Editorial

What is new in autoimmune vesicobullous disorders?

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The pathogenesis of autoimmune bullous diseases (ABD) is yet to be completely deciphered. Consequently, there has been enormous development in the fields of immunopathology, diagnostics and treatment of ABDs and there is still a long way to go. The last century saw the management of these disorders improve by leaps and bounds due to the demonstration of acantholysis as the primary pathology in a majority of intraepidermal bullous diseases, identification of various autoantibodies with their pathogenic significance and a great reduction in mortality with the discovery and widespread use of corticosteroids. However, these disorders are still associated with significant morbidity, considerable mortality and impaired quality of life. Mazotti *et al.*[1] found strong associations between psychological distress and excess expenditure in one's appearance corresponding with a perceived high disease severity in pemphigus vulgaris (PV).

NEWER CONCEPTS IN PATHOGENESIS OF AUTOIMMUNE BULLOUS DISEASES: DELVING DEEPER INTO THE PROCESS OF ACANTHOLYSIS

ABDs are broadly classified into intraepidermal and subepidermal bullous disorders. The most common intraepidermal ABD is pemphigus, with a worldwide prevalence of 0.1–0.5 per 100,000 population, which can be as high as 3.2 per 100,000 in certain races.[2] A genetic predisposition to develop pemphigus has been documented, which, in the presence of certain environmental triggers, results in acantholysis. Narbutt *et al.*[3] evaluated the polymorphisms in genes encoding co-stimulatory receptors – cytotoxic T-lymphocyte antigen 4 (CTLA4) and inducible T-cell co-stimulator (ICOS) – on T cells and concluded that the expression and function of these genes is significantly altered in PV and pemphigus foliaceus (PF). In PV, autoantibodies are primarily directed against desmosomal cadherins, desmoglein (Dsg) 3 and Dsg 1, whereas PF patients only have antibodies against Dsg 1. Mao *et al.*[4] identified autoantibodies to Desmocollin 3 as of pathologic importance in PV.

Although acantholysis as the basic pathomechanism in pemphigus is well accepted, the mechanism by which disruption of adhesion between keratinocytes occurs is not fully elucidated. Binding of autoantibodies to their antigens can disrupt adhesion of the bound antigens by steric hindrance. Secondly, the antigen–antibody complex induces production of plasminogen activator, which in turn leads to the production of active plasmin culminating in cell dissociation. Thirdly, the autoantibodies may lead to reorganization of the keratinocyte cytoskeleton, leading to cellular shrinkage and separation of keratinocytes.[5] Using atomic force microscopy, it is seen that PV-IgG directly interferes with homophilic Dsg 3 transinteraction. PV-IgG Fab reduces the binding activity of Dsg 3 by ~60% through inhibition of Dsg transinteraction.[6] In contrast, neither PV-IgG nor PF-IgG directly interacts with homophilic Dsg 1. They reduce Dsg1 transinteraction indirectly via cellular mechanisms. Thus, the molecular mechanisms in PV and PF pathogenesis differ. However, electron microscopic

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findings reveal early widening of the intercellular space (ICS) and the absence of half desmosomes in acantholytic Nikolsky-positive skin, supporting the "basal cell shrinkage theory" and arguing against direct steric hindrance as a cause of acantholysis in pemphigus.[7] Few recent studies have also reported profound changes in actin organization to accompany acantholysis in PV.[8]

Approximately 85% of the pemphigus patients develop antibodies against keratinocyte acetylcholine receptors (AChR) – AChR α9 and Pemphaxin.[9] PV-IgG binding to AChR α9 may block Ca++ influx involved in desmosome assembly and in protein kinase C (PKC) activation that induces changes in gene expression through protein phosphorylation. PV-IgG weakens intercellular adhesions between keratinocytes via inactivation of the cholinergic receptor-mediated physiologic control of cadherin (Dsg) expression and/or function and causes acantholysis.

Although the autoantibodies have been shown to be pathogenic, the role of the cellular immune system is unclear. Toto *et al.*[10] found CD28-deficient mice (lacking a co-stimulatory signal for T-cell activation) to be five-fold more sensitive to the development of PV than wild-type mice when PV-IgG was passively transferred to them. Additionally, lower levels of IL-10 mRNA were found and passive transfer of patient's sera in IL-$10^{-/-}$ mice increased blisters compared with controls, which was reversed on administering rIL-10. One of the earliest pathogenic events in PV is the activation of protein kinases, including the protein kinase R (PKR) -like endoplasmic reticulum kinase (PERK). Decreased expression of PERK *in vivo* has been shown to reduce the effects of PV serum on the cell cycle and keratinocyte viability, two key events in PV pathophysiology.[11]

Bullous pemphigoid (BP) is a group of subepidermal bullous autoimmune diseases of the skin caused by autoantibodies against the epidermal basement membrane zone (BMZ). It is the most common autoimmune blistering disease in the Western world. Hemidesmosomal proteins are the targets of autoimmunity in many subepidermal blistering diseases. Autoantibodies against BP230 and BP180 are associated with BP as well as with pemphigoid gestationis (PG), lichen planus pemphigoides (LPP) and mucous membrane pemphigoid (MMP), whereas autoantibodies against the linear IgA disease antigen (LAD-1), which is the soluble shed ectodomain of BP180, are found in linear IgA disease (LAD). Recently, plectin, involved in anchoring of intermediate filaments to the plasma membrane and nuclear membrane as well as the cross-linking of intermediate filaments and interlinking intermediate filaments with microtubules and microfilaments, has been shown to be a minor pemphigoid antigen with an immunodominant epitope located on the central rod domain.[12] In 1990, a new subepidermal blistering disease was described, distinct from previously known BP and epidermolysis bullosa acquisita (EBA), where the circulating autoantibodies did not react to any known autoantigen but to a 200-kDa molecule (p200) from dermal extracts.[13] Recently, the identity of p200 has been unmasked as laminin γ1, an extracellular matrix glycoprotein composed of several forms of laminin heterotrimers. Hence, it has been renamed as anti-laminin γ1 pemphigoid.[14]

CLINICAL TYPES OF AUTOIMMUNE BULLOUS DISEASES: THE NEWLY DESCRIBED ONES

Traditionally, pemphigus has been classified as PV and its variant pemphigus vegetans; PF and its variant pemphigus erythematosus; drug-induced pemphigus; and the newer variants, namely pemphigus herpetiformis, paraneoplastic pemphigus (PNP) and the intraepidermal IgA pemphigus. Gharami *et al.*[15] reported a newer morphologic variant of PV, dyshidosiform PV, presenting as a pompholyx-like eruption on the soles. In 1996, a new entity by the name of paraneoplastic autoimmune multiorgan syndrome (PAMS) was described where, in addition to skin and upper digestive and respiratory tract mucosa, deposits of autoantibodies are present in the kidney, urinary bladder and smooth as well as striated muscle.[16] PNP is now considered as an epithelial variant of PAMS. Clinically, PAMS may present with pemphigus-like, pemphigoid-like, graft versus host disease-like, erythema multiforme-like or lichen planus-like eruptions and may be associated with leukemias and lymphomas, Castleman's disease, thymoma, retroperitoneal sarcoma and other malignancies.

The subepidermal disorders include BP, mucous membrane pemphigoid, LAD, EBA, bullous systemic lupus erythematosus, PG and dermatitis herpetiformis. Typical patients of the newly described anti-laminin γ1 pemphigoid are approximately 50–70 years old,

often having pre-existing psoriasis.[14] The patients develop tense blisters and urticarial eruptions closely resembling BP. On indirect immunofluorescence microscopy on 1 mol/L NaCl-split skin, anti-laminin γ1 pemphigoid IgG reacts with the dermal side of the basement membrane, whereas BP IgG shows reactivity with its epidermal side. In addition, MMP IgG and EBA IgG show reactivity with the dermal side of the basement membrane in salt-split skin. However, MMP mainly affects the ocular and oral areas, and develops clearly demarcated bullae and blisters without surrounding urticarial eruptions. Typical EBA patients also develop non-inflamed mechanical bullae that heal with atrophic scarring. However, clinical presentation may be indistinguishable from anti-laminin γ1 pemphigoid or BP in many cases. Abrams *et al.*[17] reported the first case of congenital EBA due to transplacental passage of autoantibodies, which was self-limiting in nature. Among the drug-induced ABDs, biologic response modifiers like adalimumab have been reported to cause both BP and PV.[18]

Another area of interest is the association between BP and neurological disorders. Bastuji-Garin *et al.*[19] identified the risk factors for developing BP as presence of neurological disorders, particularly dementia and Parkinson's disease, psychiatric disorders, bedridden condition and chronic use of several drugs. In a study by Taghipour *et al.*,[20] at least one neurologic diagnosis was present in 42/91 (46%) BP patients compared with 16 controls (11%). Four major neurologic diagnoses were observed (cerebrovascular disease, dementia, Parkinson disease and epilepsy), with a highly statistically significant association for cerebrovascular disease and dementia.[20]

DIAGNOSIS OF AUTOIMMUNE BULLOUS DISEASES: FROM IMMUNOFLOURESCENCE TO ENZYME-LINKED IMMUNOSORBENT ASSAY

Diagnosis of ABD is based on clinical grounds coupled with detection of tissue-bound and serum autoantibodies. Direct immunoflourescence (DIF) microscopy from perilesional skin remains the gold standard for diagnosing ABD. DIF on telogen hair root sheath has shown promising results in diagnosis and follow-up in cases of pemphigus.[21] Other methods include indirect immunoflourescence (IIF) and immunoblotting. Recently, several enzyme-linked immunosorbent assays (ELISAs) using extracts of bovine skin and recombinant portions of Dsg 3 and 1 expressed in *Escherichia coli* have been developed to detect circulating autoantibody levels and have been found to be superior to IIF microscopy due to less interpreter dependency and greater standardization.[22] Schmidt *et al.*[23] analyzed the efficacy of a novel ELISA system using ectodomains of Dsg 3 and 1 expressed in human cell lines (HEK293) as target antigens and found it to be sensitive and specific in both the diagnosis and monitoring of PV and PF. Similarly, Powell *et al.*[24] found the BP180 NC16a ELISA to be highly sensitive and specific in differentiating PG from polymorphous eruptions of pregnancy. It has been proposed that measurement of B-cell activating factor (BAFF) belonging to the tumor necrosis factor (TNF) family may be a useful marker to detect early activation of an autoimmune diathesis as it is thought to play a critical role in triggering activation of self-antigen–driven autoreactive B cells in BP.[25] C3d immunohistochemistry has been devised as a valuable tool for the diagnosis of BP and PV.[26] Mueller *et al.*[27] used Collagen (COL) VII-NC1 ELISA in the diagnosis of EBA and found it to be a powerful tool in diagnosing EBA with COL VII-specific IgG correlating with disease activity, and IgG reactivity was found to be associated with T-cell recognition of identical subdomains of COL VII-NC1. Commercially available ELISA assays are now used to detect autoantibodies against p-200 antigen.[28]

TREATMENT OF AUTOIMMUNE BULLOUS DISEASES: IMMUNOMODULATION RATHER THAN IMMUNOSUPPRESSION

Treatment of autoimmune blistering diseases is based on the use of systemic glucocorticosteroids, either orally in conventional daily dosage or in intravenous pulse form, usually in combination with additional immunosuppressants. A recent systematic review included 11 studies with a total of 404 participants. Although it found some interventions to be superior for certain outcomes, it was unable to conclude which treatments are superior overall.[29] Strowd *et al.*[30] proposed a therapeutic ladder for treating pemphigus, where they treated patients initially with a combination of oral prednisolone and mycophenolate mofetil. Cyclophosphamide, intravenous immunoglobulins (IVIg) or rituximab were used in cases of treatment failure. Fourteen of the 18 patients in this study were able to achieve complete disease control with a combination of prednisolone and mycophenolate mofetil, while another two required rituximab for

disease control. The remaining two patients not responding to conventional therapy refused treatment with rituximab due to the high cost of therapy. Nearly 90% of the patients achieved complete clearance in an average of 4.5 months.

High-dose IVIg is a refreshing approach in treating recalcitrant pemphigus because it works by selectively and rapidly decreasing the circulating levels of pathogenic antibodies by more than half within 1–2 weeks of initiation of treatment. The decrease is selective because total concentrations of IgG increase rather than decrease.[31] Administered at a dose of 2 g/kg bodyweight over 3–5 days every 4 weeks, it results in clinical improvement within days of its initiation.[32] The effectiveness of IVIg improves with the concomitant administration of cyclophosphamide or azathioprine.[33] Ahmed and Dahl[34] recently published a consensus statement on its use in the treatment of autoimmune mucocutaneous blistering diseases. Another promising modality is rituximab, which is an anti-CD20 humanized monoclonal antibody, leading to transitory B-cell depletion and was originally developed for the treatment of non-Hodgkin's lymphoma. In ABD, it has been used at a dose of 375 mg/m^2 weekly for 4 weeks.[35,36] In most patients, resistant lesions cleared within 1–4 months. Response was associated with reduction in serum anti-epithelial antibodies. Patients on rituximab should be closely monitored for infectious complications and infusion-related symptoms. Rituximab may be a valuable treatment for refractory pemphigus but warrants further studies to evaluate the risk–benefit ratio of its use. Both IVIg and rituximab are expensive treatment options and should be applied to patients who are refractory to conventional treatment regimens or to those who have contraindications for the administration of steroids. Etanercept, a TNF-α antagonist, has also shown encouraging results in the treatment of pemphigus.[37] Iraji *et al.*[38] found pimecrolimus 1% cream to be an effective adjuvant to steroids and azathioprine in the treatment of PV. Businq *et al.*[39] found systemic tacrolimus to be effective in the treatment of recalcitrant PV in two patients. Daphentin, a novel antimalarial agent, has also shown promising initial results.[40] Successful treatment of severe refractory PV with allogenic hematopoietic stem cell transplantation following non-ablative conditioning regimen has been reported.[41]

Other novel approaches to the treatment of pemphigus that are currently under investigation include the intravenous administration of high-dose Dsg 3 peptides in order to induce high-dose tolerance and the selective blockage of the acantholytic activity of pemphigus antibodies with cholinergic agonists such as pyridostigmine bromide.[42] Because apoptosis sensitizes the cells to the acantholytic effects of PV-IgG, the blockade of the caspase pathway could prevent the blistering in pemphigus. Pacheco-Tovar *et al.*[43] studied the effects of caspase inhibitor Ac-DEVD-CMK in BALB/c mice where pemphigus had been induced experimentally and found the caspase inhibitor to block apoptosis and prevent blistering. It has also been studied that hyperadhesion of desmosomes makes them more resistant to acantholysis in experimental PV. Cirillo *et al.*[44] pharmacologically induced the hyperadhesive state with the PKC inhibitor Go6976 and found it to reduce both the acantholysis rate and the processing of cell adhesion molecules induced by PV serum. This offers a promising new frontier to counter the effect of autoantibodies in PV.

Newer modalities of therapy in bullous pemphigoid and epidermolysis bullosa acquisita include IVIg, rituximab and daclizumab.

CONCLUSIONS

The effective management of ABD requires knowledge of the pathophysiology of the disease process, accurate diagnosis, knowledge of the pharmacologic effects of the agents used and understanding of patient expectations. Although the use of corticosteroids and other immunosuppressive agents has decreased the mortality risk in pemphigus to less than 5%, their use is associated with significant long-term adverse events and prolonged morbidity. With the advent of newer therapies like rituximab and IVIg, it is hoped that both mortality and morbidity due to ABD will fall further along with an improvement in patient's quality of life. However, these are costly therapies and long-term studies are still awaited to observe their side-effect profile.

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