Autoimmune blistering skin diseases

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Abstract

There are many causes of skin blisters (bullae), and an accurate and timely diagnosis affects management and prognosis. The key to the diagnosis of autoimmune blistering diseases lies in the history, clinical findings and skin sampling. By determining the level of blister formation within the skin, appropriate treatment can be started. If systemic vasculitis is suspected, a full systemic screen is vital to determine and treat the underlying disease in order to prevent end-organ damage.

Keywords Autoimmune; basement membrane zone; blister; desmosome; hemidesmosome; immunobullous; immunofluorescence; linear IgA disease; pemphigoid; pemphigus; vasculitis

Key points

- The diagnostic gold standard for autoimmune bullous diseases is the immunofluorescence study, which shows deposition of antibodies (mainly immunoglobulin G (IgG) and IgA)) along the basement membrane zone (subepidermal, e.g. in pemphigoids) or intercellular space (intraepidermal, e.g. in pemphigus)
- Recent evidence has shown that systemic corticosteroids are poorly tolerated by elderly people with bullous pemphigoid, and that tetracyclines are effective and safer alternatives
- Patients with pemphigus may require long-term immunosuppression and systemic corticosteroids. They should be monitored for adverse effects. Rituximab is a promising treatment for recalcitrant pemphigus
- Vasculitis presenting in the skin should prompt further immediate further investigation to detect systemic involvement, which can be life-threatening

Introduction

Autoimmunity arises when an immunologically capable organism recognizes itself or its constituents as foreign and mounts an immune response appropriate for defence, resulting in a breakdown of naturally occurring immunological tolerance.

Blistering skin disorders can be separated into non-acquired (inherited) and acquired, as well as immunologically and non-immunologically mediated, diseases (Table 1). This review focuses on immunologically mediated blistering diseases, in particular blistering disorders classified as autoimmune. These include bullous pemphigoid (BP), dermatitis herpetiformis (DH), pemphigus vulgaris (PV), pemphigus foliaceus (PF), linear immunoglobulin (Ig) A disease (LAD) and pemphigoid gestationis (PG).

We also discuss autoimmune disorders that result in small vessel vasculitis, including diseases such as Henoch–Schönlein purpura, and vasculitides related to cryoglobulinaemia, systemic lupus erythematosus, rheumatoid disease and Sjögren's syndrome. When severe, these small vessel vasculitides also have the ability to cause skin blistering. Discussing vasculitis in its entirety is beyond the scope of this review; instead, the general cutaneous presentation, diagnostic work-up and management approach are considered.

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Acquired autoimmune blistering diseases

These primary blistering disorders carry a significant morbidity and mortality. Blisters or bullae (raised lesions >0.5 cm in diameter filled with clear fluid), are formed by the separation of keratinocytes and can be subcorneal, intraepidermal or subepidermal in origin. There is deposition of autoantibodies at the level of blister formation and at sites adjacent to blisters. These autoantibodies attack the anchoring structures that attach the keratinocytes to each other (desmosomes) and to the basement membrane (hemidesmosomes). This results in separation of these cells from each other or from the underlying dermis, causing a blister. The immunoreactant involved varies with the disease, but is typically immunoglobulin G (IgG) or, less commonly, IgA or C3. Target antigens have been identified and characterized in most diseases, although many involve multiple or overlapping antigens. BP, PG, LAD and DH are characterized by subepidermal bullae or vesicles, whereas PV exhibits flaccid intraepidermal blisters, and PF affects the subcorneal layer.

Diagnosis

The history and examination give vital clues. Diagnosis, prognosis and treatment depend on the epidermal level at which the blister forms (Figure 1). This is determined by skin biopsy and subsequent immunofluorescence (IMF) staining of the skin (direct IMF), in conjunction with serological testing for circulating antibodies (indirect IMF). IMF studies are the gold standard diagnostic tests for immunobullous diseases; their findings can help to define most immunological causes of blistering and patterns that are often diagnostic. Enzyme-linked immunosorbent assay (ELISA) confirms the types of antibody involved in disease pathogenesis and progression.

A skin biopsy should be taken from the *edge* of a fresh blister (<24 hours old) and placed in formalin for haematoxylin and eosin (H&E) histological examination. An older biopsy may show

Please cite this article in press as: Taghipour K, Perera GK, Autoimmune blistering skin diseases, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.04.007

Causes of blistering

Non-immunological causes of blistering

• Genetic	Epidermolysis bullosa — simplex (dominant)
	Epidermolysis bullosa — junctional (recessive)
	Epidermolysis bullosa — dystrophic (dominant and recessive)
	Bullous ichthyosiform erythroderma
• Physical	Heat and/or cold
	Irradiation (e.g. ultraviolet light)
	Contact with hazardous chemicals or irritants
	Friction/rubbing
	Oedema
• Inflammation/infection	Staphylococcal (e.g. bullous impetigo caused by *Staphylococcus aureus*, staphylococcal scalded skin syndrome)
	Streptococcal (including necrotizing fasciitis)
	Herpes simplex
	Herpes zoster
	Varicella
	Hand, foot and mouth disease (coxsackievirus)
	Fungal
	Eczema
	Erythema multiforme (including Stevens—Johnson syndrome)
	Insect bites
• Underlying systemic disease	Carcinoma (paraneoplastic)
	Amyloidosis
	Porphyria cutanea tarda
	Diabetes mellitus
• Immunological causes of blistering	Bullous pemphigoid
	Mucous membrane pemphigoid
	Pemphigus (vulgaris, foliaceus)
	Dermatitis herpetiformis
	Pemphigoid gestationis
	Linear IgA disease
	Epidermolysis bullosa acquisita
	Lupus erythematosus
	Vasculitis
	Bullous lupus erythematosus
	Lichen planus
• Drug reactions	Fixed drug eruptions (e.g. barbiturates, aspirin, paracetamol)
	Photosensitive eruptions (e.g. phenothiazines, naproxen)
	Pemphigus (e.g. penicillamine, angiotensin-converting enzyme inhibitors)
	Toxic epidermal necrolysis (e.g. non-steroidal anti-inflammatory drugs, sulphonamides)

Table 1

only inflammatory debris and re-epithelialization, which obscures the level of the split — a feature vital in diagnosis. Perilesional skin with intact epidermis (approximately 1 cm from a blister) should be supplied for direct IMF and must be frozen immediately at −70°C or placed in a suitable transport medium (e.g. Michel's medium) for later testing. Failure to preserve samples adequately results in rapid degradation and loss of immunoreactants, leading to false-negative results.

Indirect IMF is performed on normal human skin or other substrates depending on the differential diagnosis. Using 1 M saline-split skin (which separates the epidermis from the dermis along the lamina lucida) increases the sensitivity and provides further information about the antibody-binding site. ELISA can detect specific autoantibodies to the immunodominant epitopes in pemphigoid (BP180, BP230) and pemphigus (desmogleins 1 and 3).

Pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune blistering disease in the developed world and usually affects elderly individuals, with an average age of 80 years. The estimated incidence in the UK is 4.3/100,000 persons per year.[1]

BP is characterized by large tense bullae on an erythematous base (Figure 2a), with de-roofed blisters occurring as a result of excoriation or rupture. The bullae usually start on the limbs and spread to the trunk. The mucous membranes are rarely involved

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