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Pyoderma Gangrenosum and Palisaded Neutrophilic Granulomatous Dermatitis in a Patient with Rheumatoid Arthritis Treated with Apremilast

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Abstract

Background: Pyoderma Gangrenosum (PG) and Interstitial Granulomatous Dermatitis (IGD) are rare manifestations in association with chronic inflammatory rheumatic diseases. Conventional therapeutic strategies involve Glucocorticosteroids (GC), DMARDs (Disease Modifying Drugs) and TNF antagonists.

Method: We report a case of a rheumatoid arthritis patient suffering from a reactive granulomatous dermatitis manifesting with features of a PG and IGD refractory to treatment with high dose GC and infliximab.

Result: Upon addition of apremilast to infliximab and glucocorticoids the skin cleared and the glucocorticoids dose could be tapered.

Conclusion: Apremilast may be a therapeutic agent in PG and IGD refractory to conventional therapeutic strategies.

Keywords: Pyoderma gangrenosum; interstitial granulomatous dermatitis; glucocorticosteroids; in liximab

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Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease that mainly affects the joints. Skin manifestations of RA include the rare neutrophilic dermatoses. These are a heterogeneous group of skin disorders characterized by sterile neutrophilic epidermal, dermal or subdermal infiltrates. Cutaneous findings include vesiculopustular lesions, plaques, nodules, or ulcers.

Sweet Syndrome, Pyoderma Gangrenosum (PG), rheumatoid neutrophilic dermatitis, Palisaded Neutrophilic Granulomatous Dermatitis (PNGD) and Interstitial Granulomatous Dermatitis (IGD) may be associated with RA [1]. PNGD and IGD are uncommon diseases with a polymorphic clinical presentation. PNGD may present as tender, erythematous to violaceous papules, plaques or nodules affecting the extensor surfaces of the limbs [2]. Annular plaques or rope-like cords favoring the lateral trunk are typical clinical manifestations of IGD [3]. PNGD and IGD are considered to be within the same clinicopathologic spectrum by some clinicians [4] whereas others consider these to be different entities [5].

Case Presentation

We present a 76 year old male patient with seronegative, Anti-Citrullinated Protein Antibody (ACPA) negative, non-erosive RA under treatment with Infliximab (IFX), an inhibitor of TNF. Previous therapies with methotrexate were either insufficient or, in the case of tocilizumab, led to a gastrointestinal perforation in association with diverticulitis. Under 5 mg IFX/kg BW (Body Weight) every 8 weeks RA low disease activity (DAS28 ≤ 3.2) was established. After 3 months of IFX treatment, PG developed on the right hand and abdomen (Figure 1A). In addition, an interstitial neutrophilic dermatitis occurred 3 weeks later on the right arm (Figure 1B).

After initial treatment with 250 mg methylprednisolone daily and subsequent tapering from Prednisone (PRD) 1 mg/kg BW, the PG improved. However, the skin disease flared after

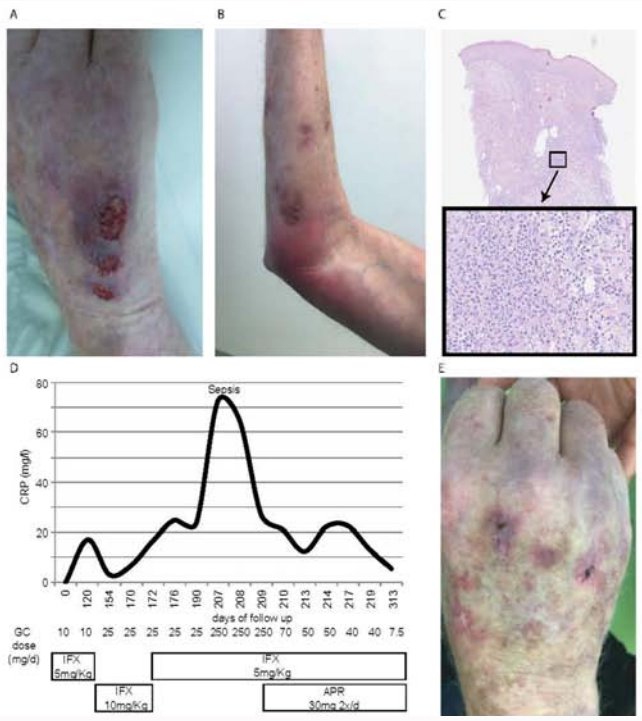

Figure 1: A) Progressive, painful ulcers occurring after sterile pustules of the right hand. B) Interstitial neutrophilic dermatitis of the right arm. C) Hematoxylin-eosin staining of a skin biopsy of the patient's right dorsal hand showing neutrophilic infiltrates (insert) typical for pyoderma gangrenosum. D) Therapeutic course and CRP levels during follow up. E) Improving PG of the right hand.

tapering the PRD dose below 30 mg daily. It was apparent that the signs and symptoms increased towards the end of the infusion intervals. IFX was increased to 10 mg/kg BW every 6 weeks. In addition, the PRD dose was increased again to 40 mg daily with subsequent tapering to 20 mg daily. After an initial response, IFX had to be decreased again to 7.5 mg/kg BW and finally to 5 mg/kg BW due to increasing transaminases. Subsequently, new erythematous, tender nodules on the right arm appeared (Figure 1B). Histologically an interstitial neutrophilic dermatosis with coexisting interstitial and palisaded inflammatory patterns was identified, representing a PNGD with aspects of an IGD (Fig 1C). Given the patient's clinical features, coexisting history of RA and histological findings, PNGD was diagnosed. High dose glucocorticoids treatment needed to be re-instated to control the newly developing PNGD on the right arm.

Thereafter, the patient was hospitalized for antibiotic treatment with 2000 mg cefepime daily for 12 days for *Serratia marcescens* sepsis which resulted from an infection of persistent skin lesions. In addition, PRD treatment was not well tolerated by the patient and he developed concomitant diabetes mellitus and steroid myopathy.

After an inadequate response to the combination of PRD and IFX, apremilast, an oral small-molecule phosphodiesterase-4 inhibitor, was added in a dosage of 30 mg twice daily. Under combination of apremilast, PRD and IFX 5mg/kg BW the patient's PG on the right hand and abdomen as well as his PNGD on the right arm improved markedly within two weeks (Fig 1E). The PRD dose could be decreased rapidly to 7.5 mg daily.

Discussion

To our best knowledge, this is the first case of a patient with a generalized neutrophilic dermatosis (PG and PNGD) improving under apremilast treatment, after a partial response to a TNF-α-antagonist and high-dose glucocorticoids. Laired et al. [6] previously reported the effect of apremilast in a patient with localized PG [6].

The histological features described in our case suggest the coexistence of PNGD and IGD, but in the clinical context we favor the diagnosis of PNGD. Coexistence of both entities has recently been reported, suggesting a substantial overlap. Rosenbach and English suggest using the unifying term "reactive granulomatous dermatitis" to encompass PNGD, IGD, and interstitial granulomatous drug reaction due to diverse clinical and histopathological reaction patterns in response to underlying systemic disease like mainly RA, systemic lupus erythematosus and inflammatory bowel disease [7].

Until now, treatment of PG remains based on anecdotal reports due to lack of study data and guidelines [8]. So far, IFX has the largest body of evidence among biological therapies as treatment of PG [9].

The pathogenesis of neutrophilic dermatosis remains unclear. It is considered to be an auto inflammatory disease with characteristic sterile neutrophilic dominant inflammatory skin lesions rarely associated with infestations of internal organs. Specific autoantibodies are not found. In classic PG, there is an upregulation of IL-1β, IL-8, TNF-α, IL-6, IL-17 and IL-23 [8]. Chu et al. [10] proposed that PNGD progresses through a series of histologic stages with early (dense inflammatory infiltrates composed of lymphocytes, neutrophils, histiocytes, and eosinophils) to late stages (palisading granulomas with fibrosis) [10].

Phosphodiesterase 4 (PDE4) is an enzyme involved in the intracellular degradation of cyclic Adenosine Monophosphate (cAMP), which is a second messenger of G-protein coupled receptor signaling. In monocytes and macrophages PDE4 inhibition leads to decreased TNF-α-production. This could provide a rationale for the proven effect of apremilast in diseases where TNF-α-inhibitors are effective, including psoriatic arthritis and Behçet's disease [11]. Apremilast also decreases levels of interleukins (IL)-2, IL-12 and IL-23 [12]. Whether these additional effects of apremilast treatment were essential for the control of the disease activity in this patient remains open.

The combination of IFX and apremilast was well tolerated in this patient. So far, combination therapy of IFX and apremilast has not been reported. While serious infectious complications are known under combination biologic therapy with IL-1 and TNF- α-inhibitors or with Abatacept, this did not occur in the case presented [13].

Conclusion

This patient's favorable response to the treatment with apremilast suggests a potential role of this substance in the treatment of neutrophilic skin diseases. Further studies are needed to assess the potential promise of apremilast for the treatment of neutrophilic skin disorders.

Authors Contribution

Treatment of Patient, Interpretation of Data, Writing of the Manuscript: Armin Zgraggen, Lara Valeska Maul, Paul Hasler and Ruediger B Mueller.

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