An overview on -Indigenous and Conventional Treatment for Pemphigus

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Abstract— Pempigus encompasses autoimmune bullous conditions, which affect both mucous membranes and the skin. The condition commonly runs a chronic-relapsing cours, with a potentially ruinous on the patient's quality of life. Pempigus pathogenesis is related to IgG autoantibodies targeting several adhesion molecules in the epidermis, including desmogelin (Dsg) 1 and 3, major elements of desmosomes. Clinical operation of pemphigus is beginning to move down from broad-range immunosuppression and towards B-cell targeted curatives, which reduce numerous cases symptoms but can have significant side effects. Then we've review the threat factors regarding pemphigus. The remedies should be specified only when proper diagnosed is done. Both conventional and modernistic methods of recovery remedy have been discussed.

Keywords: Corticosteroid, Desmoglein, IgG autoantibodies, Pemphigus foliaceus, Pemphigus vulgaris.

I. INTRODUCTION

Autoimmune bullous diseases (AIBDs) are caused by self-reactive immune responses that attack the skin's desmosomes or the basement membrane, resulting in the loss of skin integrity and varied degrees of excruciating blistering. Because the skin's function is to defend the body from invasive germs, those who have bullous disorders may experience chronic pain, reduced quality of life, and repeated, sometimes fatal infections are observed [1].The two primary subtypes of AIBDs are pemphigus and pemphigoid disorders. Pemphigus, derived from the Greek word "pemphix" (blister), is a diverse collection of AIBDs that affect the stratified squamous epithelia and are in charge of causing intraepithelial blistering, which is brought on by autoantibody deposits between keratinocytic layers. In contrast, the pemphigoid group has unique clinical features since it affects the skin's sub-epithelial layers or mucous membranes, which causes sub-epithelial blistering [2]. All Pemphigus varieties cause erosions and flaccid blisters on the skin or mucous membranes, although they differ in their aetiology and clinical presentation. Histologically, they are all marked by acantholysis, a process in which keratinocytes split apart [3].

In this instance, the production and deposition of IgG auto antibodies against the desmosomal structural proteins desmoglein (Dsg) 1 and/or Dsg3 results in an autoimmune disruption of the desmosomes, which are specialised adhesive protein complexes that tie neighbouring keratinocytes to one another and cause acantholysis [3]. The three main types of pemphigus are paraneoplastic pemphigus (PNP), pemphigus foliaceus (PF), and pemphigus vulgaris (PV). PV is the primary site of autoantibodies directed against Dsg3 and Dsg1, with anti-Dsg1 autoantibodies serving as the serological marker for PF [2]. Furthermore, it has been documented that autoantibodies against non-Dsg antigens, such as IgG against the alpha9 acetylcholine receptor, different mitochondrial subtypes of the nicotinic cholinergic receptor, and desmogellins, are present in PV patients[4].PNP patients have been reported to have a range of IgG autoantibodies, including IgG against the plakin family adhesion proteins, plakophilin 3, desmocollins 1 and 3, Dsg1, and Dsg3, as well as a 170 kD protein that was recently identified as the protease inhibitor, alpha-2 macroglobulin-like 1 (A2ML1)[5].

We will summarise recent developments in our knowledge of the aetiology and pathogenic processes of pemphigus in this review. We will also go over the conventional approach to treating this difficult group of illnesses and identify important directions for further study and advancement.

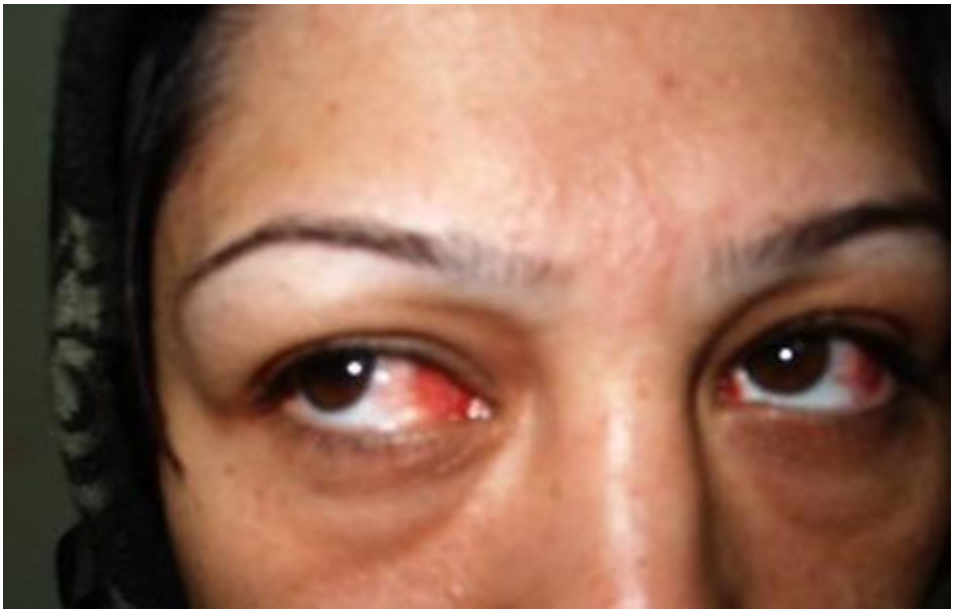

Fig 1. Pemphigus

II. EPIDEMIOLOGY

II.I. PARANEOPLASTIC PEMPHIGUS (PNP)

Paraneoplastic pemphigus is one of the type of the Pemphigus. It is associated with neoplastic diseases, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, waldenstrom macroglobulinemia, Castleman disease [6,7].On the diagnostic basis, of literature analysis, recognized two minor and three major for diagnosis of PNP. Minor basis i) lichenoid or acantholysis interface dermatitis on histopathology and ii) direct immunofluorescence staining, showing intercellular and basement membrane staining. Major basis i) concomitant internal neoplasm, ii) serological evidence of anti-plakin antibodies, and iii) mucositis with or without cutaneous involvement [10].

It has a polymorphic clinical appearance, related to presence of different IgG autoantibodies in addition to antiDsg3/Dsg1 IgG [11].

Paraneoplastic pemphigus	Age	Case frequency
	45-75	5%

TABLE1. PNP Age and Case frequency [8,9]

II.II. PEMPHIGUS FOLIACEUS (PF)

Pemphigus foliaceus second of the type of the Pemphigus. It associated within subcorneal layer of epidermis, more amount flaccid and fragile blisters include the skin and spare the mucous msembranes. [12]. Fragile blisters are infrequently seen due to their fragility. Skin lesions can increase more to exfoliative erythroderma. Moreover, the scaly erythema on scalp may be misdiagnosed. The endemic variant of PF is pathologically and clinically undifferentiated from the rare one [2,13,14].

Pemphigus seborrhoicus is exact surface variant of PF with wide covering surface area and erythematous plaques affecting areas, specially the face.[2,14]Moreover, anti-Dsg1 are their , conforming fot the nonappearance of mucosal lessions in PF[15].In general case frequency of Pemphigus foliaceus is 27% of cases in France [16,17].

II.III. PEMPHIGUS VULGARIS (PV)

A common symptom of PV type of pemphigus disease is mucosal involvement in form of painful blisters and attritions that predominate the oropharyngeal mucous membrane. However, 90% of cases with mucous membrane involvement, and the oral cavity [18].Blistering in buccal mucosa, tongue, mouth, lips region symptoms ranging from

mild discomfort to high severe pain during eating that fast weight loss is seen. The nasal, pharyngeal, laryngo oesophageal, urethral and conjunctival mucosae membrane are involved [19,13].

A large number of PV cases shows a change from a mucosal dominant to a muco cutaneous phenotype with skin lesions that is from Dsg3 to Dsg1 [20]. The population, PV affects the adult from age of 45 – 65 years and moderately female dominance.Regardless of the population, PV typically affects adults between the age of 45 and 65 years, with a slight female predominance[12,5].

III. DIAGNOSIS

Diagnosis of pemphigus begins with a thorough history and physical test. PV and PNP always involve the mucosa, while PF and IgA pemphigus generally do not. Importantly, mucosal involvement in pemphigus cases can be inconspicuous, and mucosal outsides routinely visible during standard physical examinations, similar as the eyes and lips, may not be involved. Clinicians should be sure to estimate for optical symptoms, hoarseness of voice, dysphagia, and dyspareunia to assess for involvement of all mucosal outsides.

Recent studies have demonstrated that thiol and phenol- predicated medicaments are most nearly linked to medicine-convinced pemphigus. Some of the most common triggering medicaments involved in specific- convinced pemphigus include penicillamine, captopril, tiopronin, aspirin, heroine, rifampin, levodopa, non-steroid anti-inflammatory drugs, and calcium channel blockers(37).

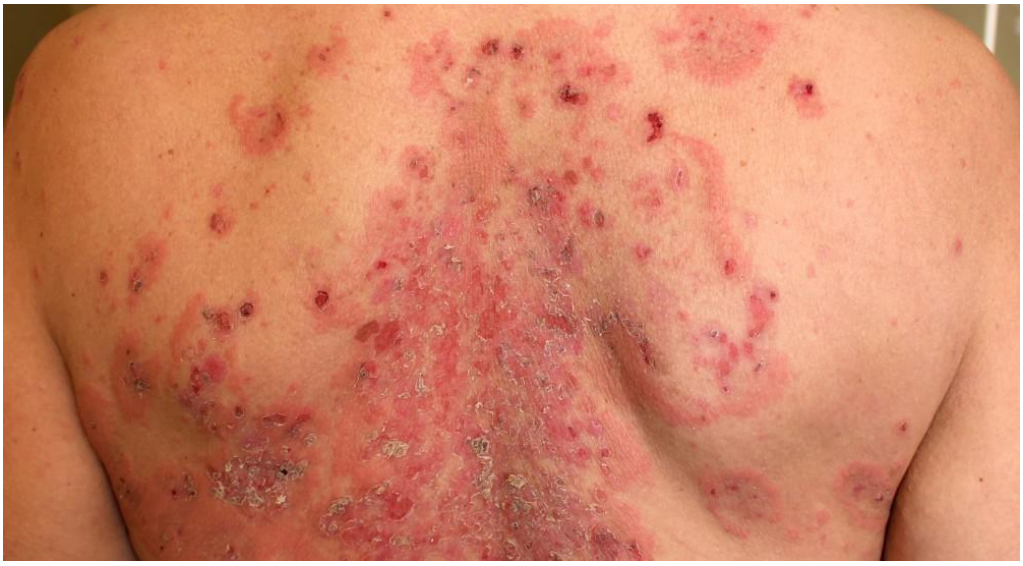

Fig 2. Symptoms of PF

IV. TREATMENT

The treatment of pemphigus has progressively evolved since the development of targeted treatments. Up until recently, the cornerstones of pemphigus therapy have been immunosuppressants and systemic corticosteroids (CS). The EADV and BAD guidelines recommend azathioprine (AZA) and mycophenolate mofetil (MMF) as first-line steroid-sparing agents among conventional adjuvant immunosuppressants[21]. However, a number of factors need to be considered, such as the expenses, the comorbidities of the patients, their experience in a particular institution, and other medications that show benefit, including cyclophosphamide and methotrexate. Interestingly, the primary action of these medications is CS-sparing as opposed to morbostatic[22].Consequently, they do not increase remission rates, but they do lower the chance of relapse by 29% when compared to CS alone . The use of RTX as a first-line adjuvant therapy for pemphigus is now supported by a recent prospective multicenter research by Joly et al., which demonstrated improved efficacy compared to CS alone and a decreased incidence of major side events and overall mortality linked to CS. Patients with severe or resistant PV may benefit from intravenous immunoglobulin (IVIg) or immunoadsorption (IA) therapy. Suggested protocols for both induction and maintenance of therapy[23].

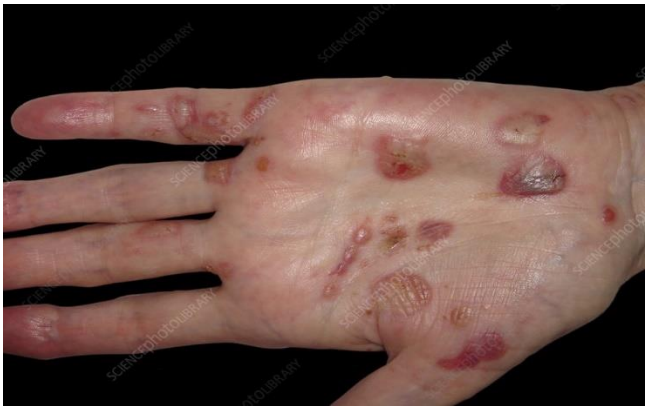

Fig 3. After treatment

V. CORTICOSTEROID

As a first-line treatment for pemphigus, prednisolone is advised in conjunction with an immunosuppressive medication, such as azathioprine (AZA) and mycophenolate mofetil (MMF), or RTX. Furthermore, in patients who cannot get treatment with RTX or other immunosuppressive adjuvants, prednisolone alone at a dose of 1-2 mg/kg/day is still advised as first line therapy. If within three weeks there is still no improvement in disease control, higher dosages of CS (up to 1.5 mg/kg) may be given. Every other week, the doses should be decreased by 25% as soon as disease control is achieved. To bring about disease control, CS should be increased till two steps back at the prior dose if lesions reappearance. However, randomised clinical trials (RCTs) have not been used to establish the ideal dose [24].

To lower the danger of side effects, a pulse treatment should be taken into consideration if the recommended daily dose of CS is greater than 100 mg. However, there is disagreement on the benefits of taking oral CS pulses along with immunosuppressive adjuvants [25]. Long-term CS therapy patients have reported a number of side effects, such as increased vulnerability to infections and infestations overall, osteoporosis, secondary adrenal insufficiency, transitory hyperglycemia, hypertension, and posterior subcapsular cataract[26].

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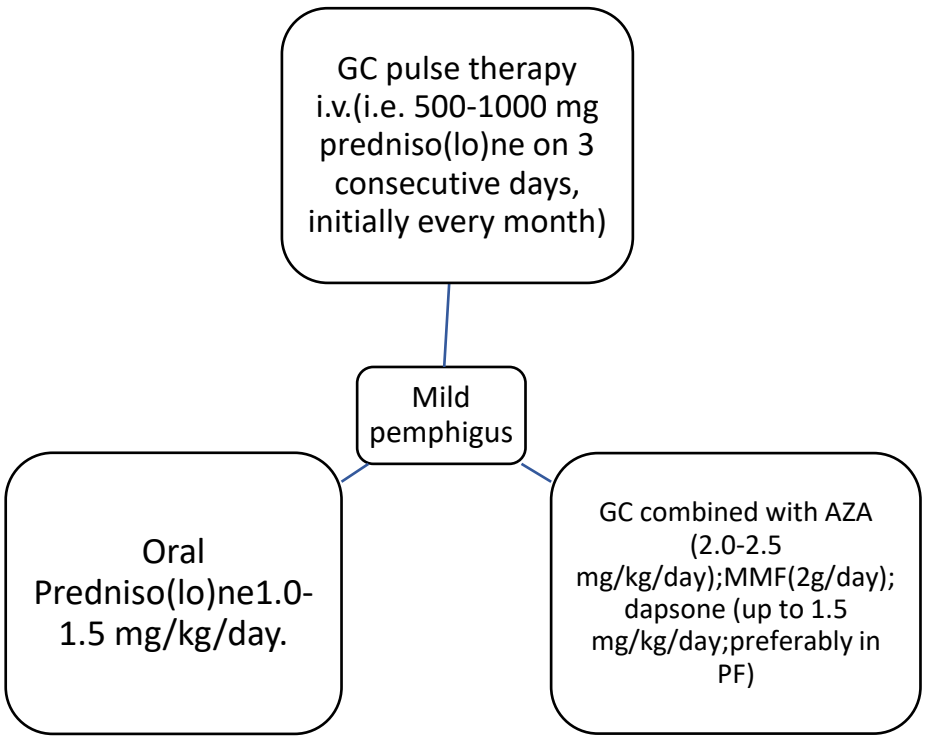

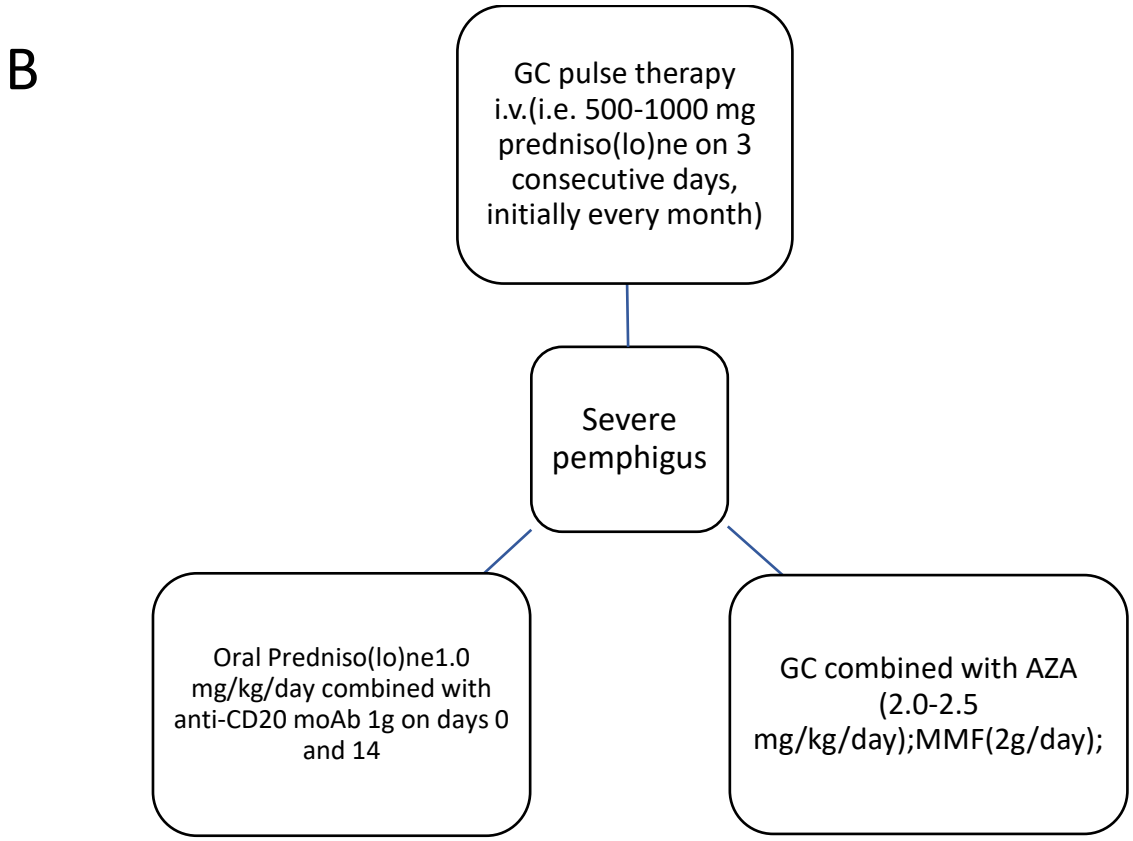

Fig 4. Induction therapy in pemphigus. (A) mild pemphigus; (B) severe pemphigus. AZA. Azathioprine; GC, glucocorticoids; MMF, mycophenolate mofetil; moAb, monoclonal antibody.

VI. IMMUNOSUPPRESSANTS

The first line of treatment for pemphigus is often immunosuppression with systemic corticosteroids, such as oral prednisone or prednisolone. Depending on the severity of the disease, different dosing schedules are used. In order to achieve initial control of the disease, the usual starting dose is 0.5 to 1.5 mg/kg/day. However, in more extreme cases, treatment options include either intravenous pulse methylprednisolone (500–1,000 mg daily for three to five consecutive days) or dexamethasone (100 mg daily for three consecutive days), with or without concurrent cyclophosphamide[27].When evaluated collectively, the early attempts to treat pemphigus with non-steroid immunosuppressive medications such azathioprine, mycophenolate mofetil, and cyclophosphamide appeared to lower the likelihood of relapse. Nevertheless, compared to corticosteroids alone, these drugs did not demonstrate superior efficacy in inducing remission, decreasing mortality, or preventing relapse. However, azathioprine and cyclophosphamide both exhibited steroid-sparing properties, while mycophenolate showed a noteworthy impact on illness management. Generally, a dose of 2-3 mg/kg/day of azathioprine, 2-3 g/day of mycophenolate mofetil, and 75–150 mg/day or 500–1,000 mg monthly intravenously of cyclophosphamide are administered[28].

Dihydrofolate reductase inhibitors like methotrexate were the first steroid-sparing medication used to treat pemphigus. Because of the related toxicities at larger doses, it lost popularity. It wasn't until later that it reemerged as a secure and successful adjuvant therapy for pemphigus, at low to moderate doses (range from 15–20 mg/week)[29].Pemphigus foliaceus, IgA pemphigus, and pemphigus herpetiformis are among the pemphigus with a primarily neutrophilic infiltration that are frequently treated with dapsone due to its capacity to obstruct neutrophil chemo-attractants.[30].

VII. RISK FACTORS

Pemphigus has emerged as a result of a variety of factors, including heredity, environment, pre-existing medical disorders, pharmaceutical use, and even reactions to vaccination. We will go over some of the most recent findings in this section, which are helping to provide a picture of the conditions and processes leading to the clinical manifestation of pemphigus.

VII.I. GENETIC RISK FACTORS

There is a strong genetic component to vulnerability, as seen by the familial clustering of specific pemphigus variations, its predisposition for particular ethnicities, and the co-occurrence of other autoimmune disorders in individuals. The relationship between PV and HLA class II genes is currently the strongest that has been found[31].In addition to the HLA susceptibility studies, other studies have found correlations between PV and immune gene sequences or autoantigens: in both the British and Indian cohorts, specific Dsg3 haplotypes were significantly associated with PV, and in two patients, single nucleotide polymorphisms within the variable region of the immunoglobulin heavy chain VH3 gene were associated with PF . Variants affecting the TAP2 gene, which encodes a protein involved in peptide assembly and transport to HLA class I, and genetic variants of the cytokine genes TNF-α, IL-6, and IL-10 have also been linked to PV[32].

VII.II. THERAPEUTIC RISK FACTORS

The drugs can cause pemphigus which have three primary drug classes that have been linked to the beginning or worsening of pemphigus are phenol medications, non-thiol/non-phenol pharmaceuticals, and thiol drugs. As thiol medicines contain a sulfhydryl (-SH) group in their chemical structure, they are most likely the pharmacological class with the most research on their role in the pathophysiology of pemphigus. Penicillamine, captopril, and bucillamine—drugs of the thiol class—were the most frequently reported medicines to cause pemphigus in a comprehensive evaluation of 170 cases of drug-induced disease[1].

Subsequent in vitro studies revealed that thiol medications (captopril, thiopronine, piroxicam, and d-penicillamine) can cause acantholytic splitting in human skin cultures or fragments when pemphigus antibodies are not present (i.e biochemical acantholysis).In addition to medications, immunisations have also been shown to cause or worsen pemphigus. They include vaccinations against rabies, tetanus, influenza, hepatitis B, and, more recently, SARS-COV2. Although the processes underlying vaccine-induced pemphigus remain unclear, various alternative possibilities to those suggested for drug-induced pemphigus have been put forth[33].

VIII. AYURVEDIC TREATMENT

Traditional (allopathic) anti-inflammatory medications are the cornerstone of care for a variety of autoimmune diseases.Due to the negative effects and high expense of commonly used anti-inflammatory medicines, patients are increasingly turning to complementary and alternative medicine (CAM) therapy techniques. Owing to the patient's poor financial situation, a biopsy or tzanck smear study was not feasible for a diagnosis.Owing to the therapy's significant relief, the patient was referred for Ayurvedic treatmen[34].The patient was admitted to the hospital's indoor patient department after being clinically diagnosed with visphosis (bullous skin disorder) and placed under the recommended Ayurvedic care.The symptoms of Visphotaka are blisters all over the body, a burning feeling, fever, and thirst, as mentioned in the traditional Ayurvedic texts[35].

The patient was prescribed either oral administration of Gandhaka Rasāyana or Arogyavardhini Rasa, one gramme of each, and a mixture of powders of Guḍūcī, Khādira and Vasā. Adhatoda vasica Nees., three grammes each, applied twice a day; local application of concentrated Pañcavalkala Kvātha was prescribed for the duration of the therapy term. He was assessed for standard haematological, urinalysis, and biochemical procedures both at admission and prior to discharge.After local application, there was a decrease in pain and burning feeling.Generalised itching was seen on the sixth day of hospitalisation, but a decrease in the production of new bullae was noted[36].

IX. CONCLUSION

The last ten years have seen an increase in the number of therapeutic choices for treating pemphigus, along with improvements in our understanding of the pathogenicity of the disease. More targeted medications and improved diagnostic methods are starting to appear. A deeper understanding of the early phases of pemphigus, the function of innate and adaptive immune cells—particularly dendritic cells—and a thorough examination of the biology of the relevant B cells will be necessary. Skin and mucous membranes are affected by the Pemphigus family of uncommon autoimmune bullous dermatoses. Classically, flaccid bullae are associated with acantholysis, a histopathologic finding, in PV and PF. Clinically, IgA pemphigus presents with pustular lesions that are consistent with comparable findings observed with light microscopy. The presence of anti-plakin antibodies is the common denominator among the widely varied clinical and histopathologic features associated with PNP, a paraneoplastic disease. It has been discovered that ayurvedic medication is a good alternative therapy for autoimmune bullous illness; nevertheless, long-term prospective research are needed to support the findings.

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