Autoimmune blistering diseases

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Autoimmune blistering diseases are common, also in the tropical context; these are diseases in which the patient’s immune system attacks its own antigenic determinants.

The blisters can be divided in intra-epidermal and sub-epidermal blisters. Disruption above the basement membrane results in *flaccid* bullae (sometimes no bullae are seen and there are mostly erosions).

Disruption *at* the basement membrane results in *tense* bullae. To determine the level of blistering in the skin the Nikolsky sign can be used. When the blister is intra-epidermal Nikolsky 1 and 2 may be positive. For a positive Nikolsky 2 the blister should not be too fragile.

*Figure 1. NIKOLSKY 1* is positive when slight rubbing of the skin results in exfoliation of the skin's outermost layer.

*Figure 2. NIKOLSKY 2 (ASBOE-HANSEN SIGN)* is positive when downward pressure is applied to a blister and it will extend laterally.
The diagnosis of the different blistering diseases can be made based on the clinical picture together with the Nikolsky sign. When available histopathology is useful to determine the level of the blister together with other characteristics. Sophisticated immunohistopathology is needed to demonstrate antibodies in the epidermis of patients (direct immunofluorescence): antibodies from the serum may react with epidermal cells (indirect immunofluorescence). Antibodies can also be demonstrated using an ELISA technique or Western blot. This paper will only focus on the clinical picture and treatment of the most common autoimmune blistering diseases since (immuno)histopathology will not be available most of the time.

**INTRAEPIDERMAL BLISTERS**

Pemphigus vulgaris constitutes the majority of the intra-epidermal bullous diseases in most parts of the world: up to 70-80%. However, it is reported that pemphigus foliaceus constitutes the majority of the cases in some areas, e.g. Mali, Libya, rural Tunisia, the Kilimanjaro region of Tanzania, Colombia and areas in Brazil, notably Acre (Fogo Selvagem).

**Pemphigus vulgaris**

**Clinical features:**

In 50-70 per cent of patients the first symptoms are blisters and erosions on the oral and genital mucous membranes. Later the blisters can appear all over the body. Nikolsky 1 and 2 are positive. In coloured skin the blisters may be less flaccid because the epidermal intracellular cohesion in coloured skin is greater than in white Caucasian skin. The Nikolsky signs may therefore be more difficult to evoke. PV affects both genders equally and occurs mostly in patients between the fourth and sixth decade. However, any age may be affected including children and neonates. The course of the disease is protracted with remissions and relapses. PV may be exacerbated by UV-light. It may also be induced by drugs, mostly D-penicillamin and captopril. Pregnancy may precipitate or aggravate PV.
Treatment:
This consists of prednisolone, at first in a high dosage of 1-2 mg/kg/bodyweight daily to be tapered down in several months. Pulse treatment approach with megadoses of methylprednisolone or betamethasone has also shown to be effective. Azathioprin 50-150 mg daily can be added. Cyclophosphamide, mycophenolate mofetil and high dose intravenous immunoglobulin are used. The new biological treatments are promising. Treatment is prolonged and should preferably be done in referral centres. PV is often lethal if left untreated, and mortality rates may still be as high as 20 per cent in treated patients, mostly due to severe infections during immunosuppressive treatment.

Pemphigus foliaceus
This disease is relatively common in some areas in Africa, South America and the Middle East. Pemphigus foliaceus is less severe than pemphigus vulgaris. As the blisters are very superficial, they are often not seen. They leave well demarcated crusted erosions. The erosions may be painful and extensive; eventually the patient may become “erythrodermic”. Some remark that the smell is typical. The misdiagnosis of erythrodermic psoriasis may be made. Lesions of PF heal without scarring. In contrast to PV oral lesions are not present. PF affects males and females equally and usually appears in the fourth or fifth decade of life but any age may be affected, including children. The onset of PF is slow or abrupt and its course is protracted but generally benign. UV-light may aggravate or precipitate the disease. PF may also be induced by drugs like rifampicin, drugs with sulfa-groups, D-penicillamin and captopril.

Figure 4. Pemphigus foliaceus
Treatment
This consists of potent topical steroids or prednisolone in a dosage of 20-40mg/day. Azathioprine, cyclophosphamide or methotrexate can be used as additives. Dapsone has also been used successfully. Treatment of the more severe cases should be done in referral centres.

SUBEPIDERMAL BLISTERS
Bullous Pemphigoid
BP is the most common autoimmune blistering disease with a reported incidence of 10 cases per one million population.

Clinical features:
Generally it starts with an itchy non-specific rash which may be urticarial or eczematous. Later, dome shaped tense blisters appear. These do not break easily. The Nikolsky sign is negative. Predilection sites are the inner or anterior thighs, groin, flexor surfaces of the upper extremities and lower abdomen. Any skin area may, however, be involved. Oral lesions are rare and usually transient. Lesions of BP heal usually without scar formation.
BP affects mainly elderly people but can also occur in infants and children. No ethnical or gender predominance is observed. BP may present as a paraneoplastic disease. Some gastric and bladder tumours can express bullous pemphigoid antigens. Drugs like furosemide, sulphasalazine, captopril, penicillins and antipsychotic drugs may induce pemphigoid. It has also been observed after chronic diarrhoea.

Untreated the disease runs a chronic self-limiting course over an average of 3-6 years; however, it may be only months. When extensive, it may be lethal in the elderly patient.

Treatment:
Prednisolone (dosage 60mg/day or even less and can be tapered off to 20-40mg/day reasonably quickly) with or without adjuvant azathioprine or cyclophosphamide. In some patients erythromycin or tetracyclines, with or without nicotinamide, have been shown to be effective, as has methotrexate. Sometimes potent topical steroids can be considered, especially in localized or not too extensive cases. Mortality is often treatment related. But extensive involvement in elderly people is reported to be fatal if untreated in up to 30% of cases.
Chronic benign bullous disease in childhood
This condition is common in Africa and other low-income areas in Asia, but rare in Europe.

Clinical features:
Most of the afflicted are toddlers and pre-school children. The onset is usually acute and the disease may have remissions and exacerbations. Symptoms vary from a mild itch to severe burning. In young children the face and genital areas are often involved.

The lesions are erythematous hyperpigmented papules and plaques, annular or polycyclic, arranged with blistering around the edges. New lesions appear around the old lesions forming the “strings of pearls” sign. Mucosal involvement is common. The disease is often mistaken for a bullous impetigo.

Figure 5. Chronic bullous disease of childhood

Treatment:
Dapsone is the treatment of choice but sulphamethoxypyridine and sulphapyridine can also be used. Success has been claimed for erythromycin and tetracycline with or without nicotinamide, also the newer macrolides have been used. In a few patients steroid, azathioprine or ciclosporin is needed.
Cicatricial pemphigoid
CP is a chronic progressive disease with insidious onset. The prognosis depends on the site of the lesions, number of affected areas, time of establishing the correct diagnosis and efficacy of treatment.

Clinical features:
Blisters and erosions on mucous membranes including the eyes (ocular pemphigoid) oro-pharynx and oesophagus causing scarring. CP affects mainly elderly persons, females more than males. It has also been reported in children. No ethnical or geographic predominance was observed. CP is a rare disease; however, its incidence is not exactly known.

Treatment:
CP is not easy to treat. Patients with mild localized disease may benefit from topical steroids but patients with more extensive disease require systemic therapy with prednisone and/or steroid-sparing agents, such as cyclophosphamide, azathioprine, cyclosporin, mycophenolate mofetil. Dapsone and thalidomide are also used.

Pemphigus gestationes
Clinical features:
This rare and extremely itchy condition, also named herpes gestationes due to the size, the distribution and grouping of the lesions, like in herpes, occurs during pregnancy. It usually starts around the umbilicus with urticarial plaques and wheals, and thereafter involves the rest of the abdomen and body. It usually starts around the 28th week of pregnancy, but may occur at any moment during pregnancy, or even shortly after delivery. It is terribly pruritic. The disease activity abates at the end of term but exacerbations of skin lesions immediately or shortly after delivery are common. HG is a rare disease and can affect any race but is more common in Caucasians.

Treatment:
In general it is self-limiting. The disease is associated with premature delivery and low-birth weight. Patients with mild disease can be treated with antihistamines and midpotency topical steroids. However, these are usually ineffective in more severe cases, and systemic steroids remain the mainstay of therapy.

EPIDERMOLYSIS BULLOSA
In epidermolysis bullosa the blisters are mechanically induced. The inherited forms usually start early in life. They can be divided in epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB) and epidermolysis bullosa dystrophia (EBD). The
differences are based on the specific genetic defect and the resulting weakness and level of the blister formation. Besides the skin, nails, hair and mucous membranes may be involved.

- All forms lead to blisters after trauma, which may heal with atrophic or hypertrophic scarring. Sometimes milia (small epidermal cysts) can be seen. Superinfection is common. In severe cases the electrolyte balance can be disturbed and there is protein loss.
- Management includes: trauma prevention, protein rich diet, wound care, infection prevention and treatment. The acquired form benefits from immunosuppression (steroids, azathioprin). The development of squamous cell carcinoma is feared. Treatment is for specialized centres.

DERMATITIS HERPETIFORMIS
Dermatitis herpetiformis is not uncommon anymore in Africa and South America, due to the introduction of the gluten-rich Western diet (wheat).

Clinical features:
The patient has intensely pruritic lesions and these heal with scar formation. At times only excoriations are seen. At this stage, the disease may be clinically confused with scabies, eczema and insect bites. The typical lesions are herpetiform (grouped) arranged vesicles. The distribution of the lesions is characteristically on the tip of the nose, the extensor sides of the limbs, elbows and knees, the lower back, buttocks, natal cleft and in the nape of the neck and on the shoulders. All patients have gluten-sensitive enteropathy although only 10% have clinical manifestations.

Treatment:
Dapsone or sulphonamides should be given. Some consider dapsone a diagnostic tool. If there is no response, the diagnosis should be doubted. Potent topical steroid treatment may also be of help. A gluten-free diet is very effective if it is kept consistently.