Pemphigus: Pathogenesis to Treatment

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ABSTRACT

Pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP) are a group of rare and fatal blistering diseases involving autoantibodies that target desmosomal proteins. The pathogenesis of pemphigus involves the production of activated B-cells and IgG with stimulation by IL-4 by T-helper 2 cells. Clinically these diseases present most often with epidermal erosions of the mucosae and skin caused by rapid rupturing of flaccid bullae. These lesions correlate histologically with splits forming in the epidermis, leaving a blister roof composed of a few cell layers. Standard treatment of pemphigus involves oral corticosteroids, often with the addition of adjuvant therapies, to improve disease control, minimize corticosteroids side-effects, and increase the odds of remission.

KEYWORDS: pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, desmoglein 1, desmoglein 3, corticosteroids

INTRODUCTION

Pemphigus includes a group of blistering diseases involving autoantibodies that target proteins found in the desmosome, intercellular adhesion protein complexes. Most forms of pemphigus are classified as being a subtype of pemphigus vulgaris (PV), pemphigus foliaceus (PF), or paraneoplastic pemphigus (PNP). They are a rare group of disorders that have an incidence of 2-10 cases per one million inhabitants in some areas of the world and a prevalence of 0.1-0.7 per one hundred thousand inhabitants.[1,2] Pemphigus was a highly fatal disease until the introduction of corticosteroids (CS) which have reduced its mortality rate from 75% to less than 10% ,with most morbidity and mortality today due to iatrogenic causes rather than the disease itself.[3,4] The one exception is paraneoplastic pemphigus, which has a mortality rate around 50% ,most often due to pneumonia, the associated malignancy, or pulmonary involvement, resulting in bronchiolitis obliterans, despite treatment.[5]

PATHOGENESIS

The pathogenesis underlying all forms of pemphigus involves the development of autoantibodies to the desmosomal proteins, which can be found in many areas of the body, but which play a major role in the epidermal layers of the integumentary system. PV and PF are caused primarily by antibodies to desmoglein 1 (Dsg 1) in PF, desmoglein 3 (Dsg 3) in mucosal dominant PV, or both in mucocutaneous PV.[6] Dsg 1 and 3 are found in varying amounts in the epidermis of the skin and mucosa. Dsg 1 is found in higher amounts in the upper layers of the epidermis, especially on the skin, while Dsg 3 is found in the lower layers of the epidermis with higher concentrations in the mucosa and skin.[2,6] It is this variability in distribution which explains the 3 distinct clinical diseases.

The disease usually occurs in patients with certain HLA genotypes who generate B-cells responsible for the specific autoantibodies. The activation of these B-cells requires a complex interaction with CD4+ T helper 2 (Th2) cells and it is this Th2 cell over-activation that leads to the autoantibody production that is necessary for PV and PF.[1,2,6] Th2 cells are known for secreting multiple interleukins (IL), of which IL-4 plays a major role in pemphigus and the humoral immune response.[2] IL-4 promotes antibody production by primed B cells and an isotype switching from IgG1 to IgG4 antibodies which have been shown to be important in the active form of PF and PV.[2,6] IL-4 also perpetuates the disease by causing naïve CD4+ T cells to differentiate into Th2 cells.[6] The production of autoantibodies and epitope binding is sufficient to cause loss of adhesions between desmosomes leading to separation of keratinocytes which is directly related to disease activity.[1] Therefore the disease does not require other components of the immune system for activity, such as complement or cytotoxic T cells. Based on this pathogenesis, treatment for pemphigus focuses primarily on the prevention of antibody production and prevention of isotype switching from an IgG1 to IgG4. When pemphigus enters remission there is a known upregulation of IL-10 and a T helper 1 response that induces antibody isotype switching from IgG4 back to IgG1.[1,2,6] Tumor necrosis factor α, IL-1, and other cytokines also play a smaller role in the pathogenesis of pemphigus.[2]

PNP is unique from PV and PF in that it may contain autoimmune antibodies to Desmoglein 1 and 3, but has more specific antibodies to envoplakin and periplakin.[7] While envoplakin and periplakin are the most specific for PNP, patients with this disease can develop multiple autoantibodies primarily to desmosomal proteins, including the

plakin family of proteins (plectin, BP230, and desmoplakin), desmocollins, and alpha-2-macroglobubin-like antigen-1.[5,8]

CLINICAL

While pemphigus is classified as an auto-immune blistering disease, usually the most prominent findings are epidermal erosions from rapid rupturing of blisters with thin roofs. PV often begins with oral erosions primarily involving the buccal and gingiva mucosae. If patients have developed antibodies to both Dsg 1 and 3, they will likely manifest erosions and flaccid bullae on the skin over weeks to months. Generally the chest, face, scalp, upper back, and areas of trauma are common sites for cutaneous involvement.[1,6,9,10] PF often can present very similarly to the cutaneous involvement of PV. Clinical differences include the lack of mucosal involvement and an exfoliative presentation due to the shallow depth that the erosions occur in the epidermis.[9] (**Table 1**)

PNP, due to the presence of multiple different autoantibodies, may have a more variable clinical presentation. All patients present with severe involvement of at least a single mucosal surface, with the majority reporting oral involvement. However, there is a high percentage of patients who have involvement of the ocular, genital, and nasal mucosa.[5] Up to two thirds of patients will have cutaneous involvement presenting with classic erosions of pemphigus. But as many as 50% of patients will present with cutaneous lesions similar to erythema multiforme, bullous pemphigoid, and lichen planus. The most commonly reported malignancies with PNP are lymphoid malignancies, most often non- Hodgkin lymphoma and chronic lymphocytic leukemia, followed by Castleman disease, thymoma, and a mix of other solid organ tumors.[5,7] Of note, only two thirds of patients will have been diagnosed with a malignancy when presenting with PNP.[9]

The diagnosis of any patient with a clinical suspicion for pemphigus is best confirmed with a combination of histopathology and laboratory testing. Most commonly a biopsy of a fresh vesicle or the edge of a blister, with adjacent non-blistered skin, should be performed for histopathology. A biopsy of normal skin at least 1cm away from any blistered or inflamed skin should also be obtained and sent for direct immunofluorescence (DIF).[9] The key histological feature of pemphigus is an intra-epidermal split with the loss of adhesion and separation of normal appearing keratinocytes referred to as acantholysis. In PV, the histology shows suprabasilar split with acantholysis of keratinocytes and DIF will be positive for intercellular IgG involving the entire epidermis. PF will have a subcorneal split with acantholysis of keratinocytes and a DIF showing positive intercellular staining in the upper epidermal layers.[9] PNP can have a histology and DIF with variable amounts of suprabasal acantholysis, lymphocytic infiltrate, and necrotic keratinocytes.[7] (Table 1) Histopathology and DIF can have overlapping features between the various forms of pemphigus. But the histologic picture may be non-diagnostic and serologic studies are recommended. Enzyme-linked immunosorbent assay (ELISA) to quantitate Dsg antibody titers can be done or, if unavailable, serum should be sent for indirect immunofluorescence (IIF) on monkey esophagus for a qualitative measurement of serum Dsg antibodies.[8-10] Specific to PV, ELISA can be used to monitor Dsg 3 antibodies which can correlate with disease severity.[10] Specific to PNP, if suspected, IIF can be performed on monkey or rat bladder urothelium which lacks Dsg 1 and 3 but still contains plakins making it a specific test for PNP.[5,8]

TREATMENT

Due in part to its rarity and the lack of standard definitions for tracking disease activity, studies on the treatment of pemphigus are few and limited by small sample sizes.[3] First-line

Table 1. Summary of disease classification, clinical features, autoantibody targets, histological, and immunofluorescence findings.

Disease	Clinical Features	Autoantibodies	Histology	Direct Immunofluorescence	Indirect Immunofluorescence
Pemphigus Vulgaris – Mucosal Dominant	Mucosal erosions and flaccid bullae	Desmoglein 3	Suprabasilar split with acantholysis	Intercellular IgG on the entire epidermis	Intercellular IgG on Monkey Esophagus
Pemphigus Vulgaris – Mucocutaneous	Cutaneous and mucosal erosions and flaccid bullae	Desmoglein 1 and 3	Suprabasilar split with acantholysis	Intercellular IgG on the entire epidermis	Intercellular IgG on Monkey Esophagus
Pemphigus Foliaceus	Cutaneous erosions and exfoliative dermatitis	Desmoglein 1	Subcorneal split with acantholysis	Intercellular IgG on the upper epidermis	Intercellular IgG on Monkey Esophagus
Paraneoplastic Pemphigus	Severe mucosal involvement, pemphigus-like, erythema multiform-like, or lichen planus-like cutaneous lesions	Envoplakin Periplakin Plectin BP230 Desmoplakin Desmocollin Desmoglein 1 and 3 Alpha-2-macroglobubin-like antigen-1	Suprabasilar split with acantholysis, lymphocytic infiltrate, and necrotic keratinocytes	Intercellular IgG on the entire epidermis	Intercellular IgG on Monkey Esophagus, Rat Bladder, and Monkey Bladder

therapy for all forms of pemphigus should be CS. Initial daily doses equivalent to 0.5 to 1.0 mg/kg of prednisone are recommended. However, smaller studies have shown that there may be no difference in outcomes for either initial dose.[3] IV methylprednisolone has been shown in pemphigus patients to decrease tumor necrosis factor α and interleukin 6.[2]

With the initiation of a CS it is common practice to also start an adjuvant therapy for disease control. The exact mechanism of immunosuppressive medications in pemphigus is unknown but it is believed that these therapies act by inhibiting B cell and autoantibody production which contribute to disease activity.[2] Adding an adjuvant agent is proven to lower the risk of relapse. However this effect is lost when comparing specific adjuvant medications. Also, adjuvant therapy does not improve remission rates, time to disease control, time to relapse, or the incidence of death in pemphigus.[3,4]

In addition to traditional immunosuppressive medications, another recently utilized adjuvant is intravenous immunoglobulin (IVIG). IVIG has been shown to decrease IL-1 levels in patients with PV and also provide immune modulation and reconstitution.[2] IVIG also causes a decrease in IgG4 and IgG1 antibodies to Dsg 1 and 3 within 2 weeks of therapy.[11] A recent meta-analysis demonstrated that IVIG was the only adjuvant that improved disease control compared to more traditional immunosuppressive medications.[4] In combination with CS, IVIG has been shown to induce clinical improvement in over half of treated patients.[11]

B-cell depleting therapies have also been studied as standard adjuvant therapy for the treatment of pemphigus and have increased remission rates up to 65%.[10] Rituximab is a monoclonal antibody against the CD20 surface glycoprotein on mature B cells while sparing plasma cells. In pemphigus there is a decrease in autoantibodies to Dsg and peripheral blood B cells that lasts several months. Those levels may rise with the return of peripheral B cells and this may signal a relapse. However, not every patient with this reconstitution relapses, suggesting a restoration of immune tolerance.[10]

Tumor necrosis factor α inhibitors have also been studied as adjuvant therapy as well in pemphigus. However, these agents may not be as successful in inducing remissions and the role of TNF-α in pemphigus is still not well understood.[2] While IL-4 has been shown to play a major role in the pathogenesis of pemphigus and currently there are medications that block IL-4, such as dupilumab, no studies evaluating its role in the treatment of pemphigus have been published.[6]

Expert consensus panels have convened to define goals for treating patients with pemphigus as well as the doses required before considering a treatment to be a failure. [9,12] Per such consensus, "disease control" was defined as no new lesions forming and established lesions improving over several weeks. CS doses should be maintained until no new lesions have developed for at least 2 weeks and most erosions have healed.[9,12] Doses of 1.5 mg/kg of prednisone or an alternative CS equivalent should be used daily for 3 weeks with or without an adjuvant before a patient has been deemed to have failed treatment. Failed adjuvant doses are defined as 12 weeks of daily oral regimens of 2mg/kg of cyclophosphamide, 2.5 mg/kg of azathioprine, 3 grams of mycophenolate mofetil, or a weekly dose of methotrexate at 20 mgs.[12]

European guidelines have since recommended that all patients with pemphigus be treated with prednisone initially. Second-line therapy involves the addition of azathioprine, mycophenolate mofetil, or mycophenolic acid as an adjuvant. Third-line therapy is the replacement of the failed adjuvant with an anti-CD20 antibody, IVIG, immunoadsorption, cyclophosphamide, dapsone, or methotrexate.[9] An alternative proposed algorithm included starting all pemphigus patients with CS and an adjuvant initially. If the treatment fails after 3 months of therapy the adjuvant therapy should be replaced with rituximab at 4 weekly doses of 375 mg/m^2. For patients with PNP, CS with rituximab as an adjuvant are recommended as first line therapy, often due to the concurrent Non-Hodgkin lymphoma.[13]

CONCLUSION

Despite the rarity of pemphigus in the general population, research continues to better elucidate the mechanisms underlying this group of diseases. Treatment regimens with long-term remissions and new medications are being evaluated as potential treatment options.

References

1. Di Zenzo G, Amber KT, Sayar BS, Müller EJ, Borradori L. Immune response in pemphigus and beyond: progresses and emerging concepts. Semin Immunopathol. 2016 Jan;38(1):57-74. PubMed PMID: 26597100.
2. Giordano CN, Sinha AA. Cytokine networks in Pemphigus vulgaris: An integrated viewpoint. Autoimmunity. 2012 Sep;45(6):427-39. PubMed PMID: 22686612.
3. Martin LK, Werth VP, Villaneuva EV, Murrell DF. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. J Am Acad Dermatol. 2011 May;64(5):903-8. PubMed PMID: 21353333.
4. Atzmony L, Hodak E, Leshem YA, Rosenbaum O, Gdalevich M, et al. The role of adjuvant therapy in pemphigus: A systematic review and meta-analysis. J Am Acad Dermatol. 2015 Aug;73(2):264-71. PubMed PMID: 26088689.
5. Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol. 2015 Dec;173(6):1447-52. PubMed PMID: 26358412.
6. Tavakolpour S, Tavakolpour V. Interleukin 4 inhibition as a potential therapeutic in pemphigus. Cytokine. 2016 Jan;77:189-95. PubMed PMID: 26440137.
7. Zimmermann J, Bahmer F, Rose C, Zillikens D, Schmidt E. Clinical and immunopathological spectrum of paraneoplastic pemphigus. J Dtsch Dermatol Ges. 2010 Aug;8(8):598-606. PubMed PMID: 20180886.
8. Poot AM, Siland J, Jonkman MF, Pas HH, Diercks GF. Direct and indirect immunofluorescence staining patterns in the diagnosis of paraneoplastic pemphigus. Br J Dermatol. 2015 Nov 11;PubMed PMID: 26556228.
9. Hertl M, Jedlickova H, Karpati S, Marinovic B, Uzun S, et al. Pemphigus S2 Guideline for diagnosis and treatment--guided by

the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2015 Mar;29(3):405-14. PubMed PMID: 25338479.

10. Feldman RJ, Christen WG, Ahmed AR. Comparison of immunological parameters in patients with pemphigus vulgaris following rituximab and IVIG therapy. Br J Dermatol. 2012 Mar;166(3):511-7. PubMed PMID: 21967407.
11. Green MG, Bystryn JC. Effect of intravenous immunoglobulin therapy on serum levels of IgG1 and IgG4 antidesmoglein 1 and antidesmoglein 3 antibodies in pemphigus vulgaris. Arch Dermatol. 2008 Dec;144(12):1621-4. PubMed PMID: 19075146.
12. Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol. 2008 Jun;58(6):1043-6. PubMed PMID: 18339444; NIHMSID: NIHMS82304; PubMed Central PMCID: PMC2829665.
13. Hertl M, Zillikens D, Borradori L, Bruckner-Tuderman L, Burckhard H, et al. Recommendations for the use of rituximab (anti-CD20 antibody) in the treatment of autoimmune bullous skin diseases. J Dtsch Dermatol Ges. 2008 May;6(5):366-73. PubMed PMID: 18201220.

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