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Report of two cases of ulcerative colitis complicated with pyoderma gangrenosum

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Keywords: Ulcerative colitis; Pyoderma gangrenosum; Inflammatory bowel diseases; Dual targeted therapy; Extraintestinal manifestations.

Abbreviations: UC: Ulcerative Colitis; PG: Pyoderma Gangrenosum; IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; CMV: Cytomegalovirus; 5-ASA: 5-Aminosalicylic Acid; TNF-α: Tumor Necrosis Factor-alpha; IFX: Infliximab; ADA: Adalimumab; UST: Ustekinumab; VDZ: Vedolizumab, ECCO: European Crohn's and Colitis Organization; DTT: Dual Targeted Therapy.

Abstract

Ulcerative Colitis (UC), an idiopathic chronic inflammatory disease, is more complex than expected, affecting the digestive tract and extraintestinal tissues (e.g., bones, joints, skin) and worsening patient's conditions. Pyoderma Gangrenosum (PG), a typical UC cutaneous manifestation with unclear pathogenesis, complicates diagnosis and treatment. Though guidelines for Inflammatory Bowel Disease (IBD) extraintestinal manifestations exist, standardized therapies for UC-associated PG (UC-PG) are lacking.

A case report described two UC-PG patients with massive mucopurulent bloody stools and multiple skin ulcers. After biologic dual-target therapy, their gastrointestinal mucosa repaired, stool symptoms improved, skin ulcers healed (with new granulation), and clinical remission was achieved, enhancing quality of life.

This study analyzed two representative UC-PG cases to explore effective treatments. It aims to summarize reproducible clinical experience, offering references for medical professionals managing such patients.

Introduction

Inflammatory Bowel Disease (IBD) primarily encompasses UC, Crohn's Disease (CD), and undefined enteritis. UC represents a chronic, nonspecific intestinal inflammatory disorder characterized by recurrent inflammation restricted to the colonic mucosa. The etiology remains unknown, and a cure is currently unavailable. The clinical manifestations predominantly consist of colitis-related manifestations, acute complications, and extraintestinal manifestations [1]. Extraintestinal manifestations can involve multiple organ systems and exert a significant influence on organ function and the quality of life of patients. Its pathogenesis remains unclear, and it is hypothesized that gastrointestinal mucosal lesions might trigger the immune response in the exterior of the intestine due to the existence of common epitopes [2]. Pyoderma Gangrenosum (PG) constitutes one of the cutaneous manifestations of UC among the extraintestinal manifestations.

PG is a rare, chronic, recurrent neutrophilic dermatosis characterized by rapidly evolving painful skin ulcers featuring marginal destruction and surrounding purplish flushing [3]. It is frequently secondary to systemic diseases such as IBD, multiple myeloma, lymphoma, and connective tissue disease. Approximately 10-15% of PG cases are secondary to UC, mostly occurring in individuals aged 20-50 years, with no significant gender disparity. Skin lesions typically arise on the surface of the extensor muscles of the lower limbs, face, trunk, neck, and

breast [4]. Although the two cases in this paper indicated that PG emerged during the active stage of UC, there is no explicit evidence demonstrating a direct connection between the two [5].

Case reports

Case 1

An early 40s male patient was admitted to the hospital due to "repeated mucous and blood stool for more than 2 years and repeated for 2 months". He had been experiencing these symptoms about 4-5 times a day without formed stools for two years before being diagnosed with Ulcerative Colitis (UC). Despite initial relief from oral salazopyridine and mesalazine treatments at a local hospital followed by non-compliance with medical advice led to recurrent symptoms over time. Upon admission he presented with blood-like stool frequency ranging from 5-6 times per day accompanied by fever (38.5℃). Physical examination revealed tenderness in the left lower abdomen along with ruptures on his right eyebrow arch as well as left cheek showing sighs of infection (Figure 1A).

The patient's hemoglobin concentration was measured at 96 g/L while erythrocyte sedimentation rate stood at 69 mm/h; fecal occult blood test returned positive results alongside elevated fecal calprotectin levels reaching up to 1356.08 ug/g. Colonoscopy confirmed inflammatory changes in colorectal tissue further supporting diagnosis of active stage chronic relapsing type UC affecting the left hemicolon region which was also supported by biopsy pathology revealing Cytomegalovirus (CMV) positive. Skin biopsy pathology indicated cellulose deposition within vessel walls accompanied by neutrophilic infiltration along large tracts displaying degenerative necrosis surrounded by mixed inflammatory cell infiltration dominated primarily by neutrophils.

Based on this data set forth above it was determined that this patient suffered from "UC (chronic relapsing type affecting left hemicolon region during an active stage), Pyoderma Gangrenosum (PG), intestinal human cytomegalovirus infection". Treatment options included adalimumab combined with vedolizumab supplemented by ganciclovir antiviral medication alongside localized symptomatic support for affected areas as well as nutritional support measures.

Following completion of one course under this regimen significant improvement was observed regarding hematostoecium symptoms while rupture sites behind right eyebrow arch along left cheek gradually healed over time (Figure 1A); half month later colonoscopic re-examination showed improved condition status (Figure 1B). At present follow-up examination have shown stable intestinal conditions devoid any recurrence or appearance bloody stools while ulcerated skin surfaces have healed leaving behind old scars.

Case 2

A late 20s female patient sought care at our Dermatology Department due to "painful ruptured skin located behind her left ear lasting more than 2 weeks". Two weeks prior she experienced redness swelling induration coupled noticeable tenderness around area whereupon ulcers developed prompting visit dermatology clinic where diagnosis suggested "skin soft tissue infection without exclusion special pathogenic bacteria infection". Wound debridement and dressing change treatment was given, but the symptoms did not improve significantly. With a 10-year history of UC and long-term oral mesalazine treatment yielding poor symptom control, the patient presented with recurrent diarrhea, bloody stool, mucus drainage, and frequent bowel movements (6-8 times daily).

Upon admission, the patient exhibited anemia, skin graft appearance on the left face, a ulcer behind the left auricle with significant tenderness and extensive grayish white tissue at the wound base (Figure 2A). Given the absence of positive results in etiology and pathology testing for the wound along with the patient's UC history, a diagnosis of "PG" was considered. Subsequently referred to gastroenterology for continued hospitalization. Blood tests revealed severe anemia (hemoglobin concentration: 38 g/L), elevated erythrocyte sedimentation rate (80 mm/h), positive fecal occult blood test, fecal calprotectin >3600 μg/g; however no positive findings were obtained from fecal etiology-related tests. Pelvic MRI showed diffuse slight thickening of sigmoid intestinal wall while colonoscopy indicated inflammatory changes throughout large intestine (Figure 2B). Biopsy results further supported UC diagnosis. Consequently, diagnosed with "UC (severe) and PG". Treatment options included adalimumab combined with vedolizumab therapy alongside local symptomatic skin treatment, iron supplementation, nutritional support etc.

Following two courses of treatment marked improvements were observed in diarrhea symptoms as well as hematochezia; hemoglobin levels rose to 110 g/L while fecal calprotectin decreased to 1013.53 μg/g. The skin behind ear began healing (Figure 2A). Nine months later re-examination colonoscopy revealed scattered ulcer scars in sigmoid without abnormalities in remaining colorectal mucosa (Figure 2B). Patient showed stable intestinal symptoms during follow-up without recurrence of diarrhea or bloody stool; healed skin ulcer surface leaving old scars.

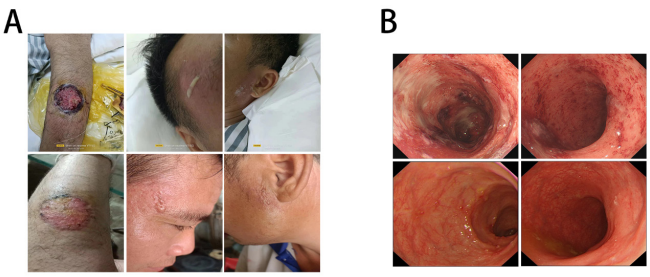

Figure 1: Skin changes before and after treatment (top is before treatment, bottom is after treatment); Endoscopic changes before and after treatment (top is before treatment, bottom is after treatment).

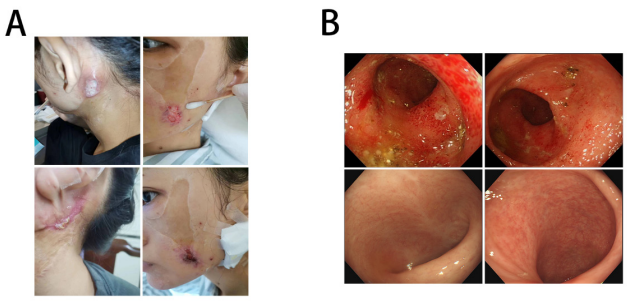

Figure 2: Skin changes before and after treatment (top is before treatment, bottom is after treatment); Endoscopic changes before and after treatment (top is before treatment, bottom is after treatment).

Discussion

Drug therapy for UC is designed to induce and maintain remission, thereby enhancing the patient's long-term quality of life and reducing the risk of surgical resection and colorectal cancer. Drug selection should be based on the clinical type, disease activity, lesion involvement, and response to previous treatment. The two cases described herein were patients with moderate-to-severe, active UC who had previously received 5-aminosalicylic acid (5-ASA) treatment. The traditional step-up treatment strategy advocates the utilization of biologics only when repeated hormonal induction therapy proves ineffective. Nevertheless, with the advancement of medical research, such as the 2019 ACG guidelines beginning to weaken the concept of step-up therapy [6], and the 2020 AGA clinical practice guidelines recommending the early application of biologics in patients with moderate-to-severe UC and not advocating the gradual increase of use following 5-ASA failure [7]. For the treatment of PG patients, there is currently no evidence suggesting a significant difference in outcomes between IBD patients and non-IBD patients. The existing treatment regimens for PG mainly comprise traditional drugs such as glucocorticoids, immunosuppressants, and biologics, as well as local treatment [3,4,8,9]. However, clinical evidence for the majority of studies on PG treatment is insufficient. Glucocorticoid serves as the first-line drug for the treatment of PG, capable of promptly controlling inflammation and disease activities. However, there are risks of infection, gastrointestinal mucosal injury, osteoporosis, and other risks in short-term or long-term usage, and PG may relapse during the reduction process, thus combination therapy or substitution with other treatment options should be contemplated. Immunosuppressants also carry the risk of increased infection, bone marrow suppression, liver function impairment and other hazards. Therefore, the application of biological agents has gradually come into people's purview.

Since the introduction of the first biologic Tumor Necrosis Factor-Alpha (TNF-α) monoclonal antibody (Infliximab, IFX) for the treatment of CD in China in 2007, the application of biologic agents in the treatment of IBD has gradually expanded. In 2019, the indication of IFX was extended to UC, and subsequently Adalimumab (ADA), Ustekinumab (UST) and Vedolizumab (VDZ) were also approved for the treatment of IBD. Two placebo-controlled RCT studies involving a total of 620 patients with moderate-to-severe active UC suggested that VDZ had a higher clinical response rate with induction therapy (RR=2.14, 95%CI: 1.03-4.43) [10,11]. In addition, multiple systematic reviews and meta-analyses [12-14] have indicated that IFX can induce and maintain remission in patients with moderate to severe UC. There is a growing body of literature supporting the use of TNF-α inhibitors in the first-line treatment of PG, especially IFX and ADA. For instance, in 2016 the European Crohn's and Colitis Organisation (ECCO) proposed in [the First European Evidence-Based Consensus Opinion on Parenteral Manifestations of Inflammatory bowel Disease] that ADA could be utilized to induce and maintain remission in patients with extraintestinal manifestations [8]. Domestic expert consensus also indicates that the application indications of IFX encompass active UC featuring prominent extraintestinal manifestations (such as arthritis, pyoderma gangrenosa, erythema nodosum, etc.) [15]. A multicenter open study conducted in Japan [16] encompassed a total of 22 PG patients, including 4 UC patients with PG. 54.5% of the patients achieved wound healing at week 26 of ADA treatment, and the earliest wound healing occurred on day 52 after ADA treatment. Based on this study, Japan expanded the ADA indication to the treatment of PG patients [3].

However, the efficacy of a single biological agent is hard to be significantly enhanced. Despite the growing variety of biologics approved for IBD, the proportion of primary and secondary non-responsiveness remains high [17,18]. Therefore, how to address this ceiling issue constitutes the current hotspot and difficulty in IBD treatment. On one hand, it is necessary to develop new drugs with distance mechanisms; on the other hand, it is necessary to optimize the drug use strategy of existing drugs. Combination Therapy strategies involving biologics include combinations with conventional immunosuppressants, sequential therapy, and Dual Targeted Therapy (DTT), where DTT refers to the combination of two biologics and/or small molecules. On one hand, multiple inflammatory pathways may be concurrently activated in the intestinal mucosa of patients with IBD; on the other hand, major inflammatory pathways may undergo dynamic alterations. According to the mechanism of action at different stages of the disease or whether multiple systems are involved, the corresponding treatment plan might be more conducive to disease control. However, there is currently a lack of sufficient consensus guidance on which patients should opt for DTT and which biologics or small molecule drugs to select for combination therapy. Besides considering the mechanism of action, onset speed, and safety of drugs, it is also necessary to comprehensively take into account the age of patients, disease-related risk factors, previous drug history and other factors. At the same time, aspects such as the timing of combination therapy, withdrawal time, and pharmacoeconomics should also be given attention. It has been proposed that DTT might be a rational option for patients with both IBD and extraintestinal manifestations, or for patients with refractory IBD lacking effective alternatives [19,20].

A multicenter study from Italy demonstrated that 3 IBD patients with extraintestinal manifestations achieved favorable outcomes after VDZ + ADA combined treatment [20]. In the treatment of patients with moderate and severe UC combined with PG, our center also tends to select DTT. The TNF-α inhibitor combined with VDZ is the most widely reported DTT regimen, but the specific selection of TNF-α inhibitor is currently inconclusive. On one hand, ADA has received approval for its indication in Japan for the treatment of PG; on the other hand, ADA is a fully human anti-TNF-α monoclonal antibody, while IFX is an anti-TNF-αhuman and mouse chimeric immunoglobulin G1 monoclonal antibody, both achieving therapeutic effect by blocking the inflammatory pathway of TNF-α monoclonal antibody. To minimize the risk of immunogenicity, we ultimately

chose the combination therapy of VDZ + ADA. In the two cases reported in this paper, the intestinal and skin effects were satisfactory after treatment.

Conclusions

Extraintestinal manifestations significantly increase disease burden among IBD patients necessitating early identification for accurate treatment strategies to prevent serious adverse outcomes. However, consensus guidance is lacking regarding optimal biologics/small molecule drug programs that maximize therapeutic benefits while minimizing risks. Currently active exploration into DDT exists within cancer, rheumatic diseases, and dermatology fields offering potential insights through ongoing clinical studies. We anticipate future high-quality evidence supporting efficacy, safety data across different DTTs leading to improved IBD treatment outcomes.

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