

Original Article

A case report on generalized pemphigus vulgaris treated with rituximab

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Abstract

Background: Pemphigus vulgaris has an obscure etiology; the presence of autoantibodies is coherent with an autoimmune disease. Rituximab a monoclonal antibody that specifically targets the CD20 antigen of B lymphocytes, has arisen as a novel treatment approach for pemphigus vulgaris.

Case presentation: A 39-year-old male patient presented with a three-month history of mouth ulcers, poor oral hygiene accompanied with heavy tobacco smoking and alcohol consumption. He was diagnosed with pemphigus vulgaris. The disease gradually progressed to involve other body parts. The patient had shown partial improvement after conventional therapy (oral cefuroxime, oral prednisolone with azathioprine) and was later on successfully treated with rituximab. After 90 days of follow-up, no future recurrence was observed.

Conclusion: With this case, the authors would like to aware other clinicians of the potential use of rituximab in treating pemphigus vulgaris, especially when the conventional therapy fails.

Keywords: Autoantibodies; Pemphigus, Rituximab, Oral Hygiene, Ulceration, Tobacco Smoking, Alcohol consumption, India

Background

The term pemphigus implies a group of autoimmune, mucocutaneous blistering diseases, in which the keratinocyte antigens are the target of the autoantibodies, prompting acantholysis and the formation of blisters. Main variants of pemphigus include pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the most common subtype and represents well over 80% of cases. As being a serious and potentially life-threatening condition, early treatment is of utmost importance [1]. The advent of corticosteroids in the amelioration of pemphigus has dramatically changed the outlook of this perpetually disastrous disease; thus, corticosteroids have become the cornerstone of pemphigus therapy. One case reported favorable outcomes with combined therapy of high-dose corticosteroids and other immunosuppressants. However, such a high dose of corticosteroids can cause serious adverse events such as several metabolic problems, global reduction of

immune system efficacy, antecedent risk of serious infections, and mortality [2]. To overcome these long-term events, Pasricha and Gupta introduced dexamethasone cyclophosphamide pulse (DCP) therapy in 1984 [3]. Later on, DCP and oral corticosteroids with or without adjuvant immunosuppressants (azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporine) have emerged as the backbone of pemphigus treatment, however, they are associated with the high death rate in pemphigus [4]. With these conventional treatments, some patients fail to improve or some have contraindications for their usage, or some encounter relapse. Hence, advanced research has continuously been going on for finding newer molecules in pemphigus. In 2001, Heizmann et al. [5] first used rituximab for the therapy of autoimmune bullous diseases. He reported a case of paraneoplastic pemphigus favorably managed with rituximab, since then there was a drastic development in the pemphigus treatment era. Rituximab chimeric monoclonal antibody selectively acts on the CD20 expressing B cells, which are known to secrete auto-antibodies targeting the epidermal desmogleins (DSG). It has been used nearly in one million patients for treating lymphoma worldwide. Recently, rituximab has been approved for rheumatoid arthritis that is unresponsive

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to tumor necrosis factor alpha (TNF- α) inhibitors. Rituximab is off-label and used for various autoimmune disorders including, PV due to potential therapeutic effects in the modulation of pathogenic B cells [5]. We report a case of generalized PV, treated with rituximab.

Case presentation

A 39-year-old male patient who lives in Surat, Gujarat, was referred with a 3-month history of painful ulcerated lesions in the oral cavity. On enquiring about the patient's history, we came to know that initially, the patient had difficulty chewing food and the severity increased gradually. The ulcerations caused considerable discomfort, affecting his normal oral functions. Subsequently, fluid-filled lesions developed involving the scalp, trunk, limbs, and axilla. Lesions were increasing in size and number and had little tendency to heal. Blisters were flaccid and burst on their own to form erosions within 2-3 days. Medical and family history was non-contributory. No history of fever, joint pain, malaise, and photosensitivity. He had weak oral hygiene due to the bad habit of taking betel quid with tobacco five times a day and smoking seven bidis per day for the past 12 years. Further, he consumes two-quarters of alcohol on an alternative day for the last 12 years. History of any drug intake before the appearance of lesions was also absent. Intraoral examination revealed that approximately 1.0 \times 1.5 dimensions ulceration lesions were present on the buccal mucosa. Dermatological examination revealed multiple vesicular lesions ranging from 0.3 \times 0.3 to 1.5 \times 1.5 involving the face, trunk, upper limbs, and dorsum of the penis (Figure 1a-i).



Figure 1: Showing (a) ulcerative lesions present on the buccal mucosa (b) multiple vesicular lesions present on the face (c) multiple vesicular lesions with erosion present on the lower neck (d) multiple vesicular lesions present on the umbilicus (e) multiple vesicular lesions with erosion present on the upper limb (f) multiple vesicular lesions with erosion present on the back (g) multiple vesicular lesions with erosion on the axilla (h) flaccid blister lesions on the scalp (i) multiple vesicular lesions present on the dorsum of the penis.

There was a positive Nikolsky sign and a bulla spread sign. The clinical manifestations of oral ulcers, flaccid bullae, and positive Nikolsky sign hinted at the provisional diagnosis of

PV. Mucous membrane pemphigoid, bullous lichen planus, paraneoplastic pemphigus, chronic ulcerative stomatitis, recurrent herpes lesions in immunocompromised patients, and erythema multiforme were the potential differential diagnosis of this condition. Regarding this, a biopsy was performed from a new vesicle to confirm the diagnosis. Histopathological examination revealed an intraepidermal suprabasal acantholytic blister. Several acantholytic cells and neutrophils could be seen in the blister. The floor of the blister showed a tombstone pattern with occasional acantholytic cells. A moderately dense superficial perivascular mixed infiltrate was present in the dermis. Mild spongiosis with neutrophils was present at the periphery of the blister (Figure 2).

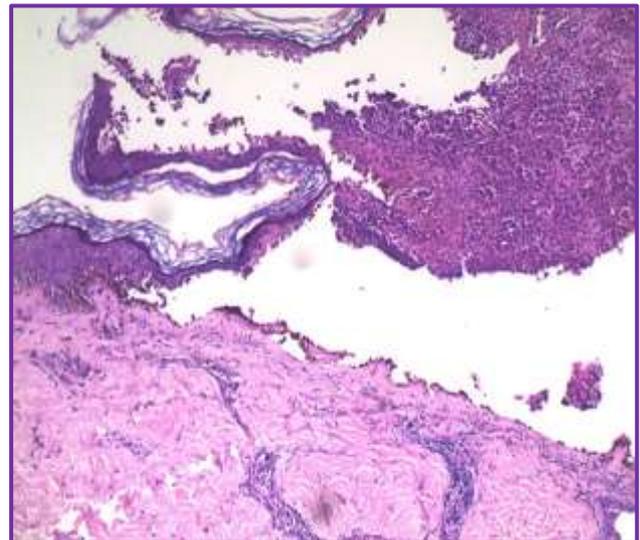


Figure 2: Photomicrograph showing acantholysis of the keratinocytes, tombstone appearance, epithelium exhibiting spongiosis, and superficial perivascular mixed infiltrate (H & E stain, $\times 5$).

The hematological test had all findings within standard limits and, routine urine examination was unremarkable. In accordance with these findings, the definite diagnosis of PV was made and the treatment with oral cefuroxime (500mg twice a day) and oral prednisolone (20mg twice a day) with azathioprine (50mg twice a day) was started. Topical antibiotics and triamcinolone gel are advised for local application in the oral cavity. The dose of oral prednisolone was gradually tapered to 20mg, 10mg, 5mg, and 2.5mg (twice a day) every 30 days. The patient was maintained on the same dose of azathioprine (50mg twice a day) for one year. With the given therapy, complete remission was not achieved. Also, azathioprine was discontinued due to an elevated level of liver enzymes. Hence, the patient was shifted to rituximab therapy. The patient was initially given three doses of rituximab 1 gm each on days 1, 15, and 45. As premedication, ceftriaxone 1gm intravenously, hydrocortisone 100mg intravenously, paracetamol 650mg stat orally, and pheniramine maleate 2cc stat intravenously were given, sequentially on the day of infusion. After 30 minutes of these premedications rituximab (1gm) intravenously in 500ml of normal saline was given slowly over six to eight hours. The last dosage of rituximab was given after 3 months. Administration of rituximab lead to decrease Dsg 3 antibody levels which in turn resulted in the complete remission of the skin lesions within the next year (Figure 3a- g).



Figure 3: After rituximab therapy, almost complete healing of (a) ulcerative lesions in the mouth (b) vesicular lesions on the face (c) lesions on the lower neck, umbilicus, and upper limb (d) lesions on the back (e) multiple vesicular lesions with erosion on the axilla (f) blister lesions on the scalp (g) vesicular lesions of the dorsum of penis.

The level of Dsg 1 and Dsg 3 was detected by the commercial enzyme-linked immunosorbent assays MESACUP Dsg test 'Dsg 1' and MESACUP Dsg test 'Dsg 3'. The level of Dsg 3 and Dsg 1 was found to be 252.6 μ /ml and 178.8 μ /ml, respectively, before treatment, however, it was reduced to 45.89 μ /ml and 1.76 μ /ml, respectively, after treatment. Lesions healed with post-inflammatory hyperpigmentation without any scarring and milia formation. The patient was followed up 90 days after the last injection and no future reoccurrence of lesions was observed. All the patient's pictures are belonging to the authors.

Discussion

The introduction of rituximab in pemphigus has been the first major progression in the treatment of the disease over 60 years. Many authors have used rituximab in the treatment of multiple immunobullous diseases including PV and PF [5, 6-15]. Based on the literature review; we have noted that the use of rituximab in the treatment of pemphigus has exponentially increased in the globe. Rituximab binds particularly to the transmembrane antigen CD20, which is present on B lymphocytes from the pre-B-cell stage to the pre-plasma-cell stage. CD20 is neither expressed on hematopoietic stem cells nor plasma cells. The binding of rituximab to CD20 triggers B-cell depletion by diverse mechanisms: antibody-dependent cellular cytotoxicity, complement-mediated lysis, direct disruption of signaling pathways, and triggering of apoptosis [4]. This may be the presumable mechanism of action for treating PV in our case. At present, a proper treatment algorithm pertaining to optimal dosage and schedule is not established for the use of for rituximab to treat pemphigus. Multiple treatment protocols are available, from which lymphoma and rheumatoid arthritis protocols have been extensively used in literature. In lymphoma protocol, patients received a total of four infusions of rituximab

at the dose of 375 mg/m² on a weekly basis. As per rheumatoid arthritis protocol, the patient received two infusions of 1,000 mg each 15 days apart [6]. Apart from these, various modified treatment protocols that show promising results were also used [6 -15]. In the present case, the patient was not completely improved with conventional treatment of oral cefuroxime, and oral prednisolone with azathioprine; therefore, based on the empirical experience, we treated a patient with our own modified protocol in order to get relief as well as the more beneficial effect. Rituximab is contraindicated in various conditions such as hypersensitivity to rituximab or other murine proteins, active severe infections, The human immunodeficiency viruses (HIV) infection with CD4 cell count <250/^ml and severe heart failure, children, pregnancy, and lactation. Rituximab may also be associated with severe adverse effects that can cause mortality, including infusion reactions, serious skin and mouth reactions, hepatitis B virus reactivation, and the developing multifocal leukoencephalopathy. Moreover, tumor lysis syndrome, serious infection, heart problems, kidney problems, stomach, and serious bowel problems might be possible side effects [6-15]. Due to such detrimental side effects, rituximab should always be received under a physician's guidance. Recently, U.S. Food and Drug Administration (USFDA) has approved Rituxan® (rituximab) in treatment-resistant rheumatoid arthritis (with another prescription medicine-methotrexate), Wegener's granulomatosis and microscopic polyangiitis (with glucocorticoids) and PV [16]. In the past, it has been off-label used for these indications. Currently, no randomized control studies are available comparing the efficacy of rituximab to conventional treatment modalities. Most of the data was obtained from a large case series and prospective open-labeled trials. In a new era, future studies will pave the way in providing patient care with this molecule.

Abbreviation

PV: Pemphigus Vulgaris; PF: Pemphigus Foliaceus; DCP: Dexamethasone Cyclophosphamide Pulse; Dsg 3: Desmoglein 3; USFDA: U.S. Food and Drug Administration; DSG: Desmogleins; TNF- α : Tumor Necrosis Factor Alpha; HIV: Human Immunodeficiency Viruses.

Declaration

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Availability of data and materials

Data will be available by emailing sakhiya.academic@rediffmail.com

Authors' contributions

Jagdish Jadavbhai Sakhiya (JJS) was the principal investigator of this manuscript and approved the final manuscript. Dhruv Jagdish Sakhiya (DJS), Jashmine Mukeshbhai Gandhi (JMG), and Feral Ravi Daruwala (FRD) were responsible for the study concept, design, writing, reviewing, and editing of the manuscript in its final form.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013). Ethical approval was obtained from Sakhiya Skin Clinic, Surat, Gujarat, India. (Approval No: 2023/06). Consent forms were signed by patient. He was informed that he had the right to withdraw from the study at any time without any consequences. All pictures reported in this case-report study belong to Sakhiya Skin Clinic, Surat-395003, Gujarat, India.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

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References

- Grando SA. Pemphigus autoimmunity: hypotheses and realities. *Autoimmunity*. 2012 Feb;45(1):7-35. doi: 10.3109/08916934.2011.606444.
- Lever WF, Schaumburg-Lever G. Immunosuppressants and prednisone in pemphigus vulgaris: therapeutic results obtained in 63 patients between 1961 and 1975. *Arch Dermatol*. 1977 Sep;113(9):1236-41. doi: 10.1001/archderm.1977.01640090084013.
- Pasricha JS, Gupta R. Pulse therapy with dexamethasone-cyclophosphamide in pemphigus. *Indian J Dermatol Venereol Leprol*. 1984; 50:199-203.
- Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. *Arch Dermatol*. 1996 Sep;132(2):203-12.
- Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. *Am J Hematol*. Feb 2001;66(2):142-4. doi: 10.1002/1096-8652(200102)66:2<142::AID-AJH1032>3.0.CO;2-0.
- Food and Drug Administration. Rituxan label; 2012 [cited Feb 2, 2021]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5373lbl.pdf.
- Belgi AS, Azeez M, Hoyle C, Williams REA. Response of pemphigus vulgaris to anti-CD20 antibody therapy (rituximab) may be delayed. *Clin Exp Dermatol*. 2006 Jan;31(1):143. doi: 10.1111/j.1365-2230.2005.01941.x.
- Schmidt E, Seitz CS, Benoit S, Bröcker EB, Goebeler M. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol*. 2007 Feb;156(2):352-6. doi: 10.1111/j.1365-2133.2006.07646.x.
- Barrera MV, Mendiola MV, Bosch RJ, Herrera E. Prolonged treatment with rituximab in patients with refractory pemphigus vulgaris. *J Dermatolog Treat*. 2007 Jan;18(5):312-4. doi:10.1080/09546630701323988.
- Faurschou A, Gniadecki R. Two courses of rituximab (anti-CD20 monoclonal antibody) for recalcitrant pemphigus vulgaris. *Int J Dermatol*. 2008 Mar;47(3):292-4. doi: 10.1111/j.1365-4632.2008.03423.x.
- Craythorne EE, Mufti G, DuVivier AW. Rituximab used as a first-line single agent in the treatment of pemphigus vulgaris. *J Am Acad Dermatol*. 2011 Nov;65(5):1064-5. doi: 10.1016/j.jaad.2010.06.033.
- Horváth B, Huizinga J, Pas HH, Mulder AB, Jonkman MF. Low-dose rituximab is effective in pemphigus. *Br J Dermatol*. 2012 Feb;166(2):405-12. doi: 10.1111/j.1365-2133.2011.10663.x.
- Craythorne E, Du Viver A, Mufti GJ, Warnakulasuriya S. Rituximab for the treatment of corticosteroid—refractory pemphigus vulgaris with oral and skin manifestations. *J Oral Pathol Med*. 2011 Sep;40(8):616-20. doi: 10.1111/j.1600-0714.2011.01017.x
- Kim JH, Kim YH, Kim MR, Kim SC. Clinical efficacy of different doses of rituximab in the treatment of pemphigus: a retrospective study of 27 patients. *Br J Dermatol*. 2011 Sep;165(3):646-51. doi: 10.1111/j.1365-2133.2011.10411.x
- Kasperkiewicz M, Shimanovich I, Ludwig RJ, Rose C, Zillikens D, Schmidt E. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. *J Am Acad Dermatol*. 2011 Sep;65(3):552-8. doi: 10.1016/j.jaad.2010.07.032
- Investor update. Basel; June 12, 2019. [cited Feb 5, 2021]. Available from: <https://www.roche.com/investors/updates/inv-update-2019-06-12.htm>.