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Pyoderma gangrenosum in a patient with multiple sclerosis under natalizumab treatment: a case report

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Abstract

Background Pyoderma Gangrenosum (PG) is often considered an immune-mediated disease. Up to 50% of PG cases - a rare, non-infectious inflammatory skin disease characterized by painful necrotic ulcers -are associated with underlying systemic diseases like Rheumatoid Arthritis (RA), and Inflammatory Bowel Disease (IBD), moreover with monoclonal antibody therapy.

Case presentation We described a 38-year-old female patient with multiple sclerosis (MS) who was treated for three years with Natalizumab. Myalgia, fever, and erythematous plaques accompanied by painful lesions in both upper extremities manifested with the fifteenth dosage of NTZ. After comprehensive testing and a Magnetic Resonance Imaging (MRI) scan, we excluded other systemic diseases and a recurrence of multiple sclerosis, respectively. After consulting a dermatologist, a skin biopsy was performed, and pathology report confirmed PG. Eventually, the lesions began to heal after stopping NTZ injection without receiving any dermatological care.

Conclusion Based on PG incidence, it was associated with some medications like Rituximab and Ocrelizumab, on the other hand, after discontinuation of NTZ the lesions started to heal even without dermatological treatment. In our situation, it is conceivable that NTZ injection, and PG incidence are connected.

Keywords Pyoderma gangrenosum (PG), Multiple sclerosis (MS), Natalizumab, Monoclonal antibody

Background

Multiple sclerosis (MS) is a chronic inflammatory disease of central nervous system and the most common progressive neurological disorder among young adults [1, 2]. Disease-modifying drugs (DMDs) have altered the long-term prognosis of the condition and enhanced patients' quality of life [3]. Although these drugs are very effective, they are associated with both frequent and unusual adverse effects (AEs). Natalizumab (NTZ) is a humanized monoclonal antibody targeting alpha4-integrins, preventing the adhesion of leukocytes to the endothelial cells and trafficking across blood-brain barrier. NTZ was approved by the Food and Drug Administration (FDA) as a second-line therapy with a high efficacy in reducing relapse rates and disease progression [4–6]. Despite NTZ generally is safe and well tolerated, several rare side effects, apart from progressive multifocal encephalopathy (PML), were reported in the literature [7]. Monoclonal antibodies, such as NTZ, can cause a variety of skin reactions. These can range from mild rashes to severe conditions like Chronic Spongiotic Dermatitis [8].

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Pyoderma Gangrenosum is a rare, non-infectious inflammatory skin disease which is considered within the spectrum of neutrophilic dermatoses that is characterized by painful necrotic ulcers [9]. PG is frequently considered an immune-mediated condition, despite the fact that the pathogenesis of the condition is still incompletely understood. Immune response modifications are believed to be essential in the pathophysiology of PG; up to 50% of cases are linked to underlying systemic diseases. This rare skin disorder was reported with various systemic diseases, such as inflammatory bowel disease (IBD), rheumatoid arthritis(RA), seronegative arthritis, hematological malignancies, or monoclonal Gammopathies. It was reported with monoclonal antibodies such as Secukinumab and Adalimumab [10–15].

Hence, we report a rare instance of PG in an MS patient on NTZ. This report informed the physician of a potential link between NTZ injection and PG. Certainly, additional exploration needs to be performed to confirm a relation between biological agents, and adverse cutaneous reactions, but the clinician should be knowledgeable of their possible presence.

Case presentation

A 38-year-old female patient with a 12-year history of Relapsing-Remitting Multiple Sclerosis (RRMS) was evaluated. There was no personal or familial history of other autoimmune disorders. MS was diagnosed in March 2011 based on the interpretation of brain and spinal cord MRI results. The patient originally rejected pharmacological treatment. However, after a disease flare-up in May 2014, she got intravenous corticosteroid treatment. Subsequently, treatment with interferon beta-1a was initiated. Due to ongoing disease activity and progression, interferon therapy was escalated to Fingolimod after two years. Fingolimod therapy was initiated in 2016 and was well-tolerated. The patient has remained relapse-free and clinically stable with an Expanded Disability Status Scale (EDSS) score of 2. In 2019 NTZ was introduced in anticipation of a planned pregnancy, which, however, did not occur. She remained on treatment until February 2023, when she discontinued medication in terms of the emergence of painful cutaneous lesions. Over a 3-year period, the patient received injections at a frequency of every 55 days. No adverse reactions were reported during or following infusions. The patient denied using any new medications or herbal agents. Throughout this period, the patient remained clinically and radiologically stable with no evidence of disease exacerbation.

The initial presentation occurred in November 2022 with the development of erythematous plaques on both upper extremities. This onset occurred subsequent to the administration of the 15th dose of Natalizumab. The excruciating lesions that are accompanied by myalgia, fever, and periodic exacerbation. Insect injuries and pathergy were excluded due to the patient's history, the characteristics of the lesions, and their duration. The patient's condition showed a gradual deterioration. Laboratory evaluation revealed elevated levels of Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP), indicative of an inflammatory process. A diagnosis of cellulitis was established at an external medical center, and the patient received intravenous antibiotic therapy without achieving clinical improvement.

The patient presented to our clinic only after painful skin lesions had progressed to necrotic ulcers. As an initial step in the evaluation, brain and cervical spine MRI examinations were performed to exclude a new disease relapse(Fig. 1). She referred to a dermatologist for consultation and further investigation. Additional test for anti-nuclear antibody (ANA), anti-phospholipid antibody, cytoplasmic ant neutrophil antibodies (c-ANCA), perinuclear autoantibodies(p-ANCA), Anti-cardiolipin antibodies(ACA), lupus anticoagulant antibody, C3, C4 and CH50 were within normal limit and viral hepatitis serology was negative. Skin biopsies were obtained. Negative results were obtained when microorganisms, such as bacteria, fungi, and acid-fast bacilli, were stained. A diagnosis of PG was made on the basis of the clinical presentation and histopathological findings. Topical Pipecuroniums and Mupirocin were also prescribed, in addition to oral Prednisolone 50 mg daily with a subsequent three-month cessation. Although oral prednisolone therapy resulted in a significant diminution of pain, complete ulcer healing was not achieved. Consequently, the dermatologist recommended intra lesion corticosteroid injections to optimize treatment outcomes(Fig. 2).

Discussion

PG is a rare skin condition and is mostly related to an underlying systemic disease which can be a possible triggering event as the uncommon AEs of certain medications [16]. In several literatures there are reported cases of PG among individuals who were receiving chemotherapy agents including Imatinib [17, 18], Sunitinib [19], Lenalidomide [20, 21], Lenvatinib [22, 23], cabozantinib [24]. Furthermore, two instances of induced-PG have been documented in patients who were treated with ciprofloxacin [25] and insulin [26]. Nevertheless, there is a lack of information regarding the precise pathological pattern of drug-induced PG. Cholelithiasis (1%) and hypersensitivity responses (4%) were severe adverse events that occurred in patients receiving NTZ [27]. The most frequently observed adverse events were arthralgia, fatigue, and headache. The novelty of our case is in terms of the occurrence of PG under NTZ treatment (around the 15th dose), it was previously reported to be extremely rare.

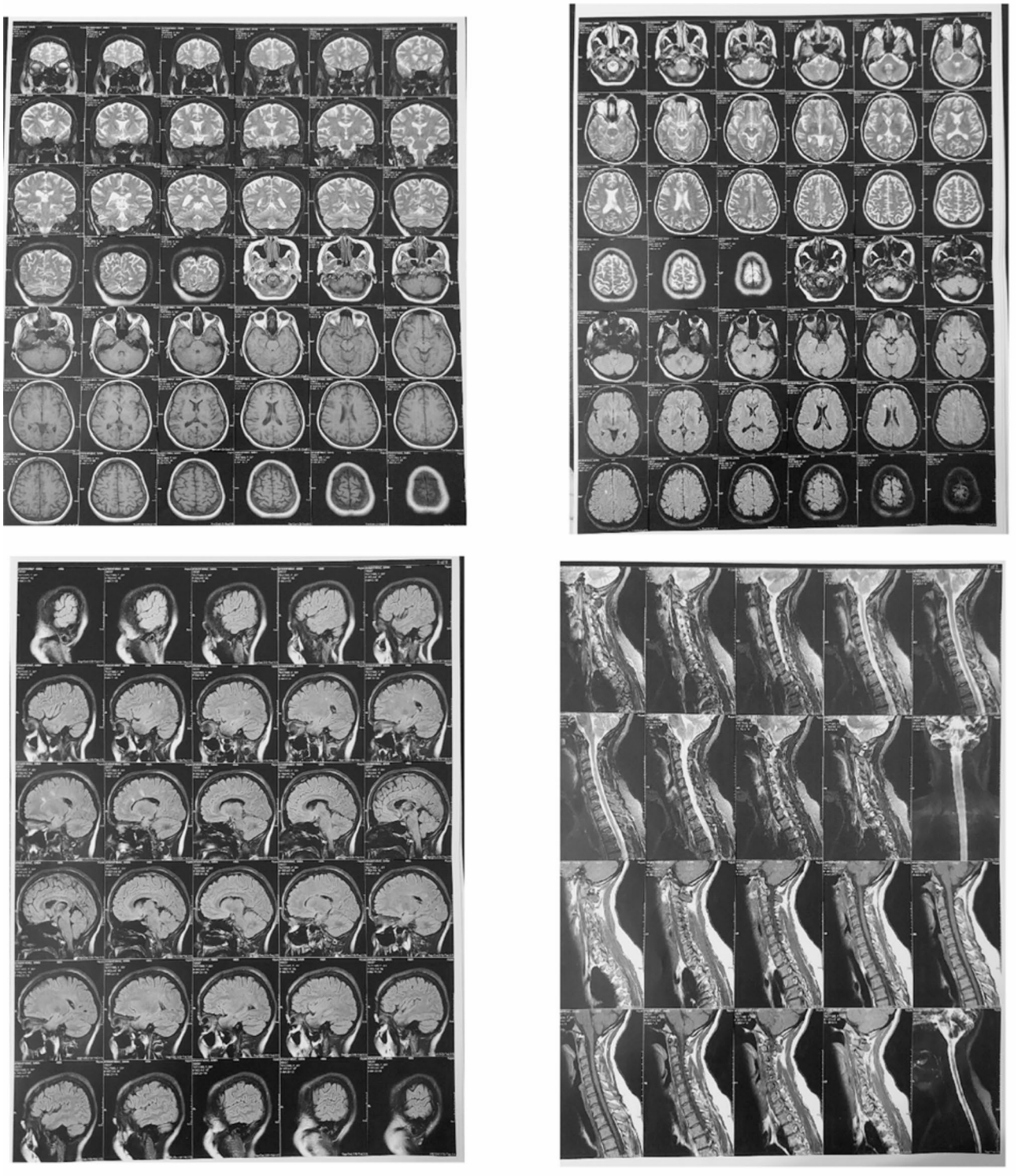

Fig. 1 Brain and cervical cord MRI performed after the onset of skin lesions and discontinuation of natalizumab

Besides, prolonged B cell (anti CD20) therapies may increase the risk of infections however regarding the incidence of neoplasms data are controversy [28]. B-cell agents are more likely to affect patients' skin and the prevalence of skin reactions are considerably high; as well as higher risk of developing psoriasis [29]. Reactions to Rituximab usually present with cutaneous repercussion, often at the first injection, that include generalized pruritus and urticaria [30]. Additionally, Daclizumab may induce skin reactions, such as psoriasis, alopecia,

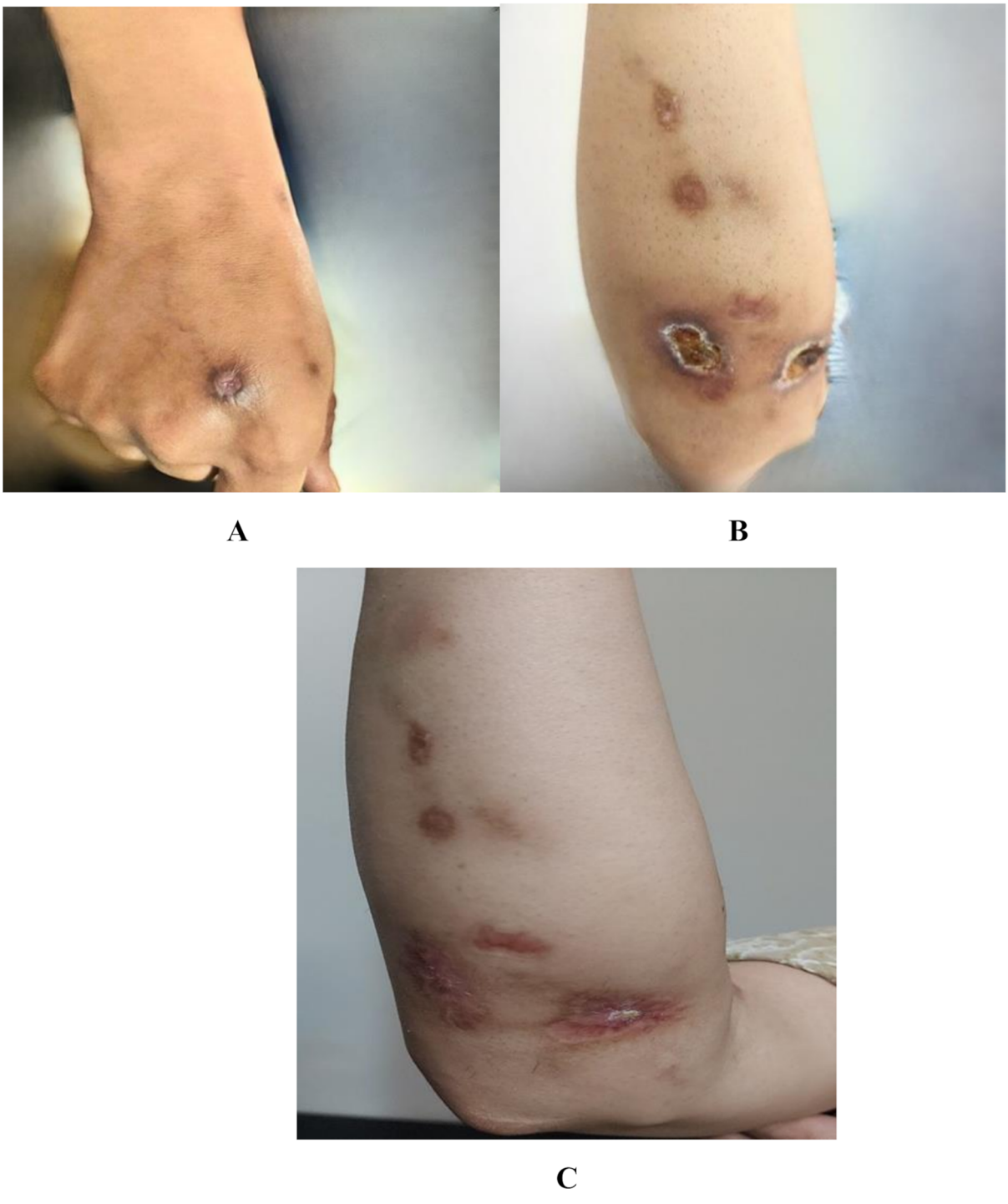

Fig. 2 The legend will be necrotic skin lesions affecting forearm and dorsum of the hand (**A**, **B**) before and after treatment (**C**)

pruritus, pityriasis roses, exfoliated dermatitis, seborrheic dermatitis, eczema, urticaria, contact dermatitis, folliculitis and erythema nodosum [31]. Regarding PG, as an adverse effect of B- cell agents, a case of vulvovaginal PG in a female MS patient under Ocrelizumab treatment was reported in the literature [32]. Moreover, two MS cases [33] and a case of rheumatoid arthritis [34] with induced-PG on Rituximab were reported. There are a lot of hypotheses on the processes behind the development of PG after rituximab, such as neutrophilic granulocyte activation and cytotoxic T cell responses being dysregulated as a result of B cell depletion [35]. Ocrelizumab's mechanism of action is similar to Rituximab's with the difference that it was humanized to decrease

immunogenicity, moreover based on an important case-report one of the causes of PG in a patient treated with Ocrelizumab, was the previous injection of NTZ [32]. Given the numerous studies that demonstrate that some medication can cause PG, it seems probable that the NTZ injection was the cause of PG in our patient.

Conclusion

PG was associated with medications like Rituximab and Ocrelizumab. Interestingly, in our case, PG lesions started healing after NTZ withdrawal, even without dermatological treatment. In our situation, it is conceivable that NTZ injection and PG incidence are connected.

Limitation

The precise etiology of PG remains elusive, although it is widely considered to be an autoimmune disorder. This lack of a definitive understanding significantly hampers the development of targeted therapeutic approaches. Additionally, the difficulties associated with the establishment of optimal treatment regimens and the commission of meaningful comparisons of different therapeutic interventions are emphasized by the heterogeneous response of PG patients to various treatments.

Abbreviations

MS	Multiple sclerosis
RRMS	Relapsing-Remitting MS
PG	Pyoderma Gangrenosum
RA	Rheumatoid Arthritis
IBD	Inflammatory Bowel Disease
NTZ	Natalizumab
MRI	Magnetic Resonance Imaging
DMDs	Disease-modifying drugs
AEs	Adverse Events
FDA	Food and Drug Administration
PML	Progressive Multifocal Encephalopathy
EDSS	Expanded Disability Status scale
ESR	Erythrocyte Sedimentation Rate
CRP	C-reactive protein
ANA	Anti-nuclear antibody
c-ANCA	Cytoplasmic antineutrophil antibodies
p-ANCA	Perinuclear autoantibodies
ACA	Anti-cardiolipin antibodies

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Author contributions

Kosar Kohandel: data gathering and drafting the manuscript. Sara Ala: data gathering and drafting the manuscript. Banafshe Tamizifar: Manuscript revision and prepared figures. Maryam Karaminia: Manuscript revision and prepared figures. Mohammadali Sahraian (corresponding author): Providing expertise background for study design and manuscript revision. Giving the final approval for the manuscript to be submitted.

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Data availability

Data is provided within the manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All the objectives of our study were defined for the MS patient and written informed consent was obtained from her. She agreed if her name and details were not specified.

Consent for publication

Our patient granted written consent for the use and publication of their personal or clinical data, as well as any identifying images, within the scope of this research; this consent for publication was "informed."

Competing interests

The authors declare no competing interests.

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