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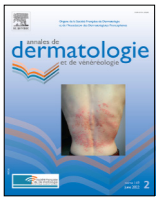

Letter to the editor

Azacitidine-related pyoderma gangrenosum

A 58-year-old woman with no pre-existing medical conditions was referred to the Haematology Department for evaluation of her anaemia. Bone marrow aspiration revealed increased granulocytic and monocytic cell growth, decreased maturation in the granulocytic series, dysplasia in both the granulocytic and erythroid series, and a 3% presence of blast cells with reticulin fibrosis. Although chromosomal analysis did not identify any abnormalities, next-generation sequencing (NGS) revealed the presence of gene mutations in the following genes: *SETBP1, ASXL1, ETV6*, and *CSF3R*. The patient was diagnosed with chronic myelomonocytic leukaemia (CMML) and underwent allogeneic haematopoietic stem cell transplantation (ASCT) with a fully matched sibling donor. However, when her CMML relapsed eight months after ASCT, she was treated with subcutaneous azacitidine (AZA) at a dose of 75 mg/m^2 for seven days in a 28-day cycle.

During the 10th cycle of AZA, the patient presented with fever of 38.8 °C and an elevated CRP level. Physical examination revealed a very painful, exudative, erythematous, inflammatory ulcer measuring 20 × 18 cm in the right lower quadrant of the abdomen. Necrotic areas were observed at the centre of the ulcer. There was no purulent discharge and no crepitation on palpation (Fig. 1a-c). Ultrasonography revealed oedema, changes in echogenicity, and increased thickness in subcutaneous tissue. Following investigation, necrotizing fasciitis was ruled out by the general surgery department. A CT scan of the abdomen revealed an increase in thickness along the anterior abdominal wall in the lower abdomen, extending into the right upper quadrant, as well as increased density indicative of oedema and inflammation in subcutaneous adipose tissue, which was also considered to be cellulitis. A bacteriological aetiology was excluded based on the negative culture of a swab, and a fungal infection was ruled out by histological examination. Furthermore, the skin biopsy revealed the presence of acanthosis, spongiosis, and dyskeratosis in the epidermis, accompanied by neutrophil-rich inflammatory cell infiltration and the formation of abscess foci. Additionally, vascular proliferation and the presence of neutrophils within the lumen of the vessels were observed (Fig. 2). The diagnosis of myelodysplasia cutis (skin infiltration of leukaemia) was ruled out by the pathologist. After exclusion of possible causes such as vasculitis, cancer, and infectious diseases (most commonly deep fungal infection), a diagnosis of pyoderma gangrenosum (PG) was considered. Once fungal and bacterial infections had been excluded, a treatment regimen comprising methylprednisolone 1 mg/kg/day and cyclosporine 4 mg/kg/day was initiated orally. In addition, clobetasol and fusidic acid were given topically, as well as meropenem and daptomycin for antimicrobial prophylaxis. Given the occurrence of PG on the abdominal skin at the injection site associated with AZA treatment, AZA was switched to decitabine 20 mg/m2/day for 5 days. At follow-up, PG regression was observed in the first week and the steroid dose was tapered and stopped at the end of week 6 (Fig. 1d).

PG is a non-infectious, inflammatory and very painful disease that is currently classified within the category of deep neutrophilic dermatoses. The four clinical subtypes of PG include classic ulcerative, pustular, bullous, and vegetative PG (superficial PG). Ulcerative PG typically presents as tender papules or pustules that progress to painful and rapidly expanding ulcers. PG is associated with a number of conditions, including inflammatory bowel disease, inflammatory arthritis or vasculitis (Takayasu arteritis), monoclonal gammopathy of cutaneous significance (IgA gammopathy), myeloid hemopathy, and genetic components. However, it may also be idiopathic. Haematological disorders represent the third most common systemic association of PG [1]. However, cutaneous manifestations considered as myelodysplasia cutis may occurred in CMML patients, and histopathological confirmation is recommended [2]. Previous studies have shown that neutrophilic dermatoses occurring during myeloid malignancies are distinguished from the malignant clone [2]. Given that a neutrophilic infiltrate in PG may be clonal, the use of myeloid NGS may offer a distinct advantage over the analysis of a skin biopsy, particularly in determining whether the infiltrate is clonal and shares the same mutational landscape as that observed in bone marrow NGS [3]. Historically, PG has been regarded as a diagnosis of exclusion. Diagnostic criteria have been proposed based on a Delphi consensus of international experts, who identified neutrophilic infiltrate as the primary diagnosis criterion and four out of eight minor criteria for diagnosing ulcerative PG [4]. The patient diagnosed with CMML presented with a rapidly progressing ulcerative lesion. Histological examination of a biopsy revealed a neutrophilic infiltrate, and infection was excluded. Moreover, the ulcerative lesion healed within a month of initiating immunosuppressive medication that included steroid and cyclosporin. Following subcutaneous administration of AZA, cutaneous reactions, including local erythema, may be experienced by up to 95% of patients [5]. However, AZA-related PG is very rare, with only three cases reported in the literature [6–8]. AZA-associated PG may be observed regardless of the injection site, including the abdomen and upper extremities. Pathergy has been identified as a significant precipitating factor for postpartum haemorrhage, with a reported incidence of 20% to 30% in cases where a minor trauma preceded the onset of bleeding [9]. The formation of lesions at the injection sites in the AZA group indicates the occurrence of cutaneous pathergy. In our patient, PG developed after prolonged azacitidine exposure. In previously reported AZA-related cases of PG, the disease occurred in early courses of AZA treatment. Our case demonstrated that AZA-related PG is not dose-dependent and may manifest at any stage of treatment.

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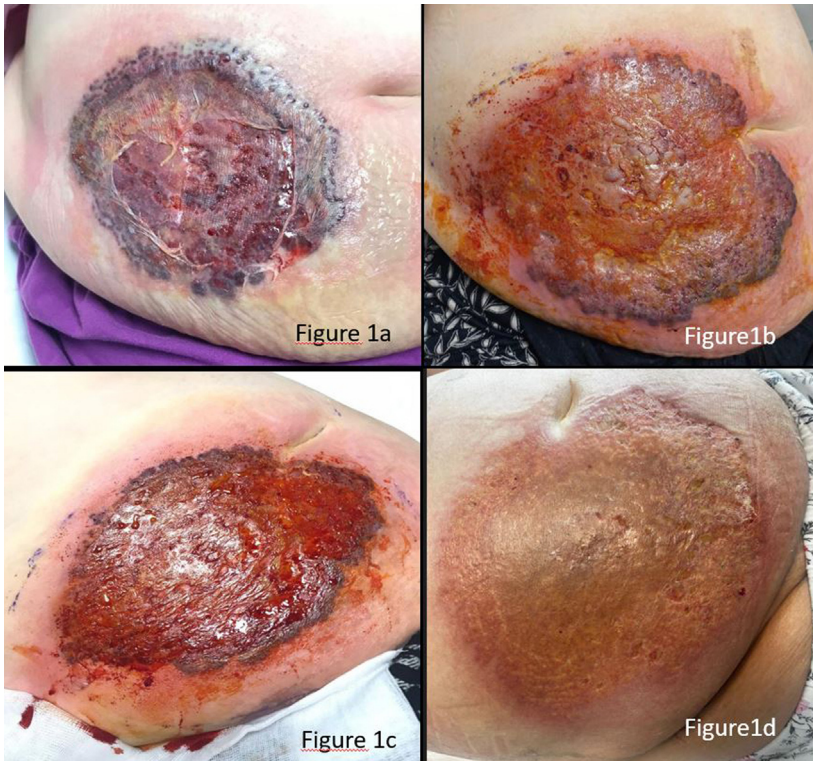

Fig. 1. a-c: Necrotic centre of the ulcer on different days. 1d: Significant regression of the necrotic ulcer after 6 weeks of treatment with cyclosporin as well as systemic and topical steroids.

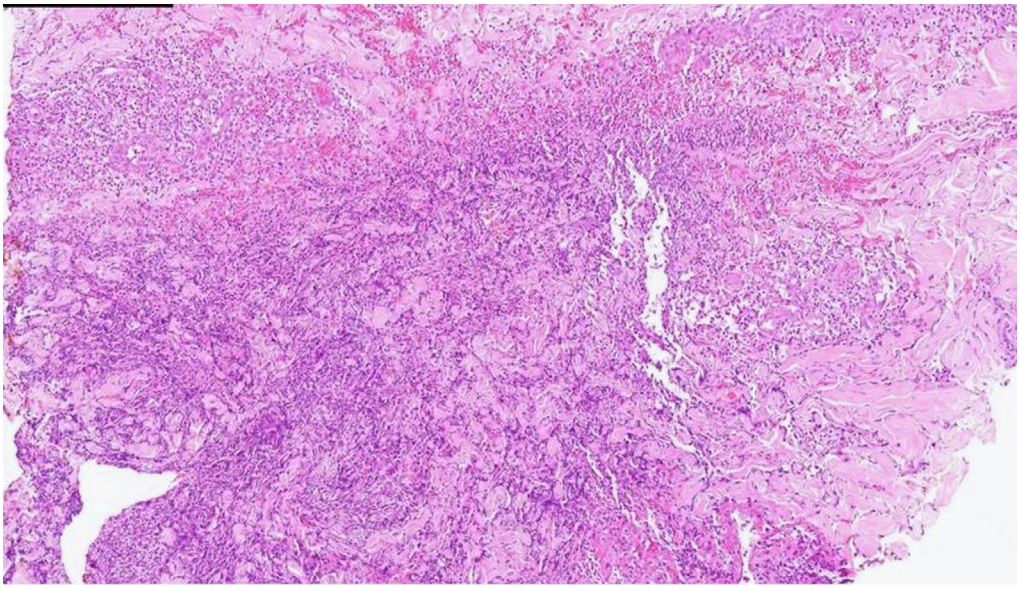

Fig. 2. Dermal inflammatory infiltrate of neutrophils and extravasated erythrocytes throughout the dermis.

In one published case, no relapse of PG occurred despite the continuation of AZA, subsequent to a change in the route of administration from subcutaneous to intravenous and the resolution of PG by oral prednisone [7]. In the literature, the most efficacious treatments for PG include systemic corticosteroids and cyclosporine [10,11]. Nevertheless, 32% of cases of hematologic malignancies demonstrated complete or partial remission with the administration of systemic corticosteroids alone [1]. In this setting,

the use of corticosteroids alone, without cyclosporine, may be a safer option for immunocompromised patients. A switch was made from AZA to decitabine, and systemic steroid and cyclosporine therapy was initiated to safeguard the patient from the potential long-term adverse effects of steroid exposure.

In conclusion, although PG may develop in haematological malignancies, it may manifest at the subcutaneous sites of AZA injection in patients with CMML. Due to the rarity of this clinical entity, the diagnosis and management of PG can be challenging.

Ethics approval and consent to participate

All procedures conducted in studies involving human participants were carried out in accordance with the ethical standards set forth by the institutional and/or national research committee and with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. The patient provided informed consent.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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