Ustekinumab in the treatment of acute disseminated pyoderma gangrenosum in a patient with Crohn's disease

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Abstract

Pyoderma gangrenosum (PG) is an auto-inflammatory dermatosis characterized by lesions that often cause ulcers. We present a case of successful ustekinumab treatment for acute general PG in a 31-year-old woman with coexisting Crohn's disease (CD). For a month, the patient suffered from skin ulcers, two of them deep and necrotic; a histopathological examination revealed PG. Treatment included: methylprednisolone, azathioprine, betamethasone, gentamicin and zincic ointments, antiseptic compresses, and adalimumab therapy. Due to resistance to the implemented treatment, the patient was enrolled in a clinical trial that included the administration of an anti-cytokines drug, ustekinumab. Subsequently, a significant reduction was observed in the severity of symptoms of PG with no relapse. The use of ustekinumab in patients with PG who have an inadequate response to current treatment or cannot receive first-line treatment can be considered. This applies especially to patients with accompanying autoimmune diseases such as CD.

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Introduction

Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis characterized by rapidly evolving ulcers with a violaceous undermined border and a purulent base.[1] Classically, skin lesions begin as tender pustules or vesicles that can rapidly cause ulcers with irregular borders with accompanying peripheral erythema.[2] The etiology of PG is complex and based on the coexistence of systemic inflammation, neutrophil dysfunction, abnormal response to injury, and genetic factors, and has not yet been fully understood.[3] Disturbed neutrophil function, along with an increase in the number of crucial proinflammatory and chemotactic neutrophil factors within the lesioned skin, appears to be of key importance in the pathogenesis of this disease.[3] Furthermore, in up to 50% of patients with PG, an underlying systemic condition is found.[3-5] The most common of them comprise inflammatory bowel disease (IBD) - up to 30%, but also rheumatoid and seronegative arthritis, hematologic malignancies or monoclonal gammopathies, and other malignancies.[4]

Optimal management should include all clinically important aspects of PG, such as proper wound care, appropriate pain management, or reducing associated inflammation leading to skin ulceration.[6] Glucocorticosteroids are usually the first line of systemic treatment to obtain rapid disease control, but immunosuppressive drugs can also be administered.[4] Due to the insufficient effect of these drugs, the use of new agents is considered, including biological treatment.[7,8] One of these is ustekinumab, a monoclonal human immunoglobulin G1 kappa antibody directed against interleukin(IL)-12 and IL-23.[9] Therefore, we want to present a case of treatment results of acute general PG with ustekinumab administrated for the treatment of CD.

Case Report

A 31-year-old woman diagnosed with steroid-dependent Crohn's disease (CD), on maintenance treatment with infliximab, an anti-tumor necrosis factor-α (anti-TNF-α), was admitted to the hospital due to another flare-up of Crohn's disease. For a month, she had been suffering from skin lesions (originally shaped as papules and then exacerbating), epigastric pain, diarrhea, and cyclic emesis. The symptoms were accompanied by multiple joint pain that was assessed by the patient for 2/10. Furthermore, the patient had been diagnosed with iron deficiency anemia. The previous medical history showed the diagnosis of CD six years earlier. The treatment applied so far included courses of infliximab and adalimumab.

The currently administrated medications were: oral mesalamine (2 grams per day) with oral iron, vitamin D supplementation, and anti-TNF-α every month. Physical examination revealed skin lesions on the lower legs, pubic region, torso, and scalp (Figure 1). Most of the lesions were erythematous and covered by scabs. On the posterior surface of the left lower leg, there were two bleeding, deep, and necrotic wounds. Magnetic resonance enterography showed inflammatory lesions in the distal small intestine, thickening of the intestinal and sigmoid wall, and lack of haustrations, indicating subacute and chronic inflammatory processes. A sigmoidoscopy of the distal 70 cm of the large intestine revealed ulcers in the sigmoid colon. The gastroscopy examination was normal. Considering that the patient suffered from severe abdominal pain, diarrhea, lack of appetite, skin lesions similar to pyoderma gangrenosum, mild joint pain, and general malaise for more than a week, the Crohn's disease activity index (CDAI) was estimated at 308 points (moderately active Crohn's disease).

A histopathological examination of the lesions was performed, revealing changes characteristic of PG. The treatment was implemented cooperating with the dermatologist and included: methylprednisolone 28 mg, azathioprine 150 mg, an ointment with betamethasone and gentamicin, zincic ointment, and antiseptic compresses. Furthermore, infliximab therapy was switched to adalimumab (160 mg subcutaneous). Subsequently, a clinical improvement was observed - healing ulcerations and improvement in gastrointestinal symptoms: the resolution of diarrhea, emesis, and abdominal pain.

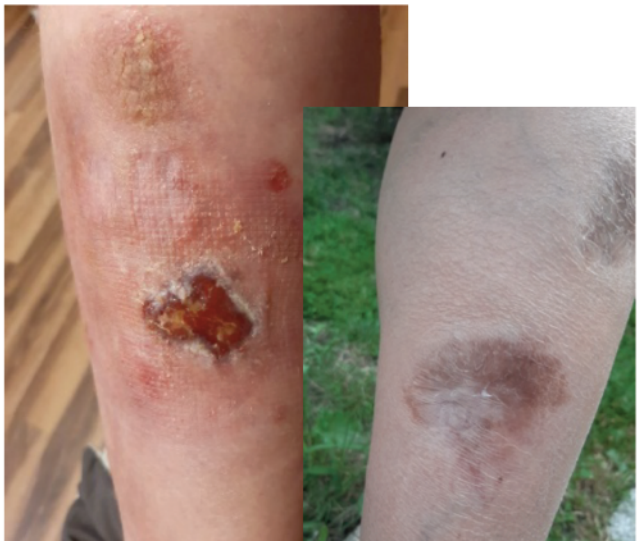

Figure 1. Pyoderma gangrenosum ulcers on the right lower leg. Photos before and after ustekinumab treatment.

One year later the patient presented new, acute, painful, necrotic lesions typical for pyoderma. They were extensive and covered almost all parts of the body. In the most acute state of the PG, 38 necrotic lesions were found. The patient reported loose stools and mild abdominal pain, indicating an exacerbation of CD. Due to resistance to the implemented treatment, the decision was to enroll the patient in an external clinical trial that included the administration of ustekinumab (control group) or guselkumab (study group) every two months.

After 6 months of experimental treatment, a significant reduction was observed in the severity of PG and CD symptoms. After a year the study was unblinded – the patient was treated with ustekinumab (the IL-12 and IL-23 antibody). The size of the ulcers decreased and there was only one healing ulcer. The patient had two loose stools per day and CDAI was estimated at 83 points (remission of the disease). To date (24 months of treatment) the patient lost a response to treatment due to the exacerbation of CD, but there was still no relapse in PG and the only sign of PG are scars at places of previous lesions.

Discussion

In the presented case, in addition to the diagnosis of PG, the patient had a long medical history related to CD. Interestingly, the patient's first episode of PG occurred during a CD exacerbation, under treatment with an anti-TNF-α agent. There are no conclusive data in the literature on the correlation of PG with the activity of IBD disease. However, a systemic review by Agarwal and Andrews showed that PG appears predominantly during active IBD.[10] There are no significant differences in the incidence of PG between patients with CD and ulcerative colitis.[10] Interestingly, patients with PG have a significantly higher risk of death compared to patients with IBD without PG, probably due to increased inflammatory response.[11] In the presented case, the patient experienced an extensive exacerbation of PG manifested by the occurrence of skin lesions on the whole-body skin during azathioprine and anti-TNF-α therapy, therefore, it was necessary to change the regimen of treatment administered. Only the use of the new biological agent, ustekinumab, resulted in the relief of persistent symptoms associated with PG.

PG is a severe condition causing painful ulcerations that significantly reduce patient quality of life. PG has a complex etiology – cytokines: TNF-α, IL-1β, IL-6, IL-8, IL-17, and IL-23 appear to be particularly important.[4,5] Still, there are no clear standards for treating patients with PG, and data from large-scale randomized controlled trials are missing.[4] The course of PG can vary significantly, and the disease can range from relatively indolent to aggressive or even explosive course. Therefore, it is necessary to adjust the intensity of the applied treatment to the symptoms presented by the patient and his general condition.[12] For this purpose, the establishment of clear therapeutic guidelines could facilitate the management of patients with PG. Glucocorticosteroids are usually the first line of systemic treatment to obtain rapid disease control. Immunosuppressive drugs can also be administered, primarily cyclosporine, in combination with glucocorticosteroids as well.[4] The use of new agents is being considered, including biological treatment[7] – the anti-TNF-α antibodies: infliximab and adalimumab are successfully administered. However, novel anti-

cytokine drugs have also recently been studied.[4,6,8]

One of these is ustekinumab, an anti-IL-12/IL-23p40 human immunoglobulin G1 kappa monoclonal antibody.[9] Gene expression analyses identified elevated levels of numerous pro-inflammatory cytokines in PG, predominantly IL-1, but also IL-12 or IL-23.[2] The role of IL-23 is to activate the IL-23–IL-17 axis by activating Janus kinase 2 and stimulating the transcription 3 activators. This causes the formation of IL-17A, which is essential for neutrophil migration. Moreover, Guenova *et al.* proved that tissue sample analysis in a recalcitrant PG lesion shows a highly elevated expression of IL-23 at both the transcriptional and protein levels.[13] In the presented case, almost a complete skin lesions cure was visible after 6 months of treatment, and it was maintained during therapy. Numerous authors have reported similar efficacy of PG treatment with ustekinumab.[13,14] There are also some systematic reviews of the literature showing its effectiveness.[15] However, it should be noted that there is currently no large-scale randomized clinical trial that could assess the efficacy of ustekinumab in patients with a severe course of PG. Further research may confirm the efficacy of ustekinumab in refractory PG. Observational and experimental studies can help to determine the features that are the probable predictor of response to treatment with IL-12/23 antibody and better understand the involvement of IL-23 in the pathogenesis of PG. Ustekinumab is also an agent with proven effectiveness for induction and maintenance of remission in CD.[16,17] In the IM-UNITI study, the randomized controlled trial of ustekinumab for CD, the continuation of subcutaneous ustekinumab therapy maintained clinical response and remission for 3 years in most patients responding to inductive therapy and was well tolerated.[18] In the updated European Crohn's and Colitis Organization guidelines on therapeutics in CD, ustekinumab has an extended position within approved biologicals, as it can also be used as a first-line biological agent.[19]

Comorbidities are a very important factor in the management of PG - although PG can be idiopathic, this disease is very often accompanied by other systemic, predominantly autoimmune diseases, such as IBD or rheumatoid arthritis. PG is the second most common cutaneous manifestation of IBD - its frequency in patients with IBD is 0.5%.[4,6] In moderate to severe CD treatment, there are several different classes of drugs available, including corticosteroids, immunosuppressive drugs, TNF-α antagonists, anti-integrin agents, and interleukin 12/23 antagonists.[16] These agents have a modulating effect on the immune system and suppress the inflammatory response, which constitutes the common etiology of PG and its selected comorbidities. Thus, the efficacy of this treatment could also be expected in the management of PG, as confirmed by clinical experience.[4] Therefore, it seems that the application of biological treatment may bring the most benefits to the group of patients suffering from more than one inflammatory disease. However, there is no consensus in the literature on whether biological treatment should be used in the early stage of PG therapy or whether it should be reserved as a second or subsequent line of treatment. Some authors suggest that novel antibodies are useful only as second and third-line therapies.[6] However, in the treatment of patients with PG, it is important to achieve all 3 therapeutic goals: reduce inflammation, limit symptoms, and prevent infection.[3] Therefore, it seems that biological drugs aimed at an anti-inflammatory effect can bring therapeutic benefits from the very beginning of the therapy, especially in patients who have already undergone biological treatment for a different reason. In patients with a severe course of PG, especially with the presence of other autoimmune diseases, including CD, the administration of biological agents as an early treatment strategy may be associated with a distinct clinical benefit.[4]

Conclusions

Our case demonstrated that ustekinumab is an effective treatment for severe PG in patients with CD. Existing evidence suggests that the use of ustekinumab in patients with PG who have an inadequate response to current treatment regimens or who cannot receive first-line treatment can be considered. This applies in particular to patients with accompanying autoimmune diseases such as CD. In addition, the use of ustekinumab should be considered in patients with PG and previous ineffective anti-TNF-α therapy.

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