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Update on clinical and laboratory diagnosis for bullous diseases

Speaker: Dr. Chan Po-Tak
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Autoimmune bullous diseases are blistering cutaneous diseases due to the development of autoantibody to components of desmosomes (that mediate keratinocyte cell to cell adhesion) or dermoepidermal junction. The majority of the molecular targets of these antibodies, together with their DNA sequences have been identified. By recombinant DNA technology, these molecules have been synthesised in vitro and are employed in research, diagnosis and disease monitoring. The most common autoimmune bullous diseases in Hong Kong are bullous pemphigoid, pemphigus vulgaris and pemphigus foliaceus.

Pemphigus refers to a group of blistering skin diseases secondary to the loss of keratinocyte cell to cell adhesion. The major forms are pemphigus foliaceus, pemphigus vulgaris, IgA pemphigus and paraneoplastic pemphigus. Diagnosis requires clinicopathological correlation and positive direct immunofluorescence (DIF) on skin biopsy. All pemphigus have intercellular staining pattern on DIF. Pemphigus foliaceus and pemphigus vulgaris are the most common forms of pemphigus mediated by antibodies to desmogleins 1 and 3. Desmogleins 1 and 3 are differentially expressed in various layers of the epidermis. In majority of cases, desmoglein compensation hypothesis predicts the disease phenotype based on antibody profile.

Bullous pemphigoid is the most common subepidermal blistering disease. It is characterised clinically by intact blister +/- erosions, histopathologically by subepidermal blister and linear IgG and C3 deposition in the basement membrane zone. The molecular targets are two hemidesmosomal proteins: BP 230 and BP 180. A common technique employed in the diagnosis of bullous disease is DIF of perilesional skin biopsies. This highlights bound immunoreactants on the biopsied specimen by a fluorescent compound conjugated antihuman antibody. By definition, all immunobullous diseases should have a positive DIF; a negative DIF is almost always secondary to errors, such as in tissue sampling or staining. Indirect immunofluorescence test (IIF) is used for estimation of the amount of circulating anti-skin antibody. A rough correlation is found between antibody titre and disease severity in pemphigus vulgaris and foliaceus but not in bullous pemphigoid.

With advances in molecular biology, recombinant proteins can be produced in vitro. Commercial ELISA kits for desmogleins 1 and 3, BP 180 are available for estimation of titre. Such methods have the advantages of being objective, not being

substrate dependent (thus less intra-assay and inter-assay variability), provides a continuous score that reflects the amount of antibody, differentiates the antibody activity between anti-desmoglein 1 and desmoglein 3, and allows testing of a large amount of sample each time. However, the disadvantages of ELISA are that it can only study antibody to one antigen at a time and it is dependent upon the availability of pure antigen.

Learning points:

Bullous pemphigoid, pemphigus vulgaris and pemphigus foliaceus are the three most common forms of autoimmune bullous diseases in Hong Kong and their diagnosis requires clinicopathological correlation. The identification of most antigenic targets of bullous diseases has facilitated the understanding of disease pathophysiology and application in clinical practice in improved diagnosis and management.

Flexural dermatoses

Speaker: Dr. Cheng Tin-Sik
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Many skin ailments have flexural involvement. Some entities involve flexures only, e.g. intertrigo; while others also affect non-flexural sites, e.g. psoriasis. When the skin rash affects flexures only, typical features of the skin disease may be lost, resulting in diagnostic difficulties, e.g. typical silvery scaling is usually not found in inverse psoriasis. Moreover, the clinical picture may sometimes be obscured by maceration and superimposed infection.

Skin tag, also known as acrochordon, is a very common condition affecting the skin flexures. It usually occurs after 30 years of age. Common fungal infections over flexural skin include dermatophytosis and candidiasis. As almost all fungal groin infections are acquired from patients' own feet, their feet should be examined for any involvement and treated accordingly. Central clearing often occurs in tinea cruris while satellite papules or pustule are characteristic of candidiasis. In erythrasma, there is pink fluorescence on Wood's light examination. A distinct, foul smell is a characteristic of group A beta-haemolytic streptococcal intertrigo, an under-recognised cause of intertriginous eruptions in children. For patients with scabies infestation, erythematous papules may be found around axillae.

Some inflammatory dermatitides affect mainly the flexural skin. In atopic dermatitis, after the infantile phase, the typical sites of involvement include the elbow and knee flexures. Seborrhoeic dermatitis may also affect flexural skin. In infantile seborrhoeic dermatitis, salmon-coloured patches with greasy scaling are found in the intertriginous areas and scalp. However, there is no pruritus and the infant remains healthy and asymptomatic. Irritant contact dermatitis occurs more often than the allergic counterpart in flexural site. Common culprits include fragrances, antiperspirants and topical medications.

Psoriasis is sometimes difficult to be differentiated from dermatophytosis or eczema in the flexural area. In flexural psoriasis, lesions are bright red with well demarcated margin. The degree of erythema is even throughout the lesion. However, silvery scaling is not seen in flexural psoriasis. Hidradenitis suppurativa is a chronic suppurative and scarring disease in axillae, groin and perineum. It usually occurs after puberty and has a female preponderance.

Some congenital conditions may affect the flexures. Hailey-Hailey disease involves mainly the flexures, presenting as erythematous patches with erosions, oozing, cracks and fissures. In Darier's disease, brown keratotic papules are found mainly in seborrhoeic areas; however, the flexures may also be involved. Axillary freckling is almost pathognomonic of neurofibromatosis.

Malignant conditions may also affect the flexures. Langerhans' cell histiocytosis can mimic seborrhoeic dermatitis but perifollicular purpura may be found. Extramammary Paget's disease may also involve axillary or anogenital skin. It is important to screen for the presence of any underlying carcinoma in this condition. Symmetric, dark brown, dried skin with velvety surface is found in acanthosis nigricans. When associated with underlying malignant diseases, acanthosis nigricans develops more rapidly and suddenly with oral mucosa involvement and hyperkeratosis of palms and soles. Pseudoacanthosis nigricans, a benign flexural dermatosis, is usually associated with obesity and insulin resistance.

Learning points:

Flexural skin is thin. It is a semi-occluded area and is prone to formation of striae and atrophy. Thus when topical steroid is used in flexural dermatoses, milder agent is usually employed. It is also important to keep the flexures dry and correct any possible exacerbating factors such as infection, excessive sweating and incontinence when dealing with flexural dermatoses.

Cutaneous manifestations of systemic diseases

Speaker: Dr. Hau Ka-Lam
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Skin is sometimes involved in systemic disease. By appreciating cutaneous manifestations of systemic diseases, physicians can better determine the most appropriate management or need for referral to dermatologists. Dermatology has also been a major beneficiary of the advances in cell and molecular biology, immunology, and genetics during the past several decades. Many of the skin diseases we deal with daily are related not only to complex interactions between environmental factors and an individual's genotype, but is also a holistic representation of human body as a whole.

Skin is an effective and readily available indicator of serious diseases. Even an untrained observer should be able to recognise the pale, ashen appearance of a patient in shock, the cyanosis associated with cardiac failure, or jaundice as the first sign of obstructive biliary disease. A complete physician, however, must also be able to detect the more subtle skin signs of life threatening diseases. None of these changes should be overlooked or disregarded, as these are the callings for our intervention. In addition, as clinicians, we know that dermatologic disorders are significant causes of human suffering.

Examples of various cutaneous manifestations of systemic diseases were given. They can be classified as 1) nutritional: protein, vitamins, fatty acids, Fabry disease, lipoid proteinosis; 2) cutaneous mineralisation and ossification, porphyria; 3) heritable disorders of connective tissue with skin changes; 4) heritable diseases with increased sensitivity to cellular injury, basal cell naevus syndrome; 5) neoplastic diseases: Langerhans' cell histiocytosis, cutaneous nonhistiocytoses X, the mastocytosis syndrome, carcinoid; 6) cutaneous manifestations according to system: haematologic, gastrointestinal, hepatobiliary, renal, cardiopulmonary, peripheral vascular, endocrine, neurocutaneous and rheumatological diseases; 7) skin changes and diseases in pregnancy; 8) inflammatory diseases: Behcet's disease, scleredema; 9) paraneoplastic syndromes.

Learning points:

Systemic diseases can present to dermatologist with a variety of skin manifestations. These should be recognised early in order to provide early intervention of serious underlying diseases.