Hong Kong J. Dermatol. Venereol. (2016) **24**, 41-48

Reports on Scientific Meetings

The 24th European Academy of Dermatology & Venereology Congress

Reported by BS Tong 唐碧茜

Date: 7-11 October 2015
Venue: The Bella Center, Copenhagen, Denmark
Organiser: European Academy of Dermatology & Venereology

Basal cell carcinoma

Speaker: Ervin Epstein
Children's Hospital Oakland Research Institute, Oakland, United States of America

Studies of the hereditary predisposition to developing basal cell carcinomas (BCCs) in patients with the autosomal dominantly-inherited basal cell naevus syndrome (BCNS) / Gorlin syndrome led to the finding that inappropriate reactivation of the hedgehog (HH) signalling pathway is the fundamental molecular abnormality that drives all BCCs, be they sporadic or hereditary. In 2012, vismodegib was approved by the US Food and Drug Administration (FDA) for the treatment of locally advanced or metastatic BCC. It selectively inhibits Smoothened (SMO), a key transmembrane protein involved in HH signal transduction of cancerous epithelial cells. A second HH pathway inhibitor, sonidegib, was approved by the FDA in 2015. Although 50% of advanced BCCs respond initially, within the first year of treatment, a significant proportion of these patients develop secondary resistance. This resistance is accompanied by reactivation of HH signalling, often due to mutations in the target of the small molecule such that the drug no longer can bind to its target. On the contrary, non-advanced BCCs in Gorlin patients do not develop resistance, and all their tumours typically disappear both clinically and histologically. However, when drug treatment is stopped the BCCs reappear to cover the same area as pre-treatment. Thus despite an often spectacular clinical response, there remain challenges – how to prevent the resistance of advanced BCCs and how to convert remission of smaller BCCs into actual cure.

Learning points:

Although not without adverse effects, systemic treatment with oral HH inhibitors can be life-altering in the appropriate patients with BCCs.

Contact allergy

Speaker: Klaus Ejner Andersen
University of Southern Denmark, Odense University Hospital, Odense C, Denmark

The patch test is used for diagnosing allergic contact dermatitis (ACD). It is a biologic assay with inherent pitfalls and results may vary depending on many factors such as patch test technique, status of the patient's skin, reading and interpretation of the test reactions. The challenge is to examine the patient with

dermatitis and establish the suspicion of ACD, to select the allergens to be tested, read and interpret the test reactions. The correct diagnosis of ACD may be missed if the allergen in question is not tested, and ACD is often a complicating factor aggravating other eczematous diseases. The use of a baseline patch test series comprising the most common allergens in all patients with suspected ACD is widely accepted. However, supplementary patch tests with working materials, gloves, topically applied products, and extra allergens selected on the basis of patient history and known exposures are often required to establish the correct diagnosis.

A working group under The European Society of Contact Dermatitis (ESCD) has published guidelines for diagnostic patch testing with recommendations on best practice.

Patch testing may be considered in patients with:
1. Suspected contact dermatitis, acute or chronic, including dermatitis related to occupational exposures.
2. Other types of chronic dermatitis not improving with treatment.
3. Skin and mucous membrane eruptions including delayed type drug eruptions in which delayed hypersensitivity is suspected.

The dermatologist must always assess whether an established contact allergy is present, past or unknown relevance, or is attributable to cross-reactivity. Both personal and occupational exposures need to be addressed.

In the case of unknown relevance of a positive patch test reaction, it is recommended to repeat the clinical examination, re-evaluate the history and exposure, and to perform use-test, spot tests, chemical analysis and worksite visits, where indicated.

Fragrance allergy is frequent and involves great complexity with more than 2,000 substances involved. Fragrances are often used in deodorants, lotions, fragrances and topical medicaments. There are many sensitisers such as natural products and chemicals. Sometimes air oxidation can lead to the formation of allergens: fragrance allergens are formed in the product – oxidised limonene and oxidised linalool. As a result, improved patch test screening materials are needed, e.g. testing with patients' own products. This requires a dedicated patient and a collaborative cosmetic manufacturer willing to supply product ingredients for supplementary testing.

Ethylhexylglycerin is an emollient solvent and fixative with antimicrobial properties and enhances preservative effects and can be found in emulsifiers and surfactants. Allergic contact dermatitis can therefore be caused by emulsifiers. Although rare, it may cause severe dermatitis. There are no definite patient risk factors and the concentration required for patch testing is difficult to establish. Sometimes, the compounds themselves are also irritants.

Another point of interest is biomaterial hypersensitivity – whether it is possible for patients to develop allergic reactions following total knee arthroplasty. This is an uncommon complication but must be recognised to ensure the health and satisfaction of patients. Some studies acknowledge the correlation but do not identify a causative relationship for metal hypersensitivity reactions after total knee arthroplasty. It is recommended that clinicians should refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic or has a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider. The clinical work-up of a patient suspected of having an allergic reaction to a metal implant should include patch testing and possibly *in-vitro* testing.

Learning points:

Clinicians should refrain from routine patch testing prior to total knee arthroplasty unless the patient has already had implant surgery with complications suspected to be allergic or has a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or clinician.

How to approach vasculitis

Speaker: Cord Sunderkötter
Department of dermato-infectiology, University of Münster, Münster, Germany

Vasculitis involves a wide clinical spectrum, often involving other organs, and with several different pathophysiological mechanisms, sometimes closely related to the process of granulocyte transmigration.

Vasculitis encompasses several serious diseases which, if left untreated, may run a severe, sometimes even fatal course (e.g. ANCA associated vasculitis) or result in permanent damage (e.g. blindness in giant cell arteritis). Since most vasculitides present with characteristic cutaneous signs or symptoms, it is important to recognise any red flags that indicate complications.

Histological and clinical algorithms are useful. Histological algorithm is determined by the size of vessels, type of affected vessels and type of inflammatory cells.

The multifaceted clinical algorithm of vasculitis can be seen in small vessel vasculitis. The combination of palpable purpura with a predilection for the lower legs, decrescendo-like reduction of lesion number cranially and "koebnerisation" by vasodilatory stimuli is pathognomonic for immune complex vasculitis, the most common form of cutaneous vasculitis. Screening for vascular IgA deposits and renal involvement should be performed in these cases. Whenever this pattern presents with deviations such as necrosis at cold exposed sites or additional nodes, a different disease should be suspected e.g. cryoglobulinaemia or ANCA-associated vasculitis.

Scientifically, immune complex vasculitis reveals the vital process of granulocyte transmigration, because it takes place at exactly the same site where all inflammatory cells transmigrate into the tissue, usually without damaging the vessel wall. In the future, research on vasculitis may reveal special features of transmigration and therapeutic approaches which target the pathogenesis less widely than glucocorticoids

Learning points:

The size of affected vessels determines clinical signs, and clinical algorithm is a primary step to establish the diagnosis of vasculitis. Dermatologists should be aware of the red flags and sometimes interdisciplinary approach is necessary.

Autoinflammation, autoinflammatory disease and the skin

Speaker: Lars French
Department of Dermatology, Zurich University Hospital, Switzerland

Autoinflammatory disease is a relatively newly described subset of diseases that are pathogenetically and clinically distinct from allergic or autoimmune diseases. Skin signs are a common feature of various inherited and acquired autoinflammatory diseases and should be recognised by dermatologists. Autoinflammatory diseases are characterised by seemingly unprovoked episodes of inflammation, absence of high titre autoantibodies and/or antigen-specific T-cell response, frequent presence of

sterile neutrophilic tissue inflammation and, in certain situations, dysregulation of interleukin (IL)-1b.

Several autoinflammatory diseases are monogenic and caused by mutations in genes regulating the function of cytoplasmic innate immune complexes, termed inflammasomes, resulting in enhanced secretion of the proinflammatory cytokine IL-1b. Recent experimental evidence also points to a role of the inflammasome and IL-1b in more commonly acquired inflammatory skin and systemic diseases characterised by an altered pathogen-host interaction or a biological response to endo- and/or exogenous danger signals.

Prototypic inherited autoinflammatory syndromes are the Cryopyrin-Associated Periodic Syndromes (CAPS) that have recurring fever and urticarial-like lesions, namely Muckle-Wells syndrome, familial cold urticaria syndrome, and chronic infantile neurological cutaneous and articular syndrome.

Gradually the clinical spectrum of accepted autoinflammatory diseases has broadened to include acquired abnormalities in proteins involved in the inflammasome and IL-1 pathway, polygenic and even inflammatory diseases with unresolved genetic mutations. Of interest, these also include PAPA (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne) syndrome, PASH (Pyoderma angrenosum, Acne, and Suppurative Hidradenitis) syndrome, SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) syndrome, Sweet syndrome, neutrophilic panniculitis and delayed pressure urticaria.

Insight into the molecular pathways and the pattern of activation and maintenance of the inflammatory response underlying these disorders have led to the discovery of new molecular therapeutic targets. The most well-known is the dramatic response to anti IL-1 drugs in CAPS, which completely dampens inflammation in these severe disorders by selective blockade of a single crucial cytokine.

Learning points:

The IL-1 family and its members are key mediators of inflammation and may have been generally underestimated in their importance. Autoinflammatory diseases are often associated with skin manifestations that histologically show neutrophilic infiltration of the skin.

Resistance to STIs

Speaker: Colm O'Mahony
Countess of Chester Hospital, Chester, United Kingdom

Resistance to antibiotics is an inevitable consequence of use whether it is controlled or uncontrolled. *Neisseria gonorrhoeae* (GC) has developed resistance to all of the antibiotics ever used against it. GC resistance to cephalosporins is ominous. The first identified case was found in a female sex worker in Japan in 2011. Currently, efforts to stem the spread of cephalosporin resistance are focused on: 1) Dual therapy, using azithromycin or doxycycline along with ceftriaxone; 2) Targeting core groups. 3) Efforts to stop the acquisition of GC by education and condom use. These strategies may delay but will not halt the world-wide emergence of totally resistant GC. Gonorrhoea Antimicrobial Surveillance Programme (GASP) is in place in some countries.

It is thought that much resistance occurs through coincidental oropharyngeal infections with GC and other bacteria types. The oropharynx has such a collection of bacteria, all carrying genomes for resistance that it is easy for these to be transmitted to a transient gonococcal infection. The use of two antibiotics, i.e.

ceftriaxone and azithromycin for treating GC in genital sites is a good idea but it must be remembered that many individuals will receive a single antibiotic, e.g. for chlamydia, who do not have genital GC but are carriers of low numbers of GC in the oropharynx.

Common infections like urethritis are becoming more difficult to control, as chlamydia and mycoplasma become more resistant, even in countries with good services. Mycoplasma rapidly develops resistance particularly if short treatment courses are used. Fortunately, resistance to chlamydia is still rare with most continuing infections actually being reinfections.

Macrolide resistance has developed in syphilis and the initial high hopes for azithromycin 2 g stat dose for managing early syphilis have largely been dashed. Injection therapy is still required, posing a greater drain on resources especially for poor countries.

Finally, resistance to anti-HIV drugs is already well-established and we are seeing a worrying increase in the number of new infections already multi-drug resistant.

Learning points:

GC resistance to Cephalosporin is inevitable. Strategies to identify and minimise resistance in STDs are crucial.