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Basic dermoscopy

Speakers: Dr. Wilhelm Stolz,¹ Dr. Ralph Braun²

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Since the last decade, dermoscopy has been widely used by dermatologists in the Western countries, where the incidence of malignant melanoma is high, for evaluation of pigmented lesions. Also known as skin surface microscopy or epiluminescence microscopy, it is non-invasive and allows the visualisation of submacroscopic morphologically important structures of pigmented lesions from epidermis to upper dermis.

Two types of dermoscope

The first type is non-polarised dermoscope which uses gel or oil as the interface reflective medium that makes direct contact with the skin, rendering the cornified layer translucent, to aid the observation in epidermis and superficial dermis. The second type was invented in 2001. It utilises polarised light and does not require direct skin contact to visualise the upper dermis. Since the

two types have different strengths in visualising various layers of skin, the diagnostic accuracy and confidence are different. Non-polarised dermoscope is better for diagnosing seborrheic keratosis and dysplastic naevi, while dermoscope which utilises polarised light is better for diagnosing melanoma and basal cell carcinoma. They are best to be used complementarily together. Notably, most published articles and atlas utilise non-polarised images.

Two-step algorithm of classification of pigmented lesions

At the World Congress of Dermatoscopy Consensus Meeting in 2001, experts agreed on the following algorithm for differentiation of pigmented lesions.

- First step: decide if the lesion is melanocytic or non-melanocytic
- Second step: when the lesion is considered to be melanocytic, then decide on its malignant potential
- If the lesion cannot be differentiated in the first place, then it should be assumed to be melanocytic. Biopsy should be performed to rule out malignant melanoma.

First step: features of melanocytic lesions

- 1. Pigment network
- 2. Branched streaks
- 3. Aggregated globules
- 4. Parallel pattern (acral area) or pseudo-network pattern (face)

First step: features of non-melanocytic lesions

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| → Steal-blue area | → | Blue naevus |
| → Milia-like cyst, comedone-like opening, multiple horn pseudocyst, fingerprint-like projections fissures and ridges (cerebriform appearance) | → | Seborrheic keratosis |
| → Maple leaf-like area, arborizing vessels (telangiectasia), slate grey globules and ovoid nests, spoke-wheel areas, ulceration | → | Basal cell carcinoma |
| → Red, blue-red, or red-black (thrombosed) lacunes | → | Angioma or angiokeratoma |
| → Uncertain | → | Melanocytic lesion |

Second step: features to differentiate between benign and malignant melanocytic lesions

- The modified pattern analysis
- Menzies scoring method
- The seven-point checklist
- The ABCD rule of dermoscopy
 - Asymmetry (in one or two axes)
 - Border (abrupt ending of pigmented pattern)
 - Colour (variegation: white, red/brown, blue gray, black)
 - Differential structures (network, streaks, globules, dots, regression zones)

Most malignant melanomas have multi-component asymmetric dermoscopic findings, like disorganised architecture, variegated colour and regression zones. One exception is dermatofibroma, which is a benign, firm nodule resembling a melanocytic lesion with a central white scar and peripheral pigmented network or streaks under a dermoscope. It is sometimes mistaken as melanoma and biopsied.

Diagnostic accuracy and application

The most practical application of dermoscopy is to try to differentiate melanoma from other benign pigmented lesions before deciding on skin biopsy. In a meta-analysis of 9004 patients in 22 studies, experts with dermoscopy achieved a 35% increase

in diagnostic accuracy compared to clinical assessment, yielding diagnostic sensitivity of 89% and specificity of 79%. However, it is worthwhile to note that diagnostic accuracy is not validated in early, small and featureless melanomas less than 6 mm in diameter clinically. Recent advancement with automatic computer vision system and multi-spectral images has improved the biopsy sensitivity of small melanomas (98% sensitivity with computer vision, compared to 70% sensitivity when assessed by expert alone) and has reduced unnecessary biopsies and mortality.

Learning points:

Dermoscopy represents a link between clinical and histopathological examination. In experienced hands, it is a useful and reliable discriminatory tool for the differentiation of melanoma from non-melanocytic lesions, detection of initial malignant melanoma, risk analysis of melanocytic naevi, and recently in the assessment of longitudinal melanonychia. However, a complete evaluation including history, serial clinical and dermoscopic assessments for any change in lesion is crucial for accurate diagnosis. Further data and validation in the Chinese population are needed.

New drugs, new rashes: an update on cutaneous drug reactions

Speakers: Dr. Jean Bologna,¹ Dr. Susan Burgin,² Dr. Patricia L Myskowski,³ Dr David R Adams⁴

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Adverse drug reactions are an inevitable concomitant of contemporary medical treatment. The skin occurs to be the commonest site of adverse reactions to systemic drugs. Manifestations range from mild transient exanthematous eruption to fulminant toxic epidermal necrolysis. There are also specific forms of eruption unique to certain new drugs. Dermatologists are often consulted to evaluate suspicious cutaneous eruption. The following will focus on new eruptions to new drugs, namely anti-cancer therapy and biologics.

I) Toxic erythema of chemotherapy – erythrodysesthesia and acral erythrodysesthesia

This is a toxic skin reaction associated with chemotherapeutic agents that are commonly used, including cytarabine (Ara-C), doxorubicin, 5-fluorouracil (especially with prolonged infusions) and its pro-drug (capecitabine), methotrexate, bleomycin, cisplatin and tyroxine kinase inhibitors. Patients can present from 24 hours to up to 3 weeks following administration of chemotherapy, with very painful, symmetric erythema of palmoplantar surface and skin overlying joints. There can also be erythema and oedema of the ears ('Ara-C ears'). Subsequent bullae formation is followed by spontaneous healing and desquamation. Histology shows vacuolar change, necrotic keratinocytes, spongiosis, epidermal atypia and possibly evidence of eccrine squamous syringometaplasia. The most important differential diagnosis is graft-versus-host-disease (GVHD), which can be differentiated by histology. The caveat here is that it is often misdiagnosed and treated as

septic emboli, vasculitis, hypersensitivity reaction or GVHD, when it is in fact a toxic reaction to chemotherapy, which will resolve spontaneously once the culprit drug is stopped and thus requires no specific treatment. However, toxic erythema of chemotherapy can recur if a similar dosing schedule is employed.

II) Eruptions secondary to epidermal growth factor receptor (EGFR) inhibitors

EGFR inhibitors are a novel class of targeted therapy that is specifically designed to block epidermal growth factor receptor function, to down-regulate signal transduction pathways for tumour growth and spread. They have potential efficacy without major toxicities associated with conventional chemotherapeutic agents. They are, however, commonly associated with unique and dramatic cutaneous side effects. The following are the FDA-approved monoclonal antibodies used in Hong Kong.

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| Gefitinib (Iressa®) | Carcinoma of lung (non-small cell) |
| Erlotinib (Tarceva®) | Carcinoma of lung (non-small cell) and pancreas |
| Cetuximab (Erbix®) | Colorectal carcinoma |
| Trastuzumab (Herceptin®) | Metastatic carcinoma of breast |
| Panitumab | Metastatic carcinoma of colon |

1. Characteristic acneiform eruption (85%)

Acneiform eruption is the most commonly encountered toxicity with anti-EGFR therapy. Patients present with sterile suppurative follicular lesions on face and upper trunk, occurring early on day 10 to day 14 of therapy. The lesions can also present after three to five weeks after the start of treatment. It is usually mild and well-tolerated with minimal pruritus or discomfort. Histology shows neutrophilic suppurative folliculitis with rupture of epithelial lining, hyperkeratotic or ectatic follicular

infundibula. The significance is that it has been shown to be a dose-related reaction secondary to EGFR inhibition of epidermal and adnexal epithelium and is associated with better clinical outcomes. It seldom posts a dose-limiting concern. Treatment is symptomatic. For mild to moderate eruption, there is no need for dose modification. Empirical treatment with retinoid, tazarotene, steroid or antibiotics has not been shown to have consistent benefit. However, prophylactic oral minocycline has been shown to hasten the improvement of cetuximab – related facial rash compared to placebo.

2. *Dry skin, perineal and vaginal dryness, blepharitis (4 to 35%).*

3. *Painful paronychia with pyogenic granuloma – like changes (12%)*

These cutaneous changes at nail folds or distal finger tufts occur after two to four months from the start of treatment. They are difficult to treat and may last for months even after the discontinuation of anti-cancer therapy. Doxycycline can be used for its immunomodulating effect for the treatment of these lesions.

4. *Hair growth abnormalities*

There have been reports of patients having finer, curlier and brittle scalp hair, as well as hypertrichosis and trichomegaly, which occur within a few weeks to months after the start of treatment.

III) Eruptions associated with tumour necrosis factor (TNF) inhibition

Overall, cutaneous side effects are uncommon with TNF inhibition. However, a few cutaneous eruptions have been reported with the use of this class of drug.

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| 1. <i>Hypersensitivity reaction</i> | Injection site reaction (commonest, usually in the first month, will decrease with time), infusion reaction, serum sickness, vasculitis, morbilliform eruption, urticarial, bullous, erythema multiforme-like eruption |
| 2. <i>Autoimmune/immune dysfunction</i> | Discoid lupus erythematosus (cutaneous lesions) De novo psoriatic lesion (in rheumatoid arthritis/ inflammatory bowel disease patient), eczema, granulomatous dermatitis, Alopecia universalis |
| 3. <i>Miscellaneous</i> | Folliculitis, acneiform eruptions |

Learning points:

Drug-related skin eruptions are common in cancer patients and those on multiple drug treatments. Dermatology input is crucial in making the correct diagnosis and in helping to formulate a plan for management. The decision of whether to discontinue the suspected agents requires careful evaluation and the balancing of risks and benefits.

Basic botulinum toxin

Speakers: Dr. Fredric S Brant,¹ Dr. Alastair Carruthers,² Dr. Dee Anna Glaser,³ Dr. Christopher B Harmon,⁴ Dr. Derek H Jones,⁵ Dr. Baruch H Kaplan,⁶ Dr. Mark G Rubin,⁷ Dr. David Kouba,⁸ Dr. Seth L Matarasso,⁹ Dr. Henry HL Chan¹⁰

¹Coral Gables, USA; ²Clinical Professor of Dermatology, University of British Columbia, Canada; ³Professor, Department of Dermatology, St. Louis University, USA; ⁴Clinical Instructor, University of Alabama, USA; ⁵Associate Clinical Professor, David Geffen School of Medicine, UCLA, USA; ⁶Chaim Seba Medical Center, Tel Hashomer, Israel; ⁷University of Pennsylvania, USA; ⁸Moy-Fincher Medical Group, USA; ⁹Clinical Professor of Dermatology, UCSF, San Francisco, USA; ¹⁰Honorary Clinical Associate Professor, CUHK and HKU, Hong Kong

Botulinum toxin A (BOTOX®) has been widely used for the cosmetic treatment of face and other areas of the body. Its main use is for facial wrinkle reduction. The doctor must have a thorough understanding of the facial anatomy so that the treatment can be targeted precisely. An understanding of the physiology of facial movement and expression helps to delineate their relationship to wrinkles and to explain the possible side effects from treatment. In general, wrinkles can be categorised into static and dynamic types. Static wrinkles consist of fine lines with weathered skin in cheeks, lips, eye lids and forehead. Dynamic wrinkles consist of lines, grooves and furrows on the glabella, forehead, periorbital and perioral areas.

Before start the treatment, one must be aware of the contraindications to botulinum toxin A injection, such as pregnancy, breast feeding, and various neuromuscular disorders such as myasthenia gravis, motor neuron disease and myopathies. The patient should be well-informed about the potential local and systemic side effects of botulinum toxin. Local side effects which are commonly encountered are often due to the local spread of toxin. This can range from minor facial asymmetry, ptosis, diplopia to even airway compromise. Bruising and haematoma, especially around the orbital rim, are not

uncommon. Systemic side effects are rare but can be serious.

The doctor should always use a standardised dilution to reconstitute the toxin to avoid confusion. The consensus recommendations on the use of botulinum toxin A in facial aesthetics suggest that a range of dilutions and injection volumes are acceptable, which depend primarily on the number of units to be injected and the preference of the doctor. There is no significant difference in treatment outcome and adverse effect with different dilutions. Studies have also shown that botulinum toxin A maintains its potency at 4°C from one week to six months after reconstitution.

Pre-treatment preparation is useful. Bruising can be minimised with the avoidance of aspirin and non-steroidal anti-inflammatory drugs seven days before treatment. In the periorbital area, patients with too much laxity of skin in lower eyelid are not good candidates for treatment.

In the treatment of localised hyperhidrosis of the axillae, studies have shown that botulinum toxin A is better than placebo, and there was no significant difference in outcome between 50 units and 75 units of toxin used. In the treatment of square face in Hong Kong Chinese, the injections are targeted at the masseter muscle. Usually, a five point injection method is used and 50 units are injected on each side. In the treatment of hypertrophy of lower legs, the calf muscles are targeted.

Different brands of botulinum toxin in the form of uncomplexed botulinum toxin A have appeared in the market, and they appear to function very similarly to Botox® in terms of efficacy and adverse effects. Reloxin®, Xeomin®, PurTox® are examples of uncomplexed botulinum toxin A. They are very pure forms of the toxin, and the reduced amount of protein should reduce the risk of immunogenicity. In a few years time, these uncomplexed forms of toxin will be approved for aesthetic uses and serve as alternatives to Botox®.

Learning points:

Botulinum toxin A is a powerful tool in cosmetic dermatology. Thorough understanding of the physiology and anatomy of various body areas will improve the outcome of treatment. The significance of local and systemic side effects should not be overlooked. The development of new, uncomplexed botulinum toxin A offers perhaps safer and better alternatives to the current botulinum toxin A.

Difficult paediatric dermatology disorders

Speakers: Dr. Lawrence A Schachner,¹ Dr. Elizabeth A Connelly,² Dr. Ronald C Hansen³

¹Professor and Chairman, Department of Dermatology, School of Medicine University of Miami, Miami; ²Assistant Professor of Dermatology and Pediatrics, Department of Dermatology, Division of Pediatric Dermatology, University of Miami; ³Chief of Pediatric Dermatology, Phoenix Children's Hospital, Phoenix, Arizona; Professor of Dermatology and Pediatrics, University of Arizona, Tucson, USA

I. Severe atopic dermatitis

The psychosocial significance of atopic dermatitis in infants, pre-schoolers and school age children should not be overlooked. The effects in severe cases can range from problems in bonding to anger and social withdrawal. Children with severe atopic dermatitis can cause significant financial burden and psychosocial impact to their families and society.

There are several points that should be noted to avoid treatment pitfalls. These include the use of step-wise treatment regimen titrated to severity, treating any infections, prescribing adequate volume of medications, doing patch tests to exclude allergic contact dermatitis and providing appropriate psychosocial support to the families.

In a recent review of controlled clinical trials of phototherapy in the management of atopic dermatitis, nine trials with a total of 363 patients were analysed. Three studies showed that UVA1 is faster and more efficacious in treating acute atopic dermatitis. Two trials revealed that the combination of UVA and UVB was superior to UVA alone. Two studies showed that narrow band UVB is more effective than UVA or UVA1 for chronic atopic dermatitis.

Cyclosporine A inhibits the transcription of interleukin 2 and several other cytokines, thus inhibiting the activation of T cells. The major side effects are nephrotoxicity, hypertension and gastrointestinal discomfort. In a recent review and meta-analysis of cyclosporine A in the treatment of patients with atopic dermatitis, 15 studies with 602 patients were analyzed. The duration of treatment varied from six weeks to twelve months. Nine studies used higher dosages of cyclosporine A (4-5 mg/kg) and showed an average 40% change in mean disease severity after two weeks compared to an average 20% change in disease severity in four studies using lower dosages (2.5-3 mg/kg). The relapse rate after discontinuation of cyclosporine A was evaluated in three studies. In general, the relapse rate was high, and 50-86% patients relapsed from two weeks to nine months after discontinuation of cyclosporine A.

Mycophenolate mofetil (MMF) suppresses purine synthesis in B and T cells. The commonest side effect is gastrointestinal upset. Other rarer side effects include immunosuppression, opportunistic infection and lymphoproliferative disorder. A recent retrospective analysis showed the MMF was useful for severe childhood atopic dermatitis. A total of 14 patients were studied, four of which had complete remission, another four had more than 90% clinical improvement, and four other patients had 60-90% improvement. One patient failed to respond. The drug was well-tolerated with no immunosuppression and infection noted.

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, have been shown to be safe and efficacious for the treatment of atopic dermatitis for children above the age of two. The speaker advised that topical calcineurin inhibitors should be used as an intermittent treatment alternating with topical steroid when topical steroid has failed or when one wants to avoid the side effects of topical steroid. The causal relationship with lymphoma has not been established, but discussion with patients and parents is mandatory.

II. Challenging infantile haemangioma

The patterns of infantile haemangioma (IH) have significant influences on the management and outcome in paediatric patients. This session focused on segmental lesions, which are lesions which cover a broad anatomical area or a developmental subunit. The presence of a segmental lesion often implies the involvement by other organ systems. Therefore, detail imaging studies of the relevant organ systems will help to detect extra-cutaneous involvement before the clinical manifestation of these complications.

There are four patterns of facial segmental haemangioma. Segment 1 is frontotemporal, segment 2 is maxillary, segment 3 is mandibular and segment 4 is frontonasal. The segments do not correspond to dermatomes. Lesions which are located in lower face often match the facial prominences. These lesions are eleven times more likely to be complicated by extra-cutaneous involvement. The segmental IH implies possible early developmental anomalies. They ulcerate more commonly than localised IH, and are associated with internal haemangiomatosis. 'PHACES' syndrome is a collection of anomalies associated with segmental haemangioma. 'PHACES' stands for posterior fossa and other central nervous system malformation,

haemangioma (typically segmental), arterial anomalies, coarctation of aorta, eye anomalies, sternal cleft and supraumbilical raphe. Infants with facial segmental IH, lumbosacral IH and segment 3 lesions are at risk of central nervous system vasculopathy, spinal dysraphism and airway involvement respectively.

Imaging studies are necessary when PHACES is in the differential diagnosis. Endocrine anomalies, such as hypothyroidism, are increasingly recognised. The use of high dose systemic steroid treatment for complicated IH is associated with an increased risk of infections. The speaker suggested the use of respiratory syncytial virus vaccine and *Pneumocystis carinii* vaccine as prophylaxis in infants receiving systemic steroid. Calcium and vitamin D supplement are also beneficial. For the treatment of ulcerated haemangioma, early surgical intervention together with medical therapy will help to reduce complications such as infection and bleeding. The treatment of nose tip haemangioma, 'Cyrano nose', is difficult as underlying cartilage involvement will distort the facial feature and early surgical intervention is warranted.

Learning points:

In the treatment of severe childhood atopic dermatitis, it is necessary to avoid pitfalls in the treatment regime. The use of narrowband UVB phototherapy, cyclosporine A and MMF provide alternatives to traditional treatment in recalcitrant cases. In approaching infantile haemangioma, it is particularly important to identify the segmental pattern of lesions so that any underlying systemic involvement can be detected with early intervention imposed.