Case Report

MEDICAL AND SURGICAL MANAGEMENT OF PARANEOPLASTIC PYODERMA GANGRENOSUM - A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

We present a case of a 44 year old male with pyoderma gangrenosum (PG) presenting simultaneously with diagnosis of acute leukemia. His skin disease was stabilized with corticosteroids and most lesions cleared after chemotherapy-induced remission of the malignancy, but the largest lesion remained necrotic. Surgical treatment of the large necrotic ulcer included debridement followed by split-thickness skin graft while maintaining corticoid therapy. Unfortunately, relapse of the pyoderma gangrenosum with bullous lesions heralded relapse of the ultimately fatal malignancy. This case illustrates: 1. PG presenting simultaneously with a haematologic malignancy 2. Relapse with atypical bullous lesions with return of the malignancy and 3. The use of surgical modalities in managing patients with PG, a disease notorious for surgical complications.

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare inflammatory skin disease characterized by painful sterile cutaneous ulcerations with undermined irregular indurated violacious borders with a purulent or vegetative base. It can be idiopathic, however it often develops in association with other systemic disease including but not limited to inflammatory bowel disease, rheumatic disorders, haematologic or other neoplasias.(1) Treatment usually includes immunosuppression.

Due to the phenomenon of pathergy, or development of PG lesions in sites of minor trauma including surgical incisions and venipuncture sites, which can occur in 25- 50% of cases(2), surgical management is avoided.

We present a case of a patient with paraneoplastic PG, secondary to a haematologic malignancy. The pa-

tient was treated medically with immunosuppression as well as surgically with skin grafting.

CASE REPORT

A 44 year old male presented to our clinic with a 2 week history of lower back pain, followed by fever and development of painful necrotizing skin lesions in the right groin and thigh. Skin lesions began as erythematous maculae which then developed central necrosis and ulceration, with undermined violacious borders. The ulcer in the right groin rapidly expanded to a maximal diameter of +/-20 cm with necrosis reaching the subcutaneous fat. The patient also developed necrotizing gingivitis. Skin biopsy of an early lesion showed leukocytoclastic vasculitis with massive neutrophilic dermal infiltration, compatible with the clinical diagnosis of PG. Bacterial and fungal tissue cultures were negative.

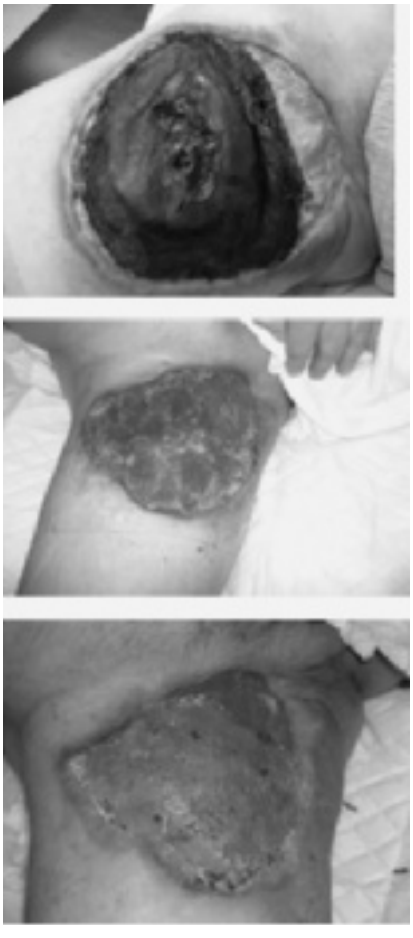

Figure 1.
PG lesion (a)after 3 months of corticoid therapy showing necrosis and a non-inflammatory border (b) after surgical debridement (c) 4 weeks after skin graft with epithelialization of the 2/3 of the lesion and a non inflammatory ulceration medially

Laboratory values were abnormal for elevated C-reactive protein (15.4 mg/dl), neutrophilia (8330/µl), and thrombocytopenia (86 000/µl). Further investigation, including bone-marrow biopsies, lead to the diagnosis of acute myeloblastic leukemia secondary to a myelodysplastic syndrome type refractory anemia with an excess of blasts (MDS-RAEB with evolution to AML).

Skin disease stabilized with glucocorticosteroid therapy (125mg methylprednisolone qd IV, slowly tapered) with concomitant chemotherapy (cytarabine, etoposide, danorubicine) and wound care. However the largest ulcer on the right thigh was slow to heal and antibiotic treatment (ciprofloxacine 500mg/d PO) of superinfection with pseudomonas aeruginosa did not lead to significant improvement.

When clinical remission of the haematologic malignancy was reached 2 months after commencing treatment, deep surgical debridement was performed, followed a few weeks later by a split thickness skin graft, with continuation of the glucocorticosteroids (methylprednisolone 16 mg qd). The graft took nicely over 2/3 of the lesion leaving a smaller ulceration in the groin further treated with wound dressings (Figure 1). There was no sign of pathergy at the donor or at the receptor site.

The wounds continued to heal nicely, but 2 months later development of new hemorrhagic bullae surrounded by erythema and superficial erosions on the hands, chest and legs heralded a relapse of the haematologic malignancy, necessitating HLA matched sibling stem-cell transplantation, of which the patient died 4 days later of complications including pneumonia, hypervolemia, and acute kidney failure.

DISCUSSION

Pyoderma gangrenosum is a skin disease thought to belong to a spectrum of diseases known as neutrophilic dermatoses, having an inflammatory infiltrate predominantly of neutrophilic polymorphonuclear leukocytes, with or without extracutaneous neutrophilic infiltrates and frequent association with other diseases(3).

Pyoderma gangrenosum lesions often begin as an inflammatory papule or pustule, or collection of papules, which then undergo necrosis and ulcerate.

Lesions are classically painful and rapidly expand centrifugally. Because there is not one pathognomonic finding, diagnosis of PG can be difficult to make, spe-

cifically in the postoperative setting. Clinicians must have a high index of suspicion for this diagnosis when a patient presents with painful inflammatory ulcers with elevated borders and negative cultures not responding to adequate antibiotic therapy.

PG can occur on any skin surface, but most commonly presents on the lower extremities, as with the primary lesions in this case. Several variants exist including ulcerative, pustular, bullous and vegetative(4).

Interestingly, our patient's relapse presented with atypical, bullous lesions which more commonly occur in the setting of haematologic disease, in this case AML. This subtype of PG presents with more superficial lesions, sometimes studded with pustules that arise rapidly, more commonly on upper extremities. It is most commonly associated with AML, myelodysplastic disorders, refractory anemia and IgA paraproteinemia(4).

Although it can present idiopathically, PG is associated with systemic disease in up to 70% of cases. The most common associations are inflammatory bowel disease (Crohn's disease, ulcerative colitis, 20-30%), rheumatologic disease (seropositive rheumatoid arthritis, seronegative arthritis, spondyloarthropathy, 20%) and haematologic disease (myelodysplasia, acute and chronic myelogenous leukemia, and multiple myeloma,15-20%). PG has been reported with other diseases including Hepatitis C viral infection, Graves' disease(5) and Takayasu's arteritis(6), as well as drug induced. Examples of drug-induced disease include propylthiouracil, pegfilgastrim – a granulocyte colony stimulating factor and gefitinib – an epidermal growth factor receptor inhibitor(1).

PG can present as a paraneoplastic phenomenon most commonly with haematologic malignancies, rarely associated with solid tumors. Timing in association with course of malignancy has not been well established.(7) This case of PG presented just prior to, or as one of the presenting signs of the diagnosis of AML and became active again as the malignancy, which had been in remission, relapsed. Case reports of PG associated with leukemia suggest PG as the presenting sign(8), and heralding relapse(9), but can present any time in the course of the malignancy as well, for instance, in the setting of pathergy.

The mainstay of treatment for this inflammatory disease is medical immunosuppression. Classically glucocorticosteroid therapy induces quick healing of lesions in a matter of weeks. Limited disease can be treated with topical or intralesional steroids, however more severe disease necessitates systemic therapy (typically immunosuppressive dose of prednisolone 1-2 mg per kg per day in the initial phase).

In addition to steroid therapy, other anti-inflammatory and immunosuppressive or immunomodulating agents have been used including cyclosporine, minocycline, dapsone, methotrexate, colchicine, thalidomide, mycophenolate mofetil, azathioprine, cyclophosphamide, chlorambucil(10). Newer anti-TNFa inhibitors have been used with success including infliximab, etanercept, and adalimumab(11). Other treatments such as intravenous immunoglobulines, granulocyte and monocyte adsorption apheresis (12) and vacuum-assisted closure(13) have been successfully implemented.

Although glucocorticoid treatment had induced healing of some of the PG lesions in this case, the largest ulcer, although stable in size, with a less inflammatory border failed to regress. Due to the phenomenon of pathergy, which can present as formation of new lesions, wound dehiscence, or periostomal disease, surgical interventions in the management of PG have been classically avoided, as the trauma of surgical manipulation of viable as well as affected tissue can induce activity of the disease and worsen the clinical course. However, multiple case reports have suggested that for recalcitrant disease, or for patients with comorbidities for whom medical treatment with immunosuppression increases risk of general deterioration, surgical management of the disease is appropriate (14) Split skin grafting with good cosmetic result has been successfully implemented with concomitant immunosuppressive therapy(15,16). The use of keratinocyte suspensions, cultured epidermal allograft, dermal regeneration template Integra(18) and bioengineerd skin Graftskin(17) have reportedly allowed accelerated wound healing allowing a shorter course of immunosuppressive therapy. When our patient's malignancy was in remission and his skin disease quiescent, we felt that surgical intervention, albeit while continuing low dose glucocorticoids, was warranted, with good result.

SUMMARY

PG is an inflammatory skin disease best treated with medical immunosuppression. Association with

systemic disease should prompt further investigations to rule out inflammatory bowel diseases, arthritis or haematologic disease. For aggressive or recalcitrant disease surgical treatment may be beneficial.

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