. PG - 3: d - Left leg ulceration

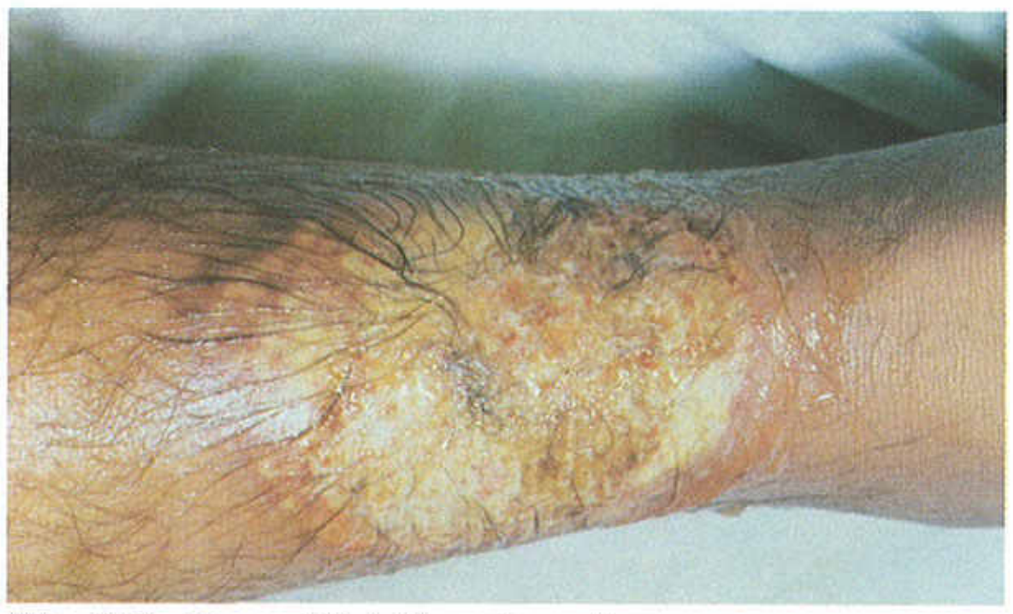


Fig. PG - 3: e - Right leg ulceration

Fig. PG - 3: f - Vasculitis with fibrinoid necrosis. Also note involvement of the sweat gland by inflammatory cells.

Fig. PG - 3: g - A pustule composed of numerous polymorphonuclear leucocytes.

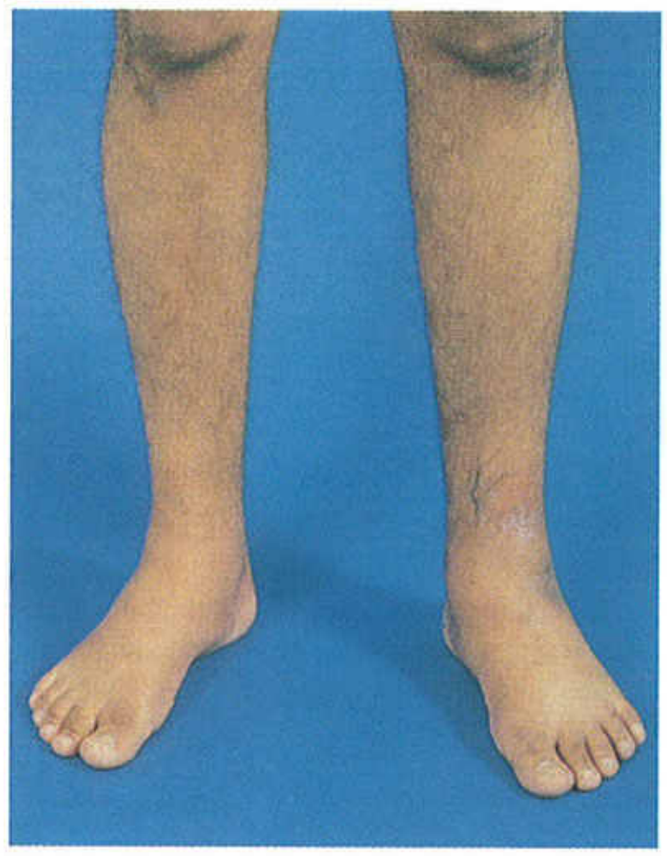


Fig. PG - 3: h - Both leg ulcers after cure

Case 4. Qatari male, 52 y.o.,with an ulcerating fluctuant nodule on the right thigh that had not responded to several months of antibiotic treatment. Vegetative or granulomatous PG was diagnosed and an associated diabetes was discovered. The ulcer healed following seven days treatment with minocycline 100mg 8-hourly and prednisolone 15mg daily (Fig. 4: a, b, c, d).

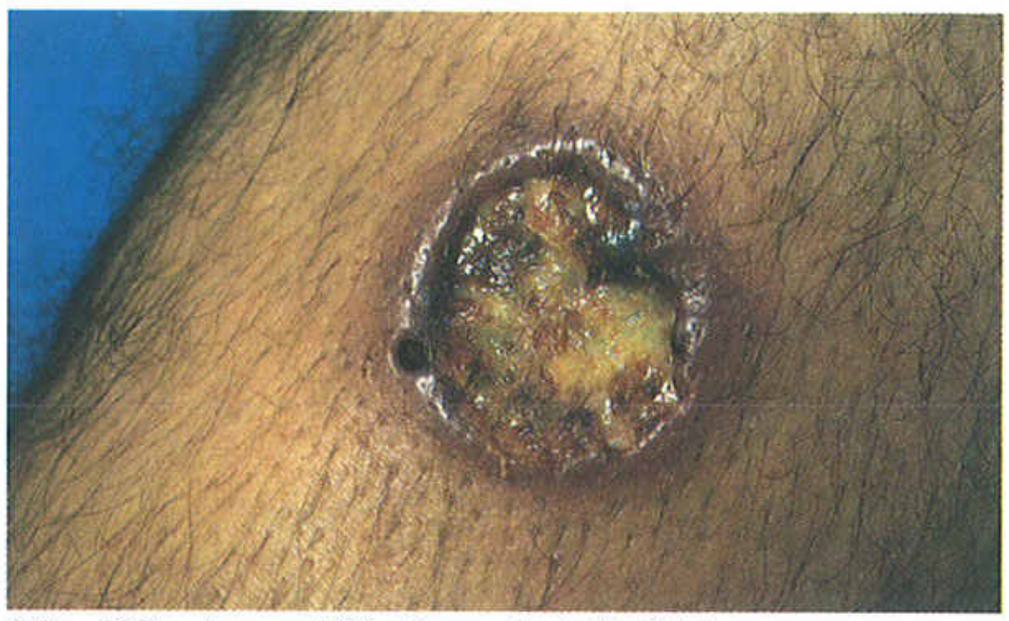


Fig. PG - 4: a - PG ulcer of right thigh

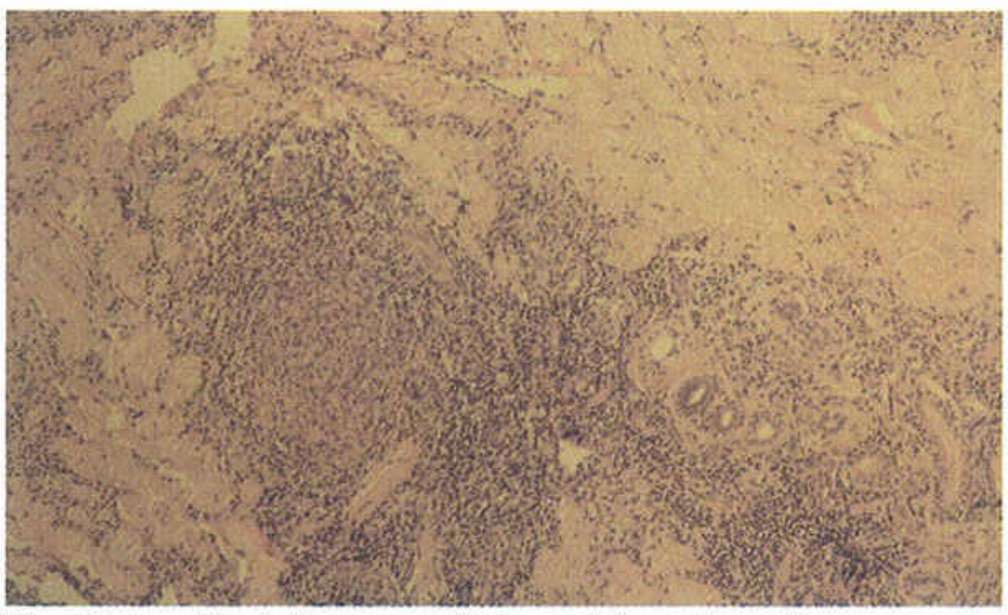


Fig. PG - 4: b - Nodular vasculitis and lymphocytic hydradenitis

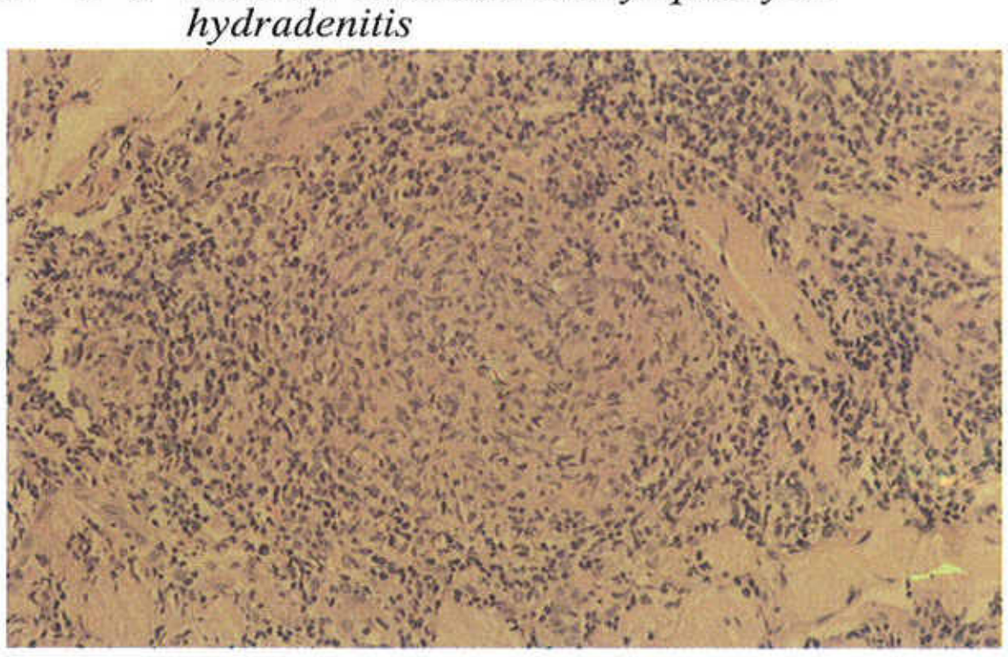


Fig. PG - 4: c - Nodular vasculitis at higher power

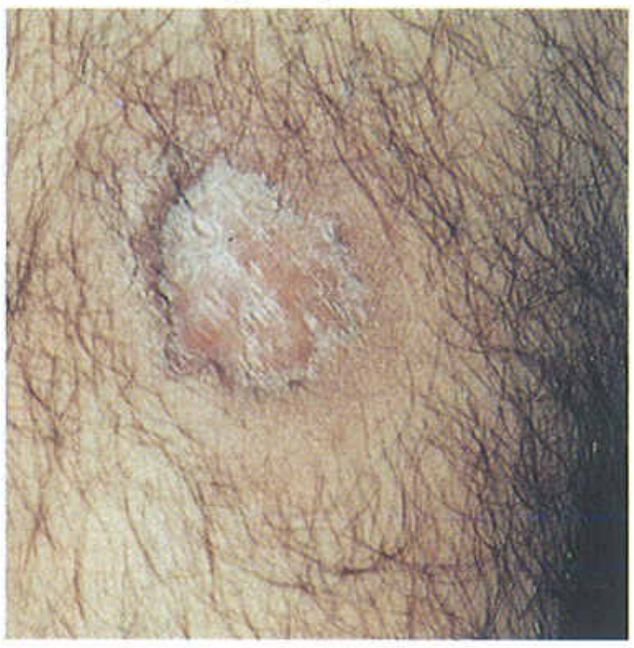


Fig. PG - 4: d - Healed ulcer with atrophic scar

Case 5. Indian male, 25 y.o., suffering for five years from papulo-vesicular and papulo-pustular eruptions of the trunk and upper limbs which became ulcerated and healed with a pigmented scar and later with erosions of the lips and inner cheek. There was no associated illness. Laboratory tests showed a high IgE (>1000 Ku/l) and a low titre of herpes simplex antibodies. Six biopsies were taken over a period of nine months. Pustular PG with a high IgE was thought the most likely diagnosis. All lesions healed with pigmented scars following treatment with systemic steroids and dapsone (Fig. 5: a, b, c, d, e, f, g, h).

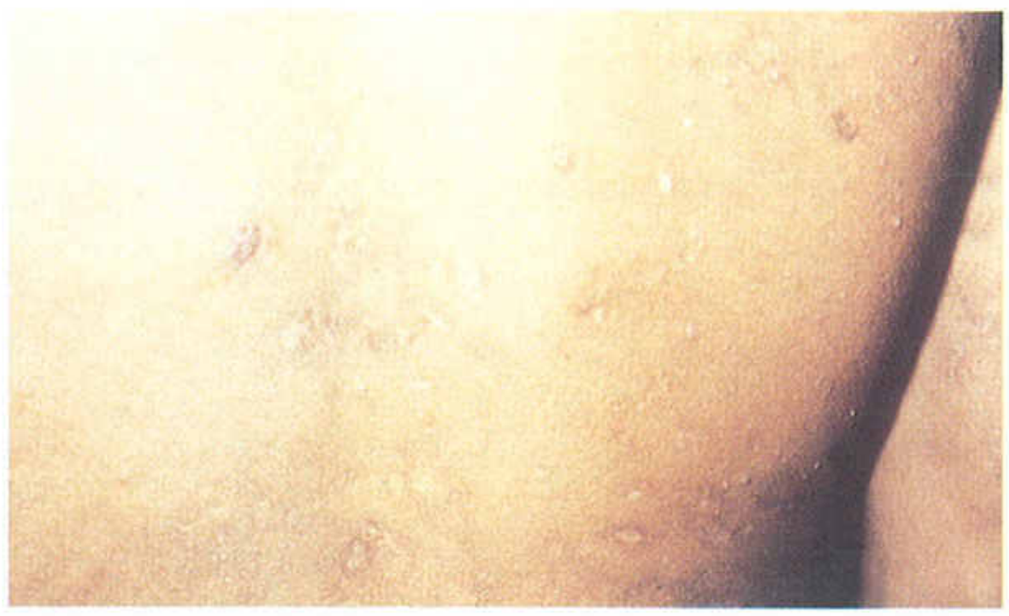


Fig. PG - 5: a - Early pustular lesion

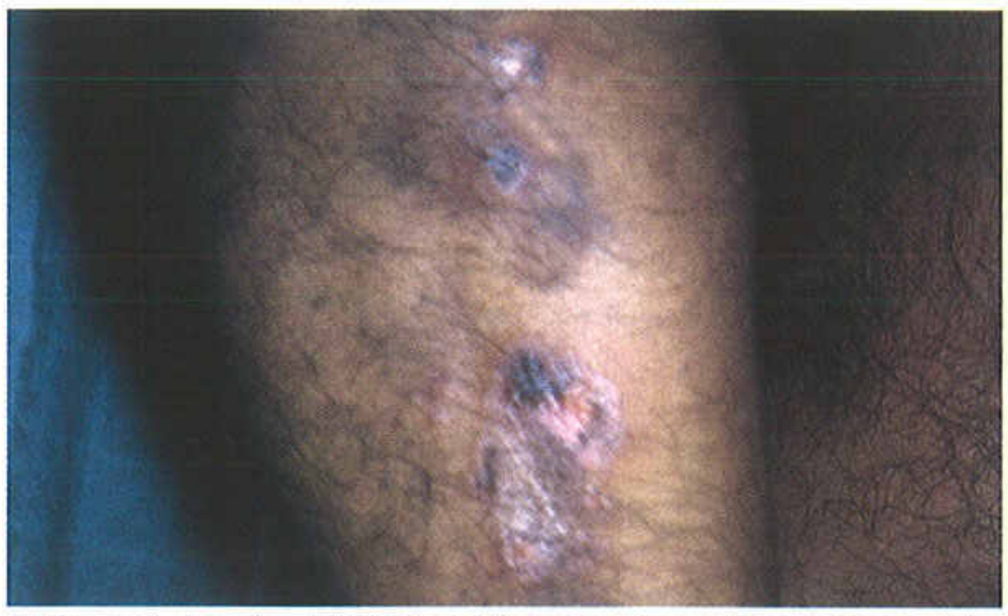


Fig. PG - 5: b - Peripheral extension of pustules and superficial ulceration

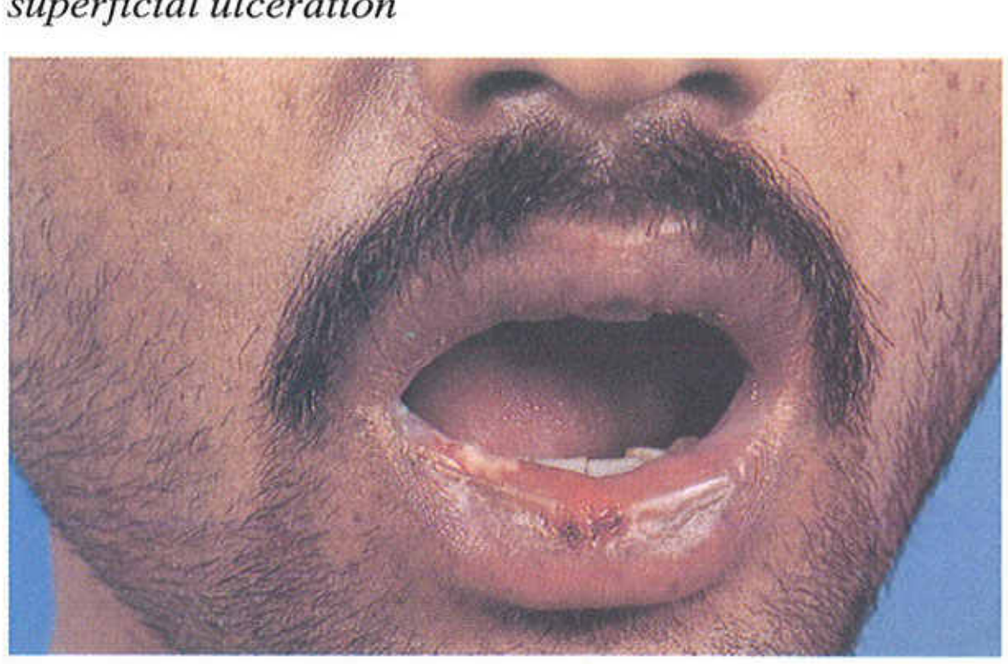


Fig. PG - 5: c - Lip affection

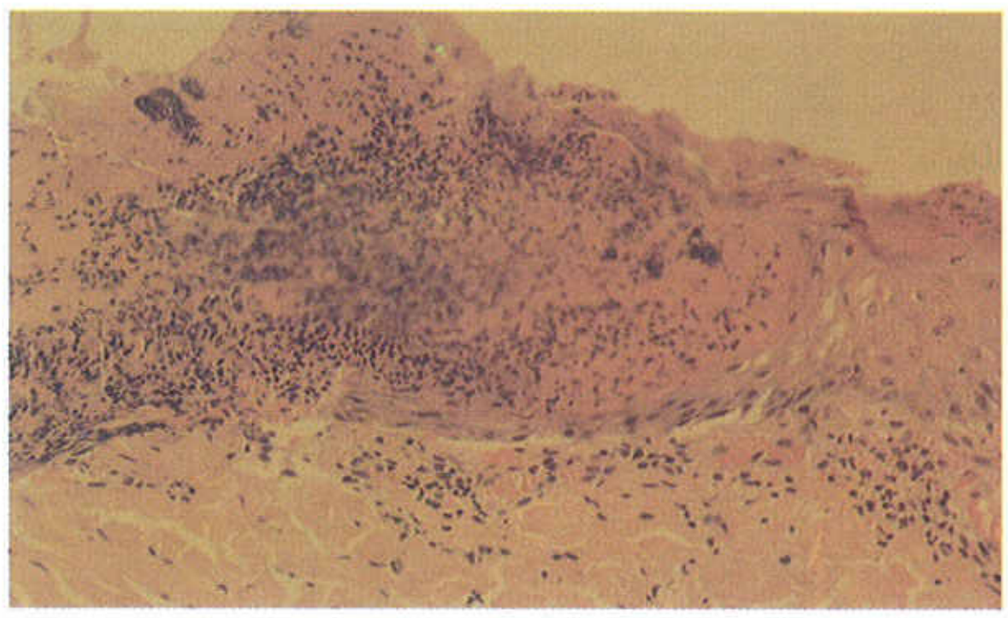


Fig. PG - 5: d - Pustules with bacterial colonies

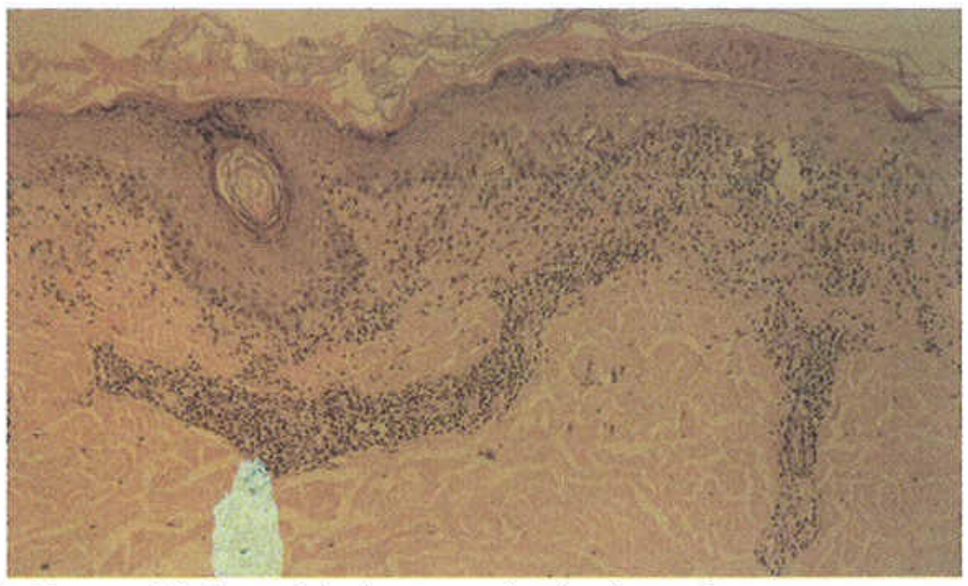


Fig. PG - 5: e - Lichenoid changes in the basal zone associated with lymphocyte vasculitis

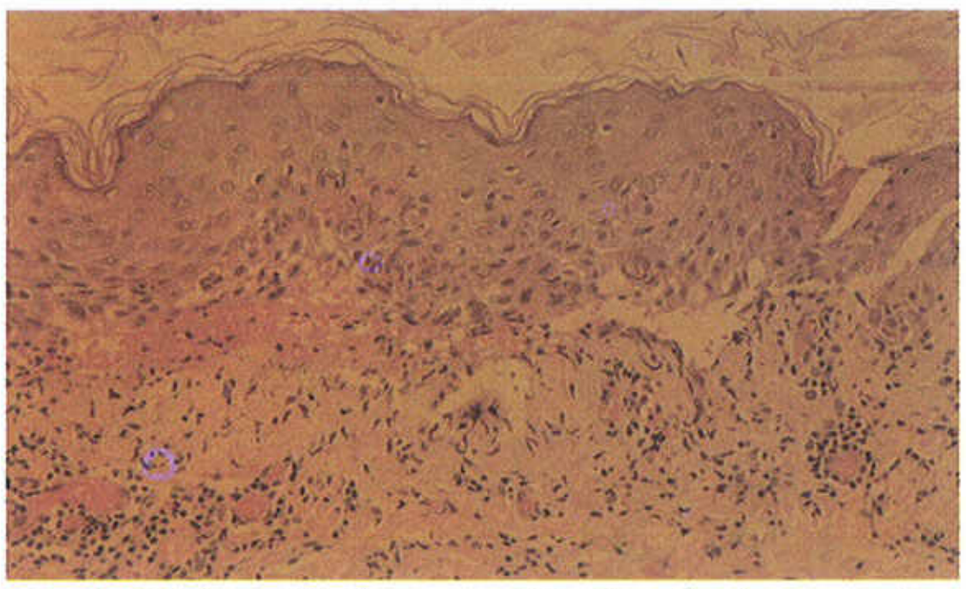


Fig. PG - 5: f - Lichenoid changes with abundant apoptosis

Fig. PG - 5: g - Healing with post inflammatory pigmentation

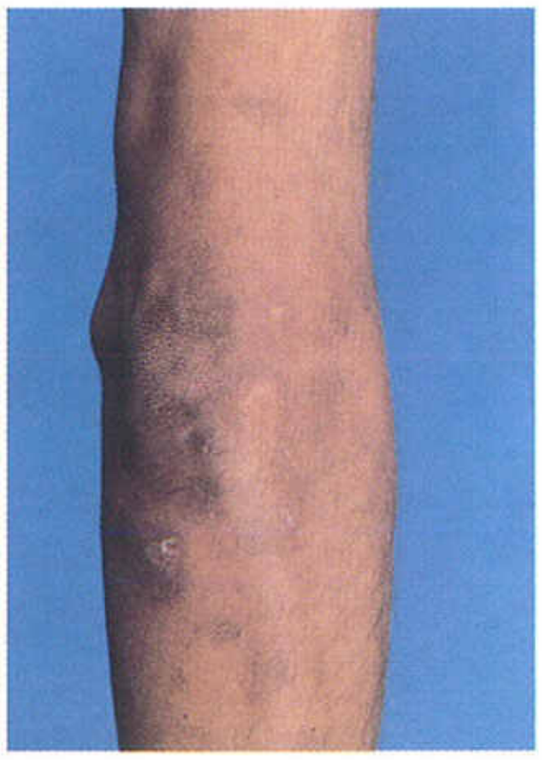
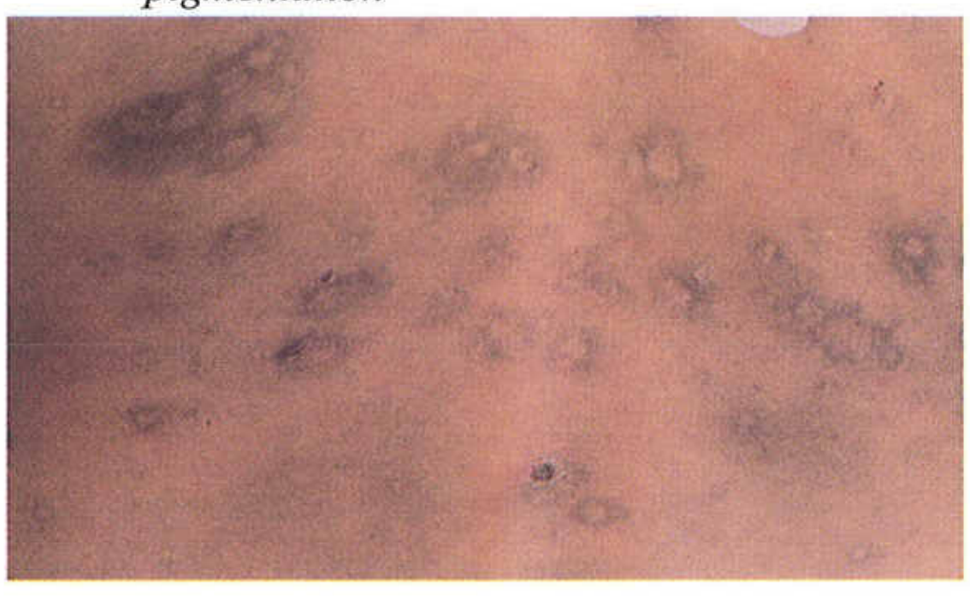


Fig. PG - 5: h - Healing with post inflammatory pigmentation



Case 6. A 16 day-old female admitted for fever, poor sucking and with dark coloured urine of two days duration. She had hepatosplenomegaly, granulocyte dysfunction and Pseudomonas sepsis. During a prolonged illness gangrenous ulcers developed on the left perianal region and both buttocks and the ulcer biopsy confirmed the diagnosis of PG. Despite several courses of ceftiazidim and intensive care she died of pseudomonas septicaemia at the age of nine months (Fig. 6: a, b).

Fig. PG - 6: a - Infarcted skin with ulceration - Note ghosts of adnexa

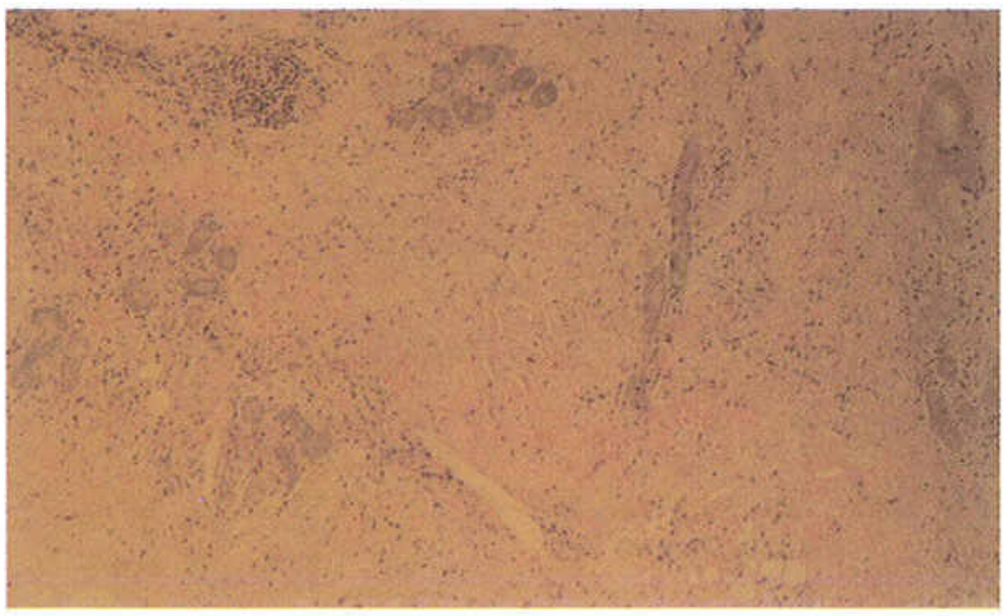


Fig. PG - 6: b - Infarcted skin and ghosts adnexa shown at higher power.

Case 7. Pakistani male, 63 y.o., on chemotherapy for malignant T-cell lymphoma since 1993, developed cutaneous involvement in 1995 with two tender boil-like lesions on his right leg. The pustular PG was treated with minocycline 100 mg 8-hourly for ten days and then cyclosporine 6 mg/Kgm/day for ten days. Because of a raised creatinine level the cyclosporine was reduced to 3 mg/Kgm/day and the creatinine level returned to normal. The PG cleared two months after the commencement of treatment and the cyclosporine was discontinued three weeks later (Fig. 7: a, b, c, d).

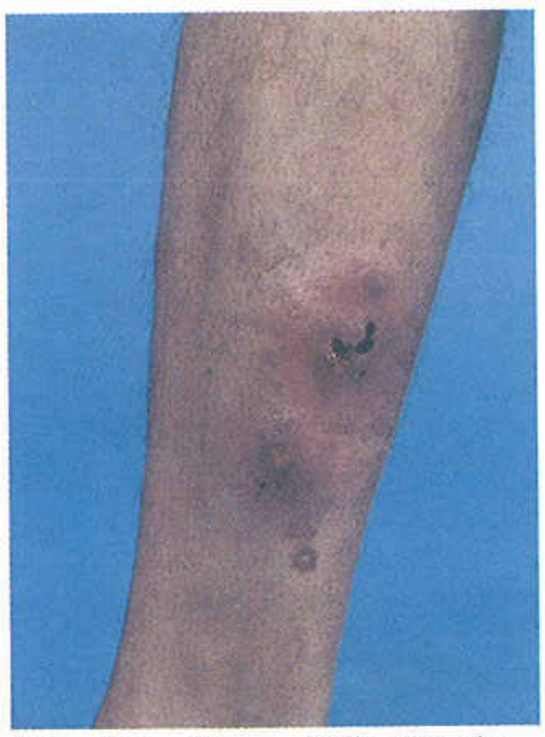


Fig. PG - 7: a - PG of right leg when disease began

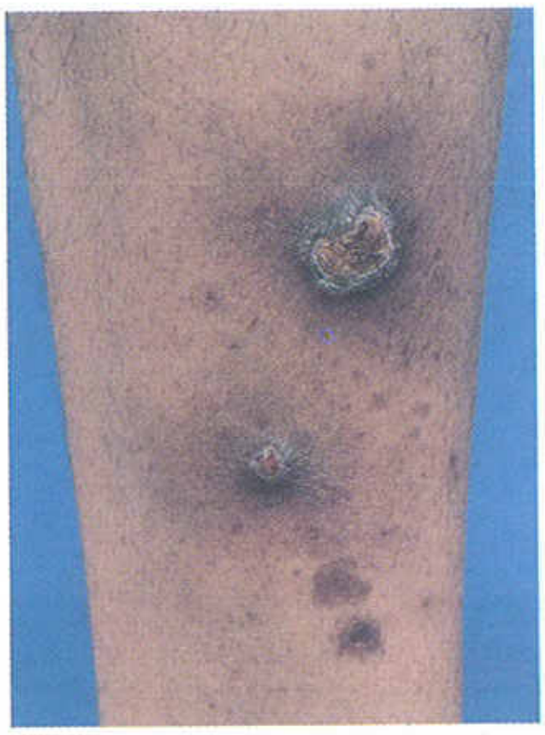


Fig. PG - 7: b - PG of right leg one month later

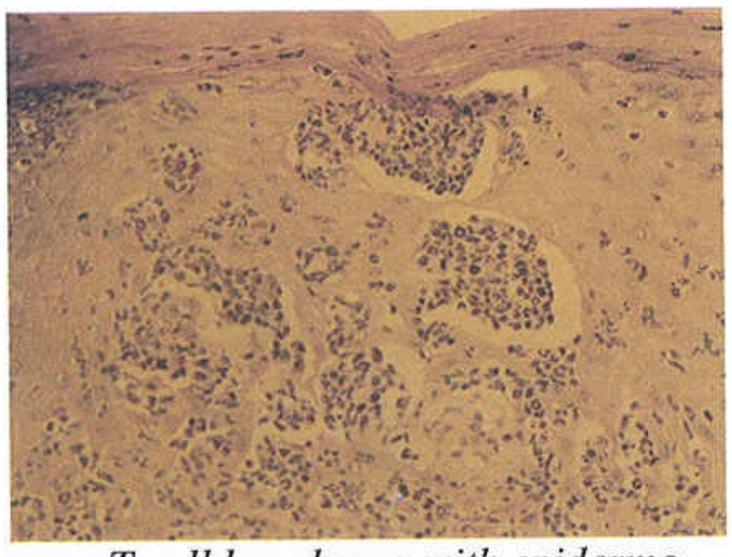


Fig. PG - 7: c - Cutaneous T-cell lymphoma with epidermotropisms and Pautrier's microabcess

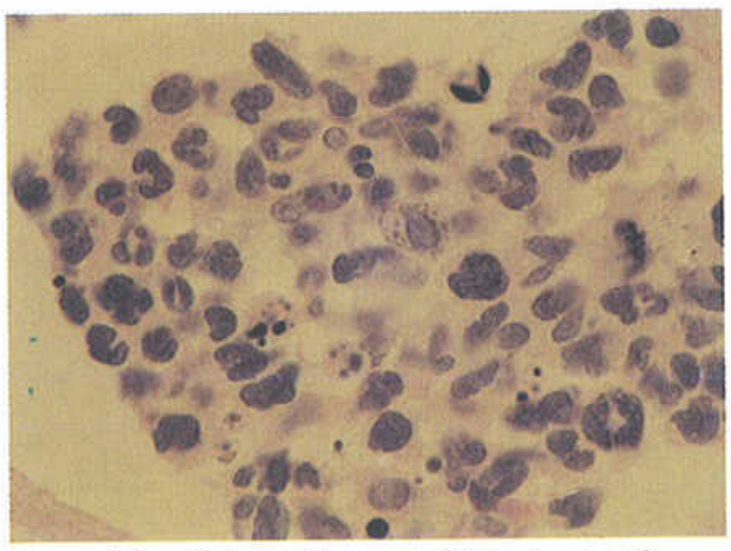


Fig. PG - 7: d - Cutaneous T-cell lymphoma: Cytological details of the malignant cells with multilobulated nuclei in a Pautrier's microabcess

Case 8. Qatari male, 68 y.o., under treatment for chronic myelocytic leukaemia for the previous ten years, developed a painful ulcerating papulo-pustular rash over both legs and both forearms. Pustular PG was diagnosed. The lesions cleared following erythropoietin 4,000 units I.M. twice a week, coliuracil, prednisolone 50 mg daily for ten days reduced to 25 mg daily for a further 45 days (Fig. 8: a, b, c, d, e, f, g, h).

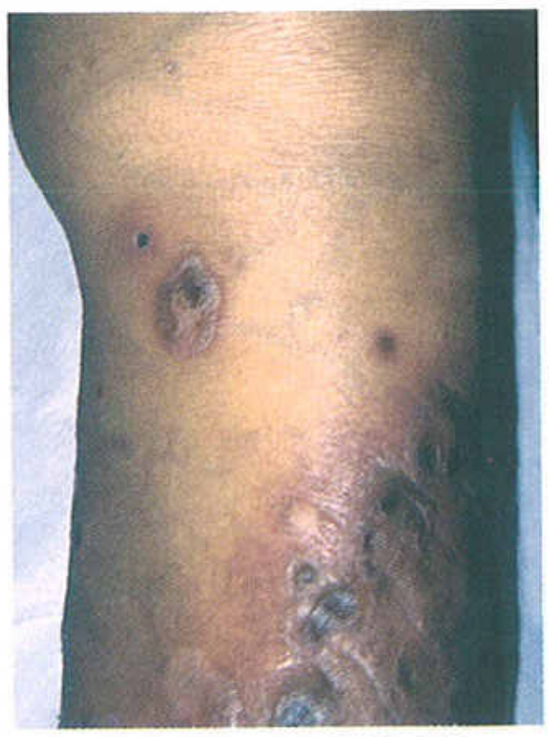


Fig. PG - 8: a - PG left leg

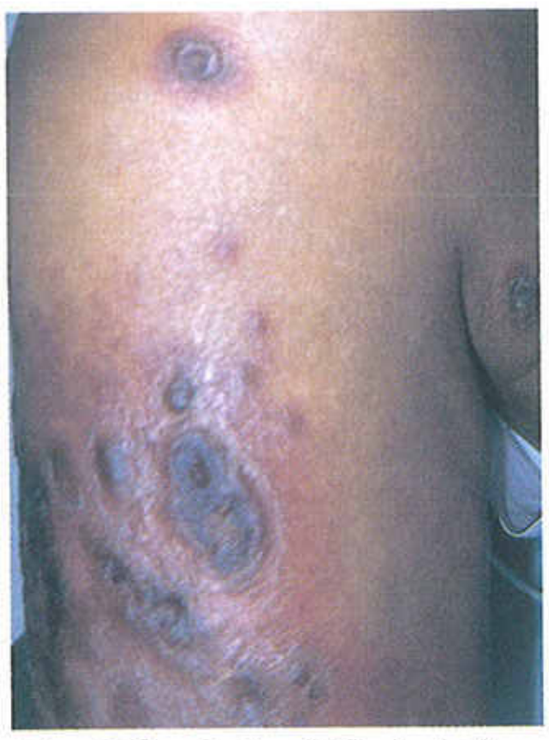


Fig. PG - 8: b - PG right leg

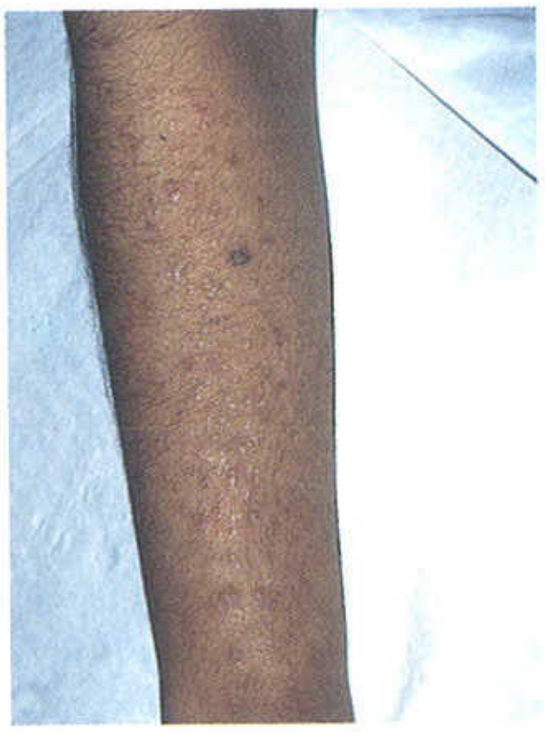


Fig. PG - 8: c - PG forearm

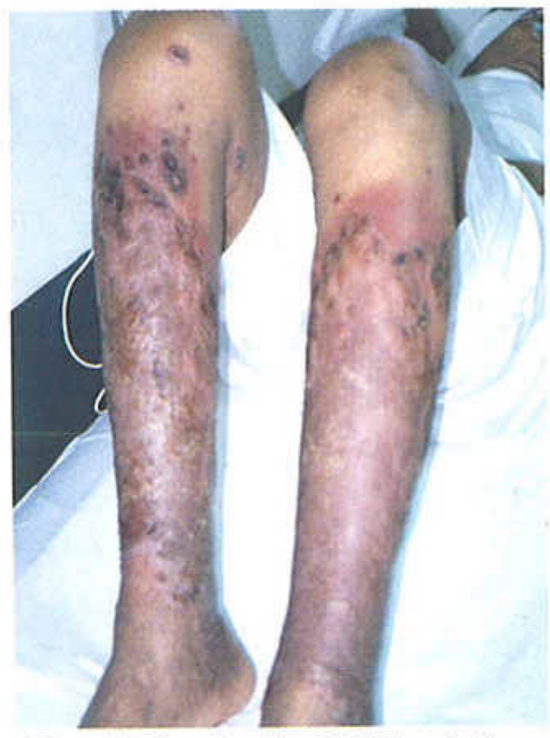


Fig. PG - 8: d - PG both legs

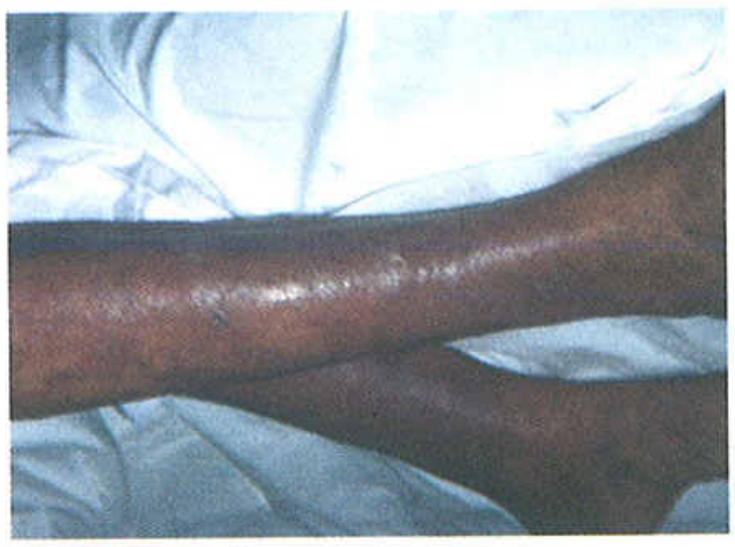


Fig. PG - 8: e - After cure - both legs

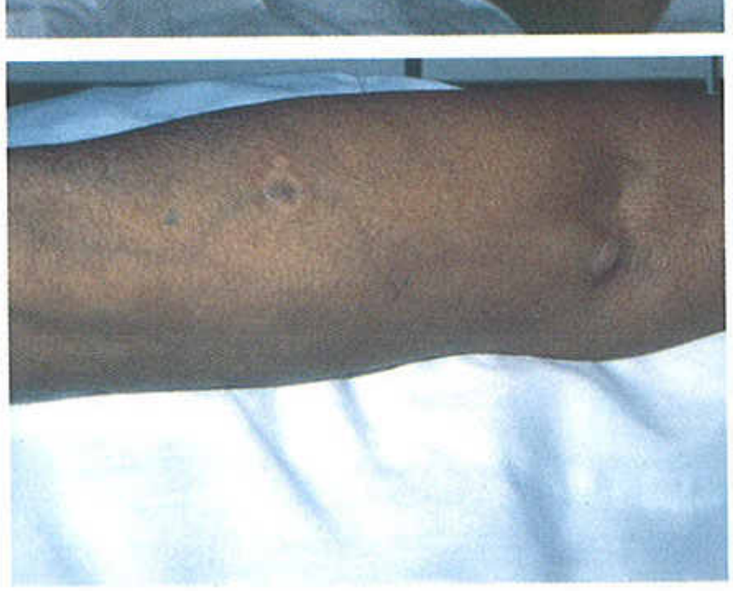


Fig. PG - 8: f - After cure forearm

Fig. PG - 8: g Dermalmono-nuclear infiltrate and prominent vessels

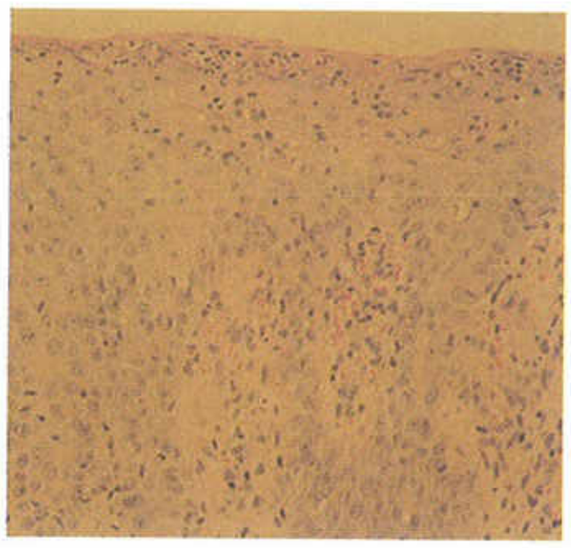


Fig. PG - 8: h - Exocytosis in the epidermis with occasional apoptosis

Case 9. Pakistani male, 21 y.o., with purpuric eruptions on both legs, failed to respond to treatment with prednisolone 30 mgm daily for one week. The lesions progressed and became necrotic. Bullous PG was diagnosed. His condition improved slowly on prednisolone 75 mgm daily plus minocycline 100 mg 8-hourly for one week. Cyclosporine 5 mg/kg/day was added, the prednisolone was reduced to 25 mg/day and the minocycline was discontinued. The slow improvement progressed to about 90 per cent after one month. The cyclosporine was discontinued after 54 days and the prednisolone was tapered gradually. The lesions healed completely with post-inflammatory pigmentation. No associated systemic disease was detected (Fig. 9: a, b, c, d, e, f, g).

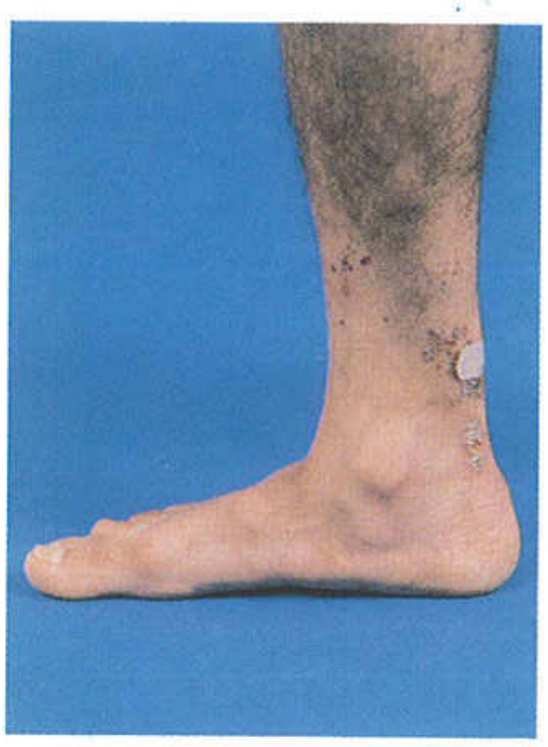


Fig. PG - 9: a - PG right leg

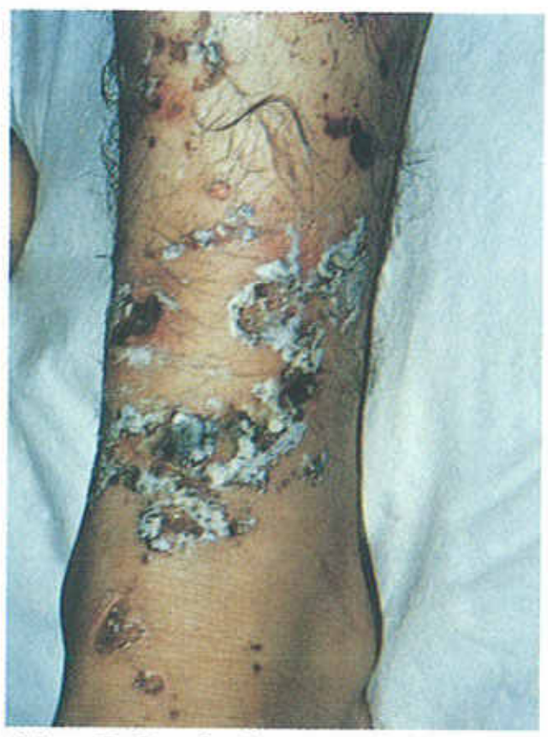


Fig. PG - 9: b - PG left leg (front)

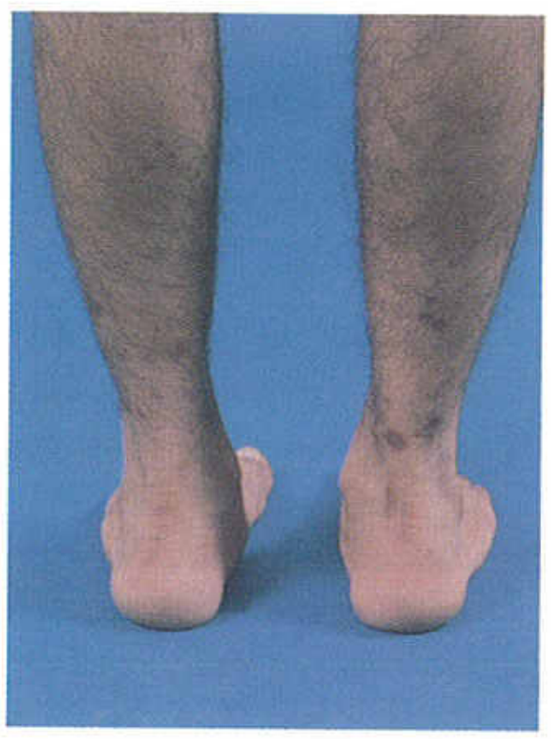


Fig. PG - 9: c - PG right leg (back)

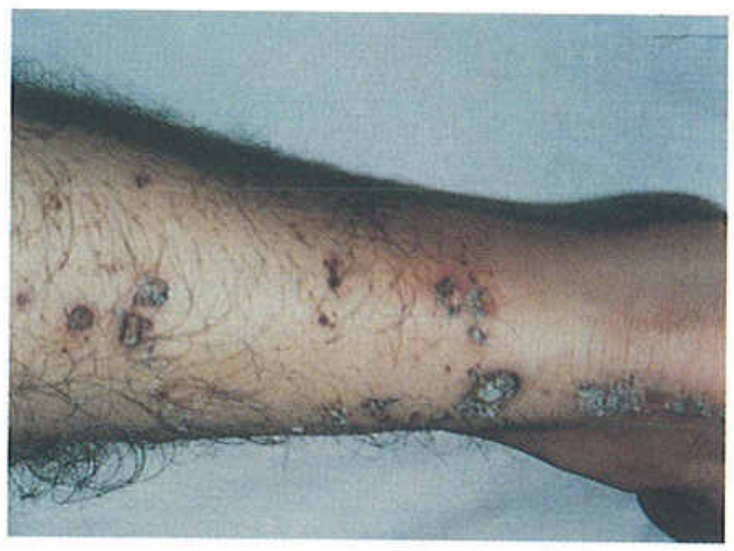


Fig. PG - 9: d - Infarcted skin with ulceration - Note ghosts of adnexa

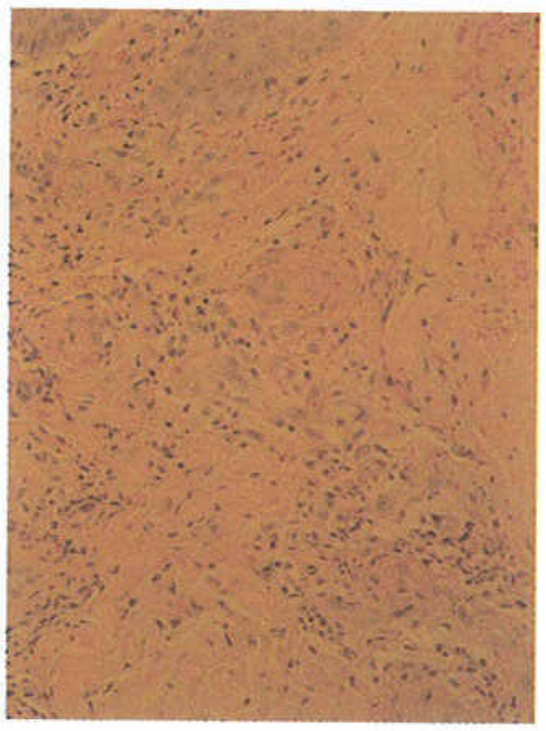


Fig. PG - 9: e - Fibrinous deposits in the walls of several vessels in the dermis.

Fig. PG - 9: f - After cure front of both legs

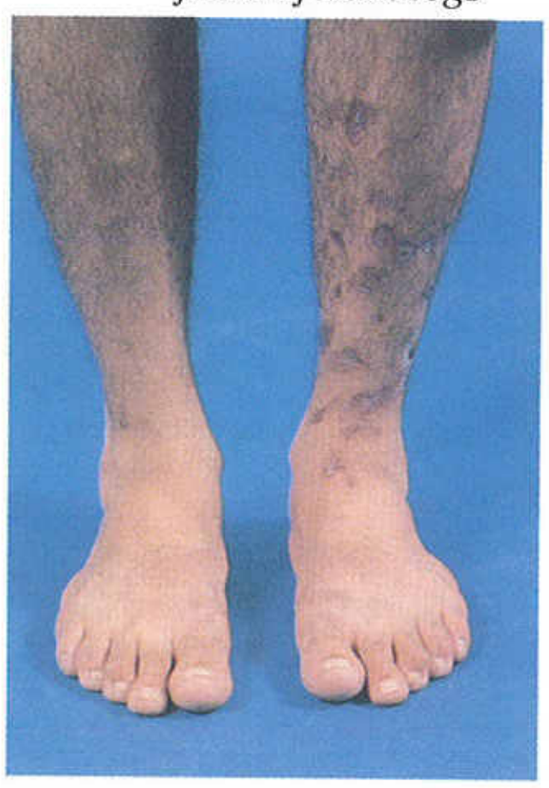


Fig. PG - 9: g - After cure back of both legs

B. Histopathology and Immunofluorescent Microscopy

These findings (summarised in table 2 and partly illustrated in conjunction with clinical pictures in Figs 1 to 9) included a combination of vasculitis, necrosis and pustules sometimes associated with bullae, apoptosis and hidradenitis.The main immuno-fluorescent features were positive stainings of the vascular walls for immunoglobulins and complement components.

DISCUSSION

The diagnosis of PG depends primarily on the recognition of the clinical features of the lesions. Microscopic features are not pathognomonic but help to confirm the diagnosis. Histopathological findings vary according to the clinical type, stage of evolution of the lesions and also depend upon which parts of the lesions have been included in the biopsy.

There may be observed a vasculitic process with endothelial damage, fibrin deposition, thrombosis, extravasated red blood cells and tissue necrosis followed by ulceration, infarction and abscess formation. In ulcerative PG an area of neutrophilic infiltration, often with abscess formation, is seen in the centre of the lesion surrounded by zones of vasculitis in the periphery, initially with mixed inflammatory cellular infiltrates which become predominantly lymphocytic in type as the disease progress. In pustular PG neutrophilic pustules are seen in subcorneal and intradermal locations as well as in and around the hair follicles. In bullous PG microscopic findings may range from subcorneal bullae, intra-epidermal oedema and bullae to dermal oedema, neutrophilic infiltrations and microabscesses.

Immunofluorescent techniques may demonstrate features reflecting a vasculitic process in some biopsies, such as stainings of the vessel walls for immunoglobulins, complement components and fibrin. This does not contribute directly to the diagnosis of the condition or the understanding of its pathogenesis. however, Immunofluorescent stainings are often necessary to exclude other diseases such as pustular and bullous dermatoses which may pose problems in the differential diagnoses.

In our nine patients, four had no detectable associated disease; the other five showed various diseases with no one being common (Table 1).

In one previous study the age of presentation of PG ranged from 30-80 years with an average age of onset of 40 years and a female to male ratio 2 : 1 [7]. In others 4% of the patients were infants and children[8]. The youngest documented case was 3 weeks old[9] and out of 46 other children affected, four (8.7%) were below one year of age[10]. In our series the youngest patient affected (and the only female) was a newborn infant (16 days old) and the ages ranged from her to 68 years.

Our nine patients are clinically described according to Powell et al[6] who related the clinical type of PG to particular associated systemic disorders. Two of our cases were vegetative (superficial granulomatous) one of whom had diabetes mellitus ; two were ulcerative (one had Crohn's disease and the second had an immunodeficiency condition), two were bullous not associated with systemic diseases and three were pustular (one had T-cell lymphoma, the second had chronic myeloid leukemia and the third had no systemic association).

The ulcerative type of PG is frequently associated with inflammatory bowel disease (IBD), arthritis and monoclonal gammopathy. The superficial bullous and pustular forms of PG are observed with myeloproliferative and lymphoproliferative disease, Wegener's granulomatosis and Takayasu's syndrome[11, 2] and the acute phase of IBD An overlap between Sweet's syndrome and superficial bullous PG has been described[12]. One of our patients who presented with bullous PG was clinically suspected to have Sweet's syndrome. The superficial bullous variant of PG has a poor prognosis.

It is estimated that 7% of PG patients have an associated malignancy which is most commonly hematologic in nature particularly leukemia[13,14]. Two of our patients had malignant disease (T-cell lymphoma and chronic leukemia).

The vegetative or superficial granulomatous PG is a superficial ulcer which is relatively non pain-

Table 1 : **Classification of PG Cases**

Patient serial number and nationality	Sex	Age in years	Associated systemic disease	Description of PG lesions	Result of biopsy	Treatment given	Result
1 Egyptian	M	52	Nil	Vegetative	PG	Minocin + Predrisolone	Cured
2 British	M	42	Crohn's disease	Ulcerative	PG	Mesalazine + Graft	Cured
3 Qatari	M	31	Nil	Bullous	PG	Minocin + Prednisolone	Cured
4 Qatari	M	52	Diabetes Mellitus	Vegetative	PG	Minocin + Prednisolone	Cured
5 Indian	M	25	Nil	Pustular	PG	Prednisolone + Dapsone	Recurs if treatment is discontinued
6 Palestine	F	9/12	Hepatospleno-megaly + granu-locyte dysfunction	Ulcerative	PG	Prednisolone	Expired
7 Pakistan	M	63	T-cell lymphoma	Pustular	PG	Cyclosporin	Cleared
8 Qatari	M	68	Myelocytic leukemia	Pustular	PG	Predrisolone	Cleared
9 Pakistan	M	21	Nil	Bullous	PG	Cyclosporin + Prednisolone	Cleared

M = male *F = female*

ful, has a benign course and is rarely associated with systemic disease[6, 14] and is characterized histopathologically by abscess granulomas[6, 14, 15].

The sites affected by PG vary but are found usually on the lower limbs. Other sites are the trunk, scalp, face, lips and eyes[16, 17]. Eight of our nine cases had the lower limbs affected. PG in infants usually runs a prolonged course with an average duration of 2.5 years[2] and there is an unusual distribution of perianal and genital lesions not often described in other age groups[10], although children appear to be more commonly affected on the head and neck[9]. The infant reported in our series had PG in the perianal region.

PG may develop in peristomal skin when colostomy is done to control inflammatory bowel disease and is considered a pathergic phenomenon[18]. Parastomal and peristomal PG rarely occur from 2 weeks to 3 years after ostomy with a female to male ratio 3:1[19, 20]. The number of peristomal PG cases reported till 1994 is 32[18, 21, 19, 20]. Peristomal PG must be differentiated from suture reaction, allergic contact dermatitis, peristomal abscess and enzymatic degradation of the skin. The presence of pain supports the diagnosis of PG[18]. Pain is a significant symptom in 65% of cases of PG[22].

Table 2 : Histopathology and Imminofluorescent Microscopy

Case	Date of Biopsies and Summary of Findings
1	27.03.87 Spongiosis, intraepidermal bullae and necrosis; lymphocytic vasculitis. Immuno-fluorescent (IF) negative except for C3 staining of the secretion in the blister. 23.04.87 Epidermal and dermal pustules adjacent to a hair follicle, lymphocytic vasculitis. 23.04.88 Pustule involving epidermis and upper dermis, vasculitis with fibrinoid changes IF: positive staining of the vascular walls and lumina for Ig G, Ig A, C3, C1q and fibrin.
2	21.12.94 Extensive abscess formation and necrosis in the skin and subcutis with lymphocytic vasculitis in adjacent dermis and lymphocytic vennulitis in fibrous septa of sub-cutaneous adipose tissue. IF: staining of the vascular walls for Ig G, Ig A, Ig M,C3 and C1q.
3	27.12.94 Necrosis of the epidermis and dermis, pustules in the dermis leukocytoclastic vasculitis with fibrinoid changes. IF: staining of the vascular walls and lumina for Ig G, Ig M, C3, C1q and fibrin.
4	03.12.95 Dermal necrosis, nodular vasculitis with angiocenteric histiocytic and epithelioid granulomata , neutrophils and nuclear debris; lymphocytic vasculitis and lympho cytic hidradenitis in adjacent and deep dermis. IF: stainig of the vessel walls for Ig G, Ig A and C3.
5	03.04.95 (Back) Pustules in the epidermis and papillary dermis, lichenoid (DLE-like) changes in the basal zone with apoptosis; lymphocytic vasculitis. 12.06.95 (Back) Pustule in the dermis in and around a hair follicle, lymhpocytic vasculitis. IF: Epidermal cell membrane staining (possibly non-specific) for Ig G, Ig A, IgM and C3. 11.11.95 (Trunk) Spongiosis, apoptosis and exravasared red blood cels in the epidermis; lymphocytic vasculitis. 13.11.95 (Lip) Epidermal necrosis, pustules in the epidermis and dermis, lymphocytic vasculitis. IF: epidermal cell membrane staining (? non-specific) as above. (Back) Epidermal necrosis and abundant apoptoisis , sub-basal bullae with hyalinised papillary dermis at the floor, lymphocytic vasculitis. 21.05.96 Pronounced apoptosis in the epidermis, lymphocytic vasculitis.
6	07.06.95 Infarction involving epidermis, full thickness of the dermis and adnexa with nuclear debris and only ghosts of adnexa visible.
7	06.09.95 Malignant T-cell lymphoma in the skin, see Figs (7, c, d) 17.04.96 Vasculitis with fibrinoid necrosis, infarctions and pustules involving mid and deep dermal layers
8	10.10.95 Striking exocytosis in the epidemis with occasional apoptosis, focal spogiosis, nuclear abnormalities and increased mitotic figures. Dense upper dermal lympho cytic infiltrates with prominent vessels and extravasated red blood cells. 09.07.96 Focal nuclear abnormalities of the basal zone with increased mitotic figures and occasional apoptosis, focal fibrinoid deposits in papillary dermis, lymphocytic vasculitis. 05.10.96 Essentialy similar to his first biopsy but with more exocytosis,apoptosis increased nuclear abnormalities and mitotic figures. Dermal lymphocytic infiltrates decreased in density.Lymphocytic hidradenitis present.
9	26.03.96 Necrosis resulting in ulceration and total loss of the epidemis and papillary dermis in ulcer base, pustules in upper dermis, infarcted dermis with ghosts of the adnexa visible; vasculitis with fibrinous thromboemboli in the lumina.

Pyoderma gangrenosum has to be differentiated from[18] atypical mycobacterium infections, Behcet's disease, spider bite, deep mycosis, cutaneous amaebiasis and amaebic abscess, facticial dermatitis, halogenoderma, pyoderma vegetans, syphilitic gumma, systemic lupus erythematosus, circulatory insufficiency, thrombophlebitis with gangrene, ulcerative necrobiosis lipoidica diabeticorum, Wegener's granulomatosis, wound infection, giant keratoacanthoma[11], necrotizing faciitis[23], necrotizing cellulitis gangrenosa, erysipelas, purpura fulminans, coumarin necrosis[24], ecthyma gangrenosa in infants[25], skin lesions after abuse injections[26] and ulcers associated with large granular lymphocytic leukaemia[27]).

It is estimated that 20-30% of PG patients do not have associated systemic disease at the time PG appeared[7, 28, 29]. PG has been also described in children without underlying systemic disorder[9, 30]. In our group of patients 44.4% were not associated with systemic disorder and 55.6% were having systemic disease (Table 1).

The highest association with PG is ulcerative colitis and it is estimated that 90% of patient with PG have ulcerative colitis[5] and exacerbation of PG usually parallels the intestinal inflammations[31]. Thirty four percent of patients with PG associated ulcerative colitis may show urticaria, erythema nodosum or erythema multiform[31]. PG is estimated to affect 0.5-5% of ulcerative colitis patients and 0.8-1.5% of patients with Crohn's disease[18-32]. In 46 children with PG, 74% of the older group had associated systemic illness most commonly ulcerative colitis and only one infant was HIV positive at time of ouset of PG[10] and half of the children had polyarthritis and pathergy was noted in many children[10].

The second commonest systemic association with PG is inflammatory polyarthritis[5] and monoclonal gammopathy[33]). Most of the monoclonal gammopathy associated with PG are of the IgA isotype. The incidence of monoclonal gammopathy increases with age and its incidence is 1-3% of adult population studied in Sweeden and U.S.A.[34]. Pulmonary abscess like involvement was reported in a patient with PG associated with IgA monoclonal gammopathy[35].

PG has been also reported with many hematological disorders such as myelofibrosis[36, 37], acute and chronic lymphocytic leukemia, myeloid leukemia, polycythemia rubra vera which progressed to myeloid leukemia[38], essential thrombocythemia, myelodysplastic syndrome, hypo gamma globulinemia, hypergammaglobulinemia, multiple myelomatosis, non Hodgkin's lymphoma, paroxysmal nocturnal hemoglobinuria[16]. PG was also reported to occur with Wegener's granulomatosis[39], psoriatic arthritis[40], colonic tuberculosis[41], anticardiolipid antibody, during treatment of a patient with granulocyte colony stimulating factor and the PG was apparently not related to the underlying systemic illness[14], in association with C7 deficiency[43], chronic active hepatitis[44], patients with defective immune reactivity and in those treated with immunosuppressive agents[45] which when given in sufficient dosage represent one of the main therapies of PG.

PG was reported to occur in HIV infected children[46], patients with paraproteinaemia[47, 48, 49], chronic venous leg ulcers in susceptible patients[50], Behcet's disease[51]), surgical wounds[52], sub corneal pustular dermatoses without monoclonal gammopathies[53], diverticular disease[54], Kertagner syndrome[55] (characterized by situs inversus, bronchitis, primary ciliary dyskinesia).

Lung involvement in PG has been reported and unilateral or bilateral pulmonary infiltrate is the radiologic feature and pulmonary and skin lesions dramatically respond to corticosteroid therapy[56]. Non infectious necrotizing tracheitis was reported and resulted in respiratory failure in an infant nine months old[57].

The diagnosis depends mainly on the clinical presentation. Investigations done may enable us to find out possible associated systemic disorders and differentiate PG from other cutaneous diseases of similar picture. These investigations should include routine blood count and ESR, blood biochemistry and because of the association of PG with monoclonal gammopathy serum protein electrophoresis and immuno-electrophoresis should be done in every case[58]. Serologic screening for hepatitis, syphilis and HIV, estimation of serum iodide, bromide, anti

phospholipid antibodies[59]), rheumatoid factor, Bence Jones proteins in urine, X ray chest, gastrointestinal tract investigations, neutrophil function, lymphocyte function and skin biopsy should be done and sent for pathology and immunohistology together with a description of the lesion, the type of the lesion, the anatomical region and the biopsied site from the lesion whether from the center or the margin or the surrounding erythema and a tissue specimen should be sent for culture for bacteria, mycobacteria, atypical myobacteria and deep fungi.

The mechanism underlying the formation of the ulceration is not clearly known. It was thought originally that streptococci had a role in its aetiology[1]. Numerous investigations postulated that a primary bacterial component causes PG[28]. Culture of early lesions failed to produce any organism[60]. It has been suggested that PG is a local inflammatory response resulting from specific sensitization of the patient to streptococci leading to changes in the skin similar to post streptococcal glomerulonephritis[61].

Many immunologic abnormalities were reported in patients with PG including humoral and cell mediated defects. A dermonecrotic factor has been demonstrated but its specificity is doubtful. This factor has the physical and immunological characteristics of IgG and is suspected to play a role in damaging the vasculature and connective tissue in patient own skin[60-62]. Abnormalities in circulating immunoglobulins with hypo and hyperglobulinemia were found[63], with variation in humoral response to salmonella antigen and tetanus toxoid.

Auto antibodies against bowel and skin were also found[61]. In PG with ulcerative colitis the skin and the colonic lesions result from a common autoimmune mechanism where antibodies attack similar autoantigens in skin and gut mucosa[64] or the primary disease is in the gut and is reflected on the skin as angiitis or Shwartzman phenomenon[65].

Intravascular coagulation with deposition of platelets and clotting proteins in small blood vessels of the skin may contribute to the development of PG[66].

In PG associated with monoclonal gammopathy there is immune dysfunction's such as invitro inhibition of neutrophil, decreased neutrophil chemotaxis, delayed migration and abnormal bactericidal ability[58, 34, 67, 68]. In PG with gammopathy the paraproteins block the surface receptors of neutrophils and monocytes[69].

T-cell imbalance and abnormality of cell mediated immunity including cutaneous anergy to candida, mumps, streptokinase, streptodornase and DNCB were found in PG[61, 70, 71].

Clinicopathologically PG evolves from folliculitis and abscess formation and may show leukocytoclastic vasculitis. The lesions then evolve to suppurative granulomatous dermatitis and regress with fibroplasia[72]. No consistant abnormalities in either laboratory or histologic studies were found[69-34]. It is suggested that immune mediated vasculitis may be a prominent feature in pathogenesis of PG[73].

The immunologic mechanism leading to vascular damage is an Arthus phenomenon[64-74]. It involves the formation of immune complexes in tissues with activation of complement cascade resulting in release of proteolytic lysosomal enzymes which are directly responsible for the damage of blood vessels and tissue. This could be demonstrated by immunofluorescence to detect the immune complexes and the result usually depends on the specific site from which the biopsy specimen is taken. The peripheral zone of the lesion corresponds with the area with active destruction.

It has been also suggested that the vascular damage in PG represent a Shwartzman phenomenon where the gram negative bacterial endotoxins produce direct toxic effect leading to direct vascular and tissue damage[65, 75].

A derangement of cell mediated immunity is in consideration as the cause of the disease . It is suggested that excess T suppresser cell function or diminished T helper cell function underlies the changes in PG and is the cause of neutrophil dysfunction seen in PG[71].

The observation of skin graft rejection in 2 adults[76] and in all children[8] raised the possibility that PG apparently represents a localized rejection

of a damaged skin[77].

PG was reported to occur in immunosuppressed patients[78].

The pathergic phenomenon manifested by localization of PG to site of skin trauma as in surgical wounds is possibly related to defective neutrophil function or may represent a localized misdirected host mediated effector cell response to cutaneous tissue antigenically changed by trauma in a patient with an altered immune reactivity[6].

THERAPY :

A - Local :

Wound care is required using saline lavage or various antimicrobial agents as povidone iodine, 0.5% silver nitrate, hexachlorophene and potassium permanganate to keep the ulcer clean. PG was successfully treated with topical 10% 5-aminosalicylic acid cream applied once daily under sterile gauze with complete recovery in 5 weeks[79]. Many other topical modalities were reported to be successful in treatment of PG as 4% cromolyn sodium[80, 81], topical 20% nitrogen mustard[82], 20% benzoyl peroxide[69]. Intra lesional triamcinolone acetonide using concentrations up to 40 mg per ml was used to treat PG and causes rapid response in peristomal PG.[69, 83, 84, 18]

It is recommended that surgery to PG patient may be done when PG is quiescent and subcuticular sutures are used to close the skin to avoid skin puncture because PG may occur in surgical wound[52].

B - Systemic therapy :

1 - Systemic steroids : Most patients respond to systemic steroid. The dose varies from 40 mg to 120 mg, prednisolone (approximately 1-3 mg/Kg/day) and up to one third of patients require long term medical management[20, 36, 6, 56].

Pulse steroid therapy was reported frequently to be effective in PG[85, 86, 87, 34]. A bolus of 1 gram methylprenisolone in 150 cc of 5% dextrose given intravenous daily for 5 days gave very good results in PG. There are potential side effects for pulse steroid therapy as hypertension, hyperglycemia, electrolyte abnormality, leukocytosis, granulocytosis, lymphopenia, eosinopenia, decrease in serum IgG and IgA, decrease in total hemolytic complement, decrease in fasting plasma cortisol levels, and a bitter metallic taste during infusion[34].

2 - Cyclosporine A:[77, 21, 88, 89, 90, 91, 92, 93, 94] Cyclosporine A appears to be the drug of choice in treatment PG. It dramatically improves recalcitrant PG. The dose used ranges between 5-10 mg/Kg/ daily. Side effects of the drug has to be carefully monitored. Intra lesional cyclosporine A was tried successfully[95]. Cyclosporine A appears to suppress proliferating helper T cells. It influences the early events in antigenic activation of helper T cells via inhibition of lymphokine production and secretion thus preventing aggregation of lymphocytes at periphery of PG lesions(10). Drugs that may interfer with cyclosporine levels include ketoconazole, erythromycin, anabolic steroids, diltiazem, phenytoin, phenobarbital, carbamazepine and rifampin[92].

3 - Diaminodiphenyl sulfone (Dapsone) : It represents a primary successful line of treatment of PG. It is given in the dose of 100-200mg/day, higher doses as 100 mg 4 times daily were also used[96]. It is usually given in combination with oral steroids. It modulates the inflammatory response by inhibiting myeloperoxidase H_2O_2-halide mediated cytotoxic system in polymorphnuclear leukocytes. It also reduces the inflammation by preventing oedema and tissue viscosity.

4 - Minocycline was found to be effective in subacute cases of PG. It is given in the dose of 100 mg twice daily and it acts through its anti inflammatory and antichemotactic properties rather than as an antibacterial agent[6, 97, 98, 99]. Other antibiotic drugs used in treatment of PG are rifampin, tetracycline, vancomycin and mezalcillin[100].

5 - Sulfasalazine[69] **:** Given 4 grams per day. It is split by bacteria into sulfa pyridine and 5-amino salicylic acid which acts on inflamed mucosa in inflammatory bowel disease at the level of inflamed mucosa by inhibiting prostaglandin and leukotriene B_4 which are both potent mediators of inflammation[101-102].

6 - Clofazimine : given in the dose of 300 mg

daily was used to treat PG[103-104] through its effect on inflammatory cells. High doses may be needed but there is a risk of splenic infarction with accumulation of the crystals in the mesenteric lymph nodes. It was reported to lead to significant improvement in five days and complete healing of PG within four weeks[105].

7 - Other immunosuppressive drugs used to treat pyoderma gangrenosum include, chlorambucil[106], cyclophosphamide[107].

Methotrexate given orally 7.5 mg/week caused decrease in the size of PG ulcer within 2 weeks and healing within 2 months. In a patient who was grafted 4 times and was on 150 mg azathioprine and 60 mg prednisolone per day methotrexate was given 15 mg per week for seven months and prednisolone was reduced to 10 mg per day. Methotrexate can be used as a primary therapy in PG and is a steroid saving agent[108].

Fk 506 an immunosuppressive drug was used to treat PG[109].

8 - Other therapeutic modalities are :

a - Hyperbaric oxygen was found to promote healing of PG and permits reduction of systemic steroid[110].

b - Potassium iodide was also used successfully to treat PG[111].

c - Intravenous human immunoglobulin given in the dose of 0.4 to 1 gram/Kg/day for 3-5 days in combination with cyclosporine A and prednisolone cause marked improvement of PG within 2 weeks[112].

d - Interferon Alfa-2 a resolved pyoderma gangrenosum associated with hepatitis C and cryoglobulinemia[113].

e - Plasmapheresis, levamesole, transfer factor, electron beam radiation were all tried[69].

Usually after complete healing, treatment can gradually be discontinued. Unpredictable intermittent reccurences occur and prolonged maintenance therapy is not justified in most patients. Treatment of underlying disease process leads to clearance of the PG.

Management of PG in childhood[8, 10] is usually difficult and satisfactory results are obtained with prednisolone, clofazimine and minocycline. Skin grafts in children are almost always rejected and are not justified as PG can occur at donor site. Local therapy is necessary but is rarely curative. Sulfapyridine was most successful when given alone or with prednisolone in the dose of 1 mg/Kg/day. With removal of the affected bowel disease of children the PG usually clears. Systemic steroids are the most frequently prescribed drug in children and is very effective.

SUMMARY

In the present study a total of nine cases of pyoderma gangrenosum (PG) were seen in two years in Hamad Medical Corporation. The clinical presentations varied and was described as pustular, ulcerative, bullous and superficial granulomatous or vegetative PG. The diagnosis was confirmed by histopathology and some were repeatedly biopsied. The most distinctive histopathologic features were summarized. Some aspects of PG were pointed out concerning its epidemiology, clinical picture, diagnosis, associated systemic conditions, aetiology and management.

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