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REVIEW ARTICLE

Review of autoimmune blistering diseases: the Pemphigoid diseases

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Abstract

Autoimmune Blistering Diseases of the Pemphigoid type is characterised by sub-epidermal blisters (SEB) with circulating autoantibodies against components of the basement membrane zone (BMZ). The main disorders to date include bullous pemphigoid (BP), pemphigoid gestationis, mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), linear IgA disease (LABD), dermatitis herpetiformis (DH), lichen planus pemphigoides and bullous lupus. This is in contrast to pemphigus and related disorders, which demonstrate intraepidermal acantholysis and a positive Nikolsky sign. The classification and management is based on clinical, histological and direct and indirect immunofluorescence findings. There are, however, overlapping clinical and histological features between the conditions and clinical heterogeneity within each disease.

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Autoimmune Blistering Diseases (AIBD) of the Pemphigoid type are characterised by sub-epidermal blisters (SEB) with circulating autoantibodies against components of the basement membrane zone (BMZ). This is in contrast to pemphigus and related disorders, which demonstrate intraepidermal acantholysis and antibodies against desmosomal components.[1] The classification and management is based on clinical, histological and immunofluorescence findings, though often features overlap between the conditions.

The diagnosis is confirmed with biopsies of lesional skin (eg. Edge of a blister) in 4% formaldehyde (10% formalin) which is stained with haematoxylin-eosin; direct immunofluorescence (DIF) on normal appearing skin at least 1 cm away from the blister (ie. 'Perilesional'), which is transported in Michel's medium or a fresh specimen on normal saline soaked gauze or snap frozen in liquid nitrogen.[2]

Indirect immunofluorescence (IIF) of serum on monkey oesophagus is not always sensitive for some of the pemphigoid diseases and often not detectable. When performed on salt-split human skin, it is more sensitive for the pemphigoid diseases and can be used to distinguish between roof and floor binding of autoantibodies. Enzyme linked immunosorbent assay (ELISA) is more sensitive and can provide a titer for the antibodies. Western immunoblotting is only available in a research setting and other diagnostic tests are available at specialist centres.

Salt split skin is a process where the perilesional skin specimen is incubated in 1M NaCl at 4 degrees Celsius for 24 h to produce a split through the lamina lucida.[3,4] Dermal staining (floor pattern) alone is seen in EBA, bullous lupus, antip200 pemphigoid and a variant of MMP in which autoantibodies target laminin332. Though BP usually has epidermal staining (roof pattern), a small percentage will show both epidermal and dermal staining.[3] Autoantibodies to BP180, BP230 and alpha 6 beta 4 integrin appear on the roof but laminin 332, p200, laminin gamma1 and type VII collagen antibodies appear on the floor.[2]

Autoimmune Blistering Diseases are often treated with systemic corticosteroids initially followed by steroid sparing agents. Patients are assessed for co-morbidities such as diabetes, osteoporosis, peptic ulcer disease and active or latent infections before commencing therapy. Pre-treatment screening tests include IgA levels, G6PD, TPMT, hepatitis B, C and HIV serology and tuberculosis testing (purified protein derivative or

QuantiFERON-Gold tests, and chest x-ray). Treatment depends on the severity, predominant cellular inflammatory infiltrate, impairment on QoL, complications of disease and therapy.

Autoimmune Blistering Diseases occurring in children can usually be managed with topical steroids with a good prognosis. Long term monitoring is recommended given the potential risk of relapse.[5]

With the advent of validated scoring systems, it is possible to objectively and subjectively monitor patients' progress and conduct clinical trials with newer therapeutic agents.[6–9]

Bullous pemphigoid

Bullous pemphigoid is the most common AIBD, accounting for two-thirds of all subepidermal blistering diseases,[10] with a yearly incidence ranging from 2.5 to 42.8/million.[11] In Germany the prevalence of BP was reported as 259 per million population.[12,13] The increased incidence of BP overtime[10] may be attributable to an ageing population, increase in the number of neurological diseases and use of triggering medications. BP is typically a disease of the elderly, with the highest incidence after the age of 90, and a mean presentation between 66 and 83 years.[12] The annual incidence of BP in a population over 85 has been reported as high as 507/million.[10] The risk of developing BP in a 90 yo is 297 times higher than a 60 yo.[14] BP affects women more than men, but this is reversed in patients older than 80.

The hemidesmosomal antigens BP 230 (BP Antigen 1) and BP180 (BP antigen 2 or collagen XVII) are the main targets in BP.[15] Autoimmunity and loss of tolerance results in IgGs targeting the non collagenous region (NC16A) of the BP 180 ectodomain.[16] Pro-Inflammatory cytokines such as IL-17 and the related cytokines including IL-13 and IL-22 play a role in the recruitment of neutrophil and eosinophils,[16,17] with elevated levels correlating with relapse of disease. Other parts of the cellular immune system such as mast cells, complement, neutrophils, macrophages, T cells, and eosinophils are thought to be involved in the pathophysiology.[18] The majority of cases are not associated with an identifiable trigger.[10] Drugs reported to trigger BP include diuretics (eg. captopril, frusemide and spironolactone), anticonvulsants, psychotropics and analgesics[10,19] and more recently, gliptins.[20] Dipeptidyl-peptidase IV inhibitors are antihyperglycaemic agents introduced to treat type 2 diabetes mellitus since 2006. Though the entire class increases the risk of BP by two-fold, vildagliptin is implicated more than the others with an increased risk of developing BP by up to 10 fold.[12] Gliptin induced BP generally does not affect the NC16A domain of BP180 resulting in a non- inflammatory presentation.[21] BP has been reported to be induced by immune checkpoint inhibitors such as cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitors (eg. Ipilimumab) and anti-PD-1/PD-L1 agents (eg. nivolumab, pembrolizumab).[12]

Drug induced BP occurs in a younger population and is less likely to recur [22] compared to BP not caused by medications. UV light, radiation and infections such as human herpes virus have been reported to induce BP.

The heterogeneity of clinical presentation of BP can result in a delay in diagnosis. Antibodies that target BP 180 at the NC16A domain result in inflammatory BP but non-NC16A targets result in a non inflammatory presentation, where there is an absence of urticaria and erythema.[23] The BP230 subtype of BP, where the BP 230 is the only autoantigen targeted, typically presents with milder disease than the classic BP.[24] Classically, patients have weeks to months of pruritus, urticaria or eczema followed by symmetric tense bullae on urticated, erythematous or normal skin on the trunk, inner thigh and flexures. Atypical presentations include an absence of blisters in up to 20% of cases, chronic itch with urticaria or eczematous eruptions, prurigo nodules and excoriations (Figs. 1, 2).[25]

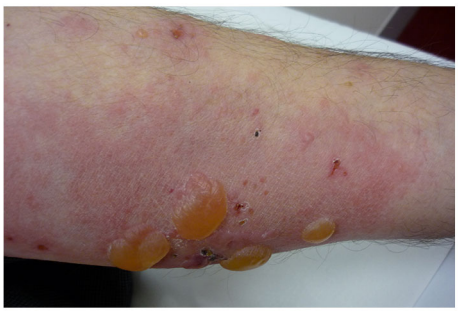

Figure 1 Large tense bullae in a background of urticarial lesions.

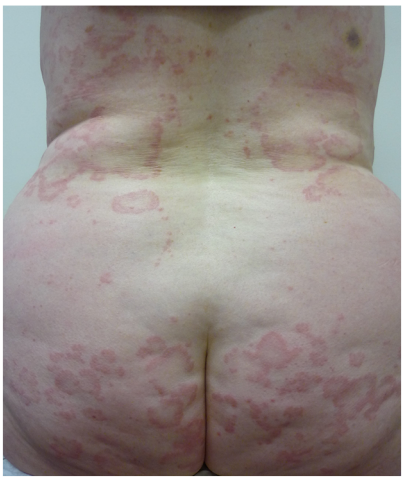

Figure 2 Bullous Pemphigoid may also appear as annular or urticarial plaques with central regression.

There are multiple variants of BP such as a localized form which affects the lower limbs; pemphigoid nodularis characterized by pruritic nodules; lichen planus pemphigoides which occurs in the context of lichen planus; acral BP; and a juvenile form.

Childhood BP affects patients less than 18 yo with similar histological and immunological findings as the adult type. It is thought to be triggered after routine vaccinations, albeit very rare.[26,27] Clinically, genital involvement is more common in children older than 1 yo, whilst infants less than 1 yo are more likely to develop acral blistering, especially of the face, palms and soles.[28] Childhood BP responds rapidly to systemic steroids with low relapse rates and good prognosis (Figs. 3, 4).[28] Neonatal BP has rarely presented in a mother with herpes gestationes or BP[29,30] but it self resolves.

Though a diagnosis of BP is made with a combination of clinical features, direct and indirect immunofluorescence on salt split skin, histopathology is usually performed to confirm BP and exclude differential diagnoses. Clinical features supporting a diagnosis of BP include age > 70; absence of blistering on the head and neck; absence of mucosal involvement; and absence of atrophic scars.[25,31] Mucosae, in particular the oral mucosa, are involved in 10–20% of cases.[2] Histopathology from the edge of the blister demonstrates a SEB with eosinophils and/or neutrophils with dermal infiltrate of eosinophils. Perilesional skin shows linear IgG +/−C3 along the BMZ on DIF, while IIF shows IgG autoantibodies against the BMZ. IIF on human split skin is more sensitive than IIF on monkey or rabbit oesophagus.[2] ELISA is not commonly available or performed in clinical practice but will show IgG autoantibodies against BP180 +/− BP230.[25] Peripheral eosinophilia is also noted.

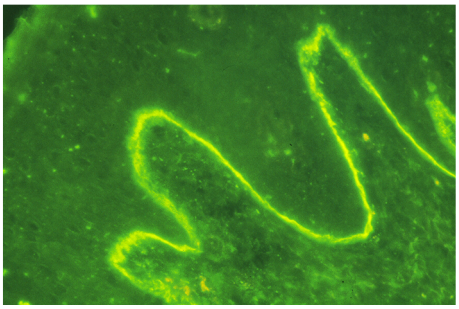

Figure 3 Linear IgG staining in Bullous pemphigoid.

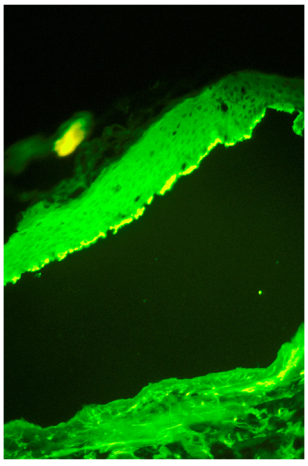

Figure 4 Roof staining in Bullous pemphigoid.

Some of the proposed associations with BP may be confounded by age. The association with malignancies is controversial with some suggesting no evidence of an association[32,33] whilst recent case series reporting a possible association with haematological malignancies.[34] The current guidelines do not recommend a routine malignancy screen for patients diagnosed with BP.[2] Cross reactivity between BP 180 and BP230 isoforms in the skin and brain may be responsible for an increased incidence of neurological disorders such as stroke, Parkinson's disease, multiple sclerosis (MS), epilepsy and dementia with BP.[35,36] Patients are 5 times as likely to have or develop neurological disorders compared to controls, and in the majority of cases this precedes the diagnosis of BP, usually by about 5.5 years.[37] MS is 12 times more likely in BP than controls. In general, neurological disorders occur 4 times more often in BP compared to other AIBD.[37] BP can co-exist with other dermatoses such as psoriasis and lichen planus.[35]

Bullous pemphigoid is associated with a prothrombotic state with a 15 fold risk of venothromboembolism in the acute phase, compared to 1.5 fold during remission.[38,39] The risk is proportional to severity of the underlying disease, with steroids contributing to the reduction of risk. Current guidelines do not routinely recommend prophylactic anticoagulation.[25]

The mortality risk is highest within the first year of diagnosis with figures from European reports ranging between 29 to 41%.[40] The reported mortality in the USA is significantly less, albeit 5 to 11% [41,42] with the majority of deaths secondary to pre-existing comorbidities, sepsis and diseases in the elderly rather than BP itself. The mortality is 2 to 6 times that of age and sex matched controls.[10,11,43] Singapore reports a 1 year mortality of 27% and a 3 year mortality of almost 50%, resulting primarily from infections especially pneumonia followed by cardiovascular disease and stroke.[44] Risk factors for increased mortality are elderly age, poor general health (as measured by a low Karnofsky score), female gender, high systemic corticosteroids (greater than 37.5 mg/d at discharge), hypoalbuminaemia and elevated erythrocyte sedimentation rate (ESR).[45–47] There are no clinical or histological features which predict the clinical course or prognosis.[48]

The safest first line treatment of localized disease is superpotent TCS (clobetasol dipropionate 0.05%), applied twice daily to the entire body, except the face, with tapering after achieving disease control. A total of 30–40 g should be used per day.[25] Second line agents include systemic steroids, tetracycline, nicotinamide and dapsone.

Superpotent TCS are just as effective as systemic steroids in generalized disease[40] with less mortality in severe BP. In clinical practice, topical applications are limited by the inconvenience of having to apply the cream all over the body twice a day and cost; in Australia, superpotent topical corticosteroids are not funded under the PBS and hence the cost is prohibitive. Overseas, larger amounts are funded when needed and there is a cost saving in terms of co-morbidity prevention.

There is no difference in efficacy between low dose (0.75 mg/kg/d) and high dose (1.25 mg/kg/d) oral prednisolone.[49] Steroid sparing agents include azathioprine, mycophenolate mofetil, MTX (15 mg/week), dapsone and combination tetracyclines (500 mg 4 times/day) with nicotinamide (500 mg 3 times/day). An RCT did not find any difference in efficacy or cumulative steroid dose between AZA or MMF, but reported less liver toxicity in the MMF group.[50] In recalcitrant disease IVIg, cyclosphosphamide, plasmapheresis, rituximab and omalizumab have been reported. An RCT of methotrexate versus topical steroid therapy for BP has been completed in France and results are eagerly awaited.[51]

A relapse or flare, which occurs when 3 or more new lesions occur in a month, is treated by increasing the frequency of application of TCS or the dose of medication to the level that controlled the disease before the relapse.[25,52] High anti-BP 180 titre on ELISA and positive DIF are associated with a higher risk of relapse. It's recommended that at least one of these tests be performed before treatment cessation.[53]

In contrast to PV, lower dosages of steroids are used in managing BP. Prednisolone is commenced at 0.75 mg/kg/day and tapered as the disease responds.[52] Tapering of prednisolone occurs at the "end of consolidation phase", which is defined as the "time at which no new lesions or pruritic symptoms have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions has healed".[52]

BP is considered a self-limiting disease, usually remitting within 5 years.[54,55]

Epidermolysis Bullosa Acquisita (EBA)

Epidermolysis bullosa acquisita is characterized by IgG autoantibodies against type VII collagen which is a major component of anchoring fibrils in the BMZ. It is a rare disease affecting about 0.2/million.[3] It can occur at any age though there is a bimodal peak in the 2nd and 7th decade.[56]

There are two major types of EBA, namely, the inflammatory (non mechanobullous) type and the more common mechanobullous (non-inflammatory) type. Inflammatory EBA can resemble BP, MMP, Brunsting-Perry pemphigoid and linear IgA dermatosis.[3,57,58]

A recent consensus on clinical features and diagnostic criteria developed by international experts highlights the complexity of this disease.[57]

Clinical features can resemble porphyria, bullous lupus and dystrophic epidermolysis bullosa- a genodermatosis with absent or reduced levels of functioning collagen VII. Cutaneous features of EBA include blisters, erosions, skin fragility, milia, atrophic scars, scarring alopecia and nail dystrophy.[3,59] EBA can affect the oesophagus presenting with dysphagia, odynophagia and heartburn and evidence of erosions and strictures on endoscopy.[60] Non inflammatory EBA is more commonly associated with mucosal involvement with stenosis and scarring.[61]

Chen *et al*. describes 5 main clinical presentations of EBA[3] which may co-exist within the same patient.

1 Classic presentation: mechanobullous lesions with skin fragility, haemorrhagic tense bullae which heal with milia and scars. Sites most often affected are those susceptible to trauma, such as the hands, elbows, knees and feet. Intraoral, scalp and nails are often affected.
2 BP like EBA: pruritus and tense bullae on erythematous or urticarial skin. There is a notable absence of skin fragility, scar and milia.
3 MMP like EBA: mucosal involvement predominate
4 Brunsting Perry presentation: localized to the head and neck
5 IgA bullous dermatosis like presentation

The most recent consensus considers BP-like EBA as the inflammatory form, though mucous membrane EBA and IgA EBA can be inflammatory. Brunsting-Perry like EBA, however, is typically considered a non-inflammatory form.[57] To distinguish between IgA mediated EBA and LABD, IIF, SSS or immunoelectron microscopy is required.[62,63] Mucous membrane EBA (MM-EBA) can be severe, requiring aggressive management.[57]

The histological findings of EBA vary with the clinical presentation. Though a subepidermal cleft is key, the degree of dermal infiltrate varies. Often there is little infiltrate in the classic mechanobullous presentation, but a prominent neutrophilic of mixed infiltrate in inflammatory EBA. Fibrosis, scarring, milia and interface damage can also occur.[57]

Though BP can resemble EBA clinically and histologically, there are some differences. In EBA, DIF typically reveals linear IgG along the BMZ, though IgA and IgM also occur. SSS is used to distinguish EBA from BP. The former has antibodies on the dermal side, whilst the latter on the epidermal side. Another feature of the DIF that distinguishes EBA from BP is the pattern. BP shows n-serrated deposits of IgG and/or C3 but EBA is u-serrated.[25] More specific laboratory investigations can be used to distinguish EBA from the other differential diagnoses. These include electron microscopy, ELISA for type VII collagen, FOAM (fluorescent overlay antigen mapping analysis), direct immunoelectron microscopy and collagen IV immunomapping

which determines the split and location of the autoantibodies with relation to the lamina densa.[63] Cost and availability of these tests limits their use.

EBA is associated with other diseases including IBD, haematological malignancies, systemic lupus erythematosus (SLE), rheumatoid arthritis, amyloidosis, thyroid disease and other autoimmune diseases.[3] IBD symptoms typically occur before or at the same time as EBA blistering.

There are currently no RCTs in EBA so good evidence on effective therapy is lacking. Treatment is often difficult and contrary to other AIBD, EBA is not steroid responsive and often refractory to many systemic agents. General measures include trauma avoidance, sun-protection and dressings. Colchicine and dapsone can be used for their anti-neutrophilic benefit.[3,64] Efficacy has been noticed with regular IVIg, high dose cyclosporine (>6 mg/kg), azathioprine, rituximab and photopheresis.[3] Antibodies to collagen VII correlate with EBA activity and can be used to monitor improvement.[63]

Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) (also referred to as cicatricial pemphigoid) is a life-threatening scarring subepidermal blistering disease with mucosal predominance with or without cutaneous involvement. MMP can affect one or multiple sites – ocular (70% of cases), oral (desquamative gingivitis in up to 65%), nasopharyngeal, laryngeal (eg. Dyspnea, dysphonia and hoarseness), oesophageal (eg. Oesophageal strictures in up to 26%) and genital involvement resulting in significant morbidity.[65,66] Ocular involvement must be detected and treated promptly to prevent significant morbidity. Ocular complications include chronic cicatrizing conjunctivitis, symblepharon, ankyloblepharon, entropion, trichiasis, glaucoma, erosions and scarring resulting in blindness.[67,68] More than 50% will have visual loss and only 35% maintain enough visual acuity to read.[69,70] Nasal involvement in up to a third of cases include epistaxis, discharge, nasal stenosis, rhinitis and airway obstruction.[61]

Disease limited to the oral mucosa alone or oral and skin combined have a favourable and benign prognosis without long term scarring. Involvement of the eyes, larynx, oesophagus, nasopharynx and genitals carry a poorer prognosis.[65]

Histology reveals a SEB with eosinophils or neutrophils. DIF shows linear IgG, IgA or C3 along the BMZ.[65] Autoantibodies target various components of the BMZ such as BP230, BP180, laminin 5, laminin 6, integrin b4 subunit, type VII collagen.[69] One study reports the relative risk of cancer is 6.8 if there are autoantibodies to laminin 332,[71] compared to other alpha-6 or beta-4 integrin autoantibodies which might be protective.[69,72,73] Adenocarcinomas occur amongst patients with anti-laminin 332 pemphigoid.[35]

Important differential diagnoses to consider are pemphigus which has intraepidermal acantholysis and intraepithelial IgG deposition on DIF; oral lichen planus with *fibrinogen* at the BMZ; lupus which demonstrates a *granular* pattern of IgG, IgA, IgM and C3 on DIF at the BMZ; and human herpes virus which has positive serology or PCR on swabs.[65] MMP can mimic lichen planus clinically with reticular and atrophic patterns and histologically with interface dermatitis. DIF is essential in distinguishing these disease.[74]

The Brunsting Perry variant is characterized by bullae on the head and neck with mild or no mucosal involvement. Scalp involvement leads to scarring alopecia.[75]

The rarity of disease, paucity of RCTs, clinical heterogeneity and system-specific staging systems have made the classification of MMP difficult. The key is to prevent misdiagnosis or delay in making the diagnosis, followed by aggressive therapy in a MDT setting to prevent irreversible scarring. A review of systems ideally flags affected organs prompting referral for specialist management. All patients should be assessed by an ophthalmologist and otolaryngologist at diagnosis. A consensus recommended that in high risk patients, defined as ocular, genital, nasopharyngeal, oesophageal and laryngeal involvement, a combination of prednisolone (1–1.5 mg/kg/s) with cyclophosphamide (1–2 mg/kg/d) or azathioprine (1–2 mg/kg/d) be used until disease control is attained. Cyclophosphamide is preferred over azathioprine because of its faster onset. Mild disease is treated with dapsone (50–200 mg/d) for 12 weeks, and if not controlled with dapsone, prednisolone and cyclophosphamide is commenced.[65] Disease limited to the oral mucosa is classified as "low risk" and can be managed with TCS, intralesional triamcinolone, nicotinamide (2–3 g/d), tetracyclines (1–2 g/d) or dapsone (125–150 mg/d).[65,76] Prednisolone, azathioprine and MMF can be added in later. Ocular MMP responds rapidly to rituximab, though additional cycles may be required.[67] Mild ocular involvement is treated with topical preservative free eye lubricants and dapsone, with systemic steroids, cyclophosphamide, azathioprine, IVIg and rituximab for recalcitrant cases.[77]

Linear IgA disease and chronic bullous dermatosis of childhood

LABD is a rare AIBD which can occur in children or adults. It can be associated with medications, infections and malignancies. The form affecting children is known as chronic bullous dermatosis of childhood usually affecting children aged between 6 months and 6 years of age and is more likely to resolve spontaneously.[78,79] It is associated with HLA B8, Cw7, DR2 or DR3.[78]

Drug induced LABD has similar clinical and histological features to the idiopathic form though there is some evidence the drug induced form is more likely to resemble toxic epidermal necrolysis with positive Nikolsky sign and larger erosions.[80] There is an absence of circulating anti-BMZ IgA antibodies. Common causative drugs include vancomycin, captopril, phenytoin, amiodarone, antibiotics and NSAIDs.[80] Clinical and histological

features of drug induced LABD rapidly resolve upon drug cessation.[78] Diseases associated with LABD include non-Hodgkin's lymphoma, CLL, bladder cancer, ulcerative colitis and SLE.[78]

Adult LABD usually occurs after the age of 60 yo and can be polymorphic with erosions, excoriations and prurigo nodules. The most common cutaneous manifestations include tense or haemorrhagic bullae sometimes on an urticated base. Bullae can form in an annular pattern and develop in rings around old bullae. These are referred to as "cluster of jewels" or "string of pearls". In children, the anogenitals, perineum, abdomen, hands and feet are typically affected. The extensor surfaces, buttocks and perioral areas are affected in adults.[78]

Mucosa are affected in up to 80% of cases with nasopharyngeal and laryngeal predominance. Cheilitis, gingivitis and pain is described.[61] Conjunctivitis, symblepharon and fibrosis does occur.[78]

Histologically, LABD has a SEB with a neutrophilic infiltrate and linear IgA staining along the BMZ on DIF. There are also circulating IgA autoantibodies against the BMZ and salt split skin on IIF shows IgA binding to epidermal side.[79]

Despite multiple proposed definitions for making a diagnosis of LABD, there is no clear consensus as the histological and immunopathological features are not specific to LABD. Linear IgA staining along the BMZ occurs in other AIBD, so staining alone or with other immunoglobulins but with an predominant IgA pattern, may not always be the only diagnostic criteria.[79] A consensus on diagnostic criteria will be useful for clinical trials and ascertaining the most effective treatment.

Treatment consists of dapsone, colchicine or prednisolone. LABD typically has a favourable prognosis though there is significant morbidity associated with ocular and nasopharyngeal complications.[81,82] In general, there is no increase in mortality.[78]

In contrast, neonatal LABD often has internal complications and has a high mortality. Thus far no cases with maternal involvement of LABD have been reported. Childhood LABD, on the other hand, is quite common and usually responds well to treatment.

Dermatitis Herpetiformis (DH)

Dermatitis herpetiformis is a manifestation of Coeliac disease (CD) with a slight male preponderance that can occur at any age, though it is becoming more common to be diagnosed after the age of 35.[83] It is not as common as CD and the incidence is decreasing compared to CD.[84]

Dermatitis herpetiformis is characterized by a symmetric extremely pruritic polymorphic papulovesicular eruption, typically involving the extensors (knees, elbows), buttocks and upper back, which heal with dyspigmentation.[85] Lesions on the toes and fingers are often purpuric. Additional clinical features include signs of malabsorption, nutritional deficiency and growth impairment in children. Clinical differential diagnoses include eczema, psoriasis, LP, scabies, EED, prurigo, papular urticaria.

Histopathological changes include a SEB with a predominant neutrophilic infiltrate, though eosinophils can occur. DIF shows granular IgA deposition along the DEJ or at the tips of dermal papillae. Given the histopathological similarities with other AIBD, such as LABD, perilesional DIF is essential to make the diagnosis as it is specific and sensitive for DH.[86] However, a false negative DIF can occur if the specimen is taken from lesional skin or if a patient is on a gluten restricted diet.

Unlike other AIBD, in DH, there are no circulating autoantibodies to components of the skin. Instead, there are IgA autoantibodies to tissue transglutaminase 2 and 3[85] which are also found in Coeliac disease. Total IgA levels are tested to exclude IgA deficient patients. Other autoantibodies in DH are IgA antiendomysium and IgA anti epidermal transglutaminase antibodies.[86]

Dermatitis herpetiformis is considered a cutaneous manifestation of Coeliac disease given the similarities in genetics (HLA DQ2 and DQ8), small bowel histopathological findings and improvement with gluten restriction.[86] The small bowel changes such as intraepithelial lymphocytes and villous atrophy, however, are not as marked as seen in CD.[84] DH is associated with and preceded by other autoimmune diseases such as type 1 diabetes mellitus, vitiligo, autoimmune thyroid disease, alopecia areata, pernicious anaemia and SLE.[84]

Dermatitis herpetiformis should be managed in conjunction with a gastroenterologist and dietician to monitor for features of Coeliac disease and provide gluten free options. Both the cutaneous and intestinal symptoms resolve and recur with gluten restriction and introduction, respectively. It takes longer for DH to respond to gluten restriction compared to CD, often taking months to years.[84] DH is a chronic disease and rarely spontaneously resolves.

It is recommended to perform investigations for complications of disease such as iron deficiency anaemia, b12/folate levels, DEXA for osteoporosis and a dental examination for caries and enamel defects.[85] Ataxia, central and peripheral nervous system diseases and myopathies are potential neurologic sequelae.[85]

Dapsone and colchicine are used first line, often with a rapid response. Importantly, only the cutaneous features (and not the intestinal symptoms) improve with dapsone, usually clearing within 3 days. Dapsone is commenced at 25 to 50 mg/d and increased gradually up to 200 mg/d. sulfasalazine can also be used.[87]

Patients require long term follow up to monitor for lymphomas especially MALT and B cell lymphomas. Non Hodgkin lymphoma and small bowel adenocarcinomas also occur. Treatment of DH and strict gluten free diets prevent lymphoma development.[84,85]

Anti p200/anti-laminin gamma1 pemphigoid

This is a recently recognised disease with autoantibodies against BP 230, 180 and p200 which has probably been diagnosed over the years as BP or EBA. It shares clinical features with BP, with tense blisters, urticarial, eczematous and prurigo changes.[88] However, it affects a younger population, with mucosal involvement in more than half and psoriasis in up to one third.[1,89] Histology reveals a SEB with neutrophilic predominance and linear IgG and C3 along the BMZ on DIF. IIF shows autoantibodies affecting the dermal side of the cleft. Immunoblotting reveals a 200 kDa antigen.[90] Treatments include clobetasol propionate, systemic steroids, and steroid sparing agents like MTX, dapsone.[88]

Pemphigoid gestationis

Pemphigoid gestationis (also referred to as herpes gestationis) occurs in the 2nd and 3rd trimester though can occur at any stage of pregnancy.[91] It affects 1 in 50 000 to 60 000 pregnancies with a mean age at presentation of 30 years of age. Patients demonstrate an increased frequency of HLA DR3, DR4,and HLA-B8.[92] Multigravidae pregnancies are associated with an earlier onset of PG compared to primigravidae (21 weeks compared with 31 weeks, respectively) and a longer time to remission.[91] Almost half the cases of PG occur in primigravids. There is no clear evidence that a change in partner will reduce the risk of PG in subsequent pregnancies.[93] PG can also occur in conditions other than pregnancy such as hydatiform mole, trophoblastic tumours and choriocarcinoma.[92,93]

Clinically similar to BP, patients develop pruritic erythema which develop urticarial papules and plaques, progressing into papulovesicles and tense bullae. Sites commonly involved include the umbilicus (87%), abdomen, trunk, legs and arms.[91,93] The mucosae are uncommonly affected.

Because of the increased rates of HLA DR3 and DR4 compared with the normal population, associations with autoimmune diseases in particular Graves' disease, Hashimoto thyroiditis, SLE, pernicious anaemia, vitiligo, alopecia areata and ulcerative colitis are common and investigated for.[94,95] The risk of Graves' disease is 20 times that of the normal population.[93]

Histologic features correlate with clinical morphology. Urticarial plaques have perivascular lymphohistiocytic infiltration with dermal oedema, eosinophilic infiltrate and spongiosis. Tense blisters demonstrate a SEB with an eosinophilic infiltrate and spongiosis.[92] DIF shows linear C3 +/− IgG along the BMZ. The majority of patients have circulating IgG autoantibodies against the BMZ on IIF. Salt split skin shows staining in a roof (epidermal side) pattern. BP180 is the major target autoantigen on ELISA and immunoblotting, though BP230 is occasionally involved. BP180 is found in both skin and placenta. Peripheral eosinophilia can also be used to correlate disease activity.[92]

Treatment consists of antihistamines (eg. Chlorpheniramine), category A TCS and if severe, oral prednisolone (0.5–1 mg/kg/d) in consultation with an obstetrician. Other reported therapies include cyclosporin, plasmapheresis, interferon- gamma and IVIg.[91]

Because of placental transfer of autoantibodies, neonatal PG occur in 2.8%–15% presenting with urticarial plaques or vesicles that typically spontaneously resolve within a month.[92,93,96] Potential complications of PG include spontaneous abortions in 16%, ectopic pregnancies, preterm delivery, stillbirth and small for gestational age.[92,93,97]

PG spontaneously resolves after pregnancy, though an immediate postpartum flare is not uncommon. Post-partum, the blisters and urticarial plaques take on average 4 and 14 weeks to resolve, respectively, without scarring.[92] PG recurs at an earlier stage in subsequent pregnancies and can recur with menstruation and OCP use in 25% of cases, though smaller studies have suggested up to 50% with OCP use.[92,93,98] PG has been reported to skip subsequent pregnancies in about 8%.[93]

Lichen planus pemphigoides (LPP)

Lichen planus pemphigoides resembles BP but occurs in the context of lichen planus (LP), affecting the extremities and a younger age group.[1] Bullae typically occur with LP lesions, though not always on the LP lesions. Mucosal involvement occur but nail involvement is rare. Palmoplantar is seen more in children.[99] Though usually idiopathic, medications (eg. ACE inhibitors) and malignancies have also been reported, though it is unknown whether a true association or causality exists.

Quality of life (QoL) measures in AIBD

Objective and subjective measures are useful in tailoring response and intensity of treatment. Disease activity scoring systems, such as the BP Disease Area Index (BPDAI) or the Mucous Membrane Pemphigoid Disease Area Index (MMPDAI) are tools for clinicians and researchers to objectively document the disease activity and damage (Post inflammatory hyperpigmentation and scarring) which in turn facilitates treatment planning and applications for expensive and novel therapies. Objective scoring systems for the EBA and LABD are currently being developed.[100]

Mucocutaneous disease has significant impacts on the QoL of patients which may not be reflected on disease activity scoring systems. The autoimmune bullous disease QoL (ABQOL) and treatment of autoimmune bullous disease QoL (TABQOL) are validated tools which identify the impact the disease has on the patient's daily activities, work and relationships as well as the cost of medication, burden of taking the medication and anxiety about the underlying disease.[8,9]

Outcome measures and disease severity scoring systems are useful tools to gauge baseline severity and monitor response to treatment. Education and patient support groups such as the

Australasian Blistering Diseases Foundation, are essential for patients with rare diseases to meet, share stories and seek counselling. The AIBD registry is a national database collecting epidemiologic and patient data to facilitate research in Australia.[101]

Guidelines for AIBD

Because of the rarity of AIBD, there is a paucity of RCTs assessing the efficacy of treatments. Differing inclusion criteria for studies and definitions of disease make comparison between the studies difficult. As a result, there has been a need to provide clear definitions of disease and management with international international consensus guidelines for the various AIBD. The international consensus guidelines for BP was published in 2012 and for MMP in 2015. Further guidelines and definitions of disease are required for EBA, LABD and pemphigoid gestationis.

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