When Recurring Infections Mask an Atypical Presentation of Inflammatory Bowel Disease (IBD): A Re-Visitation and Literature Review

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Abstract

Pyoderma gangrenosum (PG) is an uncommon and severe extra-intestinal manifestation (EIM) of inflammatory bowel disease (IBD). Head or scalp involvement in this condition is exceedingly rare. Approximately one-third of presentations can be precipitated by skin trauma or infection, a phenomenon known as pathergy. These ulcers develop acutely, do not necessarily correlate with IBD activity, and can precede IBD diagnosis. Here, we present an atypical presentation of PG that became a cornerstone finding in the subsequent diagnosis of IBD.

Introduction

This case report discusses a series of atypical soft-tissue infections which ultimately led to a diagnosis of pyoderma gangrenosum (PG) in the setting of inflammatory bowel disease (IBD), drawing attention to a lesser-known and more unexpected presentation of IBD. This article aims to additionally delve deeper into PG, both in terms of diagnosis and treatment as well as its relationship with IBD. Here, we analyze the foundation of literature upon which our current understanding of PG is built [1-4], diagnostic indicators and its association with IBD [1,5-6], and emerging treatments [7,8]. Through this discussion, a holistic picture of PG, its manifestations, its association with IBD, and potential treatment options, is formed. While there is much more to understand, our report aims to shed some more light on PG and draw together recent advances into a succinct, up-to-date description. This report represents an update to a previously published case by Davis, William D., et al entitled "S2445 When Recurring Infections Mask an Atypical Presentation of Inflammatory Bowel Disease:"

Case Presentation

A 35-year-old male with prior diagnosis of recurrent, diffuse soft tissue infections presented for management of presumed sepsis due to soft tissue infection. Two weeks prior to presentation, the patient developed a painful and purulent left lower extremity ulcer (Figure 1A, B) followed by worsening of facial and scalp ulcerations (Figure 1C).

Of note, the patient stated that his lesions started on his face in January 2020; he went four months without evaluation due to lack of insurance until they spontaneously regressed. He remained without further recurrence until March 2021 (about three months prior to the present admission), when they recurred, ultimately leading to hospitalization at that time where he improved with IV antibiotics. During that admission, he experienced some abdominal pain, leading to a CT abdomen and pelvis which showed circumferential sigmoid and rectal wall thickening concerning for colitis. After that discharge, again three months before the present admission, the patient was lost to follow-up and did not undergo endoscopy despite the recommendation to do so.

On present admission, the patient was febrile to 39.4°C, WBC count of 33k/ul and hemoglobin of 6.1 g/dl. Because of this low hemoglobin, and because he had not undergone the previously recommended outpatient endoscopy for the CT findings, sigmoidoscopy was performed showing diffuse erosive gastritis. Wound cultures of his left lower extremity (Figure 1A, B) grew staphylococcus aureus, and he was started on IV antibiotics. Initial concerns for IBD were based on the prior CT imaging, the ulcers on his leg and scalp which were grossly concerning for PG, and a three-year history of “off-and-on” watery diarrhea with occasional dark brown to black stools elicited after admission. Laboratory work-up is summarized in Table 1.

Sigmoidoscopy showed cobblestoning with non-bleeding mucosal ulcerations and sigmoid colon biopsies demonstrated severe active colitis (Figure 1D). Skin biopsy of his left cheek demonstrated disrupted follicular infundibula with adjacent neutrophil-rich mixed infiltrate and adjacent cicatrix on a fibrotic background dermis, non-specific findings which could represent early pyoderma gangrenosum, infection,
hidradenitis, acne conglobata, or other follicular disorders. Patient was started on steroid therapy with the improvement of both diarrhea and inflammatory markers. The patient was discharged on oral steroids and planned to follow up for initiation of biological therapy; he is now managed outpatient on ustekinumab.

**FIGURE 1:** Pyoderma gangrenosum (PG) lesions and endoscopy findings.

A, B: Lesions identified on patient's left lower extremity. C: Facial and scalp lesions identified on the patient. D: Sigmoidoscopy findings showing rectosigmoid mucosa with ulcerations, congestion, erythema, granularity, and loss of vascularity.
|                        | 5/25/21 | 5/31/31 | 6/7/21 | 6/10/21 |
|------------------------|---------|---------|--------|---------|
| C-reactive protein (nl 0-10mg/L) | 270     | 36      | 28     |         |
| Sedimentary rate (nl 0-15mm/hr)       | 127     |         |        |         |
| Fecal calprotectin (nl >300mcg/gm)   | >3000   |         |        |         |
| WBC (nl 4-10.8k/ul)                   | 33      | 12.2    | 14.5   | 10.5    |
| HIV                                  | Negative|         |        |         |
| HCV                                  | Negative|         |        |         |
| HBV Core/Ag                          | Negative|         |        |         |
| ANA                                  | Negative|         |        |         |
| dsDNA                                | Negative|         |        |         |
| ANCA                                 | Negative|         |        |         |
| MPO                                  | Negative|         |        |         |
| PR3                                  | Negative|         |        |         |
| Clostridium difficile                 | Negative|         |        |         |
| Ova and parasite                      | Negative|         |        |         |
| Stool culture                         | Negative|         |        |         |

**TABLE 1: Relevant labs.**

Workup elucidated significant bowel inflammation (elevated ESR, CRP, fecal calprotectin, elevated WBC), with no infectious or clear autoimmune etiology identified (negatives).

WBC: white blood cells; HIV: human immunodeficiency virus; HCV: hepatitis C virus; HBV: hepatitis B virus; ANA: Antinuclear antibodies; dsDNA: double-stranded DNA; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3.

**Discussion**

**Discussion and literature review**

IBD is associated with a broad array of extra-intestinal manifestations (EIM). Some of these findings are likely associated with the inflammatory state of the disease itself, while other findings may be related to the autoimmune susceptibility of the patients themselves, or the treatment regimens used to treat these disorders [1]. These extra-intestinal manifestations include arthritis, erythema nodosum, aphthous stomatitis, uveitis, ankylosing spondylitis, Henoch-Schoenlein purpura, primary sclerosing cholangitis, primary biliary cholangitis, arthritis, polymyositis, and many more, including pyoderma gangrenosum [1]. These EIM can be essential in supporting the diagnosis of IBD, as demonstrated in the preceding case report.

PG is an ulcerative dermatosis with an incidence of about 6 per 100,000, although given difficulties in diagnosis the true incidence is yet unknown [2]. The pathophysiology is also not fully elucidated, though there appears to be a multifactorial process at play. Histopathologically, PG lesion biopsies have been shown to contain neutrophilic abscesses, suppurative inflammation with dermal edema, and elevated levels of several pro-inflammatory cells and cytokines including IL-6, as well as a reduced ratio between T regulatory cells (which help prevent inflammation) and Th-17 cells. These biopsy findings implicate neutrophil dysfunction along with dysfunction in both the innate and adaptive immune system processes in the production of PG lesions [2]. Our biopsy report did not comment on cytokines, and otherwise differs from the above findings by its absence of neutrophilic abscesses and dermal edema, although a neutrophil-rich infiltrate was noted. This underscores the importance of clinical correlation with such non-specific findings.

About 50% of PG cases are associated with an underlying disorder, or, in some cases, pharmacological therapies [3]. Inflammatory bowel disorders - both ulcerative colitis and Crohn’s disease, account for 20-30% of these cases; however, only ~5% of patients with IBD will actually develop PG [3]. Other associated disease states include hepatitis C, seronegative rheumatoid arthritis, spondylitis, and various lymphoproliferative disorders including leukemia and lymphoma [3]. Implicated drugs include propylthiouracil, pegfilgastrim, and gefinib [3]. The role of genetics has been increasingly investigated, with multiple PG-associated genetic syndromes (PAPA, PASH, etc) found to be associated with pro-inflammatory mutations in a subset of genes.
Disclosures

led to the prompt, appropriate management of both the skin lesions and the underlying inflammatory bowel recurrent diarrhea in addition to the CT imaging demonstrating findings consistent with colitis moved the individual initially presented with recurrent spontaneous skin ulcers and infections; however, the history of This case emphasizes the importance of the history and physical exam in the evaluation of a patient. This treatment types due to data heterogeneity rate for interleukin inhibitors as a class; the study was not able to differentiate significantly among and 38% complete response rates, respectively. This led to a 70% response rate and 57% complete response which was a complete response. There was no significant difference between the usage of infliximab, TNF-alpha inhibitors in a set of 356 patients with PG noted an 87% response rate to TNF-a inhibitors, 67% of Biologic therapies have been increasingly investigated for PG treatment. A recent semi-systematic review of immunosuppressive drugs such as methotrexate, mycophenolate mofetil, and azathioprine, are used care is an important first-line treatment. This can be used in combination with topical steroids and tacrolimus. In severe cases, systemic corticosteroids, sometimes in combination with cyclosporine or other immunosuppressive drugs such as methotrexate, mycophenolate mofetil, and azathioprine, are used [5]. Biologic therapies have been increasingly investigated for PG treatment. A recent semi-systematic review of TNF-alpha inhibitors in a set of 356 patients with PG noted an 87% response rate to TNF-a inhibitors, 67% of which was a complete response. There was no significant difference between the usage of infliximab, etanercept, or adalimumab found [8]. A similar study on 81 PG patients treated with interleukin inhibitors demonstrated a 79% response to ustekinumab, 64% for canakinumab, and 59% for anakinra, with 71%, 55%, and 38% complete response rates, respectively. This led to a 70% response rate and 57% complete response rate for interleukin inhibitors as a class; the study was not able to differentiate significantly among treatment types due to data heterogeneity [9].

Conclusions

This case emphasizes the importance of the history and physical exam in the evaluation of a patient. This individual initially presented with recurrent spontaneous skin ulcers and infections; however, the history of recurrent diarrhea in addition to the CT imaging demonstrating findings consistent with colitis moved the workup beyond infectious etiologies to the ultimate diagnosis and treatment of PG and IBD. This recognition led to the prompt, appropriate management of both the skin lesions and the underlying inflammatory bowel disease.

Additional Information

Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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