ABC of Dermatology

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AUTOIMMUNITY AND SKIN DISEASE

Hypersensitivity

Circulating immune complexes

Delayed

Autoimmunity is the state where the normal mechanisms of tolerance to self antigens are broken down. Autoantibodies and autoantigen specific T lymphocytes develop.

Autoantibodies may be produced against an organ specific antigen—for example, bullous pemphigoid antigen—or against a very widely distributed antigen such as DNA, as in lupus erythematosus. Not surprisingly, the resulting disease can be organ specific or non-organ specific. The pathogenesis is complex. It is not simply the effect of T lymphocytes locking on to autoantibody coated target cells with subsequent cell death (“cytotoxic” hypersensitivity); damage due to the deposition of circulating immune complexes; or, in some instances, cell mediated (“delayed”) hypersensitivity related to specifically sensitised T cells. Defects in the control of immunological tolerance by T suppressor cells are now thought to be implicated as well.

Autoimmune diseases often run in families. Individuals with certain human leucocyte antigen (HLA) haplotypes are well known to be at risk of developing Hashimoto's thyroiditis or pernicious anaemia, and the same is true for systemic lupus erythematosus and pemphigus.

Receptor
Immunoglobulin
Antigen

The skin reflects the range of autoimmune disease

The skin is often an indicator of internal conditions, and autoimmunity is no exception. Pigmentation accompanies some organ specific disorders, such as Hashimoto's thyroiditis, Addison's disease, and primary biliary cirrhosis. A lemon yellow hue and canities occur with pernicious anaemia, and vitiligo like lesions and alopecia areata may be found in individuals with various autoimmune problems.

Non-organ specific autoimmune diseases often have prominent skin disease—for example, lupus erythematosus, systemic sclerosis, and dermatomyositis—but there are cutaneous organ specific disorders, principally pemphigus and pemphigoid.

Pemphigoid

Split at dermoepidermal junction.

Usually a condition of the elderly with a slight preponderance among women, bullous pemphigoid is characterised by large tense blisters arising on erythematous or normal looking skin. The limbs, trunk, and flexures are commonly affected; mouth lesions occur in 10% of patients. The disease responds readily to modest doses of oral prednisolone, and spontaneous remission is seen in up to a half of subjects, although relapses may occur.

Direct immunofluorescence

Indirect immunofluorescence

Indirect immunofluorescence.

Histologically, the blisters are subepidermal. Most patients have antibodies directed against the basement membrane zone circulating in their blood. These antibodies, usually of the IgG type, may be identified in serum by the *indirect* immunofluorescence method. This uses a tissue substrate (animal or sometimes human skin) cut freshly as a thin section on a slide, on to which the patient's serum is applied; the antibodies which attach to the basement membrane zone are shown by subsequently applying an antihuman immunoglobulin antibody which has been tagged with fluorescein, so that it shows up when the slide is visualised under ultraviolet radiation. The anti-basement membrane zone antibodies can be shown in a patient's perilesional skin by *direct* immunofluorescence. A freshly cut section of skin is reacted with a fluorescein labelled antibody to human IgG, and the deposited IgG can be seen as a continuous band at the basement membrane zone. The anti-BMZ antibodies are directed against bullous pemphigoid antigen, located in the lamina lucida of the basement membrane zone, and synthesised by the basal cells of the epidermis.

Other types of pemphigoid, such as cicatricial (which affects the ocular or oral membranes) or "localised" (often affecting a limited area on the head or neck), show similar histological and immunofluorescence profiles, although circulating anti-basement membrane zone antibodies are less commonly found. The same applies for pemphigoid ("herpes") gestationis, a rare but characteristic bullous eruption of pregnancy.

Pemphigus

Less common than pemphigoid and more likely to prove fatal, pemphigus vulgaris is a disease of middle life. Oral lesions signal the onset in half of the patients and often precede cutaneous disease by months. Fragile superficial blisters develop over the scalp, face, back, chest, and flexures: the bullous element may not be apparent and lesions may consist of crusted erosions. Unlike with pemphigoid, high doses of prednisolone (often with other immunosuppressive agents) are required and spontaneous remission is exceptional.

The blister is intraepidermal. Ninety per cent of patients have circulating autoantibodies, IgG in type, directed against an intercellular substance of the epidermis and identifiable by indirect immunofluorescence. The levels of these antibodies correlate with disease activity, and evidence suggests that the antibodies produce the intraepidermal split. Direct immunofluorescence shows IgG antibodies deposited on the intercellular substance of the suprabasal epidermis in almost all patients. The antigen responsible has not yet been characterised.

Intraepidermal split.

Direct immunofluorescence.

Other variants of pemphigus exist. Pemphigus vegetans gives hypertrophic, papillomatous lesions, whereas pemphigus foliaceus is characterised by shallow erosions on the face and scalp, and pemphigus erythematosus has some features of lupus erythematosus. Pemphigus is sometimes associated with myasthenia gravis, another organ specific autoimmune disease. Treatment with penicillamine can induce pemphigus: the eruption usually resolves when treatment with the drug is stopped.

Alopecia areata and vitiligo

Alopecia areata.

Organ specific autoimmune diseases are more prevalent than expected in patients with both vitiligo and alopecia areata, and afflicted patients have an increased prevalence of organ specific autoantibodies. Despite these associations, however, no direct evidence implicates alopecia areata or vitiligo as an autoimmune disease.

Lupus erythematosus

Clinical variants of lupus erythematosus

Systemic
Subacute cutaneous
Discoid
(Neonatal)

Subacute lupus erythematosus.

Discoid lupus erythematosus.

Discoid lupus erythematosus and systemic lupus erythematosus seem to be variants of the same disease, although only about 5% of those with the discoid type progress to systemic disease. A variety of autoantibodies to nuclear, nucleolar, and cytoplasmic antigens are found in lupus erythematosus. Almost 90% of patients with systemic lupus erythematosus have circulating antinuclear antibodies, but only a third of those with discoid lupus erythematosus show circulating antibodies.

Three quarters of patients with systemic lupus erythematosus have cutaneous disease. The "butterfly" eruption over the face is well known, but other cutaneous signs include photosensitivity, discoid lesions, alopecia, and vasculitis. A diagnosis of systemic lupus erythematosus requires the demonstration of multisystem disease with serological or haematological abnormalities. In addition to circulating antibodies, direct immunofluorescence of skin where there are no lesions may show granular deposition of various immunoglobulins and complement components at the dermoepidermal junction, the "lupus band" test.

In discoid lupus erythematosus, the discoid lesions typically occur in areas exposed to light, usually on the face. Circulating antinuclear antibodies and systemic symptoms are infrequent, although the "lupus band" test may be positive in lesional skin.

Patients with "subacute cutaneous" lupus erythematosus have a distinctive annular eruption, often with systemic (but not renal) disease, and usually show circulating antibodies to a cytoplasmic RNA nucleotide (Ro). Anti-Ro antibodies are similarly found in neonatal lupus erythematosus, which also has definitive skin signs.

Lupus erythematosus is often thought of as an immune complex disease with defects in T suppressor cell function. Ultraviolet radiation may generate antigenic nuclear products in the skin, with the development of clinical disease.

Dermatomyositis

The dermatomyositis-polymyositis complex is a heterogeneous group of disorders with varying involvement of skin and muscle. Associations with malignancy, particularly in men aged over 40, and connective tissue disease, especially rheumatoid arthritis and systemic lupus erythematosus, represent distinct subtypes.

The purplish red heliotrope erythema around the eyelids, cheeks, and forehead, often with oedema, is typical. Bluish red scaly plaques on the dorsal aspects of the fingers and hands (especially over the joints) and nail fold telangiectasia are other features, although the eruption can be widespread.

Abnormalities of humoral and cellular immunity suggest an autoimmune cause. Although not specific, antibodies to skeletal muscle are found, and lymphocytes from affected patients show enhanced transformation on exposure to muscle antigens. Deposits of IgG, IgM, or C3 are described in skeletal muscle blood vessels on direct immunofluorescence, and IgG or IgM may be seen in the upper dermis. Antinuclear antibodies are present in the serum of some subjects.

Systemic sclerosis and morphoea

Morphoea, localised plaques or bands of sclerotic skin, is clinically distinct from systemic sclerosis, though histologically the skin changes are similar. Morphoea is a local form of systemic sclerosis, but affected patients lack the serological characteristics of the latter, and internal disease is uncommon or mild.

Skin changes are prominent in systemic sclerosis. Raynaud's phenomenon is almost invariable: the skin of the hands and forearms becomes tight and waxy, with atrophy of the finger pulp and flexion deformities. Telangiectasia, with radial furrowing around the mouth and restricted mouth opening, are characteristic. Disease of internal organs must be expected.

Almost all patients with systemic sclerosis have antibodies to nuclear or cytoplasmic antigens in their sera. Endothelial cell damage, related to humoral or T cell derived factors, may initiate a cascade of inflammation which results in fibrosis and sclerosis of the target organ.

Graft versus host disease

Graft versus host disease occurs after bone marrow transplantation, when immunocompetent cells of the graft react against the histoincompatible tissues of the immunosuppressed recipient. Acute and chronic forms are recognised, with cutaneous changes including a morbilliform eruption, toxic epidermal necrolysis, a lichen planus like eruption, and a scleroderma like syndrome.

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Does intraductal carcinoma of the breast show up in a computed tomogram?

Computed tomography has been used to identify small tumours in the breast though not specifically those of the intraductal type.^{1,2} Only a few papers, however, describe the relative merits of this method of imaging, and they have generally concluded that the sensitivity of this method of detection is similar to that of mammography and clinical examination. Those few workers who are enthusiastic about computed tomography suggest that it may well be superior to conventional mammography in patients with dense breasts, where there is a lack of soft tissue contrast. This is, however, a minority view, and while it is true that carcinoma in the breast may occasionally be identified during the course of computed tomography, the sensitivity for the detection of these lesions by this method is inferior to that of mammography or ultrasound examination. The spatial resolution of computed tomography mammography is less than that of conventional mammography; in addition it takes longer and requires the use of intravenous contrast medium to provide tumour enhancement.

Computed tomography, therefore, has no practical role in the primary detection of carcinoma of the breast and this sophisticated, rare, and expensive resource is better applied to more appropriate diagnostic problems. Surprisingly, the even more expensive method of imaging by magnetic resonance may have a role in assessing tumours in the breast³ because it may provide useful diagnostic information on the internal structure of such tumours. Magnetic resonance may also have an advantage in its ability to display residual breast tissue when a prosthesis is in place. Further research and experience are necessary before the relevance of this imaging method in breast cancer can be determined.—D M KING, consultant radiologist, London.

1 Chang CHJ, Sibala JL, Fritz SL, *et al.* Computed tomography in the detection and diagnosis of breast cancer. *Cancer* 1980;46:939-46.

2 Chang CHJ, Nesbit DE, Fisher DR, *et al.* Computed tomographic mammography using a conventional body scanner. *AJR* 1982;138:553-8.

3 Heywang SH, Fenzl G, Han D, *et al.* MR imaging of the breast: comparison with mammography and ultrasound. *J Comput Assist Tomogr* 1986;10 (4):615-20.