CASE REPORT OLGU SUNUMU

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New-Onset Pyoderma Gangrenosum in a Patient with Moderate-to-Severe Plaque Psoriasis on Ixekizumab Treatment: A Case Report and Review of the Literature

Orta-Şiddetli Plak Tip Psöriyazisi Olan ve İxekizumab Tedavisi Almakta Olan bir Hastada Yeni Başlangıçlı Piyoderma Gangrenozum: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that can be challenging to manage. Although interleukin-17 (IL-17) inhibitors are among the treatment options for PG, recent reports have documented paradoxical cases of PG emerging in patients undergoing IL-17 inhibitor therapy for moderate-to-severe plaque psoriasis. In this letter, we present a case of newly developed PG in a patient treated with ixekizumab, an IL-17A inhibitor. While the causal relationship remains uncertain, the occurrence of PG during biologic therapy raises important questions regarding paradoxical inflammation and the need for differential diagnosis. Clinicians should remain vigilant for PG in psoriasis patients, especially when new ulcerative lesions appear during treatment. Regardless of whether it is paradoxical or coincidental, the emergence of PG warrants thorough clinical evaluation, with attention to potential systemic comorbidities often associated with both psoriasis and neutrophilic dermatoses.

Keywords: Adverse events; drug eruptions; psoriasis; pyoderma gangrenosum

ÖZET Piyoderma gangrenozum (PG), nadir görülen bir nötrofilik inflamatuar dermatozdur ve yönetimi zor olabilir. İnterlökin-17 (IL-17) inhibitörleri, PG tedavisinde etkili seçeneklerden biri olarak değerlendirilse de son dönemde orta-şiddetli plak tip psöriyazis nedeniyle IL-17 inhibitörü kullanan hastalarda paradoksal PG gelişimine ilişkin olgular artış göstermektedir. Bu olgu raporunda, IL-17A inhibitörü olan ixekizumab ile tedavi edilen bir hastada gelişen yeni başlangıçlı PG olgusu sunulmaktadır. Nedensellik kesin olarak ortaya konulamasa da biyolojik tedavi sırasında PG gelişmesi, paradoksal inflamasyon olasılığı açısından dikkatle ele alınmalıdır. Psöriyazisli hastalarda tedavi sürecinde ortaya çıkan yeni ülseratif lezyonlar PG açısından değerlendirilmelidir. Paradoksal ya da tesadüfi olsun, PG'nin ortaya çıkışı sistemik eşlikçi hastalıklar açısından kapsamlı bir şekilde araştırılmalıdır.

Anahtar Kelimeler: İlaç erüpsiyonları; istenmeyen etkiler; psöriyazis; piyoderma gangrenozum

Since biologics were approved for treating psoriasis in 2004, our experience with their efficacy and safety in the real world has increased. Due to the earlier introduction of tumor necrosis factor-alpha (TNF-α) inhibitors, paradoxical reactions (PRs) reported recently seem mostly TNF-α inhibitor-mediated.[1] However, we began to observe interleukin-17 (IL-17)-induced PRs with the introduction and the growing use of IL-17 inhibitors since 2015.

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CASE REPORT

A 50-year-old woman was admitted to our clinic with moderate-to-severe psoriasis for 20 years. She had concomitant psoriatic arthritis (PsA). Her Psoriasis Area Severity Index (PASI) was 14.3, and she had palmoplantar involvement. The patient had previously received subcutaneous methotrexate 15 mg/week and developed secondary failure at the end of 1 year. We started IL-17A inhibitor ixekizumab treatment in December 2021 for the patient who was primary unresponsive to ustekinumab. The patient achieved a PASI90 response after the induction phase. On dermatologic examination in June 2024, she had no psoriatic lesions except for a hyperkeratotic thin plaque in the lateral right plantar region. On the anterior aspect of the left tibia, a painful, irregularly shaped ulcer with a purulent base, undermined border, 3x3 cm, and violaceous peripheral erythema had developed from an acneiform pustule (Figure 1). Histopathology of the skin biopsy taken from the purplish erythematous active edge of the lesion revealed hyperkeratosis, parakeratosis, irregular acanthosis, diffuse infiltrate of neutrophilic-polymorphous leukocytes, histiocytes, and necrotic cells forming abscess formation extending from the epidermis to the reticular dermis and subcutaneous tissue. There was no growth in the cultures performed from the lesion, and the findings were consistent with Pyoderma gangrenosum (PG). Complete blood count, biochemistry, and acute phase reactants were normal. She had no signs and symptoms of inflammatory bowel disease (IBD), and screening for malignancy was negative. The patient was continued on ixekizumab due to its efficacy on psoriasis and PsA. She was given a super potent topical corticosteroid, diflorasone diacetate, ointment treatment under occlusion on the PG ulcer. At the follow-up visit 1 month later, we observed that the ulcer edges started to shrink with cribriform scarring (Figure 2).

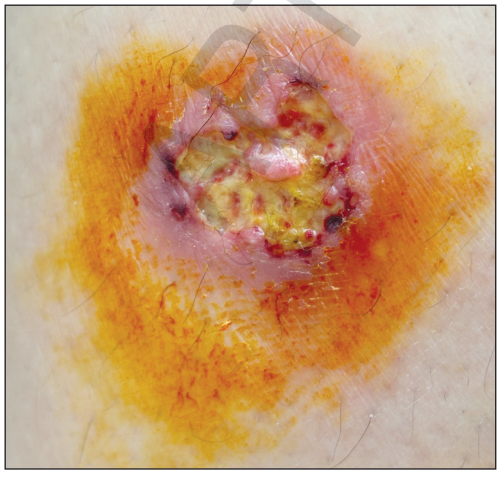

FIGURE 1: Pyoderma gangrenosum with an ulcer with violaceous, undermined borders

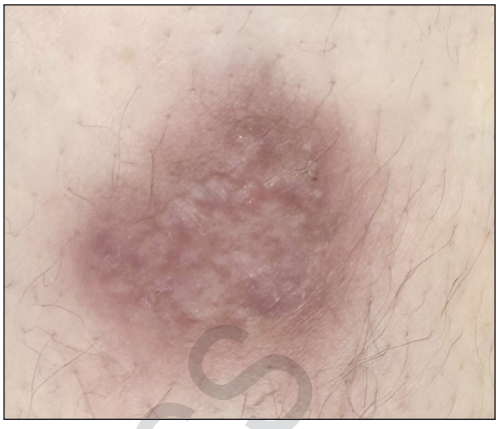

FIGURE 2: Resolution of pyoderma gangrenosum ulcer after 1 month of treatment with super potent topical corticosteroid

A written informed consent was obtained from the patient for the publication of this case report and accompanying images.

DISCUSSION

PG is a neutrophil-predominant dermatosis characterized by elevated levels of proinflammatory cytokines, IL-1, IL-4, IL-5 IL-8, IL-12, IL-15, IL-17, IL-23, IL-36, and TNF-a, in the lesional skin and serum of patients. Systemic steroids, calcineurin, and TNF-α inhibitors are successfully used in the treatment. As PG is a neutrophilic dermatosis, IL-17-mediated suppression of neutrophil migration is a reasonable target. Case reports and cohort studies showing the efficacy of anti-IL-17s have been reported in the literature.[2]

PRs refer to de novo emergence or worsening of an immune-mediated condition that already exists following the initiation of a biologic therapy. TNF-α inhibitors have been utilized in dermatology for 2 decades, particularly in the treatment of psoriasis and

TABLE 1: A literature review of new-onset pyoderma gangrenosum reactions triggered by IL-17 inhibitors on patients with plaque psoriasis

Reference	IL-17 inhibitor	Sex	Age	Immun-mediated comorbidity	Time interval for PG	New IBD	Presentation and prognosis
The present case	IXE	F	50	PsA	2.5 years	No	Solitary PG ulcer Resolved with topical super potent CS and IXE continued
Pollack et al.[8]	IXE	F	61	Not mentioned	1 year	No	Multiple PG ulcers with systemic symptoms Resolved with 3-4 mg/kg/day CycA and discontinuation of IXE
Salvia et al. (2023)[12]	BRO	F	43	HS	4 months	No	A few PG ulcers Resolved by switching to ADA biosimilar
Aromolo et al.[10]	BRO	M	51	Not mentioned	10 months	No	Multiple PG ulcers Resolved by systemic CS, CycA, and ADA
Sadik et al.[4]	BRO	F	42	Not mentioned	3 months	No	Two PG ulcers and accompanying palmoplantar pustulosis and sacroiliitis Resolved by systemic CS and switching to UST
Orita et al.[9]	SECU	M	68	PsA	1.5 years	No	Solitary PG ulcer Resolved by switching to RIS
Zhou et al.[11]	SECU	F	38	PsA	1 month	No	Multiple PG ulcers accompanying eczema Resolved by switching to ADA
Petty et al.[6]	SECU	F	50	Palmoplantar pustulosis	2 weeks	No	Recalcitrant PG ulcers Resolved by systemic CS, CycA, and UST
Wollina et al.[7]	SECU	F	33	None	1 year	No	Multiple PG ulcers Resolved by systemic and topical CS and discontinuation of SECU
Jin et al.[5]	SECU	F	47	PsA and palmoplantar pustulosis	4 months	No	Multiple PG ulcers Resolved by CycA 2.5 mg/kg/day

IL: Interleukin; PG; Pyoderma gangrenosum; IBD: Inflammatory bowel disease; IXE: Ixekizumab; F: Female; PsA: Psoriatic arthritis; CS: Corticosteroid; CycA: Cyclosporin A; BRO: Brodalumab; HS: Hidradenitis suppurativa; ADA: Adalimumab; M: Male; UST: Ustekinumab; SECU; Secukinumab; RIS: Risankizumab

hidradenitis suppurativa (HS). Consequently, they are among the biological agents most frequently associated with PRs. However, recently, IL-17 inhibitors have been linked to PRs as well, including alopecia, psoriasis, eczematous, and sarcodial reactions.[3] Cases of paradoxical PG developing with IL-17 inhibitors in psoriasis patients have also been reported. It is hypothesized that PG is caused by the paradoxical increase in IL-23 resulting from the suppression of IL-17. Reports of anti-IL-17 treatment-associated PG in patients with psoriasis are scarce in the literature and are reviewed in Table 1.[4-12]

Most (8/11) of the reported cases of paradoxical PG in patients with psoriasis, including our case, were female and aged between 40-60 years.[4-8,11,12] PRs occurred between 2 weeks-1.5 years after initiating IL-17 inhibitor treatment.[4-12] A large-scale multicenter study evaluating 9,303 PRs reported that the combination of at least 2 inflammatory diseases increased the risk of PRs.[13] Although not mentioned in some reports, psoriasis was accompanied by a second immune-mediated chronic inflammatory disease such as PsA, palmoplantar pustulosis, or HS in up to half of patients in this review.[4,5,7-12] In almost all cases, IL-17 treatment was discontinued and systemic steroids, cyclosporine, and/or switch to another biologic agent are used to manage paradoxical condition. There has only been one documented case of ixekizumab-induced PG treated with the discontinuation of IXE and introduction of cyclosporin. In this case report, PG had a severe course with disseminated painful pustular lesions that progressed to many violaceous to red papulonodules and pustules on the vagina, hands, face, and feet.[8] Our case had a milder course that benefited from topical corticosteroid treatment and did not require discontinuation of ixekizumab treatment.

Approximately 87% of PG patients are associated with a systemic disease, most commonly inflammatory arthritis and IBD. Although cases of IBD developing or exacerbated by IL-17 inhibitors have been reported, this adverse event has not been demonstrated by systematic reviews and meta-analyses.[2] In cases of paradoxical PG with IL-17 inhibitors, concurrent IBD was not found in the current case and the literature review. However, PG may be the very

first sign of IBD.[14] Therefore, dermatologists should be more cautious about IBD in patients who develop PG while using IL-17 inhibitors due to both the relationship between IBD and PG and the case reports of IBD triggered by IL-17 inhibitors.

The recent review emphasized that it is difficult to assume the causal relationship between PG and anti-IL 17 biologics.[15] More research and reports are required to accurately determine the causal relationship between IL-17 inhibitors and PG regarding PRs. However, new-onset PG may develop during the use of IL-17 inhibitors in those patients with psoriasis vulgaris, especially in female patients with comorbid immune-mediated inflammatory diseases. New-onset PG is a PR that should be considered and carefully investigated regarding possible comorbid systemic associations.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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