CASE REPORT

When a wound is the harbinger of a serious underlying systemic illness

Shweta Kishore,¹ Varun Mittal,² Shradha Ahuja,² Vikas Majithia¹

¹Department of Rheumatology, University of Mississippi Medical Center, Jackson, Mississippi, USA

²Department of Internal Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

Correspondence to
Dr Shweta Kishore,
skishore@umc.edu

Accepted 3 January 2018

SUMMARY

A 55-year-old woman presented with progressive enlarging and painful non-healing ulcers on her bilateral lower extremities; biopsy was consistent with pyoderma gangrenosum. Workup for an underlying illness revealed a cavitary lung nodule and an ulcerating mass in the anal canal. Patient did not have any respiratory or gastrointestinal symptoms. Differential diagnosis included inflammatory bowel disease, rectal carcinoma or infection such as tuberculosis, fungal process. Histopathology did not reveal any malignancy, inflammatory bowel disease or infection. Serological studies were positive for perinuclear antineutrophil antibodies specific to proteinase-3 antigen, and the patient was ultimately diagnosed with granulomatosis with polyangiitis. Intravenous pulse dose steroids were initiated followed by monthly pulse cyclophosphamide for 6 months, resulting in rapid and significant improvement of the wounds.

BACKGROUND

Granulomatosis with polyangiitis (GPA) previously known as Wegener's granulomatosis, is a systemic, necrotising vasculitis of small- to medium-sized arteries, venous and capillaries, principally involving the kidneys, upper and lower respiratory tract.

Skin involvement is seen in 10%–50% of patients. While purpura is the most common feature, manifestations can be variable but pyoderma gangrenosum

(PG) is rare. Very few reports are available with PG as the presenting manifestation of GPA. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and PG may share common pathophysiological features, as neutrophil dysregulation appears to be the main pathological and immunohistochemical substrate in both conditions.¹

Gastrointestinal (GI) tract involvement is very rare. Presentation can be asymptomatic or range from mild complications such as ulcers to life-threatening complications such as haemorrhage, ischaemia or perforation. Clinically GI GPA mimics inflammatory and infectious bowel diseases. Microscopic findings are more characteristic which may help in differentiating from other ulcerative intestinal diseases.²

Our patient had PG as the presenting manifestation of her underlying illness. More so, she had an asymptomatic rectal ulcerating mass. These lesions indicated the possibility of an inflammatory or infectious bowel disease, which led to a delay in the diagnosis. The case presented here illustrates the importance of a thorough evaluation and consideration of rarer manifestations of GPA in the right clinical setting. A literature review for concomitant presence of GPA and PG as well as GPA and rectal mass was also conducted.

CASE PRESENTATION

A 55-year-old African-American woman was admitted due to fatigue and non-healing wounds on bilateral lower extremities. The wounds started as small pustules 1 month prior and rapidly progressed in size, becoming increasingly painful. They were associated with purulent discharge. There was no associated fever, tick bite or trauma. She had failed multiple rounds of antibiotics prescribed as outpatient. All cultures done as outpatient were negative. These wounds were present on both lower extremities with areas of erythema, purulent discharge and ulceration (figure 1).

She denied any history of weight loss, rash, cough, shortness of breath, haemoptysis, nausea, vomiting, abdominal pain, diarrhoea, haematochezia or neuropathy. She had no significant medical or surgical history. The patient's family history was unremarkable; there was no known family history of autoimmune or inflammatory processes. The patient was a non-smoker and did not abuse illicit drugs or alcohol. She did not take any medication as outpatient.

At the time of presentation, vital signs were within normal limits. Physical exam was significant for

Figure 1 Right and left medial lower extremity with large ulcer, irregular, necrotic with purulence.

To cite: Kishore S, Mittal V, Ahuja S, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222491

Figure 2 Chest CT axial view showing a 2.7 cm cavitary lesion establishing contact with pleural surface without air–fluid level.

bilateral lower extremity large ulcers, which were erythematous, necrotic areas and associated with purulent and serosanguinous discharge. On admission, pertinent laboratory data were as follows: haemoglobin, 11 g/dL; leucocytes, $16.5 \times 10^9/L$; plates, $535 \times 10^9/L$ erythrocyte sedimentation rate (ESR), 88 mm/hour; C reactive protein (CRP), 10.5 mg/dL; creatinine 0.93 mg/dL, alanine aminotransferase, 132 U/L; total protein, 9.2 g/dL and albumin, 3.2 g/dL. Urinalysis showed 25 white cell/high-power field and five red cell/high-power field without any cast. Standard urine drug screen was negative for illicit substances. Serological testing for hepatitis B, hepatitis C and HIV was negative. Quantiferon gold and rapid plasma reagin was negative.

She was admitted and started on broad-spectrum intravenous antibiotics. Extensive infectious workup including cultures for bacterial, fungal and atypical pathogens returned negative. The lesions continued to worsen and became more inflamed and

Figure 3 Right lung nodule histopathology showing a granuloma with necrotic centre, surrounded by histiocytes, neutrophils and scattered giant cells.

necrotic. Skin biopsy done twice by dermatology showed dense neutrophil aggregation surrounding fibrovascular elements and some vascular necrosis, which was consistent with PG-like features. This prompted concern for an underlying malignant versus inflammatory systemic illness. On repeated questioning, patient admitted to having diarrhoea for 1 month and had noticed occasional streak of blood.

INVESTIGATIONS

A CT scan of chest, abdomen and pelvis showed a 2.7 cm cavitary lung lesion in the right lung along with multiple scattered pulmonary nodules (figure 2). A biopsy of the pulmonary nodules showed actively inflamed granulation tissue with negative results on Gram stain, cultures and acid-fast bacilli staining, as well as absent cell growth on fungal and mycobacterial cultures. In addition, there were necrotic granulomas surrounded by histiocytes, giant cells and neutrophils (figure 3).

Also seen was rectal wall thickening, hence a pelvic MRI was obtained revealing an ulcerating mass in the anal canal with extensive associated adenopathy as well as concern for rectal fistulas. Colonoscopy showed a circumferential friable tissue growth, biopsy of which showed acute inflammation and granulation tissue formation with marked lymphoplasmacytic infiltrates but no evidence of inflammatory bowel disease. Esophagogastroduodenoscopy (EGD) showed two small ulcers in oesophagus and stomach as well as multiple duodenal erosions.

Antinuclear antibody, ACE, blastomyces and histoplasma antigen were negative. Serological testing returned positive for perinuclear ANCA by immunofluorescence method, which showed specificity for proteinase-3 antigen done by ELISA on two occasions. Myeloperoxidase ANCA was negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in this patient included a variety of infections such as tuberculosis, histoplasmosis and blastomycosis. Other differentials, which were strongly considered, were paraneoplastic syndrome from haematological malignancies, rectal adenocarcinoma, inflammatory bowel disease, PG with lung involvement and GPA.

Extensive workup for infections and malignancies returned negative. Ultimately based on the presentation, positive perinuclear ANCA specific to proteinase-3 antigen and granulomatous lesions on lung histopathology, the diagnosis of GPA was made.

TREATMENT

The patient was treated with 1 g of intravenous methylprednisolone daily for 3 days followed by tapering dose of oral prednisone. The wound improved significantly within 72 hours of high-dose steroid. She also received 1 g of cyclophosphamide prior to discharge. She was then followed up in the outpatient rheumatology and wound clinic and was scheduled for monthly cyclophosphamide for a total of six infusions. She continued to show clinical improvement on her subsequent visits and prednisone was slowly tapered down.

OUTCOME AND FOLLOW-UP

At the 6-month follow-up, PG lesions had dramatically improved, except showing signs of hyperpigmentation and scarring (figure 4). On her last follow-up, ESR and CRP was normal and ANCA had become negative. She remained on 10 mg prednisone and azathioprine was initiated for maintenance therapy.

Figure 4 Right and left medial ankle after 6 months of cyclophosphamide therapy.

DISCUSSION

GPA is a systemic disease which usually affects kidneys and upper and lower respiratory tract. However it can involve other organs such as skin, GI, central and peripheral nervous system. Because of the variable and non-specific symptoms at presentation, the correct diagnosis can often be delayed or missed. Ultimately, fulfilment of histological features and detection of autoantibodies leads to the diagnosis.

Cutaneous involvement occurs in 10%–50% of the patients; usual manifestations are purpura, ulcerations, papules, nodules, digital necrosis and splinter haemorrhages. PG is very rare and even more so as the presenting manifestation. In a recent cohort analysis by the French Vasculitis Study Group (FVSG), PG was found in 0.5% of 1553 patients and occurred only in patients with GPA.³ It starts as a bullous or pustular lesion in the lower extremities, abdomen or genital region.⁴ It is an inflammatory disease characterised by rapidly progressive, painful large ulcers secondary to aggregation of neutrophils. The FVSG also pointed out poor clinical and prognosis significance of cutaneous manifestation in GPA.³ Treatment includes corticosteroids, ciclosporin, dapsone, thalidomide, colchicine, azathioprine, mycophenolate mofetil (MMF), cyclophosphamide or tumour necrosis factor alpha (TNF)- α blockers.⁵ Off-label use of rituximab in PG has been reported.⁴

GI may occur in up to one-third of the case based on post-mortem findings, but only few have symptomatic involvement.^{6,7} By the time patients present with GI symptoms, they already

have a diagnosis of GPA, and thus it remains unclear whether the GI involvement occurs as a result of the disease or the immunosuppressive therapy.^{8–11} The small bowel is the most common site involved. Pathological findings may range from multiple shallow ulcerations to intestinal perforation. Histology shows mixed inflammatory infiltrate associated with necrotising and granulomatous vasculitis of small vessels. Treatment options include cyclophosphamide, azathioprine, chlorambucil, prednisone and plasma exchange. Resection may be required in perforation, bleeding and ongoing ischaemia. Use of intravenous immunoglobulin for fulminant enteritis and haemorrhage with rapid improvement has been described.¹²

Medline literature search revealed 33 case reports or case series of concomitant GPA and PG.^{1,4,5,13–25} Of these, 19 patients had PG as one of the presenting features at the time of GPA diagnosis. Majority of these patients either had lung or renal involvement. The most popular treatment for GPA-associated PG was steroids and cyclophosphamide in 20 patients. Of these 20 patients, 5 had refractory PG with vasculitis and were eventually treated with rituximab, ciclosporin and intravenous immunoglobulin in combination with azathioprine or MMF.^{1,4,13,18} Recently, there have been good results and increasing use of rituximab in patients with GPA with lung or renal involvement. Of note, two patients received rituximab as initial therapy for GPA-associated PG with good response.^{24,25} There is not much reported use of rituximab in GPA with GI involvement or PG; however, it is imperative to note that majority of the above cases were reported when rituximab was not yet approved for treatment of GPA. Similarly, little is known about the use of infliximab in GPA associated with PG, and there are rising concerns regarding TNF- α blocker induced vasculitis.

Our patient had a rather unique presentation of GPA with PG and an asymptomatic rectal ulcerating mass who was treated successfully with steroids and cyclophosphamide. PG and GI manifestations are uncommon in GPA and can be misleading as they may precede the systemic symptoms. This report is a reminder that GPA is a systemic disease, in which cutaneous manifestation can occur in early stages of the disease. Treatment and outcome is no different from underlying vasculitis.

Learning points

- Granulomatosis with polyangiitis (GPA) is a systemic necrotising vasculitis of small-sized arteries that predominantly affects the respiratory tract and the kidneys and rarely involves skin and gastrointestinal tract.
- Pyoderma gangrenosum is a rare presenting manifestation of GPA.
- Diagnosis often gets missed or delayed due to rarity of this disease and to rule out other causes before establishing the diagnosis.
- Treatment can be challenging. Options include steroids, cyclophosphamide, rituximab, ciclosporin and antitumour necrosis factor therapy.

Contributors SK: contributed in establishing the diagnosis and management of the patient as a rheumatology consultant, extensive literature search of similar cases, initial preparation of the entire manuscript and compilation of contributions from other authors and obtaining consent from the patient; reviewed the requirements and guidelines for submission and designed the template accordingly. VMI: contributed in literature search and similar cases, found additional cases on Medline, citation management, editing of images, revision of the manuscript twice. SA: patient admitted under SA service, first suspected autoimmune disease, appropriate consultation, helped in facilitating management, prepared the abstract for the manuscript, set up the title for the manuscript, revision of the manuscript and

helped in reducing grammatical errors. VMA: served as the chief of the division and supervised all the authors, set up timeline for submission, planning the submission to BMJ, reviewed the requirements, critical revision of the article at every stage, drafted the take-home messages, gave final approval of the version to be submitted. All authors agreed to be accountable for the work and have confidence in the integrity and accuracy of the work.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- de Boysson H, Martin Silva N, de Moreuil C, *et al.* Neutrophilic dermatoses in antineutrophil cytoplasmic antibody-associated vasculitis: a French multicenter study of 17 cases and literature review. *Medicine* 2016;95:e2957.
- Deniz K, Özşeker HS, Balas S, *et al.* Intestinal involvement in Wegener's granulomatosis. *J Gastrointest Liver Dis* 2007;16:329–31.
- Frumholtz L, Laurent-Roussel S, Aumaitre O, *et al.* Clinical and pathological significance of cutaneous manifestations in ANCA-associated vasculitides. *Autoimmun Rev* 2017;16:1138–46.
- Donmez S, Pamuk ON, Gedik M, *et al.* A case of granulomatosis with polyangiitis and pyoderma gangrenosum successfully treated with infliximab and rituximab. *Int J Rheum Dis* 2014;17:471–5.
- Kędzierska K, Sindrewicz K, Smektała T, *et al.* Wegener's granulomatosis and pyoderma gangrenosum—rare causes of facial ulcerations. *Postępy Hig Med Dosw* 2016;70:210–8.
- Sokol RJ, Farrell MK, McAdams AJ. An unusual presentation of Wegener's granulomatosis mimicking inflammatory bowel disease. *Gastroenterology* 1984;87:426–32.
- Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958;2:265–70.
- Geraghty J, Mackay IR, Smith DC. Intestinal perforation in Wegener's granulomatosis. *Gut* 1986;27:450–1.
- Pickhardt PJ, Curran VW. Fulminant enterocolitis in Wegener's granulomatosis: CT findings with pathologic correlation. *AJR Am J Roentgenol* 2001;177:1335–7.
- McNabb WR, Lennox MS, Wedzicha JA. Small intestinal perforation in Wegener's granulomatosis. *Postgrad Med J* 1982;58:123–5.
- Storesund B, Gran JT, Koldingsnes W. Severe intestinal involvement in Wegener's granulomatosis: report of two cases and review of the literature. *Br J Rheumatol* 1998;37:387–90.
- Chow FY, Hooke D, Kerr PG. Severe intestinal involvement in Wegener's granulomatosis. *J Gastroenterol Hepatol* 2003;18:749–50.
- Le Hello C, Bonte I, Mora JJ, *et al.* Pyoderma gangrenosum associated with Wegener's granulomatosis: partial response to mycophenolate mofetil. *Rheumatology* 2002;41:236–7.
- Szöcs HI, Torma K, Petrovicz E, *et al.* Wegener's granulomatosis presenting as pyoderma gangrenosum. *Int J Dermatol* 2003;42:898–902.
- Jacob SE, Martin LK, Kerdel FA. Cutaneous Wegener's granulomatosis (malignant pyoderma) in a patient with Crohn's disease. *Int J Dermatol* 2003;42:896–8.
- Kouba DJ, Mimouni D, Ha CT, Ct H, *et al.* Limited Wegener's granulomatosis manifesting as malignant pyoderma with corneal melt. *Int J Dermatol* 2003;42:902–4.
- Boudny C, Nievergelt H, Braathen LR, *et al.* Wegener's granulomatosis presenting as pyoderma gangrenosum. *J Dtsch Dermatol Ges* 2008;6:477–9.
- Tashtoush B, Memarpour R, Johnston Y, *et al.* Large pyoderma gangrenosum-like ulcers: a rare presentation of granulomatosis with polyangiitis. *Case Rep Rheumatol* 2014;2014:1–4.
- Castillo RF, Cañadas-De la Fuente GA, Husein-Elahmed H, *et al.* Pyoderma gangrenosum developing over an arteriovenous fistula scar. *Intern Med J* 2011;41:436–7.
- Cone LA, Annunziata GM, Gebhart RN, *et al.* Malignant pyoderma and Wegener's granulomatosis. *Mayo Clin Proc* 1998;73:390.
- Handfield-Jones SE, Parker SC, Fenton DA, *et al.* Wegener's granulomatosis presenting as pyoderma gangrenosum. *Clin Exp Dermatol* 1992;17:197–200.
- Micali G, Cook B, Ronan S, *et al.* Cephalic pyoderma gangrenosum (PG)-like lesions as a presenting sign of Wegener's granulomatosis. *Int J Dermatol* 1994;33:477–80.
- Jiménez-Gallo D, Albarrán-Planelles C, Linares-Barrios M, *et al.* Pyoderma gangrenosum and Wegener granulomatosis-like syndrome induced by cocaine. *Clin Exp Dermatol* 2013;38:878–82.
- de Cambourg G, Mahé A, Banea S, *et al.* [Granulomatosis with polyangiitis revealed by a cutaneous ulceration mimicking a pyoderma gangrenosum: Two patients]. *Rev Med Interne* 2016;37:632–5.
- Gastman B, Hashem AM, Djohan R, *et al.* Malignant pyoderma associated with granulomatosis with polyangiitis (Wegener granulomatosis) as a unique indication for facial vascularized composite allotransplantation: Part I. *Plast Reconstr Surg* 2016;137:1007e–15.

Copyright 2018 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