Pyoderma Gangrenosum and High Titer Serum Aanti-CCP$_2$ Antibodies.

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ABSTRACT

Pyoderma gangrenosum is an uncommon ulcerative cutaneous neutrophilic dermatosis. In about 50 percent of cases, it is associated with systemic diseases like inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythromatosus, hematological diseases and various malignancies. There is no specific laboratory finding or histological features pathognomonic of pyoderma gangrenosum and it is often a diagnosis of exclusion. Here, we report an elderly female without history of any systemic disorders, presenting to us with extensive, bilaterally symmetrical, deep leg ulcers along with multiple superficial ulcers involving the right groin which was diagnosed as pyoderma gangrenosum. The only positive rheumatologic marker was serum anti-cyclic cittrulinated peptide$_2$ antibody, which was found to be strongly positive. Dramatic response to systemic corticosteroid followed by successful split skin grafting was observed in our patient.

Keywords: *Anti cyclic cittrulinated peptide$_2$, pyoderma gangrenosum, symmetric leg ulcer*

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare sterile neutrophilic dermatosis. The ulcer usually starts with some itchy skin lesions and with time, it becomes progressively deeper due to pathergy reaction. The lower extremity is most frequently involved. In 50 percent of cases, it is associated with systemic diseases like inflammatory bowel disease and seropositive rheumatoid arthritis etc.[1] PG is often the first sign of an underlying systemic disorder and therefore, early diagnosis and implementation of treatment for causative factors can halt the disease process.

CASE REPORT

A 53-year-old non diabetic, non hypertensive female presented with extensive ulcers of both the legs for the last seven years. Her lesions started insidiously in the left leg followed by involvement of the other leg within a month. It started as an innocuous itchy skin eruption following a mosquito bite. This was followed by the development of a superficial ulcer, which was ostensibly precipitated by her constant scratching. The superficial ulcer progressed gradually and became deeper (Fig. 1).

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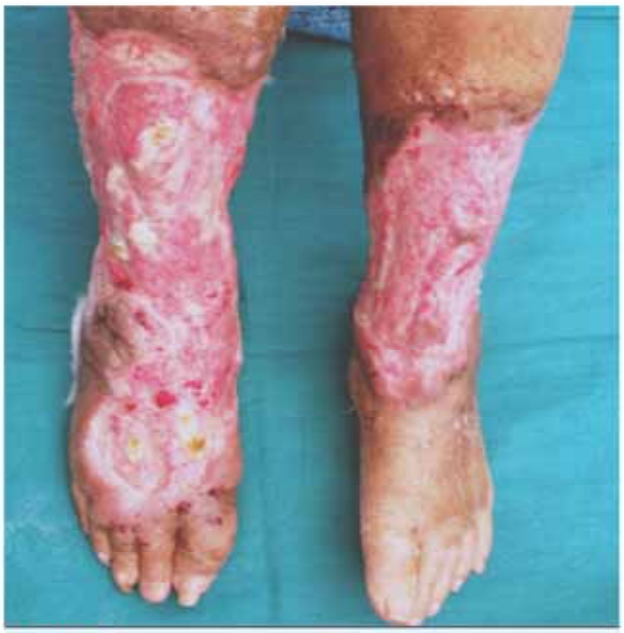

Figure 1. Pyoderma gangrenosum involving both legs.

It was very painful and was associated with a serous discharge. Six months prior to admission, another superficial ulcer developed in her right groin (Fig. 2).

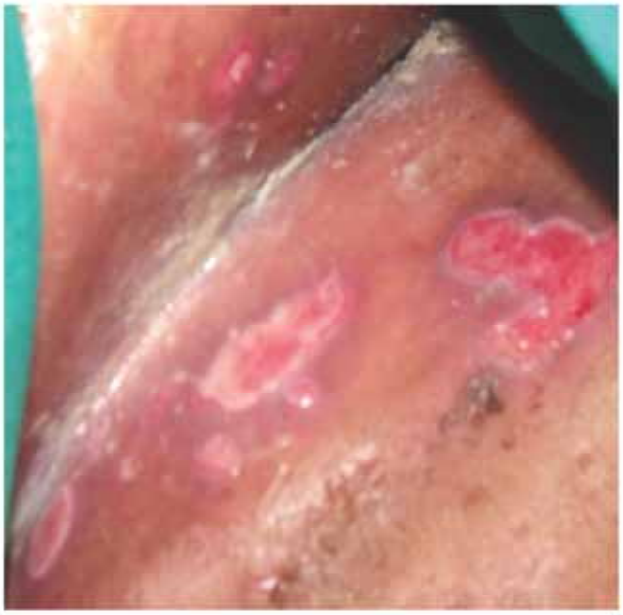

Figure 2. Pyoderma gangrenosum involving right groin.

Apart from these seemingly innocent ulcers, there were no other systemic symptoms. There was also no history of bloody diarrhea, red colored urine, overt bleeding from any site, joint pain, skin rash, oral ulcer, alopecia, bone pain, nodular swelling over the body, any significant weight loss, jaundice, fever or any drug reaction.

Local examination revealed a large deep ulcer (35X15X2.5 cm) involving each leg circumferentially, exposing the muscle and long bone. Multiple small superficial ulcers were also noted over the right groin. The edge was undermined and violaceous. Swab from the wound for microbiological examination revealed no growth of any pathogenic organisms. Systemic examinations were unremarkable.

Routine laboratory investigations revealed moderate anemia with normal serum ferritin and transferrin saturation level. The white cell count was 12,700/mm^3 with marked neutrophilia (90%). The erythrocyte sedimentation rate was 96 mm in the 1st hour. Blood sugar, urea, creatinine, lipid profile, liver function tests, thyroid function tests and blood biochemistry were within normal limits. Blood culture showed no growth of any organisms. Routine urine and stool examination was normal. It was presumed that it was a sterile ulcer and accordingly punch skin biopsy from a representative site was carried out. The histopathological examination showed an ulcer covered with inflammatory exudates and fibrin and the base of the ulcer showed granulation tissue. No granuloma was found. There was marked neutrophilic infiltration extending into the dermis and subcutaneous tissue (Fig. 3).

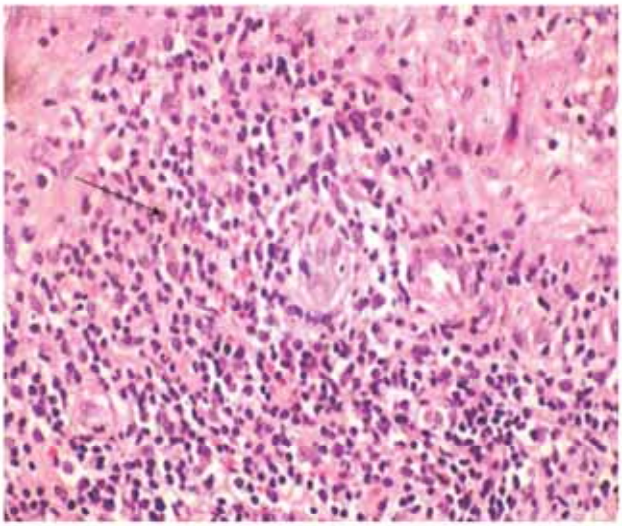

Figure 3. Histopathological picture of pyoderma gangrenosum (high power field with magnification 400x) showing extensive neutrophilic infiltration (black arrow), without granuloma formation.

All these features thus favored pyoderma gangrenosum.

A search for secondary causes was made. Serum protein immunoelectrophoresis was normal and no "M" spike was seen. Serum HBsAg, anti HCV, HIV I & II, anti mitochondrial antibody (AMA), rheumatoid factor were negative but serum anti-CCP_2 antibodies was

strongly positive (value 70U/ml, normal value <20U/ml). Moreover ANA (Hep_2) at 1:20 dilution, c-ANCA , p-ANCA and anticardiolipin antibodies of both IgM and IgG were negative. Blood for tumour markers like CA-125 and CEA were negative.

Upper GI endoscopy and colonoscopy was normal. Bone marrow revealed a reactive marrow. Ultrasound Doppler study of both lower limbs was normal. CT scan of thorax and abdomen was unremarkable. Ultra sonogram of different joints to rule out any joint erosion or signs of inflammation which was suggestive of early RA, was normal.

The patient was managed with oral prednisolone 60mg/day for 6weeks along with calcium, vitamin D_3, proton pump inhibitor and regular dressing. All the lesions healed dramatically within a week. Oral prednisolone was then tapered to 10 mg/day. After two months, split skin graft was performed successfully. She was followed up for one year with maintenance dose of 10 mg/day of oral prednisolone. No graft rejection or recurrence of ulcer has occurred till date.

DISCUSSION

Pyoderma gangrenosum is a rare sterile ulcerative skin lesion of unknown etiology and the condition was described in 1930 by Burnsting et al.[2] It usually affects men and women equally, most commonly between the fourth and sixth decades of life.[3] It is a painful condition and progresses rapidly. The pathogenesis of PG is poorly understood. Over expression of some interleukins like IL-8 and IL-16 has been reported. Pyoderma gangrenosum most commonly involves leg with preference for the pretibial area. [4] Other sites are breast, hand, trunk, head and neck and peristomal skin. Pyoderma gangrenosum is usually associated with systemic disorders in about 50% of cases, while in other 50% cases, it is idiopathic. Systemic disorders associated with PG are Crohn's disease, chronic hepatitis C, seronegative rheumatoid arthritis, systemic lupus erythematosus, lymphoproliferative disorders like leukemia, lymphoma, monoclonal gammopathy, myelodysplastic syndrome. Pyoderma gangrenosum is usually associated with rheumatoid arthritis in 37% of cases, but it classically develops in an established case. Other rare causes are Wegener's granulomatosis, anti-phospholipid antibody syndrome, HIV infection, PAPA syndrome etc. Pyoderma gangrenosum may sometimes mimic Sweet's syndrome, although the latter typically presents with fever and sudden onset of non-ulcerating lesions that generally heal without scarring. Another condition, livedoid vasculopathy, a rare thrombo-occlusive disease of post capillary venules presents with similar leg ulcers and histopathologic feature as PG. However, livedoid vasculopathy is poorly responsive to steroid therapy. All these secondary causes were absent in our case except for a high titer serum anti-CCP_2 antibodies being positive.

A high titer anti-CCP_2 antibody indicates a high likelihood of RA. It has a high specificity (98%) but less sensitivity (80%).[5] It can assess disease severity and predict future development of RA in an asymptomatic patient. But our patient did not have any history of joint pain, morning stiffness and moreover joints ultra sonogram was unremarkable. Usually PG occurs in an established RA patient. There is no specific diagnostic criterion for PG. Diagnosis of PG relies on clinical signs and histopathology. Histopathology of PG is however non specific, showing inflammatory exudates, fibrin and extensive infiltration of neutrophils and lymphocytes into dermis and subcutaneous tissue. Therefore diagnosis of PG is made by exclusion of other causes.

The drug of choice in PG is systemic corticosteroid. Initial dose is typically 0.5 to 1mg/kg of body weight of prednisolone daily. Alternatively intravenous methylprednisolone may be used in doses of 1 gm/day for three to five days followed by oral steroid until the ulcer heals. Though the ulcers healed within a week in our patient, systemic steroid was used for six weeks to prevent disease recurrence and brought the disease into remission so that split thickness skin grafting could successfully be applied without rejection. In refractory cases, steroid sparing agents like cyclosporine, azathioprine can be used with or without corticosteroids.[6] Antimicrobials like sulphones, dapsone, clofazimine and minocycline and biological agents like TNF-□ blockers have been found to be effective in treating PG associated with inflammatory bowel disease. Antirheumatic therapy should not be started based solely on positive anti-CCP_2 antibodies. Tacrolimus is a novel macrolide antibiotic having a wide range of immunosuppressive activities. It inhibits activation and proliferation of CD4 T-helper cells. The specific mode of action in PG is largely unknown, but clinical experience has shown a favorable effects in PG.[7] Surgery may have some role in managing PG.

Debridement should be avoided because it may precipitate a pathergy reaction. Split thickness skin grafting is a surgical technique, is used to speed healing of PG ulcers that are very large and should be attempted after adequate control of inflammation with high dose steroids to prevent pathergy reaction and graft loss. In our patient successful split skin grafting was successfully performed without rejection.

Such an extensive disease, with symmetric ulcers of both legs along with involvement of right groin (which is a very unusual site for PG), absence of other systemic disorders despite high titer serum anti CCP_2 antibodies, normal joint ultra sonogram and dramatic response to systemic corticosteroid followed by a successful split skin grafting have prompted us to report this case.

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