Successful Management of Severe Recalcitrant Pemphigus Vulgaris with Lenalidomide

Abstract

Pemphigus variants are treated with immunosuppressives and immunomodulators, but often, clinical remission is challenging. We report a case of pemphigus vulgaris (PV) with involvement of skin, oral mucosa, and esophagus, which failed to respond to commonly used drugs but showed a good response to lenalidomide.

Keywords: *Immuno-bullous disorder, lenalidomide, pemphigus vulgaris*

Akshay Kumar Jain, Shail Agarwal[1], Manish Gautam[2]

Department of Dermatology, GMC Kota, Rajasthan, [1]Department of Dermatology, Jhalawar Medical College, Rajasthan, [2]Department of Medical Oncology, Shanti Hospital Kota, Rajasthan, India

Address for correspondence:
Dr. Shail Agarwal, House Number 11, Durga Vihar Colony, In Front of Jhalawar Medical College, Jhalawar, Rajasthan, India.
E-mail: shailvinit@gmail.com

Introduction

Pemphigus variants are a heterogeneous group of potentially life-threatening rare autoimmune mucocutaneous blistering disorders, usually treated with systemic glucocorticoids with adjuvant immunosuppressive anti-inflammatory agents, high-dose intravenous immunoglobulin (IVIG), immunoadsorption, and monoclonal anti-CD20 antibody, rituximab. However, in some cases, conventional treatment is not sufficient to induce clinical remission. The choice of therapeutic options is often limited by their toxicity profile, adding to morbidity and mortality associated with the disease. We present a case of pemphigus vulgaris (PV), which failed to respond adequately to the conventional line of treatment, but finally, clinical remission was achieved by lenalidomide, a potent analogue of thalidomide.

Case Report

A 53-year-old male was brought to our skin outpatient department with complaints of painful oral ulcers and oral erosions for 7 months and fluid-filled blisters and raw erosions for 4 months. On obtaining a further detailed history, oral lesions started on the hard palate and spread to involve other parts of the oral cavity associated with pain and difficulty in swallowing food. Over the next 3 months, he started having fluid-filled blisters on his back which then spread to other parts of his body including the scalp, upper limbs, and chest (sparing legs). The blisters would eventually burst and form foul-smelling raw erosions with purulent discharge. He also complained of blood in stool for 7–8 days, which was diagnosed as esophageal ulcer. There was no history of itching/urticarial eruption before the onset of lesions, no history of fever/cough/joint pain, no history of abdominal pain/photosensitivity/diarrhea, no history of lesions at the site of trauma, no history of drug intake before the onset of lesions, no history of COVID-19 infection, and no history of significant weight loss.

On local cutaneous examination, the total body surface area involved was 10–12%, with cutaneous ABSIS 1012 and oral ABSIS 11/11. Morphologically, multiple crusted well-to-ill-defined lesions ranging from 1–7 cm were present. Cutaneous lesions had a violaceous hue with overlying yellowish-brown crusting adherent to lesions [Figure 1]. Perilesional hypopigmentation surrounding the lesions was present. In oral mucosa, multiple erosions on the left and right buccal mucosa, hard and soft palate, both upper and lower gingiva, with yellow slough on the tongue and teeth were seen. Crusting and swelling of the lower lip was noted with poor oral hygiene [Figure 2]. The pharynx could not be visualized due to restricted mouth opening. Other mucosa, nails, and hair did not show any significant findings. Systemic examination was within normal limits.

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On investigating the patient, a skin biopsy was taken which on histopathology showed suprabasal acantholysis and blistering favoring the diagnosis of PV. A DIF-IgG1+ linear positive result was seen along the eccrine ducts, giving a fishnet appearance: IgA- and IgM-negative. IIF-(IFS-218/21)-IgG was predominantly negative with focal floor binding. Tzanck smear from oral mucosa: giant and acantholytic cells were seen. ELISA-anti-desmoglein 3 = 4, anti-desmoglein-1 = 8. Beta-D-glucose = 43.68, LDH = 215, ANA-negative. Hba1c level-10.2. Upper gastrointestinal tract endoscopy showed grade C esophagitis. Other routine investigations and computed tomography of the chest were within normal limits. The patient was also investigated to rule out any concurrent neoplasm in the body due to the non-responsiveness of lesions to conventional line of treatment (to rule out paraneoplastic pemphigus), but values of tumor markers including AFP, CEA, beta HCG, and CA 125 were within normal limits.

Treatment history: The patient was given DCP (dexamethasone cyclophosphamide) pulse therapy (3 pulses given); systemic steroids (for 5 months), IVIG, MMF (mycophenolate mofetil), azathioprine, and 3 doses of rituximab 1 g were also given subsequently. When the patient did not respond adequately to the abovementioned drugs, and new lesions kept on coming, the patient was started on tablet lenalidomide 10 mg od along with tablet aspirin 75mg od for 21 days, and the patient responded well to this regimen leading to 80 percent resolution of lesions in the first 21 days; it was followed by a rest of 7 days; after which the patient was restarted with tablet lenalidomide and aspirin. During this cycle, all old lesions healed and no new lesions appeared [Table 1: information about immunosuppressives in chronological order]. It may be possible that lenalidomide may not be the sole agent responsible for the complete clinical remission, but the clinical response was adequately achieved only after the introduction of lenalidomide.

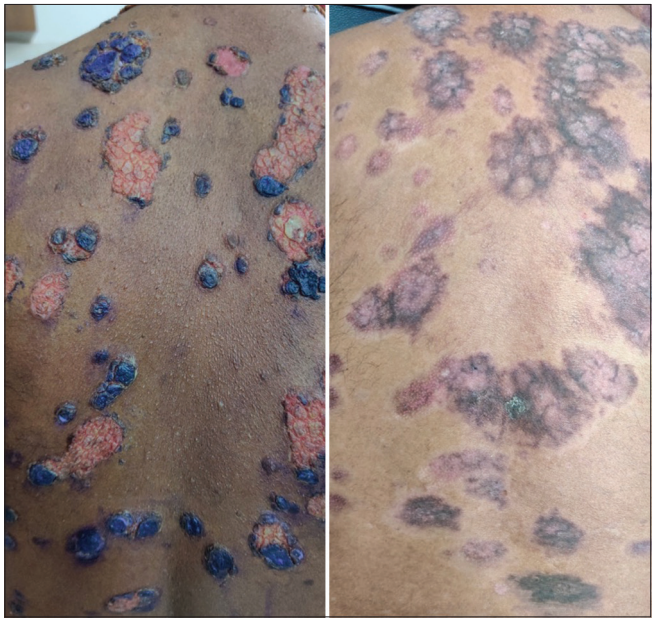

Figure 1: Multiple vesiculobullous lesions over back pre- and post-treatment

Discussion

PV is an immune-bullous disorder characterized by painful muco-cutaneous ulceration with little tendency to heal, with pathogenesis being related to IgG autoantibody directed against various adhesion molecules of epidermis including desmoglein 1 and 3, major components of desmosomes. Numerous immunosuppressive and immune modulators have been tried in the treatment of this potentially life-threatening disorder. Prior studies have reported a good

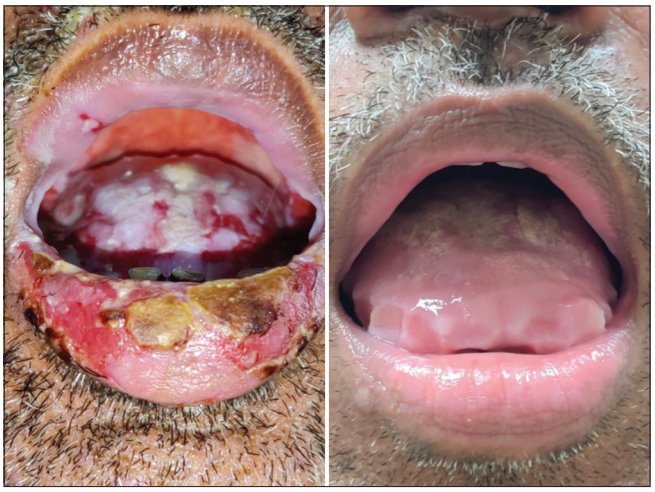

Figure 2: Multiple erosions over upper and lower lips and oral mucosa pre- and post-treatment

Table 1: Treatment (immunosuppressives) Schedule in chronological order

Name of Immunosuppressive with dose	Starting date	Ending date
Corticosteroids (1.0 mg/kg of body weight at the start for 6 weeks and then tapered)	24/1/2021	4 mg twice per week continued till the date of writing
Dexamethasone Cyclophosphamide pulse therapy (3 pulses)	25/1/21	26/4/2021
Inj. rituximab (RA protocol)	6/5/2021	20/11/2021
Tab mycophenolate mofetil (1.5 gm at the start then after 1 week 2 g/day)	30/4/2021	3/7/2021
Tab azathioprine 50 mg (TDS)	30/4/2021	25/6/2021
Inj. IVIG (2 g/day for 3 days)	6/6/2021	8/6/2021
Tab lenalidomide (10 mg)	4/7/2021	Continued till the date of writing

therapeutic response to thalidomide (an oral TNF alpha inhibitor) in a range of skin conditions.[1] Thalidomide has also been used for the successful treatment of oral and genital ulcerations including aphthous ulcers.[2,3] There are few publications on the good response of thalidomide in PV.[4,5] Lenalidomide is a more potent analogue of thalidomide, and it has been previously used in a patient with PV with myelodysplastic syndrome (MDS).[6]

Lenalidomide is licensed for use in multiple myeloma, MDS, and mantle cell lymphoma.[7] The mechanism of action of thalidomide and lenalidomide in pemphigus could be multifaceted: (1) by inhibiting the production of inflammatory cytokines including tumor necrosis factor-alpha and IL-6 and IL-2. Tumor necrosis factor-alpha is highly expressed in the skin lesions of patients with pemphigus; (2) by regulating local immunity; (3) by up-regulating desmoglein expression in epidermal keratinocytes, a mechanism compensating for desmoglein destruction.[8,9]

The safety profile of thalidomide and its analogues is of great concern, including teratogenicity, peripheral neuropathy, mood changes, constipation, tremors, drowsiness, and thromboembolic events.

In our patient, no major side effect was observed during treatment. This drug might prove to be a hope in PV cases not responding to the conventional line of treatment.

Conclusion

Thalidomide and lenalidomide can prove to be a good choice of treatment in the armamentarium of recalcitrant PV cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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