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LETTER TO THE EDITORS

# Pyoderma gangrenosum in a renal transplantation patient having immunosuppressive treatment for 5 years

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Dear Sirs,

Recently, we have reported a case with pyoderma gangrenosum in a renal transplantation patient receiving immunosuppressive treatment for 5 years. Pyoderma gangrenosum (PG) is a noninfectious neutrophilic dermatosis with unknown aetiology that is very rare [1] and is characterized by the presence of one or more ulcerations typically violaceous with an undermined border [2]. Herein, we reported an extremely rare case who had renal transplantation and developed PG under immunosuppressive treatment.

A 42-year-old man with a pustular lesion located on right shoulder, right leg and pubis was under tacrolimus 2 g/day, mycophenolate mofetil 1500 mg/day, prednisolone 5 mg/every 2 days, verapamil 240 mg/day, ranitidin 300 mg/day, candesartan 16 mg/day, hydrochlorothiazide 12.5 mg/day, allopurinol 300 mg/day and acarbose 150 mg/day for the 5 years post-transplant period. His immunosupressive treatment has switched from tacrolimus to an antiproliferative agent, sirolimus 2 mg/day for the last 2 months, because first of all his lesions were considered as a result of a malignant process as Kaposi's sarcoma.

At his dermatological examination, three lesions were detected: two of them were located at his right shoulder and leg with 0.5 cm size and a surrounding erythematous, painful two pustules. There was also a third lesion $10 \times 3$ cm sized, endured, erythematous purulant ulcerative/necrotic lesion at pubic area (Fig. 1a). At the histopathological and microbiological analysis of pubic biopsy, there was no infective cause, and histology was compatible with PG. No laboratory abnormality was detected. The patient was administered 100 mg/day methylprednisolone, and at the 15th day of his treatment two lesions were completely resolved and the pubic lesion was regressed. Methylprednisolone theraphy was gradually tapered, and as the lesions totally disappeared, it is completely discontinued at the end of 3rd month (Fig. 1b). At the 6th month visit, no recurrence was reported. As an idiopathic, rare, ulcerative, chronic, inflammatory skin disease of uncertain aetiology, PG mainly affects adults [2]. It is reported that more than 50% of PG cases are associated with systemic diseases [3]. Pyoderma gangrenosum is found in relation with rheumatological and haematological diseases [4], monoclonal gammapathies [5], iatrogenic immunosuppression [6], malignities and mostly with inflammatory bowel disease [4]. The remaining cases are considered autoimmune or idiopathic [7]. Although the pathogenesis of PG is unknown, immune-complex vasculitis, T-cell activation, neutrophil dysfunction (defect in chemotaxis with hyperreactivity) and overexpression of IL8 and IL16 are detected [8]. Lazarous *et al.* reported that the pathogenesis of the PG depends on a defect in cellular immunity and is because of anergic/delayed type hypersensitivity reaction [9]. Haim *et al.* reported two cases with PG, a kidney recipient and a pemphigus vulgaris patient receiving immunosuppression. The course, in both cases, suggested that immunosuppressive therapy (azathiopurine, methotrexate, 6-mercaptopurine, but not steroids) may play an aetiological role in the disease [6]. As antimetabolites and closely related molecules, azathiopurine and 6-mercaptopurine inhibit adenylic and guanylic acid production in the de novo purine synthesis pathway. As a result, they block proliferation of

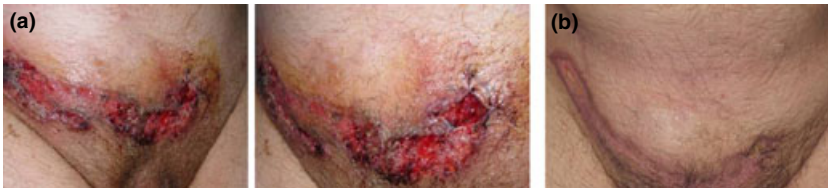


**Figure 1** (a) $10 \times 3$ cm sized, endured, erythematous purulant ulcerative/necrotic lesion at pubic area, (b) patient after his treatment at the 3rd month.

lymphocyte precursors. Methotrexate inhibits dihydrofolic acid reductase. Therefore, it interferes with DNA synthesis, repair and cellular replication. FK506 attacks calcineurin that activates NFAT, and NFAT binds to IL-2 promoter region. Interestingly, CsA and FK506 block calcineurin by binding to different proteins. Its direct effects are suppression of IL-2 production, inhibition of apoptosis, T-cell proliferation and blockage of Ab production. Sirolimus inhibits the response to interleukin-2 (IL-2) and thereby blocks activation of T- and B-cells (10). Our renal transplantation patient developed PG during the first 5 years of his immunosuppressive therapy that was consisted of sirolimus, mycophenolate mofetil and prednisolone. As the course of our case resembled previous cases, it is pointing out that the aetiology of PG could be depending on defects in both cellular and humoral immunity. The pathogenesis of PG is not only depended on the immune system defects but also on the immunosuppressive agents themselves. Besides, its unknown aetiology PG is still a challenging clinical condition with so many unanswered questions. Diagnosis of PG is based on the clinical features of the ulcer and requires exclusion of other conditions causing ulceration. The clinical variants of PG lesions have been classified into ulcerative, pustular, bullous and vegetative [2]. Our case had the ulcerative type lesions. Abdullah *et al.* reported a renal recipient who developed PG presented with multiple necrotizing skin ulcers at the extremities associated with malaise, arthralgia and low grade fever. Herein, multiple and classical ulcerative lesions were present, but he had no systemic symptoms such as fever and malaise. Histopathological examination of the advancing inflamed border reveals dense perivascular lymphatic inflammation that may at times be associated with vascular destruction. None of these histological lesions is descriptive for PG. No laboratory finding is diagnostic of PG and investigations should focus on identifying associated diseases [8]. In our case, histopathological and clinical features were compatible with PG. The first choice treatment was high dose systemic corticosteroids [2]. High-dose steroids was successful in our case for the follow-up of the clinical condition. At immunosuppressed patients, PG is extremely rare. For its conventional treatment, immunosuppressive agents are used. In this case, PG was diagnosed while the patient was on sirolimus, mycophenolate mophetil and prednisolone therapy. However, the therapy continued with high dose corticosteroids. Surgical treatment is in controversy for the present day standards, and generally, it is believed that PG is itself a 'pathergy' reaction and that trauma could aggravate the lesions. So, aggressive surgical approaches should be avoided. We had effective response to high dose steroid therapy in our case. To conclude, we considered this case of PG may be because of iatrogenic immunosuppression. However, it is not clear whether it depends on immunosuppressive therapy itself.

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