Case study

Chemotherapy-induced pyoderma gangrenosum

ABSTRACT

Pyoderma gangrenosum (PG) is a refractory, painful, non-infectious, ulcerative and inflammatory skin condition. Approximately 50% of patients with PG showed an existing systemic disease, such as inflammatory bowel conditions, haematological disorders, rheumatoid diseases or hepatopathies. Some patients developed PG following acute trauma or injury in a process known as pathergy. In the other cases, PG is characterised by isolated skin lesions with unknown causes and classified as idiopathic. However, in recent decades, PG has been reported in patients treated with certain medications. In this manuscript, we report two cases of PG, which were triggered by chemotherapy in patients with myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CMML).

Keywords Pyoderma gangrenosum, chemotherapy, azacitidine.

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INTRODUCTION

Pyoderma gangrenosum (PG) is a refractory, painful, non-infectious, ulcerative and inflammatory skin condition, which was first described by Brocq in 1916[1]. In 1930, Brunstring *et al.* named it pyoderma gangrenosum[2]. It is commonly associated with underlying systemic diseases and occurs most frequently between 40 and 60 years old[1,3-6]. Typical PG can occur on any skin surface, but is most commonly seen over lower limbs and often leaves cribriform scars after the wounds have healed[2,7].

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Approximately 50% of patients with PG showed an existing systemic disease, such as inflammatory bowel conditions, haematological disorders, rheumatoid diseases or hepatopathies[1,8]. Some patients developed PG following acute trauma or injury in a process known as pathergy[2,9-11]. In the other cases, PG is characterised by isolated skin lesions with unknown causes and classified as idiopathic[12]. However, in recent decades, PG has been reported in patients treated with certain medications. In the review by Wu *et al.*[13], 43 cases of drug-induced PG were identified. To follow is a report of two cases of PG, which were triggered by chemotherapy in patients with myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CMML).

Case 1

A 58-year-old female was diagnosed with MDS. MDS is a collection of pathologically and cytogenetically distinct bone marrow disorders characterised by peripheral blood cytopenias and will result in an increased risk of bleeding and infectious complications[14]. In addition, these patients have a tendency to develop acute myeloid leukaemia (AML)[14,15]. Azacitidine, a chemical analogue of cytosine, is a chemotherapy drug used to treat conditions that affect the blood and the bone marrow. This was given via subcutaneous injection for the patient for one week. On day 8, the patient developed non-neutropenic septic shock and multiple skin lesions were noted over her abdomen (injection site), which required admission to the intensive care unit. Initially the lesions were erythematous, which rapidly progressed into blisters and finally skin necrosis

occurred. The wounds were well circumscribed, with a ring-shaped large ulceration and elevated oedematous borders (Figure 1).

Wound culture indicated there was no particular bacterial, fungal or mycobacterial organisms. The wound biopsy demonstrated inflammatory neutrophilic dermatosis. A dermatologist was consulted and PG was finally diagnosed. Methylprednisolone 50 mg daily was commenced orally. One month following oral steroid therapy, the edge of the wound remained violaceous and it was evident that the PG was still active (Figure 2). Cyclosporine, an immunosuppressant medication, and doxycycline, a broad-spectrum antibiotic of the tetracycline class, were added to the treatment regimen. Subsequently, the wounds were less violaceous in appearance and epithelialisation was noted from the edge (Figure 3). In addition, less pain was experienced by the patient. Methylprednisolone was then decreased gradually to 5 mg with cyclosporine 70 mg and doxycycline 100 mg daily as a maintenance dose. The patient was discharged from the hospital afterwards and wound care was continued by the community nurse every alternate day.

Two months later, the patient's general condition deteriorated and her white blood cells were found to be in a rising trend during follow-up in the haematology clinic. After discussion with the patient and her family members, the patient was admitted to the hospital again and decitabine cycle 1 was given intravenously. Decitabine is another DNA methyltransferase depleting drug for the treatment of MDS[16]. Unfortunately, two weeks following the introduction of this medication, the patient reacted with neutropenic fever again and a flare-up of PG eventuated (Figure 4). Methylprednisolone 30 mg daily and cyclosporine 40 mg twice a day were recommenced, with recognised improvement in the wound (Figure 5). Dosage of both drugs was gradually decreased as the improvement continued. Conversely, another two months later, PG flared up again after decitabine cycle 2 was given. A high dose of methylprednisolone and cyclosporine were recommenced. However, the patient's prolonged neutropenic state complicated her deteriorating health and she passed away two months following active treatment.

Case 2

A 72-year-old male was diagnosed with CMML. CMML is a pathologically heterogeneous disease with overlapping morphologic features of both myelodysplastic syndromes and myeloproliferative neoplasms[17]. It is accompanied by bone marrow dysplasia, cytopenias and hepatosplenomegaly[18]. As a result of the patient having progressive anaemia and thrombocytopenia, azacitidine was commenced. The first cycle of azacitidine was well tolerated by the patient. Four days into his second cycle, multiple erythematous, painful pustular plaques with violaceous borders appeared initially on the left lower limb, then became generalised over his abdomen, chest wall and shoulder (Figure 6–9).

An incisional wound biopsy over the abdomen and left lower limb demonstrated diffuse dense infiltration of the dermis and superficial subcutaneous tissue by polymorphs with focal fat necrosis. The overall features were consistent with neutrophilic dermatosis and indicative of PG. Microbiological studies of the

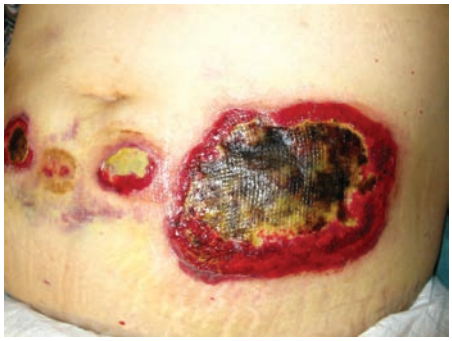
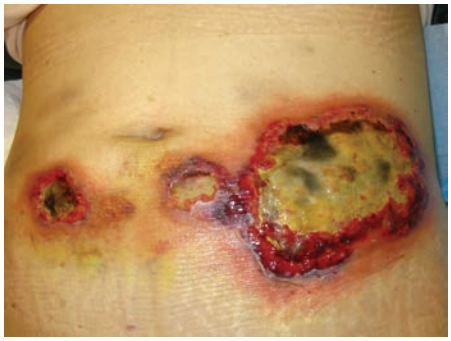


Figure 1



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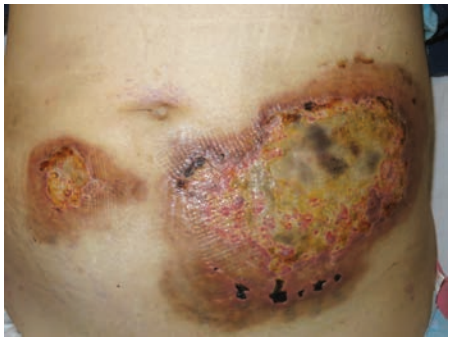

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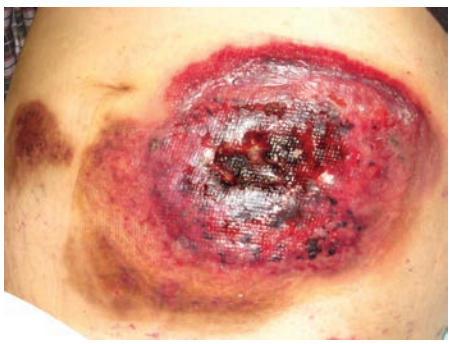

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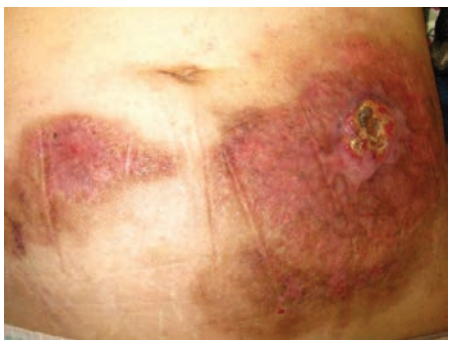

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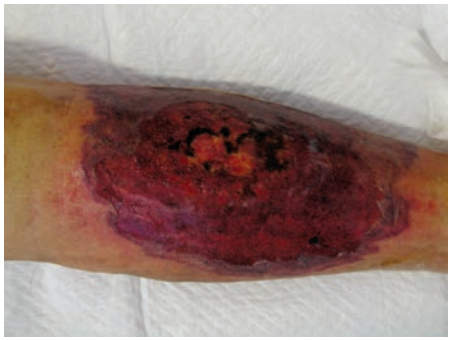

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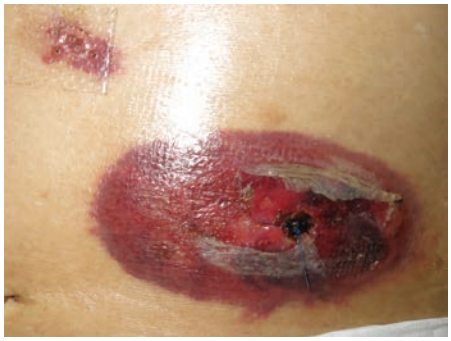

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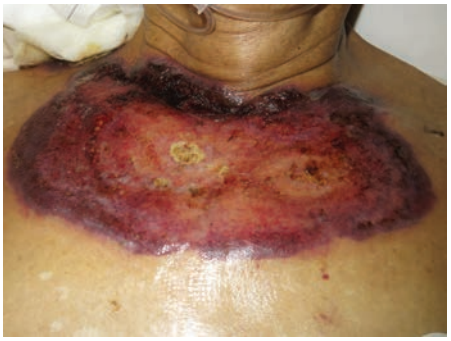

Figure 8

wounds were negative for both aerobic and anaerobic bacterial growth. However, the patient developed a neutropenic fever and multiple antibiotics were given. In the presence of a depressed immune system, the sepsis could not be controlled and the patient died two weeks following the commencement of treatment.

DISCUSSION

Azacitidine (AZA) is a DNA methyltransferase inhibitor, which has been shown to improve overall survival in patients with MDS and its sub-types[19-21]. However, AZA-induced demethylation of DNA may cause epigenetic changes, which lead to increased interferon production and cytoskeletal rearrangements; these changes may support the pathogenesis of AZA-induced PG by upregulating inflammation and neutrophil migration[13]. This side effect had been demonstrated in individual reports and literature[21-23]. The report of two patient case studies have also demonstrated AZA-induced PG.

Azacitidine can be administered by using intravenous or subcutaneous routes. However, it was known that skin lesions, ecchymosis, petechiae and skin induration following subcutaneous injection could be developed in up to 97% of patients[23-24]. Azacitidine-induced injection site PG was rare, but a single case was reported recently by Roy *et al.*[21]. In case study 1, the patient suffered from injection site complications following eight days of treatment. Some literature reported that changing the needle with no azacitidine residue before injection could reduce the incidence of injection-site reactions but control studies measuring this were limited[24].

Another drug used in case study 1 was decitabine. It is a DNA methyltransferase (DNMT1)-depleting drug approved for treatment of MDS. In 2017, Saleh and Sauntharajah reported successfully treated MDS-induced PG by using decitabine[25]. However, PG relapsed in case study 1 during the treatment of decitabine. Further studies concerning the relationship between PG and decitabine are warranted.

Wound management

Topical therapy is a significant issue in all the patients with PG but there is no consensus in the management of these wounds[1,26]. The treatment is largely empirical and depends on the severity and extent of the lesions. The overall goals of local wound management are to reduce lesion inflammation,

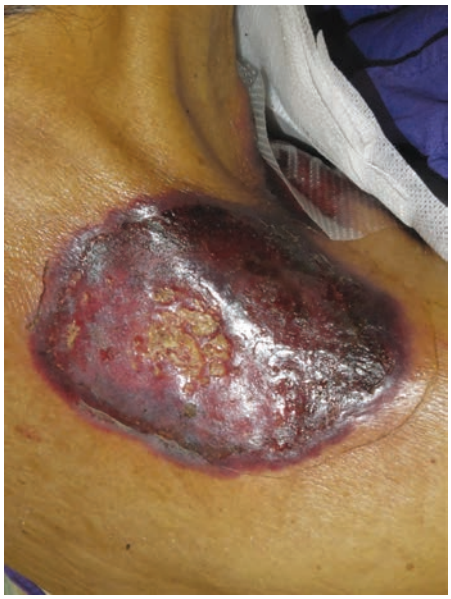

Figure 9

decrease pain and promote wound healing[1-2]. Some topical drugs, such as the application of tacrolimus, have been reported, where wounds show no further extension, regression of the inflammatory border and pain relief. However, patients' serum creatinine was increased[27-28]. Therefore, systemic absorption should be closely monitored and a clinical trial in this area is suggested to measure the risk and benefits of the topical drug.

The literature has indicated moist wound management to be the cornerstone in managing PG wounds as it can improve wound-related pain, facilitate autolytic debridement and promote angiogenesis[8]. Various dressings, such as polyurethane foam, Hydrofiber and alginate dressings, are documented in individual PG wound management with resolving erythema, flattened epibole edges and pain relief[1,29]. In the first case, the Hydrofiber dressing had been tried but the patient could not tolerate it because of severe pain. It might be due to the hydrophilic effect of the dressing. In addition, because of less exudate of the wound, the dressing adhered to the wound bed and increased pain on removal. This might also increase the potential to trigger pathergy[30]. Hydrogel dressings are formulations of water, polymers and

other ingredients. They are designed to hydrate the wound tissue, keep nerve endings moist to reduce pain and maintain a moist environment for cell migration[31]. In light of there being no bacterial growth within the tissues of the PG wounds for our two patients, Hydrogel with a tulle dressing were applied to facilitate autolytic debridement and reduce pain. On the other hand, although the underlying cause of PG is non-infectious, most of the patients are prescribed corticosteroids; therefore, caution should be made to prevent bacterial infection. The wounds were closely monitored for clinical signs of infection, such as erythema, warmth, increased pain, increased exudate and malodour[30]. Although skin flora was identified from the wound in the later stage of case 1, it was assessed that topic antimicrobial wound dressings were not necessary.

In view of the potential pathergy in the development and acceleration of the condition, both of the reported cases did not receive any surgical intervention nor conservative sharp wound debridement during the treatment period[1]. The evidence has shown that effective management of the systemic disease often results in improvement of the skin ulcerations[1,2,26]. Therefore, apart from local wound care, systemic corticosteroids and cyclosporine are recommended as first-line systemic agents for the management of patients with PG[32].

Pain control

Apart from vegetative variants, patients with PG almost entirely experience debilitating pain[26]. The source of pain may be multifactorial, but in most cases it is associated with the inflammatory process and the subsequent grave ulcer[33]. Repeated manipulation of the wound, such as wound cleansing and trauma during wound dressing removal, is a source of distress for patient[33]. Therefore, addressing the patient's pain level is crucial in treatment efficacy. Both our patients in the case studies received analgesic, Tramadol, 50 mg every six hours orally, if necessary with an additional dose during wound dressing changes in order to achieve adequate pain control. Conversely, when patients' disease and inflammation are well controlled by systemic therapy and appropriate wound management, pain may subside gradually.

CONCLUSION

The pathogenesis of PG still remains uncertain, although current evidence suggested that it has an autoimmune aetiology with defects in immune regulation of the inflammatory response. PG is also associated with various systemic conditions such as inflammatory bowel disease, haematological disorders, and autoimmune arthritis. Pathergy is an exaggerated response to minor trauma in patients with PG. However, chemotherapy is another possible triggering factor, which should be considered, particularly in patients receiving specific drug treatments. The two case studies demonstrated this serious side effect of azacitidine. Early recognition of this complication is important to avoid undue delays in the treatment of the underlying malignancy, but also to initiate appropriate therapy against PG.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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