CASE REPORTS

EXTRA-INTESTINAL CROHN'S DISEASE AND PYODERMA GANGRENOSUM AS A DIAGNOSTIC DILEMMA: CASE REPORT

Dominder Kaur, Chantel Cacciotti*, Ryan L Webb**, Jeremy Neuman**, Sarah Vaiselbuh**

Abstract

Extra-intestinal manifestations such as pyoderma gangrenosum and pulmonary nodules in Crohn's disease are rarely reported in the pediatric population. We report a 17-year-old female who presented with fulminant pyoderma gangrenosum and pulmonary nodules, as a diagnostic challenge. A review of treatment for Crohn's disease and pyoderma gangrenosum are discussed.

Keywords: Crohn's disease; pyoderma gangrenosum; pulmonary nodules; hemorrhagic pustules; inflammatory bowel disease; extra intestinal manifestation

Introduction

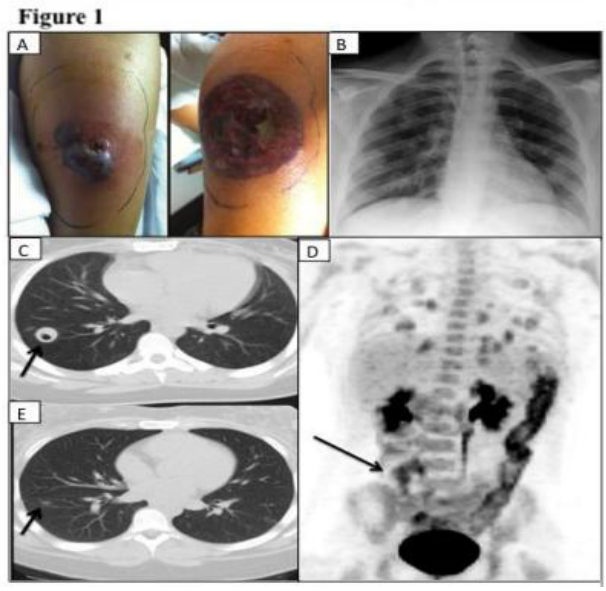
Extra-intestinal manifestations with pulmonary nodules and dermatological lesions such as pyoderma gangrenosum are unusual presenting symptoms of Crohn's disease or inflammatory bowel disease (IBD). (1-3) We present a patient with ulcerative lesions that progressed into multiple abscesses with rapid clinical deterioration, who was diagnosed with underlying Crohn's disease and pyoderma gangrenosum. In addition, the patient developed pulmonary nodules, a rare reported finding in Crohn's disease, especially in the pediatric population.

Case Report

A 17-year old female with a history of anemia, presented with acute onset of hemorrhagic skin pustules evolving into abscesses (Fig.1-A). She had a two-year history of intermittent abdominal pain and non-bloody diarrhea. Physical examination demonstrated one large loculated abscess with sero-sanguinous discharge and a black border on the right calf as well as multiple small pustules on both extremities. Laboratory analysis revealed microcytic anemia (Hemoglobin 9.3 g/dl); leukocytosis (white cell count - 14.65 x 109/L) and thrombocytosis (platelet count 582 x 109/L); elevated erythrocyte sedimentation rate (65mm at end of 1 hour); elevation of the C-reactive protein level (17.4 mg/L) and a normal coagulation profile. Blood and wound cultures remained negative. Intravenous Vancomycin and Clindamycin were started and surgical debridement was done. Due to poor wound healing, the patient underwent skin grafting.

Colonoscopy done on hospital day 5 revealed colitis of the descending colon, splenic flexure and recto-sigmoid junction. Colon biopsies confirmed chronic inflammation, with presence of T-cell lymphocytes in the duodenal mucosa and an atypical mixed lymphoid population of T- and B-cells. The histopathological differential diagnosis included chronic reactive inflammation and a possible low grade B-cell lympho-proliferative disorder such as a mucosal-associated lymphoid tumor (MALT). Treatment for colitis with prednisone resulted in minimal gastrointestinal improvement but the skin lesions continued to progress. Skin biopsies showed epidermal hyperplasia and ulceration, inflammation with intra-epidermal neutrophils, fibrinous exudate, calcifications and granulation tissue- all suggestive of pyoderma gangrenosum (PG). Serology to rule out any immunology-related conditions revealed normal titres of IgG and IgA but Anti-Saccharomyces cerevisiae (ASCA) IgA was positive (51.5) (normal reference range <25) (4), while other markers, namely reticulin antibodies, anti-neutrophil cytoplasmic antibody (ANCA), myeloperoxidase antibody, proteinase-3 antibody and ASCA IgG were negative. To rule out a PG-associated malignancy, staging CT chest was done that illustrated pulmonary nodules with central cavitation (Fig. 1-B), which were consequently monitored by chest X-ray (Fig. 1-C). Additional PET scan showed multiple bilateral scattered pulmonary nodules which were uniformly fluoro deoxy-glucose (FDG) avid along with abnormal FDG uptake in a large portion of the bowel wall, particularly the descending colon and terminal ileum (Fig.1-D). Pathology of the lung lesions was compatible with necrobiotic nodules, without evidence of malignancy. Patient was initially not responding well to intravenous steroids but after adequate antibiotic coverage did mount a response; and was discharged home on oral prednisolone. At a 6-month follow-up CT, significant internal improvement of multiple pulmonary nodules was seen with minimal residual post-inflammatory scarring identified at many sites.

Fig 1: A: Right calf loculated abscess- surrounding induration, erythema, sero-sanguinous purulent discharge. B: CT-guided biopsy demonstrates cavitary lesion (arrow). C: Chest X-Ray - multiple pulmonary nodules, some cavitary. D: Coronal PET- increased uptake within lung (maximum SUV=6.8), descending colon (maximum SUV = 12.7) and terminal ileum (maximum SUV = 11.7) (arrow). E: Follow up CT 5 months post treatment shows minimal residual inflammation or scarring (arrow).



Discussion

Pyoderma gangrenosum, initially described as an infectious entity, is now classified as a form of neutrophilic dermatosis - characterized by recurrent cutaneous ulcerations with muco-purulent or hemorrhagic exudates. (1) Despite this knowledge, its spectrum of presentation and associated diseases remains poorly understood. Our patient's presentation with ulcerative skin lesions that began as sterile pustules progressing to necrotic painful ulcers, with violaceous, edematous and serpiginously expanding borders meets the diagnostic criteria for PG. (1) Unless PG is included in the initial differential of such ulcers, it might become a diagnostic dilemma.

PG is often associated with underlying diseases, most commonly IBD, rheumatic and hematological disease or malignancy. (5) In our patient, an associated diagnosis was only entertained after the colon biopsy confirmed IBD. Pathology illustrated mucosal and submucosal involvement with focal chronic active inflammation and presence of T-cell lymphocytes in the duodenal mucosa, suggestive of Crohn's disease. Mucosal lymphocytes are described to be increasingly activated in Crohn's disease, suggesting that the exaggerated response of mucosal T-lymphocytes likely secondary to a damaged down-regulation of the CD3-dependent signaling, may contribute to the pathogenesis of Crohn's disease. (6) The mixed T- and B-cell population created a confusing differential diagnosis of possible MALT lymphoma. Colonic tissue affected by Crohn's disease maintains an increased number of mature myeloid dendritic cells in clusters with proliferating T-cells. The autocrine and paracrine actions of lymphoid chemokines are thought to be responsible for the autoimmune inflammation in Crohn's disease by causing an unusual attraction of mature DC cells towards the bowel wall. (7)

The most unexpected aspect of our case was respiratory involvement. Extra-intestinal manifestations of Crohn's disease with lung granulomas or bronchiolitis obliterans organizing pneumonia-like changes have been described as a rare entity. (8,9) However, pulmonary disease is the most frequently reported extracutaneous manifestation of PG and is characterized by patchy infiltrates, interstitial pneumonitis or cavitary pneumonia. In PG the skin lesions may appear several months after onset of lung abscesses formation, making a correct diagnosis of the pulmonary lesions more challenging (Table 1).(10)

Necrobiotic nodules are sterile aggregates of neutrophils with central hypodensity found in peripheral lung fields. (8) They have been reported either in Crohn's disease or -less frequent- associated with PG in adult patients. PG may precede pulmonary necrobiotic nodules in Crohn's disease. (11) In our patient pulmonary necrobiotic nodules were found following diagnosis of PG, confirmed by lung biopsy.

Effective treatment options for PG involve corticosteroid administration, immunomodulating agents and antimicrobial or steroid-sparing immunosuppressive drugs (Table 2). PG, as well as pulmonary manifestations of Crohns' disease, frequently responds to corticosteroid administration, which remains first-line therapy for both. Prolonged steroid treatment in our patient resulted in complete resolution of skin and pulmonary lesions (Fig.1-E). In localized PG, local wound care can be sufficient. Wide spread disease requires systemic steroids in addition to immunosuppressives and/or immunomodulators as well as management of the associated disease. (12) Biological agents have expanded the treatment options for Crohn's. (13) Studies demonstrate resolution of non-infectious pulmonary disease with infliximab therapy. (14)

In conclusion, we report an unusual presentation of extra-intestinal Crohn's disease, where the primary manifestation of pulmonary nodules and skin lesions formed a diagnostic challenge. Pulmonary lesions might first be diagnosed as malignancy or infection by radiologists and physicians. Being mindful of the extra-intestinal presentations of Crohn's disease may aid in accurate assessment of this diagnostic pitfall.

Table 1: Pulmonary manifestations in Pyoderma Gangrenosum (PG) versus Crohn's Disease/ Inflammatory Bowel Disease (IBD)

Pulmonary Nodules in PG	Pulmonary Nodules in Crohn's/IBD
- single or multiple, unilateral or bilateral	- often multiple
- usually in peripheral portions of the lung	- no specific sites noted
- solid in nature, sometimes cavitary	- cavitary in nature
- interstitial pneumonitis often ssociated	- pleural fibrosis known to be associated
- primary neutrophilic infiltrates	- infiltrates may be neutrophilic, lymphocytic or eosinophilic
- aseptic inflammatory lesions without necrotizing granulomas	- non-caseating granuloma formation sterile but necrotic/necrobiotic
- responsive to steroids	- may or may not respond to steroids, may respond to mesalazine, good response to Infliximab
- may be due to the underlying systemic disease causing PG	- known to exist without pyoderma in Crohn's

Table 2: Treatment options for Pyoderma Gangrenosum (PG) versus Crohn's Disease/Inflammatory Bowel Disease (IBD) [14, 15]

	Treatment of PG	Treatment of Crohn's Disease/ IBD
Topical Agents	Corticosteroids Tacrolimus (0.5%) Benzoyl peroxide Nitrogen mustard	Budesonide (limited for disease affecting ileum and ascending colon)
Systemic Agents Immunosuppressive	Oral Corticosteroids in pulse therapy Tacrolimus 6-Mercaptopurine Azathioprine Cyclophosphamide Cyclosporine Methotrexate Cytosine arabinoside Daunorubicin Melphalan	Chronic low dose steroids (non-responsive IBD) Tacrolimus (refractory CD) 6-Mercaptopurine Azathiopurine Cyclophosphamide Cyclosporine Methotrexate
Systemic Agents Antimicrobial	Sulfasalazine Dapsone Rifampicin Clofazimine Vancomycin Mexlocillin Minocycline	Aminosalicylates: sulfasalazine, mesalamine, olsalazine, balsalazide Ciprofloxacin Metronidazole(used to treat infectious complications CD, or mild active CD)
Anti-diarrheal Meds		Loperamide Cholestyramine
Biologic Agents	Anti-TNF therapy: Infliximab Alefacept Adalimumab Efalizumab Etanercept	Anti-TNF therapy: Infliximab (used in individuals with disease resistant to steroids and 6-MP) Adalimumab (disease resistant to infliximab) Certolizumab
		Combination therapy (infliximab in combination with 6-MP, azathioprine or methotrexate)
		Natalizumab (effective induction agent for CD)
Immune Modulators	IVIG Interferon Granulocyte apheresis	
Anti-inflammatory	Thalidomide Mesalazine Colchicine Heparin Potassium Iodide Isotretinoin	Thalidomide (refractory IBD)
Last resort	NO surgery - can make PG worse and progressive	Surgery (used in unresponsive disease or patients who develop abscess, fistula or strictures or with limited regional involvement)

Contributor's Statement

DK perceived the idea for the case report, drafted the clinical description of the case, wrote the abstract, contributed to the discussion, clinical images and tables, reviewed the manuscript and approved the final manuscript for submission. CC collected the basic reports and information for the writing of the clinical part, formulated the initial discussion draft, reviewed and revised the discussion, contributed to tables, edited and approved the final manuscript for submission. RLW performed the literary review of the radiological aspect of the case, contributed the pertinent radiological findings in the patient's imaging studies, and approved the final manuscript for submission. JN carried out and supervised the radiological literary review as well as the review of the imaging studies of the patient, selected the pertinent radiological images for the manuscript, contributed the figure legends, revised and reviewed the discussion, and approved the final

manuscript for submission. SV supervised the initial information collection and literature review for the report, contributed vital references to the discussion, revised and edited the discussion, tables and legends, and approved the final manuscript for submission.

Funding Source: None
Financial Disclosure: None
Conflict of Interest: None

References

1. Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004; 43(11):790-800.
2. Farhi D, Cosnes J, Zizi N, Chosidow O, Seksik P, Beaugerie L, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. Medicine (Baltimore). 2008;87(5):281-93.
3. Sanjeevi A, Roy HK. Necrobiotic nodules: a rare pulmonary manifestion of Crohn's disease. Am J Gastroenterol. 2003;98(4):941-3.
4. Teml A, Kratzer V, Schneider B, Lochs H, Norman GL, Gangl A, et al. Anti-Saccharomyces cerevisiae antibodies: a stable marker for Crohn's disease during steroid and 5-aminosalicylic acid treatment. Am J Gastroenterol. 2003;98(10):2226-31.
5. Farhi D, Cosnes J, Zizi N, Chosidow O, Seksik P, Beaugerie L, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. Medicine (Baltimore). 2008;87(5):281-93.
6. Jacquot S, Modigliani R, Kuzniak I, Boumsell L, Bensussan A. Enhanced CD3 monoclonal antibody induced proliferation of colonic mucosal T lymphocytes in Crohn's disease patients free of corticosteroid or immunosuppressor treatment. Clin Immunol Immunopathol. 1996;79(1): 20-4.
7. Middel P, Raddatz D, Gunawan B, Haller F, Radzun HJ. Increased number of mature dendritic cells in Crohn's disease: evidence for a chemokine mediated retention mechanism. Gut. 2006;55(2):220-7. Epub 2005 Aug 23.
8. Sanjeevi A, Roy HK. Necrobiotic nodules: a rare pulmonary manifestion of Crohn's disease. Am J Gastroenterol. 2003;98(4):941-3.
9. Betancourt SL, Palacio D, Jimenez CA, Martinez S, Marom EM. Thoracic manifestations of inflammatory bowel disease. AJR American journal of roentgenology. 2011;197(3):W452-6.
10. Brown TS, Marshall GS, Callen JP. Cavitating pulmonary infiltrate in an adolescent with pyoderma gangrenosum: a rarely recognized extracutaneous manifestation of a neutrophilic dermatosis. J Am Acad Dermatol. 2000;43(1 Pt 1):108-12.
11. Galbraith SS, Drolet BA, Kugathasan S, Paller AS, Esterly NB. Asymptomatic inflammatory bowel disease presenting with mucocutaneous findings. Pediatrics. 2005;116(3): e439-44.
12. Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43(11):790-800.
13. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and Therapeutic Management of Extra-Intestinal Manifestations of Inflammatory Bowel Disease. Drugs. 2012;Nov 27.
14. Krishnan S, Banquet A, Newman L, Katta U, Patil A, Dozor AJ. Lung lesions in children with Crohn's disease presenting as nonresolving pneumonias and response to infliximab therapy. Pediatrics. 2006;117(4):1440-3.
15. Jacquot S, Modigliani R, Kuzniak I, Boumsell L, Bensussan A. Enhanced CD3 monoclonal antibody induced proliferation of colonic mucosal T lymphocytes in Crohn's disease patients free of corticosteroid or immunosuppressor treatment. Clin Immunol Immunopathol. 1996;79(1): 20-4.

From: *Department of Pediatrics, ** Department of Radiology, Children's Cancer Center, Staten Island University Hospital, Staten Island, New York, USA.

Address for Correspondence: Sarah R. Vaiselbuh, MD; Director Pediatric Hemato/Oncology, The Children's Cancer Center - HistioCare, Staten Island University Hospital, 256-C Mason Ave, Staten Island, NY - 10305, USA. Email: svaiselbuh@siuh.edu.

E-published: 1st October 2013 Art # 62

DOI: 10.7199/ped.oncall.2013.62

Quick Response Code