Dermatology Practical & Conceptual

Persistent Nasal Skin Lesions in Pemphigus Patients and the Role of Methotrexate in Treatment: A Case Series Study

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ABSTRACT

Introduction: Nasal involvement may happen infrequently, and some lesions may not respond to conventional treatments.

Objectives: The current case series report aimed to describe the characteristics of 10 confirmed pemphigus vulgaris (PV) and pemphigus foliaceus (PF) patients with nasal skin lesions who did not respond to conventional treatment options or relapsed after a while and to evaluate the role of methotrexate in treatment.

Methods: Data regarding patient demographics, disease type and severity, nasal lesion characteristics, and treatment response were obtained from medical records and direct communication with patients between 2019 and 2023.

Results: Eight patients had received intravenous rituximab (RTX) and three had received methotrexate (MTX). Out of the eight pemphigus vulgaris (PV) patients who had undergone RTX treatment, a total of eighteen treatment sessions were carried out. Following RTX therapy, significant improvements were observed in the nasal lesions after eleven (61.1%) sessions, with eight (44.4%) achieving complete resolution within six months. Additionally, three patients who did not have satisfactory results after RTX treatment, received methotrexate, and all experienced complete recovery of their nasal lesions within the same timeframe.

Conclusions: All the patients who benefited from methotrexate had never experienced complete remission of their nasal lesions before. It seems methotrexate can be an eligible choice for recalcitrant cases.

Introduction

Pemphigus diseases are a group of acantholytic autoimmune disorders involving the epidermis and mucous membranes which usually manifest with blisters, ulcerations, and erosions. Desmosomes, proteins holding keratinocytes together, contain two main antigens, desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). These two protein antigens are targeted by autoantibodies in this group of diseases.

Pemphigus consists of two main subvariants: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Patients with PV generally present with mucosal ulcerations, mostly mouth, at the onset of the disease. After a while, most of them will develop skin involvement in later stages. The antigens that are frequently targeted in PV contain Dsg1 and 3. On the other hand, PF typically manifests by solitary cutaneous lesions without any mucosal involvement. The antigen involved in PF is exclusively Dsg1 [1,2]. Nasal involvement may infrequently happen in both PV and PF, although it has been reported previously in some articles worldwide. The nose is the most common site of localized PF, which is a rare subtype, and the involvement of other sites may follow in later stages [3,4]. Similarly, localized PV mostly occurs in the nose, scalp, and face [5].

Diagnosis of the disease is based on clinical findings combined with a biopsy for assessment of the tissue histology and by performing direct immunofluorescence (DIF). In the case of PV, histology is reported as acantholysis with blistering occurring above the basal layer, while PF exhibits blistering occurring beneath the stratum corneum of the skin. However, histological analysis of PF often reveals nonspecific results because superficial blisters may undergo roof detachment and the remaining base may look like a normal epidermis [2].

Management of PV and PF begins with the administration of corticosteroids as the first-line treatment with or without steroid-sparing adjuvant agents. Lesions should heal within the first two months in successful treatment [1], although some of these lesions may not respond to conventional treatment.

Objectives

The current case series report aimed to describe the characteristics of 10 confirmed PV and PF patients with nasal skin lesions who did not respond to conventional treatment options or who relapsed after a while.

Methods

This study was conducted at the Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran University of Medical Sciences, and all data were extracted from medical charts and through direct contact with the patients between 2019 and 2023. Moreover, informed consent was obtained from the participants. Patients diagnosed with PV and PF based on DIF and histopathological evaluations who had recalcitrant or recurrent nasal skin lesions were recruited (Figure 1). The following variables were recorded: age, sex, pemphigus type, disease and nasal skin lesion duration, Pemphigus Disease Area Index (PDAI) score on the first visit and six months after RTX therapy, history and time of RTX cycles, type of RTX therapy protocol, the medications used before and after RTX administration, and nasal skin lesions conditions before and six months after RTX therapy and on the last visit.

Results

We evaluated the histories of 10 confirmed pemphigus patients who had persistent or recurrent nasal skin lesions. All of them were male, with a mean age of 45.1, ranging from

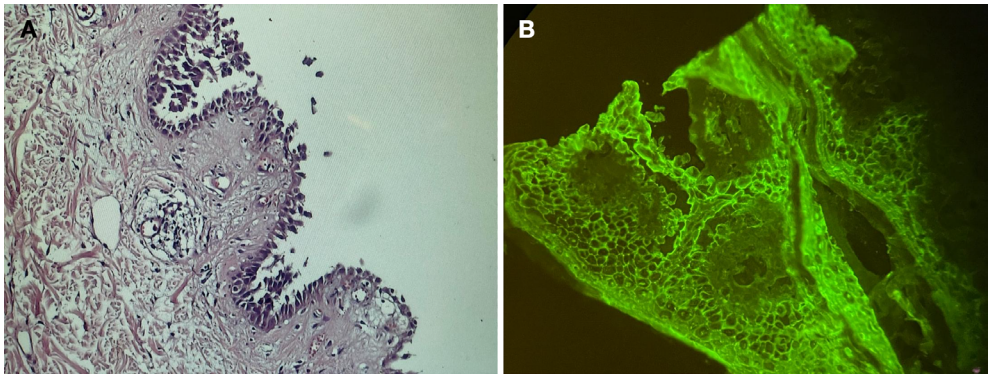

Figure 1. Histopathology and DIF images. A. Histopathology findings including suprabasilar acantholysis and row of tombstones appearance. B. Direct immunofluorescence of perilesional skin with intracellular deposits of IgG and C3 in the epidermis consistent with pemphigus vulgaris.

24 to 82 years old. The average age at disease and at nose lesion onset were 38.6 and 39 years, respectively. Eight cases had been diagnosed as PV and the other two cases as PF.

All of the patients were treated with oral corticosteroids during their treatment courses. Eight had received intravenous rituximab (all except patients N. 5 and N. 9). In addition, some patients were treated with other medications such as azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, topical corticosteroids, or intralesional steroid injection. The complete history of the patients is presented in Table 1.

A few cases showed improvement in their nasal skin lesions during their visits, while others suffered from resistant nasal cutaneous involvement. Among the eight PV patients who received RTX, 18 RTX therapy courses were administered during follow-up period. Six months after the RTX therapy, in 11 (61.1%) courses, patients showed improvements in their nasal lesions, and eight (44.4%) courses resulted in complete improvement.

Three patients who did not achieve satisfactory results after RTX treatment underwent a course of methotrexate (MTX) at a dosage of 15 mg per week. Remarkably, all three patients showed complete improvement of their nasal lesions six months after starting MTX, with no reported side effects from the medication (Figure 2). Two PF patients who did not receive RTX never showed any improvement in their nasal lesion.

Conclusions

Exclusive nasal skin lesions in the pemphigus group of disorders are very rare, although some reports have presented patients with localized nasal PV and PF [6]. One of the relatively uncommon sites on the face that is involved in pemphigus lesions is the skin of the nose.

In a study by Baykal et al., four cases of PV with nasal skin involvement without mucosal involvement were included. After 2–9 years of follow-up, it was noted that the lesions were more likely to relapse at the same place as their first presentation [7]. Moreover, a persistent nose plaque was reported in a 36-year-old male diagnosed with PV, with an uncommon patchy IgG and C3 distribution in the epidermal layer [8].

Ghoneim et al. described a case of PF with a nasal cutaneous lesion on the left nasal ala. Acantholysis was reported in pathologic examination, and DIF for intracellular anti-desmoglein IgG and C3 was positive [9].

Pemphigus vegetans, an uncommon type of PV, may also occur with the involvement of nasal skin. An 89-year-old male presented with vegetative plaques on the nasal tip and chest in addition to the nasal cavity. Further histologic evaluation revealed acantholysis and suprabasal clefts, in line with pemphigus disease findings [10].

The management of PV and PF is almost similar. The first line of treatment consists of corticosteroids mainly in the form of oral prednisolone. We can add adjuvant non-corticosteroid immunosuppressive agents such as azathioprine, mycophenolate mofetil, and rituximab, depending on the condition. In the next steps, we can use medications such as methotrexate and cyclophosphamide [2].

In the previously mentioned study by Baykal et al, systemic corticosteroids were effective in the management of nasal lesions and in preventing their recurrence [7]. In line with this study, Ghoneim et al. reported that their case was successfully controlled by an intralesional corticosteroid injection followed by a three-week topical steroid therapy [9]. The isolated nasal involvement in a patient reported by Zhang et al. was also managed with local corticosteroids; however, tapering the treatment under 2 to 3 times a week caused flare [8].

Contrary to these findings, we found that nasal skin lesions had partial or unsuccessful therapeutic response compared to other lesions elsewhere in the body. Our patients had various responses to different therapeutic strategies. None of them responded to oral prednisolone solely. Among patients who had received rituximab, some had experienced an improvement in their nasal skin lesions six months after the therapy. A retrospective study assessed the effectiveness of rituximab as a treatment option for five patients with persistent pemphigus vulgaris who had not responded to systemic steroids and at least one other immunosuppressive medication [11]. Following rituximab infusions, all patients showed complete clinical improvement with no significant adverse effects, allowing them to stop systemic steroid use and lower their initial immunosuppressive dose. On the other hand, some nasal cutaneous lesions had no improvement or relapsed a while after rituximab therapy.

Some theories may explain these results. First of all, physical triggers like scratching and ultraviolet radiation may cause epidermal cells of the nose skin to form pemphigus lesions even in the presence of lower titers of autoantibodies. In addition, the expression of Dg 1 correlates with the differentiation of epidermal and hair follicle cells. Therefore, the anatomical position of the nose can be a predisposing factor for lesion formation in different levels of autoantibodies [6,12–14].

An interesting finding that we observed was the great influence of methotrexate on the improvement of nasal skin lesions which were recalcitrant to rituximab administration. Methotrexate is a corticosteroid-sparing agent that alleviates methionine, purine, and thymidylate, and subsequent DNA synthesis. It is often used to reduce the side effects of high-dose corticosteroid regimens. Methotrexate suppresses both cell-mediated and humoral immunity [15,16]. It can be a reason why some patients' nasal lesions had a great response

Table 1. Case Characteristics, Diagnosis, Medications, and Outcomes.

Patients N./sex/ age (years)	Diagnosis / PDAI score on the first visit	Disease duration (year(s)) / nasal lesion duration (year(s))	Medication used before RTX administration/nasal skin lesion condition before RTX therapy (PDAI score)	RTX course/time of treatment (year(s))/protocol used for RTX treatment	Medication used after RTX administration	PDAI score 6 months after RTX therapy/ nasal skin lesion condition 6 months after RTX therapy (PDAI score)	Nasal skin lesion condition on the last visit (PDAI score)
1 / M / 37	PV/ PDAI = 5	9 / 9	prednisolone, azathioprine, mycophenolate mofetil, intralesional steroid injection / nose = 1	1st/ 3 years ago / lymphoma	prednisolone	PDAI = 3 nose = 2	nose = 0
			prednisolone, methotrexate / nose = 2	2nd/ 2 years ago/ rheumatoid arthritis	prednisolone, methotrexate	PDAI = 3 nose = 0	
2 / M / 30	PV/ PDAI = 12	6 / 5	prednisolone, azathioprine/ nose = 2	1st / 5 years ago/ rheumatoid arthritis	prednisolone, intralesional steroid injection	PDAI = 4 nose = 1	nose = 0
			prednisolone, intralesional steroid injection/ nose = 2	2nd/ 4 years ago/ rheumatoid arthritis	prednisolone	PDAI = 1 nose = 1	
			prednisolone/ nose = 2	3rd/ 1 year ago/ rheumatoid arthritis	prednisolone, methotrexate	PDAI = 0 nose = 0	
3 / M / 40	PV/ PDAI = 15	4 / 3	prednisolone, clobetasol/ nose = 1	1st/ 3 years ago/ lymphoma	prednisolone	PDAI = 1 nose = 1	nose = 2
4 / M / 24	PV/ PDAI = 22	3 / 3	prednisolone, mycophenolate mofetil/ nose = 1	1st/ 2 years ago/ lymphoma	prednisolone	PDAI = 1 nose = 1	nose = 1
			prednisolone/ nose = 1	2nd/ 1 year ago/ two courses of 500 mg RTX 3 months apart (due to CKD disease)	prednisolone	PDAI = 1 nose = 1	
5 / M / 39	PF/ PDAI = 10	9 / 9	prednisolone, azathioprine / nose = 1				nose = 1
6 / M / 63	PV/ PDAI = 2	2 / 1	prednisolone, azathioprine / nose = 1	1st/ 1 year ago/ rheumatoid arthritis	prednisolone	PDAI = 0 nose = 0	nose = 0

7 / M / 41	PV/ PDAI = 30	13 / 13	prednisolone, azathioprine, mycophenolate mofetil, cyclophosphamide, IVIg/ nose = 1	1st/ 11 years ago/ lymphoma	prednisolone	PDAI = 3 nose = 1	nose = 1
			prednisolone/ nose = 1	2nd/ 10 years ago/ two courses of 500 mg RTX one week apart	prednisolone, methotrexate	PDAI = 0 nose = 0	
			prednisolone/ nose = 1	3rd/ 1 year ago/ rheumatoid arthritis	prednisolone	PDAI = 2 nose = 1	
8 / M / 32	PV/ PDAI = 32	6 / 6	prednisolone/ nose = 2	1st/ 5 years ago/ lymphoma	prednisolone, intralesional steroid injection	PDAI = 0 nose = 0	nose = 0
			prednisolone/ nose = 1	2nd/ 4 years ago/ two courses of 500 mg RTX one week apart	prednisolone	PDAI = 0 nose = 0	
			prednisolone/ nose = 2	3rd/ 2 years ago/ rheumatoid arthritis	prednisolone	PDAI = 2 nose = 1	
			prednisolone/ nose = 2	4th/ 1 year ago/ rheumatoid arthritis	prednisolone	PDAI = 0 nose = 0	
9 / M / 63	PV/ PDAI = 14	7 / 7	prednisolone, azathioprine/ nose = 2				nose = 2
10 / M / 82	PF/ PDAI = 16	6 / 5	prednisolone, clobetasol/ nose = 1	1st/ 5 years ago/ lymphoma	prednisolone	PDAI = 7 nose = 1	nose = 1
			prednisolone, clobetasol/ nose = 1	2nd/ 4 years ago/ lymphoma	prednisolone	PDAI = 0 nose = 0	

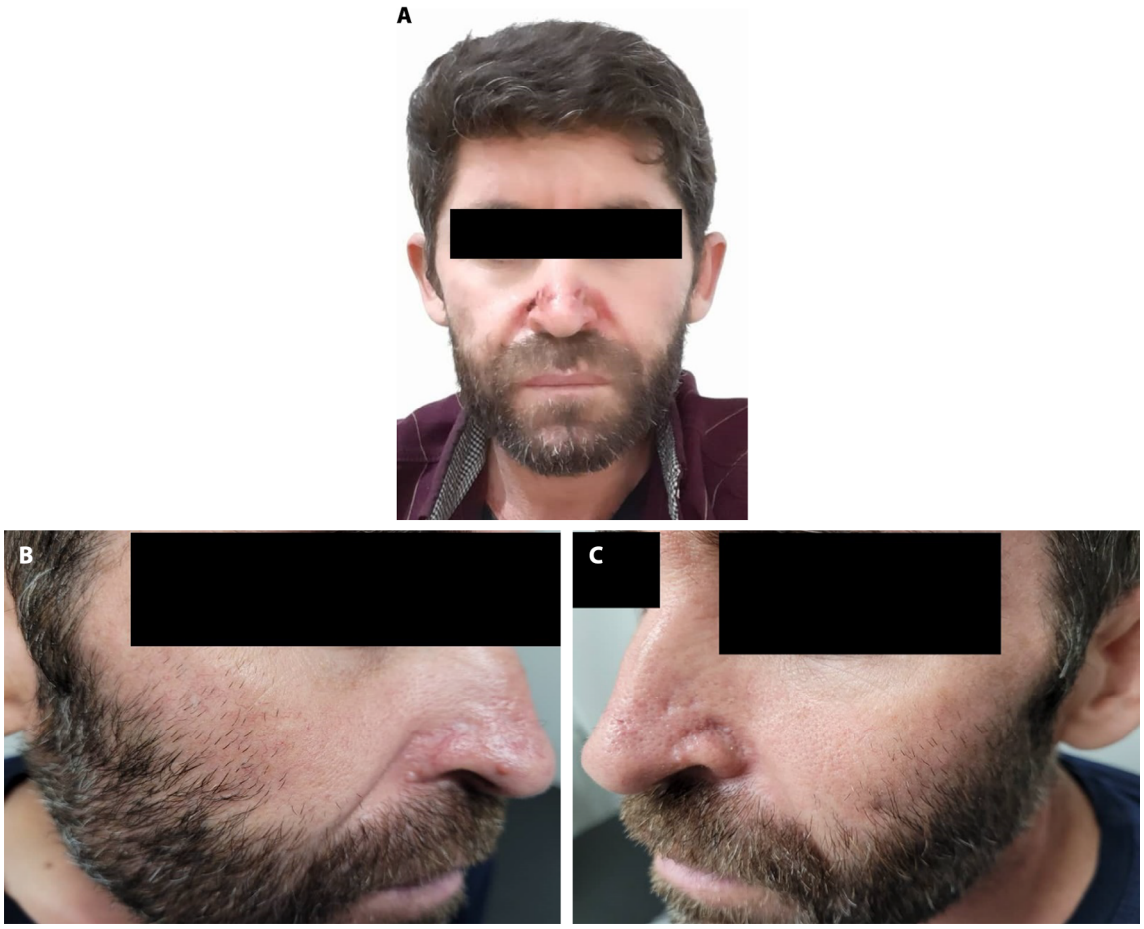

Figure 2. Bilateral nose lesions in a pemphigus patient N. 1, **A.** Persistent lesions after treatment with RTX, **B & C.** Complete improvement after treatment with methotrexate.

to methotrexate when they had previously been resistant to rituximab courses. If left untreated or delayed, nasal lesions can cause long-term problems in terms of appearance and social issues.

In our study, we utilized data sourced from medical records, which could potentially be subject to information bias. It is important to note that the lack of a randomized clinical trial and the absence of a control group may affect how the findings are understood. Consequently, additional studies that include control groups are warranted to assess the effectiveness of current management strategies and the prognosis of nasal lesions in pemphigus patients.

In conclusion, all the patients who benefited from methotrexate had never experienced complete remission of their nasal lesions before. It seems methotrexate can be an eligible choice for recalcitrant cases.

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