Case study

A BENFICIAL APPROACH OF MANAGEMENT FOR DELAYED DIAGNOSIS OF PEMPHIGUS VULGARIS: A CASE REPORT

ABSTRACT –

The most typical kind of pemphigus is pemphigus vulgaris, an uncommon chronic skin condition characterized by blisters. Desmosomes, which are skin-related elements that maintain some skin layers bonded to one another, are the target of this type II hypersensitivity reaction, in which antibodies are produced against them. In 2022, A 44-year-old female patient was admitted to the emergency department with complaints of skin lesions with burning sensation and irritation, fever and weakness of limbs. From this current case report, we concluded that how the pemphigus vulgaris can be treated if it is worsened stage and not treated immediately.

Keywords –Acantholysis, Desmosomes, Hypersensitivity, Pemphigus Vulgaris

INTRODUCTION: -

"Pemphigus is a rare autoimmune blistering disease characterized by acantholysis, which refers to the loss of cell-cell adhesion and the formation of intraepidermal blisters in the mucous membranes, skin, or both. Since the blisters are delicate, they often rupture, leaving crusty sores behind. Depending on the type of pemphigus, the symptoms may vary slightly. The skin may develop raw-looking areas where blisters have joined together, which are prone to infection and fluid oozing. Pemphigus may also affect the mouth, nose, throat, eyes, and genitalia."(1)

The incidence of Pemphigus Foliaceus (PF) was 1.138 per 1 Lakh persons internationally, while Pemphigus Vulgaris (PV) had an incidence rate of 2.059 per 1 Lakh persons (1.885 for men and 2.234 for women) (1.205 for males and 1.07 for females) (2). The incidence of Pemphigus Vegetans was 0.7 per 1 Lakh persons (1.3 for men and 2.3 for women). These are the types of pemphigus with reported incidence rates (3).

Fewer studies have been conducted in India compared to other countries about this disease. In 2001, a study was conducted, which found that the incidence rate was 4.4 per 1 million people (4). Reports indicate that pemphigus affects more women than men, with a ratio of 1.4:1 on average.(2)

Pemphigus Vulgaris can develop in people of diverse racial backgrounds, genders, and ages. It typically manifests between the ages of 30 and 60, and people of Jewish and Indian ethnicities are more likely to have it than those of other ethnicities, possibly due to hereditary reasons.(3). Symptoms of pemphigus can vary slightly depending on the type. Blisters from Pemphigus Vulgaris typically begin in the mouth, but can also later appear on the skin.(4)

A biopsy of the skin next to the lesion is typically required to diagnose Pemphigus Vulgaris. Histologically, acantholytic cells (keratinocytes) are often seen rounded and separated immediately above the basal layer of the epidermis. Suprabasal clefting can also be reported.(5) To diagnose pemphigus, direct immunofluorescence staining of perilesional skin biopsy sections is used to detect immunoglobulin (Ig)G antibodies or complement on the cell surfaces of keratinocytes. A fishnet pattern can also be used for diagnosis. Changes in antibody levels can be a good indicator of how well a treatment is working. ELISpot tests are another method for determining specific anti-dsg1 and anti-dsg3 antibody titers in blood or saliva (ELISAs). (6)

Pemphigus has no known exact cause or direct cure; however, most patients can manage the condition with medication. The first aim of treatment is to help heal current blisters and prevent relapses. The severity and stage of the disease are the main factors to be considered in treatment. Even after several years of therapy, pemphigus symptoms may persist, and most patients still need medicine to control the condition. Standard treatment for pemphigus includes corticosteroids, immunosuppressants, biological response modifiers, and antibiotics, antivirals, and antifungal medications when necessary. (7) In cases where standard treatments are not effective or the pemphigus is severe, alternative therapies may be considered. Plasmapheresis or immunoadsorption, for example, can remove pathogenic autoantibodies from the bloodstream, thereby reducing disease activity and severity. Intravenous immunoglobulin (IVIG) treatment is another option, which involves administering a large dose of pooled antibodies from healthy donors to neutralize pathogenic autoantibodies. IVIG may be especially useful in cases where conventional treatments are not sufficient or if there are concerns about the side effects of long-term immunosuppressive therapy. However, these alternative therapies are typically reserved for severe or refractory cases of pemphigus, and their use must be weighed against potential risks and benefits.. (8)

The updated S2K guidelines on the management of pemphigus vulgaris, were initiated by the European Academy of Dermatology and Venereology (EADV). (9)

Based on the above-mentioned S2K guidelines, the first-line treatment for pemphigus consists of Dapsone, corticosteroids, and rituximab at a dose of 0.5mg/kg/day. The second-line treatment involves Rituximab at a dose of 1g given over two weeks, systemic corticosteroids such as prednisolone at a dose of 0.5-1.0mg/kg/day, with or without azathioprine (1-2.5mg/kg/day). If the disease is controlled with the first-line treatment, then the previous treatment should be continued. However, if the disease is uncontrolled,

azathioprine or mycophenolate mofetil at a dose of 2g/day or mycophenolate sodium at 1440mg/day can be added to the treatment regimen.

CASE PRESENTATION:

Upon admission to the emergency department, a 44-year-old female patient reported experiencing fever for the past 10 days, as well as a burning sensation and a single episode of vomiting. She also had a history of weakness in her right upper and lower limbs over the past 10 days. The patient had been experiencing multiple erosions all over her abdomen, back, face, genitals, bilateral upper and lower limbs, and on her lips for the past 3 months (as depicted in Fig-1). Additionally, she had been experiencing skin rashes on her upper chest, face, scalp, mouth ulcers, and vesiculobullous lesions for the past 1 and ½ years.

HISTORY:

Based on the patient's symptoms and medical history, it appears that she had been experiencing symptoms of pemphigus vulgaris for the past 3 months, including skin rashes, mouth ulcers, and vesiculobullous lesions. However, the condition was misdiagnosed as psoriasis and treated with Ayurvedic medicines.

The patient's condition worsened, leading to weakness in the right upper limb and lower limb, as well as the development of multiple erosions all over the body. The patient was admitted to an outside hospital, where she had 5 episodes of seizures and was intubated. A punch biopsy performed at the hospital led to the correct diagnosis of pemphigus vulgaris. It is worth noting that the patient did not report any prior history of pharmacological, chemical, or food allergies, which may be relevant to her treatment plan moving forward.

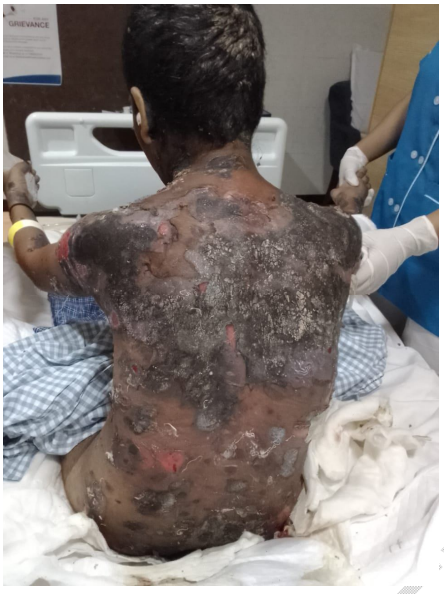

Fig-1 Serious PV erosions (Progression of blisters) on the back of the patient's body on admission.

PATIENT MANAGEMENT:

After being admitted to the MICU due to the worsening of the lesions with foul-smelling discharge and fever, the patient developed right-sided weakness and was diagnosed with CSVT with acute infarct in the precentral gyrus and hemiparesis based on imaging. The patient was put on ventilator support and started on anticoagulants (Inj. Enoxaparin sodium 0.4cc BD), antiepileptics (Inj. Levipil 750 mg BD, Inj. Lincosamide 100 mg BD), and antibiotics (Inj. Meropenem 1g) to control the seizures and infection. The consultant dermatologist started the patient on a low dose of systemic steroid (Inj. Hydrocortisone 50 mg BD), but due to the patient's non-response and thrombocytopenia, IVIG therapy was initiated, followed by four doses of Rituximab (1 dose = 500mg of Rituximab in 500ml NS).

The patient also received supportive treatment in the form of Pantoprazole 40 mg OD, vitamin supplements, calcium supplements, and syp. duphalac 20ml Ryle's tube.

RESULTS AND FURTHER ACTION: The patient's Hemiparesis condition had improved with a power of 2/5 for the upper limb and 1/5 for the lower limb. However, her pain had aggravated, and Fentanyl citrate was infused at 3 ml/hr. The culture report of blood culture and urine culture had found positive for Pseudomonas aureus and E. coli, so Antibiotic Inj Teicoplanin 400mg was added for the first 3 doses at 12-hour intervals, later once daily. Monitoring was done with respect to urine input and output observation, wound care, and oral care.

Despite improving the patient's Hemiparesis condition, the wounds did not improve. Daily Bactrim gauze dressing was given, and Ryle's tube was withdrawn. The patient was encouraged to take oral fluids, and IVF plasmalyte 1-pint 100ml/hr was given as treatment.

Later, discharge over the lesions started again. The report from the culture found it to be positive for Acinetobacter baumanii, and tigecycline and Colistimethate Sodium 1Miu STAT then 4.5Miu BD were immediately stopped. Based on the symptoms, the patient was administered Inj. Paracetamol 1gm infusion in 100ml NS and given as STAT, and later, based on the patient's pain, Inj. Tramadol Hydrochloride 50 mg was given. With the lab reports, serum creatinine, and WBC count went better, and urine input and output were balanced. Total parenteral nutrition of 30ml/hr through a central line was given. Some changes were made to the therapy concerning systemic conditions, i.e., Inj. Hydrocortisone 50 mg BD has been titrated to 100mg BD, Otski -IV, Inj. Acetylcysteine 600mg BD, and as the patient had both hypokalemia and hypo-magnesia, electrolyte supplements were administered. Zytee gel was added to the patient for local application, and for coagulation therapy, Inj. Enoxaparin sodium was stopped, and Tab. Apixaban 5mg BD was started.

Fig-2 Healing of erosions after treatment

As the patient demonstrated full consciousness and coherence, and the wounds exhibited signs of notable improvement, along with cessation of oozing, the application of betadine powder dressing was discontinued. The patient proceeded to undergo mobilization in a wheelchair, however, the rectification of electrolyte levels remained a critical concern, necessitating the administration of Magnesium sulphate IV at a dosage of 1 gram as STAT, Potassium Chloride infusion at 40 meq as STAT, and a 1-pint LDP transfusion. Subsequently, the infection rate escalated, evident by an elevated WBC count of 16000, warranting a revision of the Antibiotic regimen to include Inj. Zobapime 2.5gm BD, encompassing the amalgamation of Cefepime and Tazobactam, as well as Inj. Clinda 600 mg BD, incorporating Clindamycin. Nonetheless, following the transition to Clindamycin, the patient began exhibiting ocular irritation and redness, necessitating a further adjustment to the regimen, which included Tab.Azee 500mg BD, featuring Azithromycin. Furthermore, amidst the various stages of recuperation, an additional grievance was lodged, concerning the emergence of Mouth ulcers, ultimately diagnosed as Oral candidiasis, prompting the administration of additional anti-fungal medication, comprising IV fluconazole and Candid

mouth paste. Eventually, following the patient's favorable response to medication, and the absence of new complaints, the patient initiated physiotherapy, culminating in mobilization, and was ultimately discharged with all oral medications, encompassing Antibiotics, Antiepileptics, electrolyte replenishers, and Corticosteroids.

DISCUSSION

Pemphigus comprises a group of blistering skin and mucous membrane disorders that are potentially life-threatening and are distinguished by acantholysis - the loss of adhesion between keratinocytes. This process of acantholysis is caused by autoantibodies targeting intercellular adhesion molecules circulating in the bloodstream. Although the lesions can manifest throughout the body, they are more commonly observed on the epidermis, where intact blisters are frequently apparent, as well as on the face, pharynx, larynx, esophagus, and vaginal mucosa. (4) Although there are some physical similarities between Psoriasis and Pemphigus Vulgaris, it is important to note that Psoriasis Vulgaris is the most prevalent T-cell-mediated inflammatory disease in humans, whereas Pemphigus is an autoimmune condition characterized by blistering and caused by circulating autoantibodies that target the cell surfaces of keratinocytes. (8) The prevalence of Pemphigus is known to differ depending on the geographic location and the ethnic makeup of the population. Based on the available literature, it has been estimated that Pemphigus Vulgaris affects anywhere from 0.76 to 16 individuals per million annually in Europe. (10) The incidence of pemphigus vulgaris in India is comparatively lower than in other regions, with estimates ranging from 0.09% to 1.8%. However, pemphigus vulgaris has a prolonged clinical course, causing significant morbidity and mortality. If left untreated, mortality rates increase from 50% after two years to nearly 100% after five years, with a majority of deaths caused by systemic infections, septicemia, bronchopneumonia, electrolyte imbalances, and severe skin involvement. (10) In the case of

the patient with pemphigus vulgaris, conventional treatments such as topical and systemic corticosteroids, and immunosuppressants like azathioprine or mycophenolate were used initially. Plasmapheresis and intravenous immunoglobulin were also considered as supplementary treatments to lower the number of circulating autoantibodies. However, after trying various treatment options, it was found that IVIG therapy was the most beneficial for this particular patient. Additional doses of Rituximab, an anti-CD20 antibody, were also administered to the patient along with supportive therapy tailored to her specific symptoms.

CONCLUSION

Pemphigus vulgaris can cause significant pain and discomfort, affect the quality of life of the patient, and lead to psychological distress. The management of pemphigus vulgaris requires a multidisciplinary approach involving dermatologists, oral medicine specialists, and other healthcare professionals. The treatment aims to achieve disease control, prevent complications, and improve the patient's quality of life. The choice of therapy depends on the severity and extent of the disease, the patient's age and comorbidities, and the patient's response to therapy. Close monitoring of the patient's disease activity, side effects of therapy, and laboratory parameters is crucial to ensure optimal management and avoid treatment-related complications. Therefore, early diagnosis, prompt initiation of treatment, and close follow-up are key factors in the successful management of pemphigus vulgaris

REFERENCES:

1. Silva SC, Nasser R, Payne AS, Stoopler ET. Pemphigus Vulgaris. J Emerg Med. 2019 Jan;56(1):102–4.
2. Kianfar N, Dasdar S, Mahmoudi H, Daneshpazhooh M. Burden of pemphigus vulgaris with a particular focus on women: A review. Int J Womens Dermatol. 2022 Oct 3;8(3):e056.

3. Loewenthal R, Slomov Y, Gonzalez-Escribano MF, Goldberg I, Korostishevsky M, Brenner S, et al. Common ancestral origin of pemphigus vulgaris in Jews and Spaniards: a study using microsatellite markers. Tissue Antigens. 2004 Apr;63(4):326–34.
4. Rai A, Arora M, Naikmasur V, Sattur A, Malhotra V. Oral Pemphigus Vulgaris: Case Report. Ethiop J Health Sci. 2015 Oct 5;25(4):637.
5. Nili A, Salehi Farid A, Asgari M, Tavakolpour S, Mahmoudi H, Daneshpazhooh M. Current status and prospects for the diagnosis of pemphigus vulgaris. Expert Rev Clin Immunol. 2021 Aug 3;17(8):819–34.
6. Kilic A. Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment. In: Autoimmune Bullous Diseases. InTech; 2018.
7. Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: challenges and solutions. Clin Cosmet Investig Dermatol. 2015 Oct;521.
8. Zheng J, Liu N, Wang Y, Chen F, Ding Y. Pemphigus vulgaris with psoriasis vulgaris successfully treated with methotrexate and low□dose methylprednisolone. Dermatol Ther. 2020 Jan 15;33(1).
9. Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). Journal of the European Academy of Dermatology and Venereology. 2020 Sep 24;34(9):1900–13.
10. Huang YHuei, Kuo CFu, Chen YHua, Yang YWen. Incidence, Mortality, and Causes of Death of Patients with Pemphigus in Taiwan: A Nationwide Population-Based Study. Journal of Investigative Dermatology. 2012 Jan;132(1):92–7.