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Clinical report

Pyoderma gangrenosum and cytokine elevation associated with work-related injury

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Background: Pyoderma gangrenosum is a rare condition usually associated with underlying diseases such as ulcerative colitis, inflammatory bowel disease, or rheumatoid arthritis. However, some cases may also be traced to trauma or surgical procedures.
Objective: We reported a patient with pyoderma gangrenosum from work-related injury with abnormal cytokine elevation.
Results: Skin biopsy of the ulcer showed diffuse cellular infiltration and increased expression of granulocyte colony-stimulating factor (G-CSF). Laboratory studies revealed elevated white blood cell levels and increases in the inflammatory markers interleukin-6 (IL-6) and G-CSF. Oral doses of prednisolone were effective in treating the ulcer.
Conclusion: Measuring G-CSF and IL-6 levels may help facilitate earlier diagnosis of pyoderma gangrenosum, thereby resulting in more effective treatment.

Keywords: Cytokines, immunosuppression, interleukins, pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a rare sterile inflammatory neutrophilic dermatosis that can produce pain, disfigurement, and significant morbidity [1]. Clinically, PG can be classified into 4 types that include: ulcerative, pustular, bullous, and vegetative; all characterized by recurrent ulceration with mucopurulent or hemorrhagic exudates [1]. It can be idiopathic, but is more commonly associated with autoimmune or hematological disorders [2]. In other cases, symptoms can also appear after direct trauma [3] or following surgery [4, 5].

The etiology of PG is still unknown. A number of studies have reported varying degrees of elevated cytokine levels associated with PG, but thus far no patterns can be used to definitively link cytokine levels with progression of the disease [3]. However, by correlating cytokine levels of granulocyte colony-stimulating factor (G-CSF) and interleukin-6 (IL-6) with the clinical pattern, it may be possible to understand better the underlying pathophysiological mechanisms of PG [6].

Herein we report a case of idiopathic ulcerative PG in a man who had previously suffered a work-related inguinal injury with associated cytokine levels.

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Case report

A 66-year-old man with a history of hypertension presented with a large right inguinal ulcer. The patient had no significant family history, but had previously sustained an injury to his right inguinal region by a butt-welded drill bit welding at work. Despite initial treatment at another institution, the wound progressed and was debrided with a drain placement. However, these efforts were ineffective and the wound rapidly increased in size. Three weeks after his injury, the patient was then referred to our hospital.

On physical examination, an irregular ulcer (20 cm × 35 cm) with a distinct, purulent margin was noted (**Figure 1A**). The ulcer was surrounded by "dike-like" bulges with local hyperemia. A day later, the area of ulceration and redness continued to

increase (25 cm × 39 cm) (**Figure 1B**). Laboratory tests showed elevated white count, platelet count, and inflammatory markers, including CRP (11.9 mg/dL), IL-6 (37.4 pg/mL; normal <4 pg/mL), and G-CSF (268 pg/mL; normal <39 pg/mL).

Tests for antibodies (ANA, RF, P-ANCA, and ASO) were all negative, while bacterial, fungal, and acid-fast bacilli cultures were negative as well. Skin biopsy showed diffuse cellular infiltration from the epidermis to the dermis (**Figures 2A and B**). Since vasculitic change was not observed, a vasculitis-induced ulcer was ruled out. A diagnosis of pyoderma gangrenosum was highly favored based on the combination of histopathological findings, refractory response to antibiotic treatment, rapidly enlarging ulcer, and presence of purplish-red irregular ulcer border with surrounding "dike-like" bulges. Further immunohistochemical labeling of G-CSF in the skin tissue biopsy using rabbit anti-G-CSF (Abcam, Cambridge, UK) and visualization of labeled antigens (Histofine SAB kit, Nichirei, Tokyo, Japan; DABplus, Dako, Glostrup, Denmark) revealed that G-CSF expression was increased (**Figures 2C and D**).

After admission, patient's symptoms persisted despite intravenous antibiotic treatment (meropenem 0.5 g and clindamycin 600 mg; both three times daily for 3 days). Oral prednisolone (50 mg/day) was subsequently begun. Four days into treatment, the hyperemia began to resolve, and CRP levels rapidly decreased. After approximately 1 week of treatment, epithelialization was noted from the ulcerated border. G-CSF and IL-6 levels were also significantly declined, from 268 pg/mL to 65.6pg/mL and 37.4 pg/mL to 1.4pg/mL, respectively. The dose of prednisolone was then gradually tapered and eventually stopped. About 11 weeks after the initial visit, most of the original ulcer had epithelialized, leaving only residual pigmentation around the border with a healed scar tissue (**Figure 3**). Throughout the subsequent 30-month follow-up period, no recurrence or complications were observed.

Discussion

As PG can progress rapidly with serious repercussions, early clinical diagnosis is important to maximize treatment and avert complications. However, diagnosis may be delayed because biopsy is not always helpful [7, 8]. PG is usually associated with underlying systemic diseases, but this was not the case with our patient, who only had a history of hypertension without a family history of autoimmune diseases. Instead, the appearance of PG was linked to a work-related injury and apparently worsened with debridement through pathergy.

We found that elevated levels of G-CSF and IL-6 could be correlated with the patient's clinical progress. Indeed, elevated levels of IL-6 may not be specific for diagnosing PG; because oftentimes elevated IL-6 levels are found in many other inflammatory conditions. However, a strong correlation between concomitant elevated levels of G-CSF and IL-6 (along with symptoms and clinical findings) may suggest a more definitive diagnosis of PG. As this is only a single report and did not compare cytokine profiles in entities that may mimic or be confused with PG, elevations of these cytokines alone cannot be used

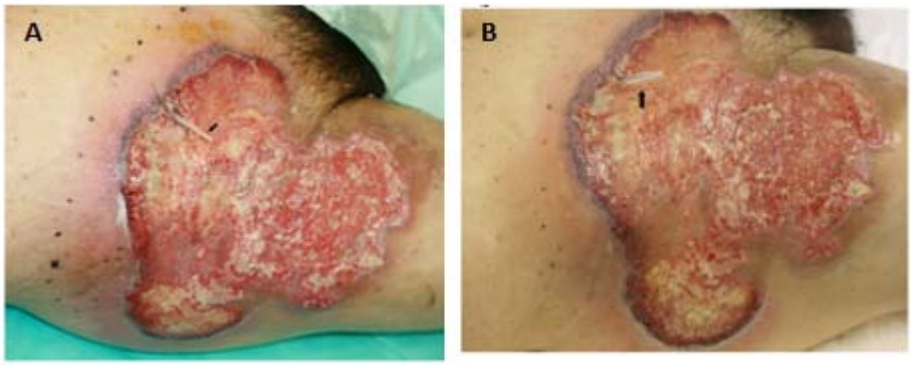

Figure 1. **A:** The patient presented with a 20 cm × 30 cm irregular ulcer with a clear border, accompanied by purulence. Dike-like bulges surrounding the ulcer and hyperemia were noted. The previously inserted drain can be seen (arrow). The patient complained of severe pain radiating from the right lower abdomen to the groin.
B: The ulceration as seen one day after the patient's initial visit. The ulcerated area, especially the area surrounding the drain (arrow), enlarged quickly. The hyperemic area had also increased in size.

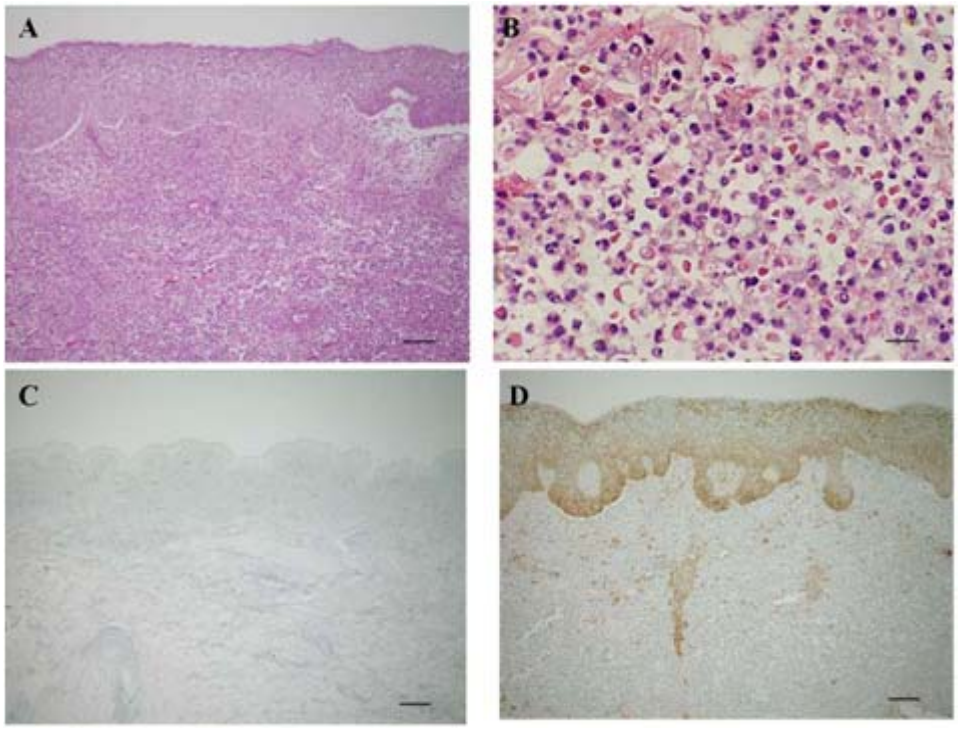

Figure 2. **A:** Severe epidermal interstitial cellular edema was apparent. Ulcer formation extended from the upper dermis to the middle dermis (100 μm, × 200). **B:** Inflammatory cells of segmented white blood cells were noted (100 μm, × 400). **C:** Granulocyte colony-stimulating factor (G-CSF) immunohistochemical staining of normal human skin (100 μm, × 100). **D:** G-CSF immunohistochemical staining of skin from the patient's ulcer (100 μm, × 100). The expression of G-CSF was markedly higher in the skin from the patient's ulcer compared with normal human skin.

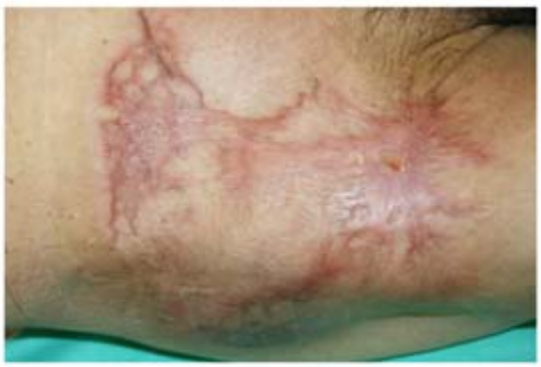

Figure 3. Approximately 11 weeks after the initial visit, most of the ulcer had epithelialized. Residual pigmentation at the border and healed scar tissue were evident.

to diagnose PG. However, our findings may serve as supportive evidence, and as shown in this case could correlate over time. Therefore, at this time, we can only consider utilizing these markers for PG in difficult-to-diagnose cases.

IL-6 is both a proinflammatory and anti-inflammatory cytokine, and can regulate immune responses and acute phase reactions [7]. When its proinflammatory activity persists, chronic inflammation, including autoimmune diseases, may

occur [9]. Conversely, G-CSF is known to be capable of regulating neutrophil development and function [10]. Inappropriate activation of G-CSF during maladaptive immune responses may manifest as autoimmunity or sterile inflammation [11]. Furthermore, PG has been reported in patients treated with G-CSF [12,13]. These observations indicate that elevated G-CSF and IL-6 may play a key role in the development of PG.

Lack of randomized clinical trials and unclear pathophysiological mechanisms involved in the development of PG have hampered attempts to develop a consistent treatment protocol. Although there is no criterion standard for treatment, most treatments include local wound management with a system for monitoring the lesions and wound dressing [14]. High doses of corticosteroids, given orally or intravenously, often with immunomodulators such as cyclosporine, are the mainstay of therapy [15].

We reported a case of PG resulting from pathergy after trauma and surgical procedures. In conclusion, measuring biomarkers, such as G-CSF and IL-6, may facilitate the diagnosis of PG if elevated and correlated over time, thereby allowing for earlier and more effective management of these challenging and disfiguring lesions. Further studies are necessary to investigate if a more substantial correlation between these cytokines and PG exist.

The authors declare that there is no conflict of interest in this article.

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