



A case of extracutaneous pyoderma gangrenosum in a patient with persistent cutaneous and systemic symptoms: Implications for differential diagnosis and treatment

Gabriella Santa Lucia, MSCR, Alexa DeMaio, BS, Samantha Karlin, MD, and Dirk Elston, MD
Charleston, South Carolina

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INTRODUCTION

Pyoderma gangrenosum (PG) is a noninfectious neutrophilic dermatosis that results in large painful ulcers with violaceous borders and cribriform pitting.¹ Altered neutrophil chemotaxis and deregulation of the innate immune system have been suggested to play roles in the pathogenesis.² The disease course is unpredictable, ranging from superficial ulcers to rare, widespread extracutaneous involvement, including but not limited to the lungs, spleen, eyes, and upper airways.³ We describe a patient with cutaneous PG who developed extracutaneous pulmonary, pericardial, hepatic, splenic, and pancreatic involvement. Colonization of sputum by mycobacteria and an indeterminate interferon gamma assay, along with a history of anti tumor necrosis factor alpha (TNF- α) therapy twice, led to the false assumption that the lung and visceral disease were infectious. This case emphasizes the importance of considering extracutaneous PG in the differential diagnosis of patients with persistent cutaneous PG accompanied by systemic lesions.

CASE REPORT

A 56-year-old woman with a history of rheumatoid arthritis and multiple myeloma status post bone marrow transplantation presented to dermatology for an ulceration of the lower portion of the leg (Fig 1), clinically consistent with PG. Biopsy showed benign ulcer with a dense neutrophilic infiltrate (Fig 2). Stains for infectious organisms and tissue cultures for bacteria, acid-fast bacteria, and fungi

Abbreviations used:

IL: interleukin
PG: pyoderma gangrenosum
TNF- α : tumor necrosis factor alpha

were all negative. Throughout the next several years, the patient continued to develop flares of PG on various sites of her extremities that were managed with systemic and intralesional steroids, adalimumab, cyclosporine, mycophenolate, and anakinra. Her rheumatoid arthritis also became better controlled with treatment of her PG.

Ten years after the diagnosis of cutaneous PG, the patient was hospitalized for new shortness of breath with associated worsening of her cutaneous PG. The patient was afebrile with an elevated C-reactive protein (14 mg/L) and a white blood cell count of 17,000 with 80% neutrophils. Computed tomography imaging demonstrated pericardial effusion and multiple large, bilateral, cavitary pulmonary (Fig 3) and splenic abscesses. The patient was admitted to an internal medicine service with concern for infection and treated with broad-spectrum antibiotics and discontinuation of immunosuppressants, which only worsened her condition. *Mycobacterium fortuitum* was isolated from sputum, but bronchoalveolar lavage, transbronchial biopsy, and 2 lung wedge resections revealed only abscess with no evidence of infection by stains, culture, or molecular studies. An antineutrophil cytoplasmic antibody test was negative. The patient's status continued to worsen despite

From the Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina.

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Correspondence and reprints requests to: Gabriella Santa Lucia, MSCR, Medical University of South Carolina, Department of Dermatology and Dermatologic Surgery, 135 Rutledge Avenue, Charleston, SC 29425. E-mail: grs200@musc.edu.

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Fig 1. Cutaneous pyoderma gangrenosum eruption of the lower leg during extracutaneous pulmonary flare.

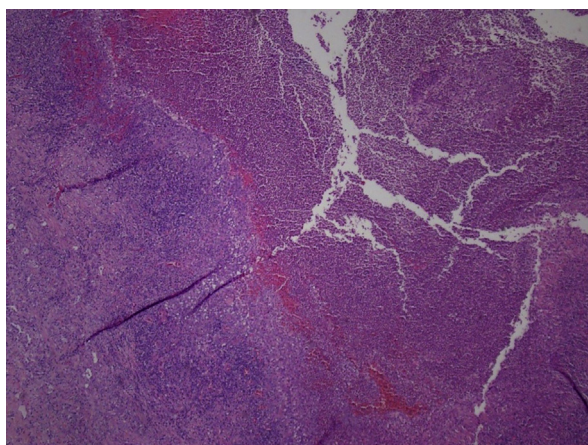


Fig 2. Lung with dense neutrophilic infiltrates including abscess formation. (Hematoxylin-eosin stain).

initiation of broad-spectrum antibiotics and systemic antifungals. Dermatology was consulted, and given the patient's concomitant flare of cutaneous PG, extracutaneous PG was considered. She was re-started on increased doses of her previous immunosuppression, and the cutaneous and visceral lesions rapidly improved. Repeat imaging showed complete resolution of the pulmonary, pericardial, and abdominal lesions.

A year later, the patient was admitted to the hospital for new nausea, vomiting, right upper quadrant pain, and a severe flare of her cutaneous PG. A computed tomography scan of the abdomen and pelvis again revealed multiple lesions throughout the lungs, liver, spleen, and pancreas.



Fig 3. Chest X-ray demonstrating pulmonary nodules.

Again, she was started on broad-spectrum antibiotics and antifungals, and her immunosuppression was discontinued by the internal medicine service. She underwent percutaneous drainage of abscesses, and again, all cultures, stains, and molecular studies were negative for infectious organisms. After dermatology was consulted, she was re-started on higher doses of her previous immunosuppression with rapid clinical improvement and resolution of all lesions.

She has since been managed with tapered doses of prednisone for periodic break-through flares, TNF- α inhibitors, cyclosporine, azathioprine, intravenous immunoglobulin, anakinra, and canakinumab. Her current and most efficacious regimen consists of tapering prednisone, azathioprine, and canakinumab, with her most recent chest X-ray displaying resolution of all active lesions.

DISCUSSION

PG is an inflammatory, neutrophilic dermatosis with 75% of cases associated with an underlying disease.¹ The association with inflammatory arthritis, hematologic disorders, and inflammatory bowel disease is well known. In rare cases, neutrophilic infiltrates can involve internal organs, such as the lungs, spleen, eyes, and musculoskeletal system. A 2019 review identified only 96 documented cases of extracutaneous involvement.⁴ These extracutaneous infiltrates can appear and flare before, during, or after cutaneous lesions surface.⁴

Pulmonary, pericardial, hepatic, splenic, and pancreatic lesions were twice interpreted by the admitting service as evidence of infection. Each time immunosuppressive therapy was held, it resulted in worsening of the patient's condition. The largest obstacle to appropriate diagnosis and care was the identification of *Mycobacterium fortuitum* in one sputum culture, in the setting of lung nodules and

cavitary lung lesions, along with an indeterminate interferon gamma assay related to anergy and anti TNF- α therapy. The sputum culture was interpreted as non-pathogenic nontuberculous mycobacterial colonization, and the visceral lesions were characterized as extracutaneous PG following the patient's worsening condition with antimicrobial treatment, subsequent healing with immunosuppression, and multiple negative transbronchial lung biopsies and aspirates.

As PG with systemic involvement is a diagnosis of exclusion, patients typically undergo extensive medical and infectious workup. They may experience critical delays in diagnosis and inappropriate management. While it is essential to rule out infection, vasculitis, and malignancy, extracutaneous PG should be included in the differential for patients presenting with flares of cutaneous PG and concomitant systemic symptoms.

While neutrophilic dermatoses can be part of the spectrum of autoinflammatory diseases, our patient did not have features of defined syndromes.⁵ A diagnosis of extracutaneous PG, PAPA (pyogenic arthritis, PG, and acne), PAPASH (pyogenic arthritis, acne, PG, and suppurative hidradenitis), and aseptic abscess syndrome rely on the patterns of presentation, associated signs and symptoms, and genetic testing.⁵⁻⁷ Our patient lacked acne and hidradenitis suppurativa, as well as any joint pain during these episodes. Antinuclear antibody, antineutrophil cytoplasmic autoantibody, and antiphospholipid antibody tests have been negative to date. Her rheumatoid factor and anticitrullinated peptide antibody have normalized with immunosuppressive treatment. Microscopically, lung tissue has consistently shown numerous neutrophils and negative infectious stains and tissue cultures, which can be seen in both extracutaneous PG and aseptic abscess syndrome. However, the patient's history of cutaneous PG flares in parallel with the extracutaneous lesions suggests extracutaneous PG as the most likely diagnosis. As we regard extracutaneous PG to reside within the spectrum of autoinflammatory disease, the distinction is not likely to affect management. The more important management issue is correct identification as inflammatory rather than infectious disease.

Immunosuppressive agents like methotrexate, mycophenolate mofetil, azathioprine, and sulfasalazine have been successful in some patients. However, recent management trends have shifted to targeted biologic therapies, including TNF- α and

interleukin (IL)-1B inhibitors.^{1-3,5} High TNF- α and IL-8 augment neutrophilic infiltration, with high IL-1 stimulating a proinflammatory response, providing a rationale for using TNF- α and IL-1B antagonists.⁸ Patients with refractory extracutaneous PG may require a multidrug regimen of general immunosuppressives and targeted biologics to control disease.

Long-term use of immunosuppressives and anti TNF- α biologics reduce cell-mediated immunity and increase the risk of nontuberculous mycobacterial disease by 8-50 times compared with the general population.⁹ Acid-fast bacteria are found in roughly half of all city water supplies, and lung colonization is common as a result of inhalation during showering.¹⁰ The risk of treating non-tubercloid colonization should be considered on an individualized basis. Our patient remains on prednisone, azathioprine, and canakinumab without antibiotics, with no progression of disease and no further evidence of the colonizing mycobacterium.

Ellen Riemer, MD contributed for pathology interpretation.

Conflicts of interest

None disclosed.

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