23rd World Congress of Dermatology

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Signature naevi

Speaker: Jean Bolognia
Yale School of Medicine, USA

As there are different types of signature naevi, it is important to recognise these to identify the correct risk category. These include solid brown, solid pink, fried egg, eclipse, cockade, perifollicular hypopigmented, halo, lentiginous, uniform pink and solid white. The uniform subtypes, cockade, perifollicular hypopigmented are usually not associated with an increased malignant potential as compared to other common naevi, whereas with halo naevi, there is a 1:1000 to 1:10,000 risk of transformation to a melanoma. One should always examine the rest of the patient's skin, especially for middle-aged patients, to look for other potentially dysplastic lesions. For borderline lesions, such as dark lentiginous or white dysplastic naevi, a second opinion for suspicious lesions is useful.

Learning points:

It is important to recognise these signature naevi and their malignant potential to manage this group of patients effectively.

Monitoring methotrexate (MTX) with liver biopsy

Speaker: Dirk Elston
Ackerman Academy of Dermatopathology, New York, USA

Currently, there are discrepancies between ACR and AAD guidelines regarding monitoring for liver fibrosis for patients on MTX. However, patients with rheumatoid arthritis are different from those with psoriasis. Patients with psoriasis are often on higher doses of MTX, have higher incidence of metabolic syndrome, obesity and alcohol consumption. Evidence from various studies have shown that liver function tests are not a good indicator of liver fibrosis and are mainly an indicator for inflammation which may not exist in MTX-induced fibrosis. Recent meta-analysis suggests that procollagen III peptide, Fibro Test and Fibroscan are better predictors for liver fibrosis. There are urine markers in development that may be useful in detecting liver fibrosis in psoriasis patients with a high cumulative MTX dose.

Learning points:

Newer technologies allow us to use MTX more safely without putting the patient through the risk of performing a liver biopsy.

Atopic dermatitis

Speaker: Sandipan Dhar
Department of Pediatric Dermatology, Institute of Child Health, Kolkata, India

The prevalence of atopic dermatitis is increasing worldwide and is putting a significant burden on healthcare systems around the world. It is known that atopic dermatitis is a lifelong disease, with a childhood onset in 60% of cases. Childhood disease is phenotypically different from adult onset disease with many potential differential diagnoses. It severely affects the patient's and the family quality of life and this aspect will need to be dealt with during the initial visit.

A thorough explanation should be given to the caregiver during the initial visit which including pathogenesis, general skin care, treatment options, addressing steroid phobia, long term prognosis and the role of food allergy. There is no consensus about optimal bathing frequency. Many parents have concerns about food allergy as a cause of disease which is often not the case. Dietary manipulation is usually not recommended, although many patients can have co-existing food allergies.

Treatment usually includes topical emollients and anti-inflammatory agents. Topical anti-inflammatory medications, such as topical corticosteroids and calcineurin inhibitors have been used successfully. Newer topical formulations are under development such as PDE4 inhibitors (e.g. roflumilast and apremilast) and JAK inhibitor (e.g. tofacitinib). For patients with severe disease, systemic immunomodulators such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil are useful for controlling the disease.

Learning points:

The prevalence of atopic dermatitis is increasing. It is important for every dermatologist to know how to manage this condition effectively. Newer topical formulations on the horizon offer alternatives to currently available anti-inflammatory medications.

Immunosuppressive/modulating modalities for treatment of urticaria

Speaker: Clive Grattan
Norfolk and Norwich University Hospital, United Kingdom

Functional autoantibodies that release histamine from healthy donor basophils and mast cells in vitro have been found in 30% of patients with chronic spontaneous urticaria (CSU), previously known as chronic idiopathic urticaria. Due to the presence of circulating autoantibodies, systemic immunosuppressive therapies have been used successfully to treat CSU. There is good evidence for using ciclosporin in patients with CSU but it should be stopped if there is no improvement after two months. It is more effective if the patient has a positive basophil histamine release assay with a short duration of disease. It is a potentially disease-modifying drug that suppresses functional auto-antibodies although this has not been well-studied. Methotrexate and mycophenolate mofetil have also been used successfully for CSU.

There is good evidence of efficacy for omalizumab which is licensed for H1-antihistamine unresponsive CSU. There are several proposed mechanisms for its effectiveness such as reduction of circulating IgE, dissociation of IgE from the high affinity IgE receptor on mast cells and basophils and subsequent reduction of high affinitiy IgE receptor density with stabilisation of mast cells and basophils.

Learning points:

There is good evidence to support CSU as an autoimmune disease and the use of traditional immunosuppressants. Omalizumab offers an exciting new opportunity to treat patients with recalcitrant urticaria.

Vitiligo and other disorders of hypopigmentation

Speaker: John Harris
University of Massachusetts Medical School, USA

Vitiligo is a complex disease in which depigmentation involves a complex interaction between abnormalities within melanocytes and autoimmune-mediated melanocyte destruction. The initial event may involve melanocyte "danger signals" that activate innate inflammatory cells leading to inflammation of the skin. Melanocyte loss in vitiligo is mediated by melanocyte-specific, cytotoxic CD8+ T cells that migrate into the skin while T regulatory cells act to control this destruction. The IFN-γ-CXCL10-CXCR3 cytokine axis is a central player in mediating the migration of these autoreactive T cells into the skin and their effector function. Armed with this knowledge, new treatments are being developed for treatment of vitiligo. There is evidence suggesting that simvastatin, inhibitor STAT1 in vitro, may be useful for the prevention and treatment of vitiligo in mouse model by reducing the number of infiltrating autoreactive CD8+ T cells. A phase II trial has since been completed with the study of which the results are pending.

Narrowband UV-B is frequently used alone or in combination with topical treatment for vitiligo. Afamelanotide, a synthetic analogue of α-MSH, has been used successfully together with narrowband UV-B for treatment of vitiligo in a small pilot study. More recently, a randomised multi-centre trial compared this combination therapy with narrowband UV-B alone and showed superior repigmentation at day 56 especially for the face and upper extremities. The author concluded that combination therapy is superior in terms of the amount and speed of repigmentation.

For patients with stable but recalcitrant vitiligo, surgical treatment should be considered. For small areas, 1 mm mini punch graft can be used to transfer melanocytes to the vitiliginous areas. For bigger areas, non-cultured epidermal suspension is the treatment of choice. The technique has undergone various modifications over the years and can be combined with hair follicle outer root sheath cell suspension. It can be used to transplant a recipient area up to 8-10 times the size of the donor site.

Learning points:

Understanding the pathogenesis of vitiligo has offered new potential treatments, such as simvastatin. A combination of newer treatments may improve treatment success for these patients.

Daylight PDT

Speaker: Rolf-Markus Szeimies
Department of Dermatology and Allergology, Vest Clinic, Recklinghausen, Germany

Topical photodynamic therapy (PDT) has been used successfully for cancerous and pre-cancerous changes on the skin by using a porphyrin precursor which is activated by visible light. It is relatively painful if the malignancy involves large areas of the face or scalp. The concept of daylight PDT was developed in Denmark in 2008 by Dr. Wulf and his team. By utilising daylight as the light source, there is continuous activation of protoporphyrin IX during its formation. Pain is reduced as protoporphyrin IX never accumulates to high level. It works with sunny and even during cloudy weather conditions and all-year round for the

equatorial regions. At places with higher/lower latitudes, seasonal restrictions apply and treatment is only suitable during late spring, summer or early autumn. As the duration of treatment varies between 30 to 90 minutes depending on the locality, this form of treatment may not be possible in adverse weather conditions. There are a few studies in Australia and Europe which showed daylight PDT to be at least as effective as and less painful than MAL conventional photodynamic therapy in treating patients with mild actinic keratosis.

Learning points:

Daylight PDT offers an inexpensive and effective way for patients with wide spread actinic keratosis to be treated. The pain during treatment is much reduced when compared with traditional PDT.

Microbiome and atopic dermatitis

Speaker: Thomas Bieber
Department of Dermatology, Friedrich-Wilhelms University, Bonn, Germany

Atopic dermatitis (AD) is now well recognised to be caused by a defective skin barrier function and abnormal host immune response. There are various aspects of defective skin barrier including defective lipid lamellae, degraded corneodesmosomes, abnormal cornified envelope that also includes filaggrin defects. Cutaneous microbiome was recently found to to play an important role in the pathogenesis of AD. The human microbiota constitutes ten times more cells than an individual and can weigh up to 1.5 kg. The birth of microbiota starts at pregnancy, birth and during lactation. Towards maturation, the core microbiota consists mainly of *Propionibacteria* and *Staphylococcus spp*. These bacteria are both found on and within the skin's ultrastructure. The host genotype and environment significantly influence the microbiome, such as the filaggrin, host physiology, lifestyle and living environment. In normal skin, there is a delicate balance between the immune system and the skin microbiome. A disruption of this balance will lead to development of AD. The example being a significant reduction of microbiome diversity in the flare-up of AD which is often associated with an increase of *Staphylococcus spp* and a restoration of diversity when the disease is settled. The *Staphylococcus spp* can also cause a lack of immune response from dendritic cells and Th17 cells. There is evidence that microbiome diversity improves with proactive treatment in AD.

Learning points:

Skin microbiome plays an important role in maintaining normal skin homeostasis. A disruption of microbiome balance is observed in disease flare-up of AD.

Food allergy and elimination diet: current scenario in atopic dermatitis

Speaker: Jon Hanifin
Oregon Health and Science University, Portland, USA

In the context of food allergy and elimination diet in atopic dermatitis (AD), inappropriate restrictions were being imposed on 80% of patients with AD in the United States. The definition of allergy is adverse health effect arising from exposure to allergens with evidence of reproducibility. It was found that about 55% of Americans had positive allergen specific IgE antibodies, but this only implies sensitisation and not true allergy. It is known that AD predisposes to multiple sensitisation and true food allergy is diagnosed by food challenge and clinical correlation. The concept of delayed eczematous response is not yet clearly defined and thus is not appropriate for use to assess the effect of food allergy. Food allergy was estimated to be present in 10-35% of patients with AD but food restriction is most appropriate

for those with proven type I allergic response. There is no evidence to support extensive use of hydrolysed formula in preventing AD.

Learning points:

Inappropriate restriction of food is common in patients with AD. Food restriction is appropriate in patients with proven type I allergic reaction.

Epidermolysis bullosa

Speakers: Leena Bruckner Tuderman,[1] Mohammedreza Barzegar,[2] Christine Bodemer,[3] Johann Bauer,[4] Kasuto Tamai,[5] Mei Chan[6]

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There has been a new approach in the classification system of epidermolysis bullosa (EB) in which old eponyms were to be eliminated. With the advances in molecular genetics, the classification will be based on major EB type present (level of skin cleavage), phenotypic characteristics, mode of inheritance, targeted protein and its relative expression in skin, genes involved and types of mutation present; the so-call 'onion skinning' approach. The classification and subclassification of EB begin with separation into one of the four major groups of skin cleavage: intraepidermal (EB Simplex), within the basement membrane zone (Junctional EB) or beneath the basement membrane zone (Dystrophic EB) and mixed pattern (Kindler syndrome). The next level of subclassification takes into account of the clinical features and distribution of disease and the severity of cutaneous and extra-cutaneous disease. Further subclassification based on the mode of transmission, specific genes involved and mutations is possible with immunohistochemical studies and mutation analysis. The eponyms used in EB classification have made comparison with other clinical entities difficult and have no immediate descriptive value, therefore, it is proposed that these should be eliminated. Examples are 'EBS, Weber-Cockayne' renamed as 'EBS localised'; 'EBS Dowling-Meara' renamed as 'EBS, generalised severe'; 'JEB, Herlitz' renamed as 'JEB, generalised severe' etc. Exceptions are Kindler syndrome and EBS-Ogna. This system includes both clinical and molecular features of each EB subtype and also allows enough flexibility to accommodate newly discovered EB subtypes in the future.

There is a new approach in the biopsy technique for diagnosing EB. Normally, *in vivo* approach to induce a blister by rubbing the skin for skin biopsy is adopted. This however is time consuming as a prolonged waiting time before biopsy is needed and the specimen obtained can be of unsatisfactory quality. *Ex-vivo* blister induction is proposed. The skin biopsy specimen (usually 4 mm in diameter) is subjected to a negative pressure exerted on by repeated drawing of a syringe in the laboratory. It usually takes few minutes to several hours for a blister to form, dependent on the subtypes of EB. A fresh biopsy specimen is required to prevent degradation of cells.

The new advances in the management of EB include the use of mesenchymal stromal cell therapy, protein therapy and gene therapy. There is evidence that cross-talk mechanism exists between bone marrow and injured tissues. The use of CD44+ rapid recycling mesenchymal cells to inject into the site of non-healing ulcer in EB significantly promotes healing. The use of recombinant type VII collagen by intra-dermal injection had been shown to produce new C7 and anchoring fibrils in EB mice model and reversal of poor dermal-epidermal adherence. Intravenous type VII collagen had also showed an effect in the mouse model. The CHO-derived type VII collagen (CHO-C7) and fibroblast-

derived type VII collagen shared the same structure and property and after intravenous injection, CHO-C7 was found in the DEJ as well as the oesophagus. No autoantibodies were produced against CHO-C7. Topical recombinant C7 was also found to incorporate into DEJ and promote wound healing in the animal model.

Learning points:

A new classification algorithm has been proposed for EB. New biopsy techniques help to obtain satisfactory skin specimen for diagnosis. Use of mesenchymal stromal cells and recombinant type VII collagen seems promising in promoting wound healing in EB.

Infantile haemangioma and vascular malformation

Speakers: Julie Powell,[1] Seok-Jong Lee,[2] Olivia Boccara,[3] Samira Syed,[4] Christine Leaute-Labreze,[5] Ilona Frieden[6]

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There has been controversy in the classification and terminology in benign vascular lesions due to the heterogeneity of clinical presentation. The International Society for the Study of Vascular Anomalies (ISSVA) had come up with a new consensus in the classification of vascular anomalies in 2014. The vascular anomalies are classified into vascular tumours and vascular malformations. The tumours are further classified into benign, locally aggressive or borderline and malignant. The malformations are classified into simple or combined; with associated major named vessels or associated with other anomalies.

There are many controversial vascular anomalies that require further study to delineate their nature. For example: the angiokeratoma and verrucous haemangioma; PTEN harmatoma of soft tissue and angiomatosis of soft tissue and fibro-adipose vascular anomaly; intravascular haemangioma and arterio-venous malformation (AVM).

In the treatment of vascular anomalies, laser had been used extensively but recurrence of lesions and complications are not uncommon. In the treatment of port-wine stain (PWS) with pulsed-dye laser, 9-10% had various degree of recurrence 2-4 years after treatment. Laser treatment should require particular caution for those lesions prone to bleeding, associated syndromes and facial lesions with visual complications. It is not suitable to use laser for rapidly progressive vascular tumours and AVM. Multiplex laser system such as Cynergy™ is used with success in the treatment of vascular anomalies such as PWS.

The US FDA has approved propranolol in 2014 as a first line treatment for proliferating infantile haemangioma (IH) requiring systemic therapy. Study showed that the numbers needed to treat by propranolol to have beneficial outcome is 1.76. There is no benefit gained by combining systemic steroid with propranolol at the initial stage of treatment. The safety profile of propranolol is good and rarely associated with serious side effects. Current recommendation is to start treatment early in an escalating dose, routine echocardiography and ECG are not required if cardiac examination is normal. However, relapses or rebound is possible and studies have showed that up to 11% needed retreatment at 24 weeks after treatment for

6 months. The use of other beta-1 selective blockers is currently under study. The advantage of using less lipophilic drugs such as atenolol and nadalol is that they do not cross blood-brain barrier. Topical timolol has been used quite often with success for superficial IH.

Sirolimus is becoming a promising emerging therapy for vascular malformations and tumours. Sirolimus worked through the PI3K/AKT/mTOR pathway by inhibiting mTOR and resulted in inhibition of downstream cellular proliferation and angiogenesis. Case series demonstrated that sirolimus significantly improve the clinical status of patients with Kaposi haemangioendothelioma and other combined vascular malformation with Kasabach-Merritt phenomenon (KMP).

Learning points:

There has been a new consensus in the classification of vascular anomalies and some controversies still exist. Multiplex laser systems are being used successfully in treating PWS. Propranolol has been used extensively for treating complicating infantile haemangioma in recent years with good safety profile. Other selective beta-blockers are under study for their better side effect profile and efficacy. Sirolimus is a promising treatment for complex vascular malformation or tumour with KMP.

Advances in atopic dermatitis: expert insights into new and emerging therapies

Speakers: Amy Paller,[1] Eric Simpson[2]
[1]Department of Dermatology and Paediatric Dermatology, Northwestern University Feinberg School of Medicine, Chicago, USA; [2]Department of Dermatology, Oregon Health and Science University, Portland, USA

There is emerging awareness that atopic dermatitis (AD) is associated with co-morbidities such as obesity, cardiovascular diseases, vitiligo, osteoporosis and alopecia areata. Currently the pathophysiology of AD stresses the interplay between barrier dysfunction, immunological dysregulation and inflammation. There may be primary immune dysfunction and resulting IgE sensitisation. Filaggrin mutation is associated with early onset AD, more persistent disease and also allergic airway disease. About 9% of Europeans carry a heterozygous mutation. The role of phosphodiesterase (PDE) had been revealed as patients with AD showed significant elevated PDE type 4 (PDE4) which resulted in an increase in proinflammatory cytokines. As a result, PDE4 inhibitors are being recognised as emerging therapeutic options for the treatment of AD. Topical agents such as crisaborole ointment (boron-based PDE4 inhibitor) and roflumilast cream have shown promising results in clinical trials. Oral apremilast, which is a small molecule PDE4 inhibitor, is also being studied in the treatment of AD. The Janus kinases (JAK) have been recognised in the pathogenesis of AD due to the effect on IL-4, IL-5 and IL-31 signalling pathways causing immune dysregulation. Topical JAK inhibitor tofacitinib has shown promising results in phase II clinical trial. Dupilumab is a newly developed fully human monoclonal antibody that blocked IL-4 and IL-13, which are key cytokines in Th2 mediated pathway in AD. It has shown significant improvement in patients with moderate to severe AD in a randomised controlled trial.

Learning points:

New treatment modailties for AD such as PDE4 inhibitor, JAK inhibitor and IL-4 and IL-13 blocker have been revealed. These medications that target different pathways in the pathogenesis of AD will revolutionise the management of severe AD patients in the near future.

Drugs in the pipeline – from small molecules to antibodies

Speakers: Bruce Strober,[1] Herve Bachelez[2]
[1]University of Connecticut School of Medicine, Farmington, USA; [2]Saint-Louis University Hospital, University of Paris, France

New targets in the pathogenetic pathway of psoriasis have been discovered. A new biologic, secukinumab that targets the IL-23/ Th17 axis in psoriasis has been launched. This is a fully human monoclonal antibody that selectively targets IL-17A, a key cytokine that directly acts on keratinocytes to stimulate the production of proinflammatory mediators. The action of IL-23 is dependent on inducing the production of IL-17A, which is the target of ustekinumab in the treatment of psoriasis. The effect of blocking IL-17A has been demonstrated in a recent study to be superior to blocking IL-23 in treating patients with moderate to severe psoriasis. The major side effects of secukinumab are opportunistic *Candida* infection and neutropenia. Ixekizumab, another IL-17A blocker, has been shown to be more effective and superior to placebo and etanercept in two phase III studies. Anti-IL-23p19 monoclonal antibody tildrakizumab and guselkumab have showed promising results in phase II studies for the treatment of psoriasis. Use of small molecules in inhibiting proinflammatory targets of psoriasis has been under extensive study. Janus kinase (JAK) signalling inhibition by tofacitinib has been demonstrated non-inferior to etanercept in treating psoriasis, which is the first oral medication to show biologic-like activity in psoriasis. Apremilast, a small molecule phosphodiesterase 4 (PDE4) inhibitor, has been shown to be effective in treating moderate to severe psoriasis and psoriatic arthritis and has recently gained approval by the US FDA and European Commission.

Learning points:

The latest development in the treatment of psoriasis includes targeting IL-17A and IL-23 axis, inhibition of JAK signalling and PDE4 inhibition.