CASE REPORT

Refractory postsurgical pyoderma gangrenosum in a patient with Beckwith Wiedemann syndrome: response to multimodal therapy

Faiza Fakhar,¹ Sehrish Memon,¹ Diane Deitz,² Richard Abramowitz,³ Deborah R Alpert⁴

¹Department of Internal Medicine, Jersey Shore University Medical Center, Neptune, New Jersey, USA
²Department of Nursing, Jersey Shore University Medical Center, Neptune, New Jersey, USA

³Department of Medicine/ Wound Care, Jersey Shore University Medical Center, Neptune, New Jersey, USA
⁴Department of Medicine/ Rheumatology, Jersey Shore University Medical Center, Neptune, New Jersey, USA

Correspondence to
 Dr Deborah R Alpert,
 dalpert@meridianhealth.com

SUMMARY

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that may be difficult to diagnose and treat. We presented a 41-year-old woman who required skin grafting following third-degree burns to her left breast. She suffered recurrent graft dehiscence and infections over many years, prompting elective bilateral reduction mammoplasty. She subsequently developed suture margin ulcerations unresponsive to topical therapies and antibiotics. Skin biopsies were non-specific, and a clinical diagnosis of PG was established. Although initially responsive to corticosteroids, wounds promptly recurred following steroid taper. She was treated unsuccessfully with various immunomodulatory agents and underwent elective bilateral mastectomy. Following a mastectomy, she developed progressive deep chest wall ulcerations. She failed numerous immunomodulatory treatments, surgical wound closure and negative pressure wound therapy. Ultimately, treatment with adalimumab, mycophenolate mofetil and prednisone, in addition to hyperbaric oxygen therapy facilitated progressive healing. Our case highlights the role of collaborative multimodal therapy for the treatment of refractory PG.

BACKGROUND

Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic dermatosis with an estimated incidence of 3–10 cases/million/year. It may be associated with various systemic disorders such as connective tissue disease, inflammatory bowel disease or haematological malignancy, or may develop at sites of trauma. PG may be idiopathic in up to 50% of cases.^{1–2} PG lesions typically begin as pustules, papules or nodules that evolve into necrotic ulcerations with undermined violaceous borders² and is a diagnosis of exclusion without pathognomonic clinical or histological findings.

First-line treatment of PG includes local wound care and systemic corticosteroids (typically 1–2 mg/kg/dose), along with treating any underlying systemic disorder. Other immunomodulatory treatments include cyclosporine, cyclophosphamide, methotrexate, colchicine, mycophenolate mofetil (MMF), thalidomide, intravenous γ globulin (IVIG) and tumour necrosis factor α (TNF α) inhibitors.^{1–5} For refractory cases, surgery, negative pressure wound therapy and hyperbaric oxygen (HBO) therapy have occasionally shown benefit.^{6–8}

There have been several reports of patients developing PG following surgery, including reduction

mammoplasty and mastectomy.^{9–11} Herein we report a patient who developed PG following reduction mammoplasty, which recurred following bilateral mastectomy. Her refractory disease required collaborative multidisciplinary and multimodal therapies to attain meaningful clinical improvement.

CASE PRESENTATION

A 41-year-old woman with Beckwith-Wiedemann syndrome, whose manifestations included macroglossia, cardiomegaly, horseshoe kidney, macromastia and cognitive disability, suffered third-degree burns to her left breast from spilling heated coffee at age 22. She required skin grafting and over many years, recurrent graft dehiscence and infections necessitated two revision surgeries. She ultimately underwent elective bilateral reduction mammoplasty at age 37. Following reduction mammoplasty she developed recurrent ulcerations at the suture margins, unresponsive to topical therapies or antibiotics. Intermittent wound cultures grew methicillin-resistant *Staphylococcus aureus* and were aggressively treated with antibiotics. Attempted surgical closure and subsequent skin grafting were unsuccessful.

The patient's mother and maternal aunt both had rheumatoid arthritis, but the patient had no clinical evidence of inflammatory arthritis, bowel disease or other connective tissue disorder or malignancy.

INVESTIGATIONS

Various skin biopsies revealed occasional giant cells with acute and chronic inflammation. There was no evidence of vasculitis (figure 1). Stains and wound cultures for fungal organisms, mycobacteria and herpes viruses were persistently negative. She was clinically diagnosed with postsurgical PG. Workup for associated inflammatory disorders was essentially negative. Erythrocyte sedimentation and C reactive protein were normal, and serology including antinuclear antibody, rheumatoid factor, ACE and antineutrophil cytoplasmic antibodies were negative. Immunoprotein electrophoresis was normal, and both a chest X-ray and contrast-enhanced CT scan of the chest were unremarkable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PG is protean and reviewed in box 1.^{12–13} Our patient was clinically diagnosed with postsurgical PG, after extensively ruling out other causes including necrotising infection, malignancy and vasculitis.

To cite: Fakhar F, Memon S, Deitz D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201084

Figure 1 Left breast ulcer biopsy. (A) Ulcerated, necrotic epidermis and intensely inflamed, focally necrotic dermis. (B) (High power) Marked acute and chronic inflammation and occasional giant cell formation. All cultures were negative.

TREATMENT

A short course of corticosteroids was beneficial, but her wounds promptly recurred with steroid taper. Over the course of 1 year, she was treated with the immunomodulatory agents hydroxychloroquine, minocycline, dapsone and chronic steroids without significant improvement. Her wounds progressed, prompting elective bilateral mastectomy at age 39.

Approximately 2 months following mastectomy, she developed progressive ulcerations predominantly over her left chest wall extending to the deep muscles and vasculature, associated with intermittent profuse bleeding. She required multiple blood transfusions and intravenous iron for resultant anaemia. She failed treatment with cyclosporine, colchicine, IVIG and MMF and required prednisone dosed up to 120 mg/day, with

occasional intravenous steroid pulses. Surgical wound closure and negative pressure wound therapies were unsuccessful. Local steroid injections at the ulcer borders led to pathergy. She remained high-dose steroid dependent for 2 years, leading to Cushingoid habitus, steroid-induced dysglycaemia and obstructive sleep apnoea. Eventually, the addition of the TNF α inhibitor adalimumab to a regimen of MMF and prednisone facilitated progressive decrease in ulcer size. HBO therapy was additionally implemented; 60 treatments of 100% oxygen at two atmospheres absolute led to further clinical improvement.

OUTCOME AND FOLLOW-UP

With this multimodal therapy, the left chest wall ulcer dimension progressively decreased from a maximum of 15 $\times$ 7.5 cm to 1.5 $\times$ 0.5 cm over 1 year (figure 2), allowing for gradual prednisone taper to a minimum of 7.5 mg daily.

Box 1 Differential diagnosis of pyoderma gangrenosum

Infection

Bacterial (streptococcal gangrene, ecthyma gangrenosum, treponemal gummatous ulcers, mycobacterial infection)
Viral (deep herpetic ulcers)
Fungal (blastomycosis, coccidioidomycosis, sporotrichosis)
Parasitic (amoebiasis, leishmaniasis, schistosomiasis)

Malignancy

Cutaneous lymphoma, squamous or basal cell carcinoma, metastatic carcinoma

Vasculopathy

Arterial or venous insufficiency, calciphylaxis, livedoid vasculopathy (often associated with hypercoagulable state such as antiphospholipid syndrome)

Vasculitis

Systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, granulomatosis with polyangiitis, Behcet's syndrome, polyarteritis nodosa, mixed cryoglobulinemia, hypersensitivity vasculitis

Exogenous tissue injury

Arthropod bite reaction, factitious panniculitis

Drug reaction

Isotretinoin, granulocyte colony stimulating factor, propylthiouracil, potassium iodide, bromide, α 2b-interferon

DISCUSSION

Herein we describe a case of chronic refractory postsurgical PG following reduction mammoplasty and subsequent mastectomy. Our patient did not have any underlying systemic disorder associated with PG, although she had Beckwith-Wiedemann syndrome, which is a genetic disorder characterised by overgrowth, tumour predisposition and several congenital abnormalities.¹⁴ We were unable to find any association between Beckwith-Wiedemann syndrome and PG in the literature. To our knowledge, this is the first case report describing PG in a patient with Beckwith-Wiedemann syndrome.

PG is an unusual complication of breast surgery, and has been reported in the postoperative period following reduction mammoplasty and mastectomy, often leading to mistaken diagnoses of necrotising wound infection.^{9–11} PG has also been reported to occur at the incision site several years following reduction mammoplasty.¹⁵ Attempts to debride PG may result in worsening of disease due to pathergy; therefore it is extremely important to correctly diagnose PG in order to avoid additional disfigurement.^{9 10 16} Even with healing, PG characteristically results in extensive cribriform scarring, as noted in our patient (figure 2).

The standard treatment of idiopathic PG is systemic corticosteroids; however, some patients may have refractory disease requiring additional immunomodulatory treatments. Our patient failed numerous immunomodulatory therapies, but ultimately responded to the addition of the TNF α inhibitor

Figure 2 Progression of left chest wall pyoderma gangrenosum wound healing, postmastectomy. (A) Wound measures 13×8×2 cm and the patient is taking prednisone 30 mg twice daily, mycophenolate mofetil (MMF) and just started adalimumab. (B) Nine months later, the patient is taking prednisone 7.5 mg daily, MMF, adalimumab and is completing hyperbaric oxygen therapy. (C) Another 5 months later, the patient is taking prednisone 15 mg daily, MMF and adalimumab. Wound is nearly closed, but with significant cribriform scarring.

adalimumab to a regimen of MMF and prednisone. Serum TNF α levels are elevated in PG and may contribute to abnormal T-cell responses, resulting in ulcerations. There are several reports discussing the benefit of TNF α inhibitors such as etanercept, infliximab and adalimumab in the treatment of refractory PG.^{17–19} In a randomised, double-blind, placebo controlled trial of 30 patients, infliximab at a dose of 5 mg/kg was found to be superior to placebo for the treatment of PG.¹² In small case series, adalimumab and etanercept have been helpful for some patients who responded suboptimally to infliximab.^{17–19}

In our patient, the inability to control her PG following reduction mammoplasty led to subsequent elective mastectomy. Despite mastectomy, disease recurred over her chest wall and failed to respond to surgical management, including skin grafting and wound closure. Surgical treatment has a controversial role in the management of PG due to risk of pathergy. However, in cases with very large wounds, exposed vital structures or significant psychological distress, surgical treatment in combination with immunosuppression and other modalities may occasionally be beneficial.^{8–16}

Our patient responded further to the addition of HBO therapy to her immunomodulatory regimen. It is postulated that increased oxygen delivery to damaged tissues leads to a cascade of events including the reduction of oedema, down regulation of leucocyte receptor sites and the promotion of neovascularisation necessary for the healing process and closure of wounds.²⁰ HBO has been successfully utilised for decades as part of a multimodal regimen for the treatment of PG.^{6–8}

Successful treatment of this complex patient over several years required the combined expertise and collaboration of

wound care specialists, rheumatology, dermatology and plastic surgery. In addition to the challenges of managing the disease process, other issues including pain management and psychological support for the patient and family continue to be addressed on an on-going basis. Our case of refractory postsurgical PG reiterates the critical importance of collaborative multimodal management of this rare, disfiguring disease.

Contributors All authors substantially contributed to the conception and design of the manuscript, acquisition and interpretation of the data, and drafting and revising of this manuscript critically for important intellectual content.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Wollina U, Haroske G. Pyoderma gangraenosis. *Curr Opin in Rheumatol* 2011;23:50–6.
- Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am J Clin Dermatol* 2012;13:191–211.
- Cummins DL, Anhalt GJ, Monahan T, et al. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007;157:1235–9.
- Sinnya S, Hamza S. Pyoderma gangrenosum of the breast treated with intravenous immunoglobulin. *J Dermatol Case Rep* 2013;7:64–8.
- Wollina U. Clinical management of pyoderma gangrenosum. *Am J Clin Dermatol* 2002;3:149–58.
- Tutrone WD, Green K, Weinberg JM, et al. Pyoderma gangrenosum: dermatologic application of hyperbaric oxygen therapy. *J Drugs Dermatol* 2007;6:1214–19.
- Fraccalvieri M, Fierro MT, Salomone M, et al. Gauze-based negative pressure wound therapy: a valid method to manage pyoderma gangrenosum? *Int Wound J* 2012;14:127–34.
- Niezgoda JA, Cabigas EB, Allen HK, et al. Managing pyoderma gangrenosum: a synergistic approach combining surgical debridement, vacuum-assisted closure, and hyperbaric oxygen therapy. *Plast Reconstr Surg* 2006;117:24e–8e.
- Duval A, Boissel N, Servant JM, et al. Pyoderma gangrenosum of the breast: a diagnosis not to be missed. *J Plast Reconstr Aesthet Surg* 2011;64:e17–20.
- Grillo MA, Cavalheiro TT, da Silva Mulazani M, et al. Postsurgical pyoderma gangrenosum complicating reduction mammoplasty. *Aesthet Plast Surg* 2012;36:1347–52.
- Leppard WM, Reynolds MF, Schimpf DK, et al. Pyoderma gangrenosum of the breast after bilateral simple mastectomies for ductal carcinoma in situ. *Am Surg* 2011;77:E144–6.
- Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006;55:505–9.
- Weenig RH, Davis MD, Dahl PR, et al. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med* 2002;347:1412–18.
- Choufani S, Shuman C, Weksberg R. Beckwith-Wiedemann syndrome. *Am J of Med Genet Part C Semin Medical Genet* 2010;154C:343–54.
- Segaran A, Mohammad M, Sterling JC, et al. Pyoderma gangrenosum arising in a breast reduction scar: seven years post-procedure. *J Plast Reconstr Aest Surg*. Published Online First: 4 Jun 2013. doi:10.1016/j.bjps.2013.05.016

Learning points

- Pyoderma gangrenosum (PG) is a rare inflammatory and ulcerative neutrophilic dermatosis that may be difficult to diagnose and treat.
- PG may occur following various surgeries, including reduction mammoplasty and mastectomy.
- First-line treatments of PG include local wound care and systemic corticosteroids, along with treating any underlying disorder.
- Refractory PG may require collaborative multidisciplinary and multimodal treatments, including immunomodulatory, surgical and adjunctive therapies.

- 16 Goshtasby PH, Chami RG, Johnson RM. A novel approach to the management of pyoderma gangrenosum complicating reduction mammoplasty. *Aesthet Surg J* 2010;30:186–93.
- 17 Charles CA, Leon A, Banta MR, *et al.* Etanercept for the treatment of refractory pyoderma gangrenosum: a brief series. *Int J Dermatol* 2007;46:1095–9.
- 18 Jacob SE, Weisman RS, Kerdel FA. Pyoderma gangrenosum—rebel without a cure? *Int J Dermatol* 2008;47:192–4.
- 19 Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol* 2005;152:1059–61.
- 20 Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med* 1996;334:1642–8.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow