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Reports written by

Dr. Adrián Alegre Sánchez

Dermatologist, Spain

Acne, rosacea, and hidradenitis suppurativa

Diagnostic and management challenge: Perianal HS and fistulising perianal IBD

Dr Afsaneh Alavi gave a presentation on the difficulty of differential diagnosis between perianal manifestations of inflammatory bowel disease (IBD, Crohn's disease) and hidradenitis suppurativa (HS) in the same area. Dr Alavi reminded the audience that in most cases of HS-related fistulas, they are not truly fistulas as they don't connect to internal organs. Rather, they should be considered tunnels. For their study, her research team selected two cohorts of patients: one with HS and the other with IBD, in both cases affecting the perianal area. The researchers found a few characteristics that may be used to differentiate the two diseases. Patients with HS tend to be younger, smokers, have a higher body mass index, more symptoms affecting the underarms and groin, a bilateral pattern of symptoms, and a greater frequency of tunnels. Patients with IBD, on the other hand, tend to be older, have worse systemic symptoms, be affected on the perineum, and present true fistulas. Analytically, both groups tended to be more anaemic, but there was a greater occurrence of neutrophilia in cases of IBD. In terms of radiological analysis, using MRI, you can see how IBD patients have intersphincteric fistulas and thickening of the rectal mucosa, while HS patients present tunnels and abscesses, with the rectum less affected.
In terms of markers, faecal calprotectin appears to be at higher levels in cases of IBD. In spite of all this, many cases cannot be differentiated and should be considered mixed cases called "perianal fistulising disease."

Spesolimab for hidradenitis suppurativa: A proof-of-concept study

Spesolimab is a new biologic drug of interest for treating hidradenitis suppurativa. Dr Afsaneh Alavi spoke about its usefulness. It is an IL-36 receptor monoclonal antibody. The IL-36 pathway is hyperactivated in patients with HS. In the study presented, researchers tracked a treatment and a placebo group for 12 weeks, then provided maintenance treatment to both groups for an additional 12 weeks. The treatment group received spesolimab at 1200 mg IV as induction therapy at 0.1 and two weeks, then 1200 mg IV every two weeks thereafter as maintenance therapy, i.e., at four, six, eight, and 10 weeks. Following the initial 12 weeks, maintenance therapy was given at 600 mg subcutaneously every two weeks. As for the results, in the treatment group, all types of lesions were

reduced at 12 weeks. The greatest difference was found in fistular lesions and tunnels, with a 40% reduction, compared to a worsening of 56.6% for the placebo group. A reduction of IHS4 scores was observed at week 12 and was maintained at week 24. As for the profile of adverse effects, most of those found in the spesolimab group were local injection site reactions or fatigue. With regard to the selection of spesolimab over other biologics, Dr Alavi indicated that spesolimab appears to be better than adalimumab for treating patients with many fistulas or tunnels.

The human-skin commensal Cutibacterium acnes induces epidermal lipid synthesis

Dr David Boudier presented a study on the ability of Cutibacterium acnes to induce lipid synthesis. The in-vitro study showed that the amount of lipids produced depends on the total amount of C. acnes and is not stimulated, for example, by S. epidermidis. Additionally, that stimulus of lipid synthesis does not depend on the C. acnes phylotype. Of the different molecules produced by C. acnes, it was shown that propionic acid is most responsible for the lipid production by keratinocytes. It appears that PPA receptors are responsible for this activation, especially PPAR-alpha. It also appears that there is feedback between the lipids generated by the keratinocytes and the strains of C. acnes to hinder their growth.

Unique molecular features of the Cutibacterium acnes 70S ribosome and its implications for antibiotic therapy in acne vulgaris

Dr Christopher Bunick reminded the audience that among all medical specialists, dermatologists prescribe the most antibiotics. Among those prescribed antibiotics, over 70% are tetracyclines because of their anti-inflammatory action. Tetracyclines can even have anti-oxidant, anti-lipase, and anti-metalloproteinase effects, among others. Their classic antibiotic action occurs when they bind with the 30S subunit of the bacterial ribosome to inhibit protein synthesis. The problem with tetracyclines is that they are broad-spectrum antibiotics and can have significant effects on the entire intestinal microbiome. Sarecycline, belonging to the tetracycline class, has a larger molecule size that allows it to be more selective for Gram-positive bacteria without as broadly affecting intestinal Gram-negative and other bacteria. Dr Bunick's team was able to show that this is because sarecycline inhibits two different spots on the ribosome, both 30S and 50S, making it the only antibiotic to have this double effect. As such, sarecycline acts against both the decoding of mRNA and the translation into proteins by the ribosomes. This reduces the risk of bacterial resistance to negligible levels. Thanks to this, using sarecycline allows us to be more selective while having fewer adverse effects, both in the treatment of acne and, in the future, other dermatological conditions.

Successful modulation of the PPAR-γ receptor in the treatment of acne vulgaris: Results of an international phase 2b study with NAC-GED-0507 gel. The GEDACNE Study

Dr Mauro Picardo presented a study of a new topical drug with the ability to modulate PPAR-gamma in moderate to severe acne. The drug in question is N-acetyl-GED-0507-34-LEVO (NAC-GED) at 5% in a gel, used in a study for 12 weeks of treatment. The study compared treatment with 5% and 2% gel against a placebo group. With regard to the results, the research team saw a 57.1% reduction in total lesions with the 5% gel, versus 33.8% using the vehicle alone. The results were significant both for inflammatory lesions and non-inflammatory lesions, but the effect was greater for inflammatory lesions. Additionally, the results were dose-dependent, with the 5% concentration of the drug producing a greater effect. As an advantage over other topical drugs, the researchers did not find adverse effects such as irritation, dryness, peeling, etc.

Combination treatment with adipose stem cell exosomes (ASCE) and fractional CO2 laser for acne scars: A 12-week prospective, double-blind, randomized, split-face study

Dr Byong Seung Cho presented a study of treatment with adipose stem cell exosomes and fractional CO2 laser for acne scars. The exosomes act as intercellular messengers and contain fragments of RNA, DNA, and proteins. There are many different types of exosomes (as many as there are types of cells). Many of them have anti-inflammatory or regenerative effects, among others. Currently, they are being indicated for many different purposes. This study did a comparison of using fractional CO2 laser + 30% exosome gel versus fractional CO2 laser + placebo gel. In total, subjects received three sessions of treatment. The treatment group showed improvement of 32.2% on the ECCA acne scar grading scale, versus 19.9% for the placebo group. Additionally, in the treatment group, erythema and recovery time were reduced.

Wound healing and keloids

Combination approach using laser-assisted drug delivery (LADD) and topical treatment for the treatment of keloid and hypertrophic scars: Case series

Dr Irmadita Citrashanty presented her experience with combining laser therapy with other treatments for drug delivery. Dr Citrashanty recommended the combination of a vascular laser, such as pulsed-dye laser or ablative fractional laser, with injection of triamcinolone and 5-fluorouracil, along with a silica-based gel applied twice a week for refractory cases. In cases that don't tolerate corticosteroid injections, topical drug delivery is a good option.

Anti-IL-17A ixekizumab for treatment-resistant chronic venous leg ulcers: A phase II randomised, double-blind, placebo-controlled pilot trial

Dr Charlotte Cox spoke about her experience with using ixekizumab (an IL-17A inhibitor) for the treatment of chronic venous leg ulcers. This type of ulcer comes at a high cost for all health systems. Their pathogenesis involves excessive pathological inflammation. Dr Cox's team treated patients who had been suffering from such venous ulcers for more than six weeks and for whom conventional treatments had failed. Although it was a preliminary study, the patients treated with ixekizumab improved faster and more fully than patients treated with a placebo.

A comparative study of efficacy of intradermal injection of hyaluronidase in combination with triamcinolone acetonide and 5-fluorouracil in keloids and hypertrophic scars

Dr Rachita Durat spoke about a study comparing injection of corticosteroids, 5-fluorouracil, and hyaluronidase. According to Dr Durat, hyaluronidase appears to be more effective in a part of keloids where mucopolysaccharides have accumulated. In her study, researchers compared the use of corticosteroids + 5-FU to the use of corticosteroids + 5-FU + hyaluronidase. The medication combined 0.4 ml of triamcinolone at 40 mg/ml and 0.6 ml of 5-fluorouracil at 50 mg/ml to produce 1 ml total. That 1 ml was mixed with hyaluronidase in the second treatment group. The study found that the volume and other characteristics of the scars were reduced more in the group treated with the added hyaluronidase. The team did not find significant differences in adverse effects.

Medical aesthetics I: Rejuvenation and skin tightening with lasers and EBDS

Recent advances in laser and energy-based devices for skin rejuvenation in skin of colour

Dr Henry Hin Lee Chan presented several new technological advancements. Regarding acne treatment, Dr Chan highlighted the new 1726-nm laser, which, being multi-pulsed and combined with powerful contact cooling, is very selective for the sebaceous gland and is safe. Another new development in rejuvenation is non-focussed ultrasound for a powerful retightening effect.

Regarding fractional laser treatments, there's the new use of "focal point technology," which makes it possible to apply non-ablative fractional treatments with much greater energy (up to 150 mj per point, versus 70 mj used previously). The procedure is still in the development stage. As for ablative fractional treatments, Dr Chan pointed to "microcoring" or "micropunching" via microextractions of tissue as the future of this type of treatment. Additionally, the microcores can potentially be used to regenerate other areas of skin.

For pigmented lesions, a potential new development is treatment using controlled cooling, which differs from typical cryotherapy treatments. This technique is also known as cryomodulation. The pigmented lesion is cooled in a very controlled fashion. Thanks to this, it takes virtually no time at all to recover. The procedure could even be used for its anti-inflammatory effects to treat inflammatory pathologies such as psoriasis or atopic dermatitis.

Laser treatments for higher phototypes

The complexity of treating patients with darker skin is rooted in the fact that the doctor must contend with the more abundant melanin in these patients.

Pigmented lesions in dark phototypes

Dr Henry Hin Lee Chan explained the treatment options for solar lentigos in patients with darker skin. The main risk of Q-switched lasers in Asian skin is post-inflammatory pigmentation. Dr Chan laid out three types of approaches for such situations:
- A more aggressive approach using treatment with Q-switched 532-nm laser in fewer sessions, i.e., one or two, but with the risk of post-inflammatory pigmentation. In this case, use a small spot of about 2 mm and low fluency of 0.6 J/cm2 with nanosecond pulses or 0.4 J/cm2 with picosecond pulses.
- An intermediate approach using longer wavelengths, whether 532 nm or 755 nm, for example, without cooling and using compression so that the treatment can be carried out without creating issues with haemoglobin. Here, the endpoint is darkening of the lesion. This is probably the preferred option for the highest phototypes.
- A more conservative approach using low-energy pulsed light combined with non-ablative fractional treatment.

For melasma, Dr Chan proposes a preparation combining different topical depigmenting agents: azelaic acid, hydroquinone, and mometasone, adding tretinoin after six weeks if there is no irritation. Doing this after laser toning with Q-switched nanosecond or picosecond laser at low fluency is the best option. Other options for melasma include non-ablative fractional resurfacing and low-energy pulsed light.

In the case of periorbital hyperpigmentation, the important thing is to determine its origin: pigmentary, vascular, mixed, caused by diving, etc. In such cases, Dr Chan recommends using a mixed approach with vascular laser and Q-switched pulsed dye laser at low fluency.

Collagen remodelling with darker phototypes

If what you're aiming for is general rejuvenation using fractional laser, Dr Chan reminded the audience that the risk of post-inflammatory pigmentation is proportional to density, more so than fluency. For this reason, he recommends for these patients that you be more conservative, and preferably use non-ablative lasers. As such, it's better to conduct more sessions with lower-density passes, obtaining the same results but with a better safety profile.

Vascular laser with darker phototypes

Here, Dr Chan reminded the audience of the importance of adequate cooling. In many cases, it would be preferable to use longer wavelengths, such as 755-nm alexandrite laser or 1064-nm Nd:YAG laser.

Tattoo removal using laser

Dr Mathew Avram reminded the audience of the importance of not underestimating the number of sessions required for tattoo removal. It is important to assess all aspects of the tattoo: whether it was done by an amateur or a professional, the colour, if it's multicolour, the skin phototype, the age of the tattoo, palpate the skin to assess the density of the ink, etc. Professional tattoos are much more difficult to remove. The colour of the ink should guide the wavelength selection. The colours that respond most poorly are yellow, orange, and purple.

We must bear in mind that even picosecond laser treatments can cause damage to epidermal cells loaded with melanin and that can cause the development of post-inflammatory pigmentation or hypopigmentation. Hypopigmentation resulting from tattoo removal is very common and can be improved with non-ablative fractional lasers or with ablative fractional lasers to obtain a consistent skin tone.

For post-treatment care, Dr Avram recommends applying Vaseline, non-occlusive dressings, compression, and avoiding friction and sun exposure. Perfluorodecalin patches during treatment help prevent skin bleaching caused by dermal and epidermal blisters. As such, they allow us to do more passes in a single session, although their long-term value still has not been fully proven.

Dr Avram recommends combining each nanosecond and picosecond Q-switched laser session with ablative fractional laser afterwards to reduce the risk of scarring or fibrosis in the treatment area. Another option would be to follow the laser treatment with microneedling or even microcoring treatment.

One type of approach being studied is the use of acoustic shock wave technology with laser treatment, which may further mobilise the tattoo ink after applying the Q-switched laser treatment. Doing this may speed up the tattoo removal, allowing for fewer session.

Fibroblast senescence in tissue decline and skin ageing: Future therapies

Dr Scharffetter-Kochanek

Ageing is a complex process due to the varied composition of tissues: epidermal and dermal cells, skin appendages, and the extracellular matrix. Fibroblasts are a key player and receive a signal from reactive oxygen species to alter their growth in all tissues, including muscle and bone, not just the skin.
It's likely that an increase in tumour development is more closely related to immunosenescence, but it also involves altered growth of senescent fibroblasts. In fact, researchers have seen more aggressive melanomas in older patients due to the immune alteration in senescent fibroblasts. When fibroblasts suffer from senescence, they reach a point where they stop dividing, but can also no longer undergo apoptosis. As such, they remain stuck in a progressive growth pattern with an inactive or inefficient metabolism.

There is a secretome associated with senescence. In it, there are specific cytokines that are generated as cells age. As such, not only does one cell age, but also the cytokines are distributed to adjacent cells, increasing the number of cells affected by this "paracrine senescence." This generates a senescent microenvironment. The senescent secretome is also associated with alteration of immune cells, such as natural killer cells, making them less capable of eliminating aged cells.

Dr Scharffetter-Kochanek proposes that there are several ways to reduce this senescence:

- Inhibit the senescent signalling: in the senescent cells, there is persistent activation of JunB in the fibroblasts, altering interactions of the stem cell niche, reinforcing ageing processes. Certain studies seem to have shown that by inhibiting that signalling, the skin returns to more normal functioning. The trade-off here is that the signalling is important for hair follicles. As such, if you eliminate the signalling, you will alter the growth of hair and of skin appendage glands. This complicates the usage of this mechanism as it requires inhibiting the senescent signalling only in fibroblasts.
- Destroy senescent cells so that they don't amplify the senescent environment: in mice, researchers have seen how eliminating these aged cells results in a much younger phenotype. There are drugs that help reduce the senescent environment, including metformin and rapamycin. Additionally, habits such as exercise and calorie restriction can help. Also, ablative laser, especially ablative fractional laser, will eliminate the cells, and it has been shown that laser treatment results in better improvement than collagen remodelling alone. This is because it eliminates a large number of senescent cells and decreases the ripple effect of the ageing signals.

It is essential to understand that cell ageing is not just a cosmetic issue and that the presence of aged cells, because of specific signals, intensifies the ageing of surrounding cells, generating a ripple effect. As such, the treatment of aged cells should be viewed as important at all levels given that there are cosmetic implications, but also implications for survival, as eliminating these cells deceases the likelihood that skin cancer will appear, in addition to decreasing the aggressivity of tumours.

Medical aesthetics II: Botulinum toxin

Neuromodulator for upper and mid face

Dr Doris Hexsel reminded the audience of the importance of knowing the anatomy, but also the dynamics, of each patient in order to come up with the most appropriate injection techniques and doses for each case. For the frontalis muscle, it's important to be familiar with the "convergence" line, which is the area of the upper frontalis in which the muscle transitions from lifting the eyebrows to pulling down the hairline. It's also important to inject botulinum toxin along that line in order to reduce

that minimal depressant effect of the frontalis muscle. Additionally, results on wrinkles of the frontalis muscle are cumulative and more pronounced after several years of repeated injections. As for crow's feet, caused by the orbicularis oculi muscle, Dr Hexsel recommends not being very intensive with the treatment of the lower eyelid so as to avoid creating bags under the eyes.

In the mid face, Dr Hexsel suggests the need to compensate for treatment of the orbicularis oculi with treatment of the "bunny lines" caused by the nasalis muscle. With a gingival smile, up to five muscles may be involved depending on if the smile line is anterior, posterior, anterolateral, etc. An anterior gingival smile line, which is the most common, should be treated by injecting BT into the levator muscle of the nasal ala and upper lip. A posterior gingival smile line should be treated via the zygomatic muscles.

Neuromodulator for lower face and neck

Dr Denise Steiner provided recommendations for the treatment of the lower third of the face and the neck. In this area, the depressor anguli oris muscle is responsible for marionette lines due to its skin insertions and its triangular shape. Dr Steiner recommends two or three injections with more units of BT in the part of the muscle near the jawline (2-3 units in that area) and just 1-2 units in the part near the mouth, and never very close to the lip, so as to avoid lip incompetence when eating or drinking. The mentalis muscle should receive injections in the lower portion, 4-5 mm below the maximum depression of the chin. Injections should be given far down to avoid problems with the orbicularis oris muscle. The platysma muscle has many insertions in the skin and on the facial fascia. The areas of platysmal bands should be marked before treatment and you should inject 2 units every 1-2 cm superficially and in a well-distributed pattern. It should be avoided in patients with lipodystrophy, relaxed muscles, or slackness. A Nefertiti lift involves applying injections to the area of the jawline. As for the masseter muscles, Dr Steiner recommends using 20-30 units per muscle, distributed in three points on each muscle.

Topical therapies I

Calcineurin inhibitors: Fears, facts, possibilities, and off-label

Calcineurin inhibitors are very useful drugs, although more often than not we use them off-label given that they are only officially indicated to treat eczema. Dr Norbert Ferenc Kiss reminded the audience of their safety profile: they do not cause atrophy, they do not cause much transcutaneous absorption, and they do not come with as much risk of flare-ups as corticosteroids. Long-term studies show that they are safe and don't increase the risk of oncogenicity. Additionally, calcineurin inhibitors can be used off-label for numerous pathologies. Such use is supported by high-quality clinical trials for conditions including seborrheic dermatitis, vitiligo, lichen sclerosus, etc. In terms of adverse effects, admittedly, tacrolimus in particular can cause irritation, probably due to excipients such as cetyl alcohol and propylene glycol.

New topical anti-inflammatory drugs

Dr Nayera Hassan Moftah gave a presentation on new topical anti-inflammatory drugs that differ from drugs we already know like corticosteroids and calcineurin inhibitors. There are three groups of these new drugs:
1. Phosphodiesterase-4 inhibitors: PDE4 is responsible for converting cAMP to AMP. By blocking this pathway, cAMP accumulates, causing an anti-inflammatory effect by blocking other cascades. One of

these drugs is crisaborole 2%, approved for atopic dermatitis. Roflumilast 0.3% is up to 200 times more potent than crisaborole for treating atopic dermatitis and psoriasis. It has been approved for psoriasis since 2022 and it is in a phase III trial for atopic dermatitis. It may be very effective for psoriasis in intertriginous areas, which are difficult to treat.
2. Aryl hydrocarbon receptor agonists and modulators: Tapinarof is a small molecule with a modulating effect on the aryl hydrocarbon receptor. At 1% in a cream, it is approved for treating psoriasis. In terms of adverse effects, it can cause folliculitis and irritation.
3. JAK/STAT inhibitors: Belonging to the family of tyrosine kinase inhibitors. The most studied topical drugs in this category are tofacitinib, delgocitinib, ruxolitinib, and brepocitinib. In the case of atopic dermatitis, the cytokines involved send signals through the JAK family, making these drugs interesting for its treatment. Delgocitinib is already authorised for this use in Japan. In September 2021, the U.S. FDA approved ruxolitinib to treat atopic dermatitis. Many of these drugs are still being studied. In particular, the use of ruxolitinib for vitiligo looks promising: this indication is already approved and the drug appears to be superior to corticosteroids and calcineurin inhibitors for this use. For psoriasis, these drugs still do not have FDA approval. For alopecia areata, they do not appear to be effective in a topical form. There are many different pathologies in which they may be effective, including skin symptoms of lupus, granuloma annulare, and seborrheic dermatitis.

As for their limitations, the safety and efficacy of these drugs still need to be studied in depth for pregnant and nursing patients. Their long-term safety also needs to be studied further.

Hair diseases: Androgenetic and cicatricial alopecia

Frontal fibrosing alopecia and lichen planopilaris

Dr Matthew Harries presented new developments relating to lichen planopilaris and frontal fibrosing alopecia (LPP and FFA). With regard to cicatricial and lichenoid alopecias, we must bear in mind that the inflammation attacks the hair follicle bulge. As the bulge is where stem cells are located, even if the inflammation goes away, there will be no more potential for regrowth from the affected hair follicle.

Both lichen planopilaris and frontal fibrosing alopecia are lymphocytic-type cicatricial alopecias and their characteristic clinical presentation as observed via trichoscopy shows perifollicular hyperkeratosis. The conditions do not necessarily present base erythema, but it may occur. The two conditions can be differentiated via their clinical presentations as histological differences have not been observed. However, it does seem that there are differences in the aetiopathogenesis as the two conditions respond differently to treatments.

Lichen planopilaris (LPP)

LPP presents clinically as irregular plaques with persistent hairs within them. It may appear to only affect one of every 10-20 hairs. There can be diffuse cases with persistent hairs, and when we look for activity, we should be looking at the margins. Alternatively, there can be small plaques with completely alopecic centres and surrounded by partial activity.
Histologically, scientists have observed the destruction of sebaceous glands, starting from initial stages and associated with perifollicular inflammation and concentric fibrosis. According to recent studies and a talk given by Dr Mariya Miteva, in LPP, we also often observe the presence of sebaceous cells (similar to the hypodermis) at upper levels of the dermis.

Current treatments are able to eliminate symptoms and halt the condition's progression, but not regrow hair. Being a chronic condition, doctors look for treatments that are safe in the long term. Treatments have varied over time and we should look for options based on our best knowledge of the aetiopathogenesis. Topical and local treatments are good options as the inflammation is superficial (the bulge is located at the insertion of the arrector pili muscle, just about 2 mm below the surface). In the future, it looks like lines of treatment will trend towards using JAK inhibitors, as well as other biologics like apremilast or drugs related to IL-17.

Due to the difficulty of reproducing views in successive visits, photographic tracking of patients with LPP is complex. Because of this, researchers are studying new options.

Female androgenetic alopecia (FAA)

The clinical presentation of FAA is distinct, but there are different variations: linear, diffuse, or pseudo-fringe (in which the alopecia maintains an initial hairline).
The presence of papules on the face is characteristic of the condition. A trick to see them well, including in images, is to use tangential (lateral) illumination. The presence of clinical signs outside of the scalp gives us hints about the development of the condition. The presence of facial papules, as well as the loss of body hair or eyelashes suggest more severe development, whereas if the activity begins in the eyebrows, the development may be milder.
As for treating the condition, you should focus on reducing inflammation via extended use of 5-alpha-reductase inhibitors. However, we still don't fully understand how they work in this condition.
During the discussion, people offered some interesting tips for tracking and treatment:
- Corticosteroid injection as a first line of treatment, using vibration anaesthesia;
- Always combine treatment with low-dose isotretinoin to treat facial papules (10 mg three times a week) as the papules alter the patient's quality of life (skin looks aged and "strange");
- Always consider the option of patch testing as the condition is increasingly being linked to situations like hypersensitivity or allergies to substances, and it appears that when the patient avoids the allergen, the clinical signs improve.
(It seems that linalool may be connected to FAA as it's present in so many cosmetic products and it causes many reactions, but data on the subject are preliminary.)
- We can't use clinical signs and symptoms to guide our assessment of the risk of progression or of response to treatment as their presence does not always imply activity. In one study of patient follow-up, Dr Saceda showed how the presence of clinical signs of inflammation is not correlated with the progression of hair loss.

Skin microbiome as bacteriotherapy for inflammatory pathologies

Dr. Masayuki Amagai

Dr. Masayuki Amagai has reviewed all the latest developments on the skin microbiome and its possible therapeutic implications. Manipulating the skin microbiome may have multiple therapeutic benefits. There are ongoing studies, focused especially on atopic dermatitis. For example, the use of *Roseomonas mucosa* in atopic dermatitis. The use of cultures of this species from people without atopic dermatitis and their application to the skin in patients with atopic dermatitis appears to have maintenance effects between flare-ups following conventional treatments and opens the door to other treatments, including monotherapy.

Another approach is the use of bacteria that can compete with and inhibit *S. aureus*. Staphylococcus homins A9 (ShA9) has antibacterial action on *S. aureus*. In a study with strains of ShA9 from healthy patients, applied in murine models with a filaggrin mutation to simulate atopic dermatitis, a significant improvement in eczema was observed. It has been tested in human patients, achieving a reduction of *S. aureus*, but without significant effect on the disease as such. The use of cultures of coagulase-negative staphylococci to compete with *S. aureus* is also being studied, in this case achieving an improvement in the control of the disease.

A different approach is the use of *S.cohnii*, which does not reduce *S.aureus* colonies but increases natural cutaneous glucocorticoids, creating a potent anti-inflammatory effect. This effect of *S.cohnii* has been studied using dermatitis and eczema models generated by imiquimod and in mutations in murine models.

News in female androgenic alopecia

Dr Ulrike Blume-Peytavi updated us on female androgenic alopecia. In women, androgenic alopecia is very different from men, since the patterns are much more varied, as is the response to treatments. In fact, the same loci related to heritability have not been observed, as is usual in males. We should call it FPHL (female pattern hair loss) and not female androgenic alopecia since its pathogenesis is not always mediated by androgens. Your approach must also be much more holistic.

The fact is that there are hormonal alterations in the blood, which appear in a small subgroup. There are many women with symptoms associated with menopause and ageing that appear to be of a different origin than those that appear in young women.
It is very interesting how cases have been observed in patients with androgen insensitivity, including cases where circulating androgens are not present, which is why not all women respond to the same treatments.

The severity indices or scales are not currently adapted to this kind of variability. It is important when we assess its severity, to also take into account the amount of hair that is falling out at any given time.

Evidence-based treatments are complex. Some that have been highlighted for their general usefulness are:

Oral minoxidil

It shows effectiveness in all studies. The increase in hair thickness and the presence of terminal hairs is dose dependent. However, so is hypertrichosis and the increased risk of cardiac side effects. However, these side effects are rare. In most countries, it must be formulated and the majority of cases with side effects are associated with errors in the formulation.

Prostaglandins

Studies have always shown that upregulating stimulants or downregulating inhibitors achieves good results. But for some reason, this has not been translated into treatments that appear on the market.

Hair transplant

This can achieve good results in women, so we should not wait for patients with advanced alopecia to offer and/or perform it. A correct technique is very important to achieve increased density, as well as reduce post-transplant effluvium. It could even improve the growth of non-transplanted hair that was already in the area by providing plenty of stem cells and growth factors.

The field of functional medicine is booming, and studies of multiple substances, many of which are natural in origin, are revealing other therapeutic options and results that can help hair growth and therefore must be taken into account.

We must always combine medical treatments with cosmetic options due to the overwhelming influence that hair has on self-perception and therefore confidence and quality of life. As dermatologists we must teach patients options that they can use and how to do it: Wigs, extensions, hair fibres, dyes, cosmetic products for hair care, etc.

Reports written by

Dr. Lee Hwee Chyen

Dermatologist, Singapore

Medical Aesthetics I: Fillers and Threads

Anatomy applied for injectable fillers
Dr Andre Braz (Brazil)

Discussed the different “standards of beauty” between females and males and across ethnicities (Asians vs Caucasians)
Discussed the key concepts of facial fillers. To consider:
1) bone anatomy
2) facial ligaments
3) fat compartments
4) vascularization
The different planes were discussed, along with danger zones and areas to avoid
Videos on various injection techniques as well as practical tips and tricks were explained

Needle vs Cannula in the Middle third: soft tissue augmentation
Hassan Galadari (UAE)

Middle third of the face includes the tear troughs and cheeks
He discussed injection of fillers for volume replacement using a single entry method
And the differences between needle vs cannula injection techniques. Of note, fewer occlusion events occur with cannula

Lower face Aesthetics and Injection techniques
Dr Ada Trindade De Almeida (Brazil)

The different ethnic and gender preferences for fillers were explained – there are different “beauty standards” for the lips, jawline and chin.

In lower face aging, mandible size and volume are reduced and there is an increased aperture of the gonial angle.
G'prime: refers to the resistance to deformation and lifting capacity of the filler. Higher G' has more lifting capacity and suitable for injection into deeper planes. Lower G' has less lift capacity, more fluid products and is easy to spread, therefore is suitable for injection into superficial planes.
Calcium hydroxyapatite has a higher G'prime when not diluted. Dilution reduces the lifting effect but allows biostimulation action.
Hybrid products are therefore suitable for injections into superficial planes.
Different injection techniques and filler combination techniques were shown for lower face contouring.
CaHydroxyapatite can also be combined with botulinum toxin injections for jawline contouring.

Nails and Nail surgery

Nail Anatomy & Anesthesia
By Dr Eckhart Haneke (Germany)

Anatomy and imaging techniques in the assessment of nail disorders were discussed.
Innervation of the fingernails are supplied by volar and dorsal nerves.
Different techniques for local anesthesia of the nail for biopsies and procedures were discussed
A) Transthecal anesthesia
B) Distal infiltration "wing block"
C) Proximal finger block
D) Metacarpal block
E) Hand/foot block (very rarely used for nail surgery)
F) Spinal block (very rarely used for nail surgery)

Different types of local anesthesia were discussed. Common amide anesthetics include lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine. Articaine can be used for patients allergic to the common amide type anesthetics.
The concentration of 1:200,000 as available in almost all fixed LA-adrenaline preparations is used multiple times without any adverse effects. But Prof Haneke general does not use LA with adrenaline, simply because he always performs nail surgery with a tourniquet.

Nail Biopsy Techniques and Handling of Nail Specimens (From OT to lab)
By Dr Adam Rubin (USA)

Special issues in Nail unit Pathology:
1. A variety of specimens can be submitted to the dermatopathology laboratory including
- Nail clippings
- Punch biopsies
- Longitudinal excisions
- Total en bloc nail unit excision
- Partial digital amputation
2. Unfamiliarity of histology staff with nail unit anatomy to perform orientation and grossing of specimen

Differences in the indications between nail bed and nail matrix punches, the procedures, were discussed.
Inflammatory nail disorders require a matrix punch biopsy

Some common tips and tricks were discussed, these include
- Inking the surface of the biopsy specimen to help orient it may help as it can shrink after being fixed in formalin
- Having a diagram demonstrating which part of the nail unit the specimen is from will also be helpful to the person handling the specimen

Matrix tangential excision originally described by Prof Eckhart Haneke was also discussed
Videos on the various biopsy techniques were shown

Surgery for ingrowing nails and Benign Nail tumours
Dr Siliang Xue (China)

Ingrown toenails – the different severity index and corresponding treatment methods were discussed
Severity Index 1 (nail is normal)
- Asymptomatic: moisturizing cream or steroid ointment
- Symptomatic: alter the conflict between the distal horn of nail plate and lateral nail folds
Severity Index 2 (where infection / granulation tissue is present)
- Curettage of granulation tissue, and then using a tube to separate to separate the nail fold from the nail plate
Severity index 3 (chronic infection/hypertrophy)
- treatment to remove the hypertrophic tissue. And then remove the lateral matrix
Pincer nail treatment
- conservative treatment
- surgical treatment including – hanekes procedure, Suzuki's variant, fanti's variant, kosaka's variant, zook's variant

He then moved on to discuss other clinical nail conditions including:
- glomus tumour
- fibrokeratoma
- onychomatricoma
- digital fibromyxoma
- exostosis and osteochondroma
- soft tissue chondroma

Nail surgery

Local anesthesia, hemostasis, and pain management, post op dressings
Dr Eckhart Haneke (Germany)

Patient preparation:
Do not operate in case of infection, except if the surgery is intended to improve the infection
No smoking before surgery
Have the patient brush the hand or foot like you would do for surgery, and to bring a large shoe for toenail surgery
Disinfect very generously
Special preparations for nail surgery in children – consider the parents! Discuss anesthesia

Local Anesthesia
Different types for different purposes:

- Distal infiltration: “wing block”
- Proximal finger block
- Transthecal block for fingers 2-4
- Metacarpal block
- Hand/foot block and spinal block (rarely used for nail surgery)
- Articaine- used for patients allergic to common amide type of anesthetics

Nail surgery is always performed with a tourniquet, so LA with adrenaline (epinephrine) is not required
Hemostasis is not a problem in nail surgery as it is done with a tourniquet.
Types of tourniquets: penrose drain for all digits, metal band tourniquet, sterile glove finger for fingernails
The neurovascular anatomy of the nail was discussed
Pain management is a very important aspect of nail surgery. It starts before surgery, is maintained during surgery and continues after surgery
Before surgery, can consider: paracetamol, ibuprofen, metamizole, tilidine, other opioids. Consider pre-operative sedation or nitrous oxide for local anesthesia in extremely anxious patients. Use distraction method or device, especially in children.

During surgery, effective local/block anesthesia is important. Inject slowly and with the smallest needle #30. Use high LA concentration to minimize volume. Buffer and warm up LA
Different types of local anesthesia administration was discussed. Transthecal anesthesia was recommended, only one needle prick is needed with no damage to the neurovascular bundle. No post-injection numbness of the side of the finger and it is as fast as a proximal block.
For pain management during and after surgery, high LA concentration works faster and longer. Use long acting LA: ropivacaine 0.5- 1%., add bupivacaine to lidocaine or inject bupivacaine after surgery.
For post-operative pain management:
instruct your patient to elevate the operated extremity for at least 48 hours. This prolongs the action of the local anesthesia, reduces post operative bleeding and swelling, improves and speeds up healing and decreases pain over the entire healing period.
Use long acting LA: ropivacaine 0.5- 1%, add bupivacaine to lidocaine, or inject bupivacaine after surgery. A study has shown that the intensity of pain during the first 24-48 hours after surgery is indicative of the pain during the entire healing phase.
Post operative pain management: Pain medication has to be adapted to the individual pain threshold and the type of surgery. Some interventions are notoriously painful, others not. Discuss pain medication with your patient.
Adapt the pain medication according to the type of surgery. Nail avulsion is very painful. Interventions touching the bone may be painful for 24-72 hours.

Post op dressings:
The dressing is adapted to the type of surgery, the extent of the wound, expected post operative pain, infection risk, age, physical activity, way/transport home.

Preferred post operative dressing:
Vaseline-based ointment to prevent dressing from sticking to the wound. Thick gauze pad to absorb blood and inadvertent shock post-op. Circular dressing with (elastic) gauze bandage.
Dressing change is recommended after 24-48 hours. A luke-warm finger or foot bath (with or without a disinfective agent) facilitates the removal of the dressing.

Antibiotics or not: routine antibiotics are not indicated as nail surgery has to be sterile. However, if you are afraid of a postop infection, do give an antibiotic that covers both staphylococci as well as enterobacteria.

Nail Bed diagnostic procedure: punch or excision biopsy
Dr Severin Laeuchli (Switzerland)

Nail unit biopsies
Indications
- Malignant tumours and precancerous conditions
- Nail bed (bowen's disease, BCC, SCC, melanoma, Kaposi sarcoma, metastatic tumours)
- Nail matrix (melanonychia stirata)
- Elderly, Caucasians
- Solitary, unexplained or new, widened, very dark, growing
- Thumb, index, great toe

- Benign tumours of the nail bed and nail matrix
- Enchondroma, exostoses, glomus tumor, pyogenic granuloma, wart, epidermal cyst, fibroma, osteochondroma, nail matrix tumours
- Inflammatory conditions
- Psoriasis
- Lichen planus
- Long standing, treatment non-responsive onychomycosis

Nail plate avulsion
Indications:
Visualization and/or biopsies of nail bed, PNF or LNF groove or matrix
Visualization and/or removal of tumors
Definitive nail removal

It should not be a treatment option without accompanying measures for dystrophic nails, ingrown nails or onychomycosis.

Nail plate repositioning:
- Protects the wound, nail bed and matrix 3- 12 weeks postoperatively
- Contraindications: nail infection, wound contamination, excessive drainage
- Make transverse, basal or lateral cuts to ensure drainage
- Place the stitches laterally or crossed over in the X-fashion
- Keep the nail plate in iodine solution until repositioning

Various videos and diagrams were displayed to show the types of approaches to nail bed biopsies and nail matrix biopsies.
In nail biopsies, when hard nail plates are encountered, it can be very frustrating, dangerous and painful.
To soften the nail plate, soak in chlorhexidine and warm water for 15- 20 minutes.

Nail bed therapeutic procedure: Glomus tumour, onychopapilloma and longitudinal erythronychia
Dr Bertrand Richert (Belgium)

What causes Longitudinal erythronychia?

Most etiologies share the same general pathogenesis. Results from matrix disturbance; the bed and plate may be innocent bystanders and/or secondarily involved.
Longitudinal erythronychia may be caused by

1. Submatrical glomus tumour
2. Onychopapilloma

Submatrical glomus tumour:
- Presents with longitudinal painful erythronychia
- Pain could be spontaneous or triggered by cold or pressure
- Notched at its end

Onychopapilloma:
- Presents with thin well defined longitudinal erythronychia, not painful
- V notch in the distal matrix
- Distal subungual hyperkeratosis
- Splinter hemorrhages
- Distal onycholysis or fissure
- Females (60%)
- Thumb +++

Various videos and diagrams were displayed to demonstrate different methods of excisions of the above tumours.

Nail matrix diagnostic procedure: Diagnostic excision of longitudinal melanonychia
Dr Chander Grover (India)

“No-go” areas in nail surgery: ventral/proximal nail matrix, distal nail matrix and the areas near the extensor tendon insertion.
The biopsy is to be taken down to the periosteum.

What is longitudinal melanonychia?
- Brown/gray/black band of nail plate
- Cause: matrix/melanocyte activation or proliferation
- Melanocyte activation – hypermelanosis of various causes
- Melanocyte proliferation: lentigo, nevus, melanoma
- Origin: distal matrix (mostly) or proximal matrix

Management of Longitudinal melanonychia
Goal: early diagnosis of melanoma
Tools for management:
- Clinical examination
- Onychoscopy (nail plate, nail matrix, hyponychium)
- Nail biopsy and histopathology: gold standard, possibly therapeutic
Different etiologies of longitudinal melanonychia were discussed (benign vs malignant causes)

Principles of matrix biopsy for LM
1. Always biopsy the origin of the band (not in between)
2. Melanotic origin should not be partially biopsied
- Does not allow complete examination of the pigmented lesion
3. Several techniques possible for removal of the melanotic matrix origin
- Choose as per the size of LM
- Choose as per location in matrix
Precautions
- Always withdraw the plunger before administering the anesthetic solution

- Nerves lie close to vascular structures
- A nerve block will have an onset over a few minutes, do wait for the complete effect before starting the procedure.

Which block to choose?
- Matrical block

- If only partial proximal nail avulsion is planned
- Proximal or distal digital block

- If more extensive removal is expected

Exsanguination and tourniquet
- Gauze strip tourniquet
- Sterile glove tourniquet
- Others: sterile penrose drain, foleys catheter

In the procedure, 2 aims
- To expose the matrix origin of the LM band
- To excist it in totality

To avulse or not to avulse the nail plate?
Advantages
- Visual confirmation that the lesion has been fully removed
- Easy harvesting of the specimen

Disadvantage
- Suboptimal histopathological specimen

Various videos and diagrams were shown to demonstrate the technique of the nail matrix biopsies for LM

Ideal nail dressing should be
- Absorbable, non adherent
- Painless removal
- Bulky dressing – adequately secured to the wrist/ankle
- Dressing with tip exposed: ideal but not practical
- Specialized footwear/sandal with Velcro straps
- Should loosen / remove dressing if throbbing pain

Conclusion
- Nail matrix is the “sanctum-sanctorum” of the nail unit; principle of operating in this area should always be kept in mind
- Matrix biopsy is indicated for any doubtful LM, better to be safe than sorry
- Tangential biopsy gives adequate tissue with least risk of scarring

Onychomatricoma and Digital Fibrokeratoma
Dr Nilton Gioia Di Chiacchio (Brazil)

Onychomatricoma
- Rare benign tumor of the nail matrix
- Probably misdiagnosed
- F>M 2.16 : 1
- 51 yrs of age
- Painless tumour

- Rare in children
- Dominance in white people
Various diagrams and videos were shown to discuss the histology of the onychomatricoma, along with the excision techniques.

Fibrokeratoma
- Common tumour of the nail folds/ matrix/bed/hyponychium
- Usually solitary
- Trauma
- Matrix: nail thickening and a honeycomb appearance of the nail on plate avulsion
- Nail bed: rim in the nail plate
Various excision techniques were demonstrated via subsequent video clips

Nail fold therapeutic procedure: Ingrown nail phenol matricectomy and other techniques
Fatih Goktay MD (Turkey)

Ingrown nail
- A painful conflict between the nail plate and periungual soft tissue
Matricectomy methods

1. Surgical
- Winograd
- Frost
- Suppan
- Selective excision of the lateral matrix horn (less invasive technique, higher success rate)
2. Physical
- Electrosurgery
- Co2 laser
3. Chemical
- 80-90% phenol
- 10% NaOH
- 100% TCA
**wedge excisions are no longer recommended

Chemical matricectomy with Phenol:
- Phenol is a carbolic acid
- Has three main properties: necrotizing, disinfecting (lower infection risk), anesthetic (phenol induces demyelination of the terminal nerve endings for several weeks,painless postoperative period)
- Phenol acts by coagulating tissue proteins and causes coagulation necrosis

How to perform phenol matricectomy?
- It is performed under digital block anesthesia
- A tourniquet is essential for bloodless surgery
- Blood neutralizes the phenol
- This is the most common cause for recurrences
- A finger of latex glow can be used as tourniquet
- At the end of the surgery, removal of the tourniquet should not be forgotten

Granulation tissue removal and nail plate avulsion
- Granulation tissues should be removed for better visualization of nail plate
- A 3-5mm nail plate strip is separated by an elevator

- This part of the nail plate is cut by a nail nipper or scissors
- It is very important to be sure that we have cut the nail plate up to its proximal edge
- Then this nail plate is removed by a hemostatic clamp

Before phenolization
- The exposed nail bed and matrix should be dried with gauze
- Periungal tissue may be protected by applying ointments (sterile Vaseline or antibiotic ointment)

Post operative oozing
- Phenol can cause post op oozing
- May continue up to 6 weeks
- What may help: gentle curettage after surgery, 20% ferric chloride application, foot baths may shorten this time

Safety and hazarads
- Phenol matrixectomy is safe for health care personnel exposed for up to 21 minutes of the procedure
- Phenol should not be used if the patient, physician or medical assistants may be pregnant

Summary
- Considering the efficacy and the side effect profiles, phenol and other chemical matrixectomies seem to be more preferable than other matricectomy methods in the treatment of ingrown nails caused by the nail plate
- Very good cosmetic results can be obtained with soft tissue excision in the treatment of ingrown nails caused by periungual soft tissue hypertrophy
- In severe cases accompanied by a wide nail plate, the above two methods can be combined.

Skin ulcers and keloids: Treatment options for keloids and hypertrophic scars

Combination Therapy for keloids and Hypertrophic Scars
Dr Peter Peng (Taiwan)

<u>Factors associated with the development of keloids and the mechanism of keloid formation:</u>
- Vascular: endothelial cell dysfunction, hypoxia, altered circulating fibrocytes, increased cytokines
- Mechanical: Mechanical clod -> mechanosignalling -> increased hypoxia, inflammation and angiogenesis pathways.
- Autoimmune: increased T cells, IL-4, IL-13 secreted by Th2 cells – these promote the synthesis and metabolism of collagen, resulting in reticular fibrin deposition
- Genetic: Epigenetic mechanisms represented by DNA methylation, histone modification and mRNA regulation -> altered collagen deposition and fibroblast proliferation
- Neurovascular: Sensory neurons -> neurotransmitters
Increased proliferation of keratinocytes and fibrocytes, Increased MMP2,9 and increased tissue remodelling, Increased expression ratio between collagens I and III, in favour of collagen type I

<u>Topical formulations targeting symptoms in skin scarring</u>
Dryness: use silicone oils and hypoallergenic moisturizing creams, vitamin E
Itching/pain: use St Johns wort, onion extract, green tea extract
Inflammation/redness: use Green tea extract, topical antibiotic ointment, topical betuline gel

Stiffness/pliability: use onion extract, imiquimod and tranilast 8% gel

Injection treatments
- Intralesional steroids, or 5FU or mixed.

Hypertrophic scars
- Conventional treatments include wound compression, laser, silicone cream, flavonoids, botox , scar excision and microneedling

Botulinum toxin for scar treatment
- In research, most clinicians have confirmed the clinical effectiveness of BTXA in the prevention and treatment of pathological scars, yet its mode of action and combination therapy need more research
- 5 u per point, can be used intraoperatively, and right after surgery to 9 days after surgery

Laser assisted delivery of corticosteroids and antimetabolites
- For triamcinolone acetonide suspension (TAC), 5FU
- The hypertrophic portions of the scare are treated with ablative fractional laser, and within a few minutes of laser treatment the solution is squirted and applied onto the treatment area. The excess may be wiped off with gauze and wound care can proceed in the standard fashion.
- This delivery of medicine is “off label”
- Can be done at intervals of 1-3 months

Keloid treatment options
- Intralesional steroid injection
- 5FU injection
- Radiotherapy
- Surgery
- Compression therapy
- Stabilization therapy
- Laser therapy
- Cryotherapy
- Photodynamic therapy (PDT)

Cryotherapy for keloids
Eva Kerby MD (USA)

How does cryotherapy work for keloids?
- It can reduce keloid size by cold-induced necrosis of the keloid tissue, and resulting in blood stasis within the keloid -> anoxia -> tissue necrosis
- Decrease pain and pruritus

Benefits of cryotherapy
- Increases MMP-9 , collagen III synthesis
- Induces differentiation of keloidal fibrolasts toward a more normal phenotype

When should cryotherapy be considered as a treatment option for keloids?
“nodular keloids

What are the different techniques for cryotherapy that can be used for keloids?
- Contact cryotherapy
- Intralesional cryotherapy

Logistics of contact cryotherapy
- LA
- 4x4 non-woven gauze into 6-8cc test tube, dip into styforam cup with liquid nitrogen
- 1 freeze-thaw cycle per session, freeze a 1-2mm margin around the keloid
- Make sure liquid nitrogen isn't dripping elsewhere onto the skin
- Tell the patient to expect blistering and drainage for the first week, then the area forms a scab
- Treat every 6- 8 weeks

Treatment is still combined with intralesional kenacort injections. Case examples shown

Post procedure care
- Cover with petrolatum, telfa and sterile gauze, and change dressing once daily
- Tylenol and ibuprofen for pain control for the first 48- 72 hours

Safety
Expected side effects:
- Pain
- Swelling
- Blistering
- Hypo or hyperpigmentation, especially in skin of colour

Less common side effects:
- Infection
- Inadvertent damage to the surrounding areas
- Cartilage cryonecrosis
- Subcutaneous emphysema

Contact vs intralesional cryotherapy: which method is better?
There was a study of 23 patients, 66 keloids
Each patient underwent single free thaw cycles monthly for a maximum of 6 months
Contact cryo:
- Complete flattening 49%
- Larger keloids did not respond as well
- Faster to perform, lower cost procedure
- Cons: most postop pain, higher risk of PIH and higher risk of post op infection

Intralesional cryoprobe
- Complete flattening 84$
- Faster response (1-2 treatments)
- Less postoperative pain
- Less hypopigmentation
- Cons: more expensive, requires more time (7-25 minutes per keloid)

Should cryotherapy be combined with ILK?
Yes, ILK +/- 5 FU should be injected intralesionally as maintenance after treatment with cryotherapy

If cryotherapy doesn't work?
Consider
- Excision + brachytherapy
- Excision + ILK & 5FU
- Oral pentoxifylline – decreases post operative keloid recurrence and pain & pruritus in existing keloids

Summary
- Cryotherapy is an effective treatment for nodular keloids
- Reduces keloid size and improves pain and pruritus
- Intralesional cryotherapy is more effective than contact cryotherapy
- Cryotherapy should be used as part of combination therapy with ILK +/- 5FU
- If not improved, consider excision with mandatory adjuvant therapy

Reports written by

Dr. Olivia Boccara

Dermatologist, France

Atopic dermatitis: new developments

Speakers:
- Disease phenotypes and comorbidities: Kenji Kabashima, Amy Paller, Christian Vestergaard, Tilo Biedermann
- Genotypes and pathogenesis: Akiharu Kubo, Stephan Weidinger, Yifeng Guo, Emma Guttman-Yassky
- Systemic and new treatments: Mette Deleuran, Andreas Wollenberg, Luca Stingeni, Carle Paul
- The barrier and classical therapies: Michael Cork, Kilian Eyerich, Linda Stein Gold
And free communications

Four sessions (two sessions of free communications) were devoted to atopic dermatitis (AD), providing a broad update on the pathophysiology of the disease and the treatments available. As the presentations were in some cases redundant, a summary is being proposed here.

AD is a multifactorial condition. It was initially considered to be a phenomenon of IgE-mediated hypersensitivity, before scientists discovered the central role of the Th2 signalling pathway, in particular IL-4 and IL-13, in altering the barrier function by reducing the expression of filaggrin and the synthesis of ceramides and antimicrobial peptides. Several endotypes have been described, depending on whether genetic determinism, the cytokine profile, the microbiome or the type of antigenic stimulation is being considered.
Filaggrin mutations are found in half of European patients; they are found less frequently in Asian patients and even less so in African American patients; their type varies depending on the population studied and is not correlated with the severity of the disease. A filaggrin mutation is neither necessary nor sufficient for the development of AD. Several dozen other genes are involved, coding for skin barrier proteins, the inflammatory and allergic response, and pruritus.
Th2 activation is constant. However, other cytokines can also be modified. Il-17 is increased in very young children, which may partly explain the frequent nummular, “psoriasis-like” form at this stage. In adults, on the other hand, CCL17 (TARC) is often increased. Gaining a better understanding of a patient’s skin cytokine profile will enable treatment to be tailored as closely as possible to their situation for greater efficacy. This is being made possible by the development of non-invasive techniques such as tape strips, which allow for the painless sampling of the surface of the skin. IL-31 seems to be specifically associated with the severity of pruritus. In addition, the specific features of pruritus, particularly its intensity, depend on the various types of nerve fibres and receptors involved.

Microbiome imbalance in terms of reduced microbiological diversity and the predominance of *Staphylococcus aureus* is a well-known mechanism; the extent of this imbalance is correlated with the severity of AD.

Lastly, with regard to sensitisation factors, allergens are large compounds that require barrier function impairment in order to penetrate the body. This is the mechanism involved in extrinsic AD, which is the most classic form and which affects around 80% of patients, who generally have elevated IgE levels. Haptens are small compounds that readily penetrate the intact skin barrier. These patients will have a Th1 cytokine profile and frequent sensitisation to metals.

Atopic dermatitis in children differs little in terms of its clinical presentation. The response to targeted therapies is comparable to that observed in adults. However, the disease is more severe after the age of 12, and the pattern of the lesions changes with age: infants mainly develop lesions on the convexities; in young children, the lesions become less exudative and mainly occur in the skin folds; and in adults, the lesions are more lichenified and excoriated.

Several studies have shown that the early application of emollients is of no benefit in preventing the onset of atopic dermatitis in infants. However, not all emollients are the same, and the use of sophisticated emollients, which supply specific fatty acids and can correct the skin's pH, could potentially help restore the skin barrier at an early stage and prevent the development of the disease. The STOP AD study showed slightly fewer cases of AD at 12 months in infants when this type of emollient had been applied; interestingly, these infants were carriers of a filaggrin mutation. The question now being asked in paediatrics in terms of therapies is whether more aggressive treatment at an early stage would modify the natural course of the disease, given that the aim of treatment, as far as possible, is to prevent AD from developing and worsening and also prevent the associated comorbidities.

There are many comorbidities associated with AD: atopy (oesophagitis, asthma, allergic rhinitis), cardiovascular and psychiatric diseases, social repercussions, contact allergy, and infections. Are these specific complications resulting from chronic inflammation, or are they consequences of being ill? It should be noted that their severity, particularly in the case of food allergies, is correlated with that of AD. Asthma patients with AD have a lower life expectancy than patients with isolated asthma. Indeed, certain comorbidities, such as asthma, oesophagitis, prurigo, infections, and psychiatric disorders, are greatly improved when AD is treated. The management of AD is essential in the management of comorbidities.

Genetic studies (single-nucleotide polymorphism (SNP) studies), which study the susceptibility of individuals to several types of diseases, show that certain polymorphisms are shared by AD patients and patients with inflammatory diseases of the digestive tract. In addition, inhibiting IL-4/IL-13 can promote inflammatory imbalance by stimulating the IL-17/IL-23 pathway, leading to the resurgence or onset of diseases such as Crohn's disease or psoriasiform eruptions. For these patients, JAK inhibitors appear to be a more appropriate option, since they inhibit several signalling pathways at once, albeit with the risk of additional side effects.

Epidemiological studies on populations living in very different environments (Greenland, India) have seemed to show that the environment, especially the climate (temperature, humidity level), probably plays a role in the severity, clinical presentation and progression of the disease. In these studies, AD was more severe and longer-lasting in Greenland than in India.

In terms of treatment, the European recommendations for the management of AD published in 2022 were reiterated, in particular the role of "classic" systemic therapies. Surprisingly, the use of systemic corticosteroid therapy is not strictly prohibited; ciclosporin, methotrexate and Imurel are still compounds that can be used, with a preference for MTX, which can be used for a longer period than ciclosporin due to their respective safety profiles. Mycophenolate mofetil should be abandoned because of its uncertain efficacy and poor safety profile, and in light of the new compounds available. The therapeutic arsenal is constantly expanding. In addition to dupilumab – which has been available since 2017 – tralokinumab and lebrikizumab, several monoclonal antibodies targeting IL-13 are

currently being developed.
A new class of compounds is being developed: OX40 (receptor on T-cells)-OX40L (antigen-presenting cells) inhibitors. One of these is rocatinlimab. Two other compounds from the same family are being studied, inhibiting the Th2, Th1, Th17 and Th22 pathways (Gottmann-Yassky et al. Lancet 2023). These compounds appear to offer a longer-lasting response with no relapse after treatment discontinuation, with a 20-week follow-up period.
Nemolizumab, an anti-IL31R antibody, specifically targets pruritus, not only in AD, but also in other pruritic diseases, such as pruritus associated with renal failure.
On the other hand, the first compound targeting TSLP has not shown to be effective, while others are currently being studied.
The systemic JAK inhibitors available are, in decreasing order of efficacy, upadacitinib, abrocitinib and baricitinib. They are superior to dupilumab in terms of short-term efficacy, particularly against pruritus; the difference in efficacy diminishes over time. The safety profile of JAK inhibitors is slightly poorer (infections, acne). Although the populations are very different, the thrombo-embolic and cancerous events observed with tofacitinib in rheumatoid arthritis call for caution, and the associated comorbidities and risk factors should be carefully considered before prescribing a JAK inhibitor, particularly for elderly patients.

New topical treatments are being developed or are already on the market in some countries. Topical JAK inhibitors, in particular ruxolitinib, a JAK1/2 inhibitor, have very low systemic uptake, even at very high doses. Efficacy appears to be rapid, from the very first days of treatment. The studies that have been undertaken have focused on patients over the age of 12 years.
Roflumilast is a phosphodiesterase inhibitor that is four times as potent as difamilast. A study is currently being conducted with patients aged six and over.
Lastly, tapinarof is an agonist of the AhR pathway. It inhibits the production of pro-inflammatory cytokines such as IL-17 (making it a potential treatment for psoriasis as well) and Th2 cytokines; it also stimulates skin barrier proteins. Its efficacy appears to be fairly slow, which means it should be reserved for moderate AD in children over the age of two years.

Paediatric dermatology: Hereditary and inflammatory diseases of childhood

Dermatoses in neonates: Hereditary diseases of the epidermis and dermis
Pierre Vabres (France)

The diagnostic approach ensuring appropriate management should be based on an analysis of the clinical signs present at birth, and on a clinical examination of the parents. Initial management should be that of a possible medical emergency. In the vast majority of cases, diagnostic confirmation is based on a molecular diagnosis, which is essential to provide families with the most accurate information possible, particularly in terms of the prognosis; indeed, the clinical presentation alone is not sufficient, and initial severity is not a predictor of future severity, and vice versa: some cases of epidermolysis bullosa simplex can have a worrying initial florid presentation, including systemic complications, but then progress more favourably and become milder.
The clinical examination of the child and their family will usually provide a strong diagnostic orientation, and the molecular diagnosis will be made using a panel. Without any diagnostic orientation, the exome or even the whole genome may be analysed. There are multiple transmission mechanisms (autosomal dominant, autosomal recessive, X-linked, possibly resulting from germline mosaicism), and de novo mutations are always possible.

Bullous lesions should suggest epidermolysis bullosa, and if there is a linear Blaschko configuration, incontinentia pigmenti.
In the event of erythroderma, histology can distinguish between a primary immune deficiency or ichthyosis.
Aplasia cutis congenita of the vertex can be indicative of rare forms of ectodermal dysplasia such as AEC syndrome; if combined with a generalised cutis marmorata appearance, it should suggest Adams-Oliver syndrome.
There are some rare hereditary forms of vascular malformations, and an examination of the parents can be very instructive.

Dermatoses in neonates: Hereditary immune deficiencies
Arti Nanda (Kuwait)

The immune system of full-term newborns is complete, particularly for innate immunity; the adaptive immune system has not yet come into contact with antigens. Premature infants have a more fragile immune system, with a reduction in gamma globulins, lymphocytes, complement, and antimicrobial peptides.
Early cutaneous manifestations are observed in almost 50% of patients with a primary immune deficiency, in addition to extra-dermatological signs such as dysmorphism, digestive signs such as diarrhoea, post-live vaccine infections, delayed growth, delayed cord separation, or a family history.
The most common cutaneous signs are early, recurring, atypical, extensive and severe infections that resist standard treatments, followed by eczematiform eruptions, which are also resistant and atypical, erythroderma, and lastly granulomatous manifestations, which are less common, particularly in very young children.

Inflammatory diseases: Atopic dermatitis (diagnosis and treatment in early childhood)
Mark Koh (Singapore)

AD in infants tends to affect the scalp, making it difficult to differentiate from genuine seborrhoeic dermatitis; it then mainly affects the convexities, followed by the skin folds in older children. The lesions are sometimes annular and can be confused with dermatophytosis; sometimes though, they are more sharply nummular. The lesions may be infiltrated, tending towards prurigo, and lichenified.
Bacterial (Staphylococcus, Streptococcus) and viral (herpes, Coxsackie, molluscum) secondary infections are common. On dark skin, follicular forms are more common, as is hypo- or hyperpigmentation.
Food allergy is not frequently associated with AD, but it should be investigated in the event of digestive signs, delayed growth, or severe skin involvement that is resistant to treatment.
Differential diagnoses in infants include zinc deficiency, Langerhans cell histiocytosis, neonatal lupus, psoriasis, genodermatoses, and primary immune deficiencies.
Topical treatments are recommended for mild forms. Topical calcineurin inhibitors are effective, with no risk of inducing lymphoma or skin cancer. Phosphodiesterase-4 inhibitors are an interesting alternative to topical corticosteroids.
For moderate forms, particularly affecting black or Asian skin, phototherapy is a good option.
Conventional systemic treatments and biotherapies should be reserved for severe forms.
The role of prevention with the early application of emollients remains debated.

Inflammatory diseases: Psoriasis (diagnosis and treatment in early childhood)
Lawrence Eichenfield (USA)

Around 2% of children worldwide suffer from psoriasis. Facial involvement is more common in children and can overlap with AD. There is often a family history. Scalp involvement is more common

in girls, while nail involvement is more often observed in boys. Early involvement of the nappy area is often confused with classic irritant nappy rash. Guttate psoriasis is a common form in children, often occurring secondary to a streptococcal infection, and the risk of it developing into a plaque form is estimated at 40%.
Joint involvement affects less than 1% of patients but warrants an ophthalmological consultation to systematically look for uveitis. The comorbidities include psychiatric manifestations such as depression, obesity, diabetes, and hypercholesterolaemia.
The therapeutic arsenal includes topical agents (topical corticosteroids, tazarotene, roflumilast, tapinarof), phototherapy, traditional immunosuppressants (ciclosporin and methotrexate) and biotherapies, which are constantly expanding, including for children. The choice of treatment will depend on the patient's age, the type and severity of their psoriasis, its repercussions and any comorbidities, the treatments already used, factors favouring flare-ups, and the preferences of the patient and family in terms of galenic formulation. The biologics available for children have a satisfactory safety profile, with ustekinumab in particular showing fewer infections than in patients treated with methotrexate or etanercept. TNF alpha inhibitors, used in other inflammatory diseases, particularly digestive diseases, cause paradoxical psoriasis, which is generally well controlled with local treatments. Several therapeutic trials are under way in children, testing apremilast, IL-23 inhibitors, and JAK inhibitors (deucravacitinib).

Paediatric dermatology: Emerging treatments in special topics

New treatment options and biologics in children
Mette Deleuran

New treatments for AD in children are gradually becoming available.
Dupilumab is authorised from the age of 6 months for severe forms; however, this situation is fairly uncommon. There were only 11 patients under 2 years of age in the 6 month-6 year therapeutic trial; there were around 150 older patients. There were only three cases of conjunctivitis in the treated group, with more infections observed in the placebo group. Tralokinumab is authorised from the age of 12, and will soon be followed by lebrikizumab. The safety profile of JAK inhibitors in children is similar to that in adults: the main side effects are acne and infections.

Emergencies including allergies in childhood
Michele Ramien

A new classification of severe cutaneous adverse reactions (SCARs) has been proposed.
The term "erythema multiforme" is reserved for the form formerly known as erythema multiforme minor, where the skin lesions are typically target lesions, which are few in number, and where mucosal involvement is often less severe. This rash is more likely to occur secondary to HSV infection.
Mycoplasma pneumoniae-induced rash and mucositis (MIRM) is specifically associated with Mycoplasma. The skin rash is bullous, but there are not necessarily target lesions. This rash can lead to disabling mucosal sequelae.
Stevens-Johnson syndrome and toxic epidermal necrolysis are grouped together under the disorder "drug-induced epidermal necrolysis" (DEN) and are therefore strictly drug-induced.
However, other infectious agents can induce the rashes described above, and in some cases, no inducing drug is found in DEN.

Urticaria and Mastocytosis

Cathryn Sibbald

In children, infections are the most common cause of acute urticaria, followed by medication, diet, and contact factors. The first-line treatment is still 2nd-generation H1-antihistamines, possibly accompanied by a short course of systemic corticosteroid therapy. After six weeks, the condition is known as chronic urticaria, whether spontaneous or induced (particularly physical urticaria). Spontaneous chronic urticaria generally resolves within a few years. In disabling forms, dupilumab and omalizumab can be used; they are generally effective at reducing pruritus and improving quality of life.
Cutaneous mastocytosis is said to be “solitary” when there are three or fewer skin lesions. The maculopapular form accounts for 70% of patients and the diffuse form less than 5%. If tryptase levels are normal, a systemic form can be ruled out. However, when tryptase is elevated, the condition is not necessarily systemic, but there is greater susceptibility to anaphylaxis.
KIT mutations are commonly found in patients, particularly the D816V mutation, in around 40% of children. In patients with another mutation, the disease develops at a later stage, and the prognosis is slightly poorer.
In terms of therapy, topical treatments such as corticosteroids and calcineurin inhibitors are used; JAK inhibitors could be considered. Omalizumab improves symptoms without altering tryptase levels. Imatinib (a tyrosine kinase inhibitor) is used in the absence of a D816V mutation, with the main side effects being cardiotoxicity and growth retardation. Midostaurin is used when there is a D816V mutation; it can induce thrombocytopenia.

Clinical features and the natural course of longitudinal melanonychia in children
Si-Hyung Lee

Longitudinal melanonychia in children is more common in the Asian population than in populations of European origin. In most cases, it takes the form of nail matrix naevi.
Cases of subungual melanoma in children are exceptional, and the few cases reported in the literature have been controversial.
Longitudinal melanonychia in children tends to disappear spontaneously.

Paediatric dermatology: Infectious diseases of childhood

Introduction of topic
Severe non-targetoid infantile exanthem
Q&As
Eduardo David Poletti (Mexico)

Dr Eduardo Poletti reviewed the main characteristics of severe exanthems in children. Acute generalised exanthematous pustulosis (AGEP) combines fever and non-follicular pustules, with no involvement of the mucous membranes, palms of the hands, or soles of the feet. Facial oedema can occur. He pointed out that in children, the rash is mainly infectious in origin.
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a febrile rash with facial oedema, adenopathy and hepatomegaly; the liver is most commonly affected internal organ. The viruses involved are HHV6, HHV7, EBV and CMV. Certain HLA groups are associated with greater susceptibility to this syndrome.
Toxic epidermal necrolysis is also associated with specific HLA haplotypes. The warning signs are highly suggestive and include a febrile syndrome with conjunctivitis, altered general condition, and

joint and skin pain. Treatment with TNF alpha inhibitors is proposed to block progression and induce healing. This treatment was also mentioned by Dr Ramien (above).
SSSS is a well-known toxin-induced exanthem related to an epidermolytic toxin that targets desmoglein 1, produced by Staphylococcus aureus, which is generally methicillin-susceptible. Recurring perineal erythema is a less well-known form of toxin-induced erythema that has not been widely reported in the literature; it is more likely to be of streptococcal origin, occurring secondary to sore throat. It is characterised by perineal involvement associated with a strawberry tongue and palmar desquamative erythema. Recurrence is frequent despite antibiotic treatment (Dr Maria Abad).
The epidemiology of dermatophytoses has changed considerably. Whereas tinea capitis used to be the main manifestation, tinea corporis is on the increase in India, with T mentagrophytes being found more frequently than T rubrum in mycological samples. Skin involvement is frequently multifocal and extensive. The speaker attributed these changes to changes in climate and lifestyle, particularly clothing (tighter-fitting clothes). This seems to be a public health problem in India today (Dr Jayakar Thomas).
The cutaneous manifestations observed during COVID were as follows: frostbite, predominantly affecting the feet, and urticarial, targetoid, vesicular, livedoid, purpuric and roseoliform eruptions. Cases of alopecia were also observed. While these manifestations appear to be non-specific, and could potentially be associated with other viruses, PIMS is a systemic inflammatory disease that seems specific, affecting older children than Kawasaki disease, with cardiovascular and digestive manifestations. The manifestations secondary to the COVID vaccine included injection-site reactions and urticarial or roseoliform eruptions (Bruno Ferrari).
Chikungunya is not uncommon in India. Several types of neonatal cutaneous manifestations can occur, secondary to maternal-foetal transmission; maternal fever in the 3rd trimester of pregnancy is often found. All the cases presented were serologically documented. Hyperpigmentation may primarily affect the face, particularly the median region and nose, or it may be more diffuse. Superficial bullous lesions may mimic SSSS, with a favourable spontaneous outcome, desquamation, and hypopigmentation. There may be deeper detachment but without any mucosal involvement and with a favourable outcome. Cases of ulcerated subcutaneous calcinosis have been described, also with a favourable outcome. Some of these cases have been published by the speaker, Sahana Srinivas.

Baricitinib is authorised for the treatment of alopecia in adults; a therapeutic trial testing ritlecitinib in children over the age of 12 has recently been published. The new drugs available include JAK inhibitors, which are more selective in theory. The aim is to improve efficacy and safety. However, it is not certain that in vitro selectivity can be reproduced in vivo, as host factors can modify this selectivity, and because of the interaction between different kinases. The results with this compound in this age group are comparable to those of baricitinib in adults, i.e. around 30% of patients are responders, with scalp hair loss reduced to less than 20%. Very severe forms with more than 94% scalp hair loss appear to be less responsive. The main side effects are acne and headaches, although there is also a risk of weight gain. Moreover, JAK inhibitors are teratogenic and require contraception, which can alter the risk of thrombo-embolic events. Several other compounds are currently being developed (Leslie Castelo-Soccio).
Pellagra, or niacin deficiency, is a less well-known deficiency disorder than acrodermatitis enteropathica and scurvy. The rash appears on the neck, neckline and face due to photosensitivity. It is associated with dementia and digestive signs such as diarrhoea. This disease is endemic in regions where the diet is restricted to maize, or in patients at risk of deficiency, due to a digestive disease for example. In addition, erythema nodosum is a possible cutaneous manifestation, although not specific to COVID (Christian Vestergaard).
Autoimmune bullous dermatoses differ little between children and adults. The most common forms in children are linear IgA dermatosis and pemphigus vulgaris. In newborns, forms of pemphigus vulgaris and pemphigoid gestationis can occur through maternal-foetal transmission (Enno Schmidt).

Paediatric Dermatology: Genodermatoses

Skin development
Muzlifah Haniffa

Muzlifah Haniffa presented the Human Cell Atlas project. Technological advances have made it possible to study genomic, transcriptomic and proteomic profiles, in other words multi-omics at cellular level, leading to the creation of a cellular atlas. This is a major tool for human physiology research. There is a prenatal skin cell atlas and a paediatric skin cell atlas. https://www.humancellatlas.org

Ectodermal dysplasias
John McGrath

Ectodermal dysplasias affect seven in 10,000 newborns. There are around 170 different types, at least 50 of which have not yet been characterised at molecular level. All modes of transmission are possible. The EDA, EDAR, EDARADD and WNT genes account for 90% of cases. Parents carrying a recessive pathogenic variant may present with minor, isolated signs. New clinical presentations and new genes are regularly being identified. Treatment remains symptomatic in most cases. However, two therapeutic trials are currently in progress, with promising results: the protocol of the EDELIFE trial involves injecting a recombinant protein (ectodysplasin) in utero. The newborns in the study were able to sweat. In AEC syndrome linked to a TP63 mutation, local application of a p53-reactivating compound leads to the re-epithelialisation of skin erosions and a major reduction in pain.

Mosaic skin disorders
Pierre Vabres

Mosaic abnormalities result from a somatic mutation, i.e. a mutation occurring after fertilisation. Any non-fatal pathogenic variant, usually responsible for a general disorder, can also induce a mosaic disorder. Nevertheless, most mosaic abnormalities result from variants that are fatal at the embryonic stage. These disorders are not inherited, whereas in a few rare cases, a non-fatal variant can be transmitted if the mosaicism affects the germ cells: this is possible for Darier disease and keratinopathic ichthyoses, for example. Lastly, some autosomal recessive diseases may have a mosaic presentation in a patient with a germline variant, in whom a second mutation occurs somatically; this is the case with certain ABCA12-mutated epidermal hamartomas.
Mosaic abnormalities related to fatal variants result from variants in genes belonging to four signalling pathways: G-protein subunits GNAQ/GNA11 (Sturge-Weber syndrome and port-wine stain, phakomatosis pigmentovascularis, congenital hemangiomas), tyrosine kinase receptors (venous malformations), the RAS-MAP kinase pathway (arteriovenous malformations; atypical lymphatic malformations: Gorham-Stout syndrome, kaposiform lymphangiomatosis; congenital naevi; epidermal naevus syndromes), and the PIK3CA-AKT-mTOR pathway (PROS, hypomelanosis of Ito). All cell types can be affected. In the field of vascular anomalies, there are some autosomal dominant diseases in which lesions appear due to loss of heterozygosity secondary to the occurrence of a second genetic event; this is the case of CM-AVM syndrome associated with RASA1 and EPHB4 mutations.

Epidermolysis bullosa
Liat Samuelov

The different types of epidermolysis bullosa (EB) were described: 1) EB simplex, associated with the following mutations: KRT5, KRT14, PLEC, KLHL24, DST, EXPH5, CD151; 2) Junctional EB (LAMA3, LAMB3, LAMC2, ITGA6, ITGB4, COL17A1, ITGA3); 3) Recessive dystrophic EB (COL7A1); 4) Kindler syndrome (KIND1). Each genetic variant is associated with specific cutaneous and extra-cutaneous manifestations (cardiac, digestive, renal), and its severity and prognosis vary; molecular diagnosis is essential for the management of these patients.

Skin tumour syndromes
Neil Rajan

Familial cylindromatosis is a disease associated with a germline mutation in CYLD, a tumour suppressor gene. The skin tumours observed include cylindromas, spiradenomas and trichoepitheliomas. They form a clinical and histological continuum. They affect the face, the sides of the nose, the scalp, the trunk, and the vulva in women, in whom the presentation tends to be more severe. These tumours gradually grow, by around 10% per year, and can be locally aggressive. Small lesions can be treated with laser therapy, but they recur and have to be treated again every two to three years. The phenotype can vary greatly from one family to the next, and even within the same family, with the same mutation. Therefore, molecular diagnosis has no prognostic value. In the event of a systemic unilateral presentation, there may be a mosaic abnormality due to the occurrence of a second somatic mutation in a patient carrying a germline variant.

New targeted therapies
Amy Paller

There are several avenues of treatment for EB:
In 2006, a child with junctional EB (LAMB3) with >60% skin involvement was treated with transgenic autologous keratinocyte transplantation; the LAMB3 gene was delivered by a retroviral vector. The result was maintained for more than six years after treatment (De Luca 2006, 2014). The same approach has been used with type VII collagen on a number of wounds, resulting in improved healing, reduced pain, and better quality of life. Studies are under way with a view to marketing this technology (Eichstadt 2019).
Topical gene therapy for type VII collagen has recently been approved in the United States.
Trials are currently being conducted on injectable recombinant type VII collagen (Nystrom 2022).
CHILD syndrome results from an abnormality in cholesterol metabolism. The clinical manifestations are related to the accumulation of the unmetabolised substrate. Topical application of a compound combining 2% statins and 2% cholesterol leads to a major improvement in the skin's condition (Paller 2011). The principle is the same for porokeratosis with lovastatin.
Since keratinisation disorders are associated with inflammatory manifestations whose mechanism is similar to that of psoriasis, the biotherapies available for psoriasis have been repositioned, sometimes with spectacular effects, and sometimes with more disappointing results.

Paediatric Dermatology: Vascular anomalies and practical therapies

Christine Labrèze, Mark Koh, Julie Powell, Margarita Larralde, Olivia Boccara

The 2018 version of the ISSVA classification of vascular anomalies was presented. A 2023 update is due to be published shortly (https://www.issva.org).
Vascular tumours in childhood include infantile hemangiomas (IHs), which are by far the most common. High-risk IHs are segmental forms in the head & neck, lumbosacral and perineal regions;

the risks are associated malformation syndrome and early painful and mutilating ulceration. Recently, the topographies at risk of PHACE syndrome in segmental facial hemangiomas have been extended to include involvement of the scalp, more specifically the cervical and retroauricular regions. Other problematic locations include the periorbital region, the tip of the nose, and the nipple region in girls. Ulceration is a very frequent complication of IHs. Patients with a hemangioma at risk of PHACE syndrome, especially if they have associated malformations, should be monitored over the long term, due to possible delayed complications: frequent headaches, deafness, neurological balance disorders, learning difficulties, etc.
Treatment with propranolol should be initiated in the first few months of life. As topical timolol is not very effective and passes into the bloodstream, it should not be used.
Congenital hemangiomas are less common. They are strictly congenital tumours that may involute completely in the first year of life (RICH); they may also partially involute (PICH, with around 30% of lesions presenting as RICH at birth) or fail to regress (NICH). Neuropathic pain is sometimes described by older children for residual lesions. In the neonatal period, if the tumours are very large, they may be complicated by cardiac hyperflow and transient thrombocytopenia. Somatic GNAQ mutations are sometimes found.
Tufted angiomas and kaposiform hemangioendotheliomas are even rarer; they may be complicated by Kasabach-Merritt phenomenon, whose prognosis been greatly improved with the use of sirolimus.
Venous and lymphatic malformations are slow-flow vascular malformations. They are benign lesions that require treatment when they are painful, bleeding or oozing or cause aesthetic discomfort. No curative treatment is currently available, so these are chronic diseases requiring long-term monitoring and adaptation of therapeutic measures as they evolve.
Lymphatic malformations are cystic lesions. The cysts vary greatly in size. Painful phenomena are linked to inflammatory flare-ups and less often to genuine secondary infections. Bleeding and oozing from superficial lymphangiectasia are very uncomfortable. In venous malformations, the pain is related to thrombo-inflammatory phenomena due to blood stagnation and chronic consumption coagulopathy. Thrombo-embolic complications are rare and occur in the context of Klippel-Trenaunay and CLOVES syndromes. All these malformations result from somatic mutations in the PIK3CA-AKT-mTOR signalling pathway and to PIK3CA mutations for lymphatic and combined malformations, whereas venous malformations are TEK or PIK3CA mutated. Identification of the responsible molecular mechanism is leading to the use of targeted therapies (sirolimus, alpelisib) in addition to traditional treatments (sclerotherapy, surgery, anticoagulants, compression therapy). Management should be tailored to each patient’s specific situation.

Reports written by

Prof. Soyun Cho

Dermatologist, South Korea

Skin aging: extrinisic and intrinsic factors – dermal skin ageing

Speakers:
- Oliver Dreesen (Cell Aging Lab, A*Star Skin Research Labs, Singapore): Identification and characterization of senescence biomarkers in aged human skin, upon UV-exposure and in UV-induced skin pathologies
- Abigail Langton (University of Manchester, Center for Dermatology Research, Manchester, UK): Extracellular matrix

- Anna Chien (Dermatology, Johns Hopkins School of Medicine, Baltimore, USA): Hypertrophic and Atrophic Photoaging
- Mauro Picardo (Dermatology, Unicamilus International University, Rome, Italy): Preventing skin ageing

Identification and characterization of senescence biomarkers in aged human skin, upon UV-exposure and in UV-induced skin pathologies

In this symposium, first Dr. Oliver Dreesen spoke about senescent cells which are irreversibly growth arrested cells that accumulate in aging tissues including human skin. He demonstrated how to characterize senescent cells within specific compartments of the skin using 3D organotypic skin models in vitro. His team found that loss of lamin B1 occurs in replicative/chronologic aging and in UV-induced aging. Therefore, in addition to HMGB1, lamin B1 is a novel senescence biomarker. Senescent cells accumulate upon UV exposure and in actinic keratosis lesions. Therefore, in actinic keratosis, a precancerous skin lesion, HMGB1 and lamin B1 expression is lost, but in SCC, lamin B1 is positive because cancer cells are non-senescent cells. Lamin B1 and HMGB1 are robust markers to identify/quantify senescent cells during aging or upon UV exposure or to test anti-aging procedures. In conclusion, his team developed a toolkit to study senescence in skin cell types.

Extracellular matrix

Next, Dr. Abigail Langton addressed the difference between intrinsic aging and extrinsic aging, where loss of elasticity is gradual and abrupt, respectively. Cutometry is a very effective non-invasive measure of skin elasticity. Disruption of the highly organized elastic fiber network and effacement of rete ridge structure coincides with a marked decline in biomechanical function. Histologically, young skin is elastic and resilient, whereas photoaged skin demonstrates solar elastosis and truncated fibrillin at dermoepidermal junction. Using a combination of histological techniques and cutometry, her team uncovered fundamental differences in skin architecture and dermal extracellular matrix (ECM) composition between black and white skin as a consequence of both time-dependent intrinsic ageing and photoaging. There was a 40- to 50-year gap in skin aging between white and black skin; however, black skin was not exempt from UVR-induced damage and therefore improved public health advice regarding the consequences of chronic sun exposure, the importance of multimodal photoprotection and the development of products and technologies that elicit skin repair and dermal remodelling are warranted for all.

Hypertrophic and Atrophic Photoaging

Dr. Anna Chien discussed two phenotypes of photoaging, hypertrophic and atrophic photoaging. Each subtype has unique clinical, histologic and molecular features. A subtype of atrophic photoaging, telangiectatic photoaging, also exists that is distinct from erythematotelangiectatic rosacea. In hypertrophic photoaging, individuals present with coarse wrinkles and a thickened skin texture. In contrast, atrophic photoaging manifests as thin skin with pronounced telangiectasias and sparse wrinkles. Hypertrophic photoaging is more prevalent in females while more males present with the atrophic variant. The main distinguishing histologic feature is the prominence of solar elastosis in the hypertrophic subtype that is lacking in atrophic photoaging. The association of atrophic photoaging with keratinocyte cancers may be attributed to the altered dermal matrix and increased vascularity seen in this subtype. Solar elastosis might be protective against tumor formation in exchange for thick wrinkles. It is critical for clinicians to be aware of these phenotypes to have the proper index of suspicion when diagnosing skin cancer as well as being more proactive in skin cancer prevention and treatment.

Preventing skin ageing

Lastly, Dr. Mauro Picardo presented various strategies to prevent skin aging. Besides sunscreen, he mentioned endogenous antioxidants, topical agents such as retinoids, topical antioxidants, systemic antioxidants including polyphenols, Nrf2 activators and nicotinamide, and nutritional intervention (balanced diet). SASP (senescence-associated secretory phenotype) is a key feature of cellular senescence, and thus immunosenescence and inflammaging go hand in hand. Senomorphic drugs work by suppressing SASP without eliminating cells. Senomorphic strategy includes energy-based devices such as lasers (fractional picosecond laser, etc.), HIFU and RF devices. Genetic variants of MC1R are important determinants for photoaging, and therefore α-MSH has photoprotective effects. It also activates PPAR-γ. He posited that perceived age is a robust marker of aging.

Skin aging: extrinsic and intrinsic factors – mechanism and factors of skin ageing

Speakers:
- Oliver Dreesen (Cell Aging Lab, A*Star Skin Research Labs, Singapore): Delineating the chain of events that trigger senescence in the premature aging syndrome Hutchinson-Gilford Progeria
- Florian Gruber (Medical University of Vienna, Dermatology/cdl skinmagine, Vienna, Austria): UV, visible light and infra-red and the skin
- Rachel Watson (University of Manchester, UK): Inflammation/inflammageing
- Ervin Tschachler (Dermatology, Medical University Vienna, Vienna, Austria): Transcriptomic differences of epidermal cells in young and older skin

Delineating the chain of events that trigger senescence in the premature aging syndrome Hutchinson-Gilford Progeria

First, Dr. Oliver Dreesen presented that lamins lie beneath the inner nuclear membrane and serve as a nexus to maintain the architectural integrity of the nucleus, chromatin organization, DNA repair and replication and to regulate nucleocytoplasmic transport. Perturbations or mutations in various components of the nuclear lamina result in a large spectrum of human diseases collectively called laminopathies. One of the most well-known laminopathies, Hutchinson-Gilford Progeria Syndrome (HGPS), is caused by a mutation in LMNA, resulting in a mutated form of lamin A, termed progerin. Progerin expression results in a myriad of cellular phenotypes including abnormal nuclear morphology, loss of peripheral heterochromatin, transcriptional changes, DNA replication defects, DNA damage and premature cellular senescence. He also showed that sequence-specific inhibition of DNA damage response of telomere improves the detrimental phenotypes of HGPS. HGPS provides a unique opportunity to identify and characterize molecular pathways and mechanisms that contribute to human aging.

UV, visible light and infra-red and the skin

Next, Dr. Florian Gruber talked about how exposure biological material to specific wavelength bands of radiation can result in oxidative modification of intra- and extracellular macromolecules. Non-enzymatic generation of reactive oxidized lipids can accumulate in and are secreted by senescent cells. These lipids can interact with proteins of the extracellular matrix and affect the biology of cells residing on such a modified matrix. Such photochemically generated or senescent cell-derived factors can modulate inflammation and facilitate the evasion of tissue clearance by phagocytic cells. His research demonstrates that lipids act as second messengers of light in extrinsic aging.

Inflammation / inflammageing

Next, Dr. Rachel Watson talked about chronic low-level inflammation associated with aging, termed inflammaging. This is characterized by increased levels of circulating proinflammatory cytokines and a shift toward cellular senescence. Senescent cells accumulate in the skin during aging, and although they are unable to divide, they remain metabolically active and exhibit an altered secretome, referred to as an SASP. The proinflammatory skin milieu derived from senescent cells facilitates the damage and remodeling of the skin's ECM while concomitantly disrupting adaptive immunity. Strategies targeting senescence and inflammation, including rapamycin, metformin and senolytics (heat shock protein 90 inhibitors, Bcl-2 family inhibitors and natural compounds such as quercetin and fisetin), may improve skin aging.

Transcriptomic differences of epidermal cells in young and older skin

Last, Dr. Erwin Tschachler showed, through single-cell RNA sequencing of epidermal keratinocytes from young (20-30) and older (65-70) individuals, that keratinocyte proliferation is decreased in older epidermis. Transcriptional differences between the two age groups were most pronounced in terminally differentiated keratinocytes, where expression of filaggrin, loricrin and corneodesmosin amongst others was significantly downregulated in the epidermis of older participants. His team also found a significantly elevated expression of several transcription factors of the AP-1 family including JUN, JUNB, FOS and FOSB in keratinocytes of the older study population. This research highlights the aging-associated transcriptional differences in epidermal keratinocytes and identifies genes responsible for epidermal structure and barrier function to be most affected.

Dermatopathology for the clinician: Advanced diagnostic tools in dermatopathology

Speakers:
- Jeffrey North (Dermatology, UCSF, San Francisco, USA): Immunohistochemistry and molecular testing for melanocytic tumours
- Dong Youn Lee (Dermatology, Sungkyunkwan University, Seoul, Republic of Korea): Nail pathology based on new molecular techniques
- Wayne Grayson (Anatomical Pathology, University of Witwatersrand, Johannesburg, South Africa): Molecular testing: non-neoplastic conditions
- Raymond Cho (Dermatology, UCSF, San Francisco, USA): Immunohistochemistry and molecular testing for inflammatory skin disease

Immunohistochemistry and molecular testing for melanocytic tumours

First, Dr. Jeffrey North introduced immunohistochemistry used for melanocytic tumors including lineage markers, proliferation markers, tumor suppressor proteins, oncogene analysis, and PRAME (preferentially expressed antigen in melanoma). If β-catenin is positive in nuclei of melanocytic lesions in the deep dermis, it's a deep penetrating melanocytoma arising in a nevus. Secondly, molecular testing was mentioned. Genomic instability is typical of melanoma; 96% of melanomas have genomic chromosomal aberrations, whereas only ~ 10% of nevi have them (Spitz 11p, etc.). Mutational profile is also used to predict melanoma prognosis; BRAF + BAP1 mutation poses low risk, whereas GNAQ mutation poses high risk. FISH is 80-90% sensitive and 90% specific. Comparative genomic hybridization (CGH) has 95% sensitivity and specificity.

Nail pathology based on new molecular techniques

Next, Dr. Dong Youn Lee explained that nail unit consists of nail-specific epithelium (nail matrix and nail bed) and nail-specific mesenchyme (onychodermis containing onychofibroblasts). Onychodermis stains positive for CD10, and onychofibroblasts, positive for RSP04. And then he mentioned onychomatricoma, a nail-specific tumor which originates from onychofibroblasts. Onychomatricoma is CD34- and CD13-positive and usually CD10-positive. In his series, the likelihood of subungual melanoma was 100% when longitudinal melanonychia width was >3 mm and 61% when Hutchinson sign was positive. PRAME is a useful genetic marker to distinguish nail melanoma from benign melanocytic lesions.

Molecular testing: non-neoplastic conditions

Next, Dr. Wayne Grayson summarized molecular testing methods for non-neoplastic conditions. General application of next generation sequencing (NGS) seems endless, he said. Through NGS, the causative mutation for keratolytic winter erythema was found in chr 8p22-p23. In molecular mycology, DNA barcoding using nuclear internal transcribed spacer (ITS) region is most widely being used. Histopathology of emergomycosis in AIDS patients mimics that of histoplasmosis, but thanks to the DNA barcoding technology, now it's correctly identified as being caused by Emergomyces africanus.

Immunohistochemistry and molecular testing for inflammatory skin disease

Lastly, Dr. Raymond Cho talked about disrupting inflammatory skin disease paradigms using patient cases where features of both psoriasis and eczema were present. In these patients, heterogeneity of skin phenotype obscures genetic features of the disease, and identifying RNA molecules and epitopes in single immune cells from skin would help reach the correct diagnosis. Skin resident T cell signatures distinguish disease states, and analysis of these cells would also help diagnose inflammatory skin conditions. He concluded that we should expand the rash X library to more powerfully distinguish skin disease states, in order to circumvent drug resistance in chronic rashes and to map clinically important classes of skin inflammation onto a principled landscape.

Skin ulcers and keloids: Chronic leg ulcers

Speakers:
- Robert Kirsner (Dermatology and Cutaneous Surgery, University of Miami, Miami, USA): Introduction
- Fatimata Ly (Dermatology, Cheikh Anta Diop University, Dakar, Senegal): Ulcers of the lower leg: Differential diagnosis and pathophysiology
- José Contreras Ruiz (Dermatology, Hospital H+ Los Cabos, Cabo San Lucas, Mexico): Malignancy and chronic leg ulcers
- Marco Romanelli (Dermatology, University of Pisa, Pisa, Italy): Compressing bandages in leg ulcers
- Robert Kirsner (USA): Surgical therapy and skin grafting in chronic leg ulcers

Introduction

First, Dr. Robert Kirsner introduced the session and the first speaker.

Ulcers of the lower leg: Differential diagnosis and pathophysiology

Dr. Fatimata Ly summarized the differential diagnosis and pathophysiology of ulcers of the lower leg, including venous ulcers which are most common, mycetoma caused by fungi, erysipelas caused by bacteria, vasculitis caused by LE and other diseases, pyoderma gangrenosum in which MMP 9 and MMP 10 are upregulated, squamous cell carcinoma (SCC) and cutaneous lymphoma. In conclusion, the epidemiology of ulcer of the leg has changed during the last decade. Many skin diseases can mimic lower leg ulcer, and some skin diseases can be a complication of chronic ulcer/SCC. Infectious etiologies can progress to chronicity. Malignancies should be ruled out. Global approach is needed.

Malignancy and chronic leg ulcers

Next, Dr. José Contreras Ruiz discussed malignancies associated with chronic leg ulcers, which as a prevalence of 4-10% of leg ulcers. Tumors that may become ulcerated include metastatic carcinoma, lymphoma, sarcoma, primary skin tumors and chronic lymphedema/lymphangiosarcoma/angiosarcoma. Metastatic carcinoma is very rare on the leg and are mostly vaginal or renal carcinoma. Primary skin tumors are BCC, SCC and melanoma. 2.6% of BCCs occur on the legs, and less than 10% of SCCs occur on the legs. Patients with leg SCC have a higher risk of multiple SCCs. In suspected lesions, biopsy should be performed from the border of ulcer and re-biopsy should be done if necessary.

Compressing bandages in leg ulcers

Next, Dr. Marco Romanelli talked about different compression therapy systems for leg ulcers including stockings, bandages, wraps, etc. Compression therapy aims to reduce venous hypertension; the mechanism of action is by reducing luminal diameter and improving valve function of leg veins by bringing venous walls closer. Contraindications for compression therapy are severe peripheral arterial disease (ABPI < 0.6 by Doppler ultrasound), cardiogenic edema caused by heart failure, diabetic microangiopathy and severe skin infection. Pressure should be applied accurately and continuously 24/7. Applied pressure depends on bandage tension, bandage overlap and ankle circumference. One should reshape the leg to obtain graduated compression, and then apply bandage from toes to knee, with ankle at 90 degrees with lower leg and skin padding to prevent damage. Inelastic/short stretch bandages are more effective. To prevent recurrence of leg ulcer, weight reduction is mandatory. Compression therapy is a main option in vascular ulcer therapy. The ability to manage exudate in a controlled fashion is key to the provision of optimal balance at the wound interface. Providing compression with moisture balance reduces the risks both of maceration and of drying out the wound.

Surgical therapy and skin grafting in chronic leg ulcers

Lastly, Dr. Robert Kirsner discussed skin grafting. Autografting with mesh formation eases pain and heals wounds faster. Alternative grafting techniques include scalpel-derived pinch grafts and fractional full-thickness skin grafting. Skin grafts are pharmacological agents. Skin grafts work by multiple mechanisms, and they can be performed simply and inexpensively. Opportunities for scarless skin grafting exist, using cell and tissue products. As of now, ‘off the shelf grafts’ do not take.

Hair diseases: Basic approaches to hair diseases

Speakers:
- Etienne Wang (Dermatology, National Skin Center, Singapore): Hair cycle and its relation to hair diseases

- Amos Gilhar (Israel Institute of Technology, Israel): The impact of immune cells in regulating the hair cycle
- Leopoldo Dualibe Santos (Dermatology, Sao Paulo School of Medicine, Sao Paulo, Brazil): Differential diagnosis of hair disorders
- Daniel Fernandes Melo (Dermatology, Universidade do Estado do Rio de Janeiro, Brazil): Dermoscopy of the scalp

Hair cycle and its relation to hair diseases

First, Dr. Etienne Wang reviewed hair cycle and how it changes in various hair diseases. Androgenetic alopecia is characterized by miniaturization of hair follicles. Telogen effluvium is stress-induced hair loss, most common after pregnancy, weight loss, COVID, etc. There are 5 subsets of telogen effluvium. Premature telogen is seen in physiological stress conditions including high episodes of fever. Prolonged anagen is seen in pregnancy. Premature exogen is seen with topical minoxidil therapy because the drug triggers release of telogen hair. Chronic short anagen is seen in perimenopausal women. Prolonged telogen is seen in change of diurnal rhythm as occurs following travel from low-daylight to high-daylight environment. Knowledge of hair cycle is important in order to understand the pathophysiology of hair diseases and to develop treatment.

The impact of immune cells in regulating the hair cycle

Next, Dr. Amos Gilhar explained about the impact of immune cells on hair cycle. Anagen stage hair follicles (HFs) exhibit "immune privilege (IP)" from the level of the bulge downwards to the bulb. Perifollicular mast cells, Tregs and other immunocytes may also contribute to HF IP maintenance in healthy human skin. Collapse of anagen hair bulb IP is an essential prerequisite for the development of alopecia areata (AA). In AA, lesional HFs are rapidly infiltrated by NKG2D + T cells and natural killer (NK) cells, while perifollicular mast cells acquire a profoundly pro-inflammatory phenotype and interact with autoreactive CD8+ T cells. Purified CD8+T-cell and NK cell populations alone, which secrete fγ, suffice to induce the AA phenotype, while CD4+T-cells aggravate it, and Tregs and iNKT cells may provide relative protection against AA development. While IP collapse may be induced by exogenous agents, inherent IP deficiencies might confer increased susceptibility to AA for some individuals. Thus, a key goal for effective AA management is the re-establishment of a functional HF IP, which will also provide superior protection from disease relapse.

Differential diagnosis of hair disorders

Next, Dr. Leopoldo Santos discussed differential diagnoses of hair loss. For evaluation of hair loss, first the pattern of hair loss should be assessed as diffuse, patchy or band-like. Diffuse hair loss indicates telogen effluvium, alopecia areata, androgenetic alopecia, or fibrosing alopecia in a pattern distribution (FAPD). Patch type hair loss indicates alopecia areata, dissecting cellulitis, lichen planopilaris, or discoid lupus erythematosus. Band-like hair loss should raise suspicion of frontal fibrosing alopecia (FFA) and traction alopecia. In FFA, eyebrow hair loss and facial hyperkeratotic papules are clues to the diagnosis. There are acute and chronic forms of traction alopecia, and biopsy reveals many sebaceous glands in contrast to FFA. In addition, pull test, midline part, trichoscopy and biopsy are used for evaluation of hair loss. Trichoscopy should be performed from 3 parts of midline. In diffuse hair loss, 4-mm punch biopsies should be done from each the vertex scalp and occipital scalp and the findings compared. In conclusion, hair loss is a broad chapter of dermatology. Clinical findings, trichoscopy and biopsy are necessary for correct diagnosis.

Dermoscopy of the scalp

Lastly, Dr. Daniel Melo talked about dermoscopy of the scalp. Trichoscopy is used for better visualization, to guide biopsy site, and to assess disease state. Alopecia can be broadly categorized as non-scarring alopecia and scarring alopecia. Non-scarring alopecia includes alopecia areata, androgenetic alopecia, trichotillomania and tinea. Alopecia areata shows signs of activity, chronicity, and hair regrowth. Tinea shows corkscrew hair. Scarring alopecia includes lichen planopilaris, LE, dissecting cellulitis, and folliculitis decalvans. In lichen planopilaris and FAPD, perifollicular scales are seen. Dissecting cellulitis shows 3D yellow dots. Folliculitis decalvans is a chronic neutrophilic scarring alopecia and shows big tufts (polytrichia), diffuse erythema, perifollicular scales, and pustules/crusts.

Lymphomas: Cutaneous lymphomas I

Speakers:
- Maarten Vermeer (Dermatology, Leiden University Medical Centre, Leiden, Netherlands): New concepts in the pathogenesis of cutaneous lymphomas
- Antonio Cozzio (University of Zurich, Zurich, Switzerland): Cutaneous CD30+ lymphoproliferative disorders (LPDs)
- Maxime Battistella (Pathology, Saint-Louis Hospital, Paris, France): Cutaneous CD8+ acral T-cell and CD4+ small/medium T-LPDs, evolution of entities
- Youn Kim (Dermatology, Stanford University, Stanford, USA): Management of aggressive T-cell lymphomas

New concepts in the pathogenesis of cutaneous lymphomas

First, Dr. Maarten Vermeer introduced 2022 WHO Classification of and new concepts in cutaneous lymphomas. He began by summarizing the antibodies being used to diagnose lymphomas. Next, he talked about the changing trend from clinicopathology to molecular genomic entities, for example, NGS combined with clinicopathological entities. Third, we are moving from tumors to individual tumor cells, e.g., Sezary cells are not always Th2 phenotype. Fourth, he mentioned the change from tumor cells to tumor microenvironment, e.g., imaging CyTOF and spatial transcriptomics. Lastly, we're moving from single centers to worldwide collaborations.

Cutaneous CD30+ lymphoproliferative disorders (LPDs)

Next, Dr. Antonio Cozzio presented cutaneous CD30+ lymphoproliferative disorders (LPDs), 95% of which are composed of lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL) and mycosis fungoides (MF)/Sezary syndrome (SS). LyP presents as a nodule < 1 cm that waxes and wanes and is self- healing. Childhood LyP requires long-term follow-up because the risk of Hodgkin's lymphoma is about 10%. LyP should be differentiated from PLEVA and reactive CD30+ T cell infiltration in scabies and arthropod bites reactions. Mucosal LyP is a differential diagnosis for lues. Cutaneous CD30+ pseudolymphomas such as drug reactions should also be differentiated. Among the numerous subtypes of LyP, subtype A accounts for >80% and is of wedge-shaped mixed cellular infiltration. Subtype B accounts for <5% and is epidermotropic; subtype C (10%) shows cohesive infiltration; subtype D (<5%) is characterized by epidermotropism and Pagetoid spread; subtype E (<5%) shows angiocentricity and angiodestruction. Prognosis of LyP is such that about 10% will get secondary lymphoma. Treatment includes wait-and-see strategy, corticosteroid, phototherapy and low-dose methotrexate. Durable complete remission is difficult to achieve. CD30+ pcALCL is characterized by de novo tumor formation without patch/plaque stage, unlike MF.

Treatment includes excision and radiotherapy. Relapse rate is 40%. If disseminated, methotrexate or brentuximab vedotin is used.

Cutaneous CD8+ acral T-cell and CD4+ small/medium T-LPDs, evolution of entities

Next, Dr. Maxime Battistella presented the evolution of the entities called cutaneous CD8+ acral and CD4+ small/medium T cell lymphoproliferative disorders (LPDs). Cutaneous CD8+ acral LPDs are CD8+, CD68+ in perinuclear dot-like pattern, and Ki67 <10%. Treatment is observation, excision, radiotherapy or corticosteroid. They have excellent prognosis, with local recurrence rate of 20%. Primary cutaneous CD4+ small/medium-sized T cell LPD is a solitary nodule that occurs on the head and neck in 50% of cases. It shows a nodular or band-like infiltration. It is diffusely positive for CD4 and positive for PD-1+ in cluster/rosette pattern.

Management of aggressive T-cell lymphomas

Lastly, Dr. Youn Kim talked about management of aggressive CTCL. Aggressive MS & SS profile includes large cell transformation, high-risk CLIPi (cutaneous lymphoma international prognostic index) and reactivity for molecular markers. For durable remission, allogeneic hematopoietic stem cell transplantation (HSCT) is the only solution. Cytotoxic CTCLs are aggressive lymphomas and include subcutaneous panniculitis-like T-cell lymphoma (SPTCL), aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (AETCL), γδ T-cell lymphoma (GDTCL) and NK/T cell lymphoma. Management is based on clinical behavior; if indolent, prednisolone, methotrexate or retinoids can be used. If aggressive, cyclosporin A (in case of SPTCL), pralatrexate, romidepsin with or without prednisolone and allogeneic HSCT are used. If the patient is transplant-ineligible, clinical trials are considered. Among chimeric antigen receptor T cell (CAR-T) therapy for CTCL, CTX130 (anti-CD70 CAR-T) clinical trial is ongoing.

Lymphomas: Cutaneous lymphomas II

Speakers:
- Shang Ian Tee (Singapore): Pseudolymphomas and differential diagnosis of CTCL
- Emmanuella Guenova (University of Lausanne, Lausanne, Switzerland): The value of clonality, morphology and phenotype in the diagnosis of CTCL
- Marie Beylot-Barry (Dermatology, University of Bordeaux, Bordeaux, France): New systemic therapies in cutaneous T-cell lymphomas
- Suzan Thornton (CEO, Cutaneous Lymphoma Foundation, USA): Impact and progress of patient advocacy in cutaneous lymphomas

Pseudolymphomas and differential diagnosis of CTCL

First, Dr. Shang Ian Tee listed the etiologies of pseudolymphomas, including drugs (38%), infections/infestations (20%) and others (42%) such as tattoo dyes, UV and piercing. Drugs induce T cells predominantly. Anti-hypertensive drugs are most common culprits, followed by monoclonal antibodies, anticonvulsants and antipsychotics. Cutaneous T-cell pseudolymphomas can have one of 3 patterns: band-like, nodular, or with prominent vascular component. Band-like pattern is mostly seen in drug-induced lesions. When nodular, it's classified as CD4+ T-cell pseudolymphoma, CD30+ T-cell pseudolymphoma, or pseudolymphomatous T-cell folliculitis. Among lesions with prominent vascular components, acral pseudolymphomatous angiokeratoma of children (APACHE) and T-cell rich angiomatoid polypoid pseudolymphoma (TRAPP) should be differentiated. APACHE occurs in

children as grouped lesions in acral areas. TRAPP occurs in adults as solitary lesions in head and neck and trunk.

The value of clonality, morphology and phenotype in the diagnosis of CTCL

Next, Dr. Emmanuella Guenova discussed clonality of CTCL. pcCTCL accounts for >70% of cutaneous lymphoma and pcCBCL for <30%. When it comes to machine learning classifiers for MF, the best performing features are nuclei detection, nuclear saturation, and nuclear brightness. Essential markers are CD3, CD4, CD2, CD7, CD8, CD20, CD30 and CD5. Also important are HTLV-1/2 serology and molecular analysis to detect clonal TCR gene rearrangement. There is normally a 1.6% chance to find identical gamma clones for TCR gene rearrangement, so if there is rearrangement, it means clonal expansion. Clonality in MF has a sensitivity of 69% and specificity of 76%, so it's far from perfect. Therefore, one should take multiple, repetitive biopsies, and if all of them are of the same clone, there's a higher chance of MF. TCRβ high-throughput sequencing identifies aggressive early-stage MF.

New systemic therapies in cutaneous T-cell lymphomas

Next, Dr. Marie Beylot-Barry presented new systemic therapies in CTCL. First, monoclonal anti-CCR4 (mogamulizumab) was mentioned. Adverse events include infusion reaction (33%) and skin rash (23%). There was better response if there was blood involvement (SS responded better than MF). Second, brentuximab vedotin (humanized anti-CD30-antimitotic agent monomethyl-auristatin E) was discussed. Side effects include peripheral neuropathy in two-thirds. Efficacy was also seen in CD30-low cases. High level of response (rapid response) was seen in advanced MF. No more than 16 cycles can be done due to peripheral neuropathy. Third, humanized monoclonal anti-KIR3DL2 (lacutamab), a cytotoxicity-inducing antibody, was mentioned, and finally allogeneic transplantation was mentioned for its curative potential.

Impact and progress of patient advocacy in cutaneous lymphomas

Lastly, Suzan Thornton, CEO of Cutaneous Lymphoma Foundation, introduced what kind of help the Foundation provides for cutaneous lymphoma patients, including full manuscript files on the newest treatment for cutaneous lymphoma, information on ongoing clinical trials, etc.

Pruritus and dysaesthesias

Speakers:
- Wei Hua (China): Comparison between cowhage-induced itch scores and the current perception threshold (CPT): use as diagnostic tools for sensitive skin syndrome
- Shi Yu Derek Lim (Singapore): In vivo imaging of patients with chronic pruritus of unknown origin reveals partial sweat duct obstruction with partial itch resolution upon retinoid treatment
- Sonja Staender (Germany): Greater reductions in pruriginous lesions with oral nalbuphine extended-release versus placebo in patients with prurigo nodularis: results from a phase 2b/3, double-blind, placebo-controlled study
- Sonja Staender (Germany): Prurigo activity and severity score: development of a tool to assess chronic prurigo objectively in clinical trials and clinical practice
- Sonja Staender (Germany): How to treat different severity stages of chronic nodular prurigo in 2023: what are the guidelines recommending and what is new?

- Karolina Swierczyneka-Mroz (Poland): Serum Level of protein-bound uraemic toxins in patients with chronic kidney disease-associated pruritus: myths and facts

Comparison between cowhage-induced itch scores and the current perception threshold (CPT): use as diagnostic tools for sensitive skin syndrome

First, Dr. Wei Hua reported the results of a clinical study on 30 participants with and without sensitive skin, where the cowhage test and measurement of CPT with its related sensations were performed. Cowhage provoked more intense itch with a longer duration in the face and forearm of the sensitive group compared with the nonsensitive group. The authors concluded that the cowhage test might serve as a better diagnostic tool for sensitive skin than CPT measurement.

In vivo imaging of patients with chronic pruritus of unknown origin reveals partial sweat duct obstruction with partial itch resolution upon retinoid treatment

Next, Dr. Derek Lim reported the outcome of isotretinoin or acitretin 10 mg/d treatment in patients with chronic pruritus of unknown origin (CPUO). In CPUO patients, sweat duct lumen is increased, and sweat leakage into the dermis may cause prickling sensation and sweat leakage into the epidermis may cause nerve irritation and itch. Based on novel imaging findings identifying partial keratinaceous sweat duct obstruction in CPUO, they instituted systemic retinoid treatment to address the underlying pathology. In patients who failed conventional therapies, the treatment appears effective and safe.

Greater reductions in pruriginous lesions with oral nalbuphine extended-release versus placebo in patients with prurigo nodularis: results from a phase 2b/3, double-blind, placebo-controlled study

Next, Dr. Sonja Staender reported the outcome of a double-blind, placebo-controlled, phase 2b/3 study of patients with prurigo nodularis (PN), where both instruments (Prurigo Activity Score (PAS) question 5a and IGA-PN activity score) showed that nalbuphine extended-release 162 mg/d treatment resulted in significant reductions in the number of excoriated skin lesions.

How to treat different severity stages of chronic nodular prurigo in 2023: what are the guidelines recommending and what is new?

Next, Dr. Sonja Staender discussed the utility of PAS. After development of the Prurigo Activity and Severity Score (PAS), it was validated in a large cohort of patients with chronic prurigo. The validation study examined interrater reliability, intrarater reliability, and the relationship to external constructs such as pruritus intensity and quality of life. PAS was shown to be a valid tool to assess the clinical picture of chronic prurigo.

Next, Sonja Staender discussed treatment options for chronic nodular prurigo including topical steroids, calcineurin inhibitors, and capsaicin, UV therapy, and systemic agents such as gabapentinoids, antidepressants, opioid receptor antagonists, and immunosuppressants. Newer treatments include dupilumab, nemolizumab (a humanized monoclonal antibody against IL-31 receptor-A), vixarelimab (monoclonal antibody against IL-31) and nalbuphine. Nalbuphine, as a dual κ-opioid receptor agonist and μ-opioid receptor antagonist, is thought to inhibit the transmission of pruritus at spinal level.

Serum Level of protein-bound uraemic toxins in patients with chronic kidney disease-associated pruritus: myths and facts

Lastly, Dr. Karolina Swierczyneka-Mroz discussed therapy for chronic kidney disease-associated pruritus (CLD-aP). First-line therapy is difelikefalin, and second-line therapy includes gabapentin and pregabalin. Uremic toxins consist of 3 groups: free low molecular weight-molecules, middle molecules (0.5 – 60 kDa), and protein-bound uremic toxins (PBUTs). So far published research regarding the role of PBUTs in CKD-aP etiopathogenesis are ambiguous and very limited. Their study did not support earlier findings about higher levels of indoxyl sulfate and p-cresol sulfate in patients reporting CKD-aP.

Vasculitis and vasculopathies

Speakers:
- Glenn Geidel (Germany): Polyarteritis nodosa reveals cerebral toxoplasmosis in an immunocompromised patient
- Mina Kang (Australia): Ultrasound-guided biopsy improves the diagnostic accuracy of cutaneous vasculitic and vasculopathic conditions
- Ayushi Khandelwal (India): Clinico-pathological and Immunofluorescence study of cutaneous small vasculitis: a hospital based cross-sectional study
- Wei Jian Russell Lim (Australia): Livedo rash in Trousseau's syndrome secondary to non-Hodgkin’s lymphoma: a case report
- Vinod Nambudiri (USA): Growing Nodule in Patient with Sneddon Syndrome
- Denya Penaloza (Argentina): Intralesional sodium thiosulfate as adjuvant therapy in severe calciphylaxis
- Swagata Tambe (India): Case series of Challenging Ulcerative lesions
- Nohemi Trejo Chavira (Mexico): Extensive mucocutaneous lesions in Behçet disease associated with Aplastic Anemia and other Autoimmune diseases

Polyarteritis nodosa reveals cerebral toxoplasmosis in an immunocompromised patient

First, Dr. Glenn Geidel introduced a rare case of cerebral toxoplasmosis that initially presented as polyarteritis nodosa. Treatment with clindamycin, pyrimethamine and folinic acid for the toxoplasmosis led to a complete healing of the polyarteritis nodosa. The presented polyarteritis was identified as an Id reaction upon cerebral toxoplasmosis, which in turn manifested under triple immunosuppression among extracutaneous sarcoidosis. Toxoplasmosis should be considered as an infectious cause of cutaneous vasculitis. Extreme caution should be taken in cases of severe immunosuppression.

Ultrasound-guided biopsy improves the diagnostic accuracy of cutaneous vasculitic and vasculopathic conditions

Next, Dr. Mina Kang introduced ultrasound-guided biopsy of cutaneous vasculitic conditions. Ultrasound is an extremely useful adjunct in guiding site selection for skin biopsies, especially in vascular conditions such as lymphocytic thrombophilic arteritis or livedoid vasculopathy. -Limitations are time-cost, steep learning curve, and expensive equipment.
Dr. Ayushi Khandelwal was not present to deliver the talk.

Clinico-pathological and Immunofluorescence study of cutaneous small vasculitis: a hospital based cross-sectional study

Next, Dr. Russell Lim presented a case of Trousseau’s syndrome in a patient with NHL who presented with extensive reticular livedoid rash over his bilateral medial thighs and lower legs, that were severely

painful to light touch. Trousseau's syndrome refers to the paraneoplastic, hypercoagulation disorder in patients with malignancy. Trousseau's syndrome should be suspected in patients presenting with a painful, livedoid rash in the context of malignancy and post-chemotherapy. Moreover, in patients without known underlying cancer, recurrent superficial thrombophlebitis should increase suspicion for Trousseau's syndrome.

Growing Nodule in Patient with Sneddon Syndrome

Next, Dr. Chong on behalf of Dr. Vinod Nambudiri presented a case of a growing nodule on the neck of a patient with Sneddon syndrome. Although initially vascular inflammation secondary to Sneddon syndrome was suspected, histopathology demonstrated a poorly differentiated carcinoma with positive staining for TTF1, Napsin-A, and pan-keratin, most consistent with a first diagnosis of metastatic lung adenocarcinoma. Dermatologists should have a low threshold for evaluating individuals with preexisting systemic vasculopathies with cutaneous manifestations.

Intralesional sodium thiosulfate as adjuvant therapy in severe calciphylaxis

Next, Dr. Denya Penaloza presented a case of severe calciphylaxis where although vascular structure could not be identified due to the severity of skin lesion, intracutaneous sodium thiosulfate injection in the lesional skin resulted in the resolution of the condition.

Case series of Challenging Ulcerative lesions

Next, Dr. Swagata Tambe presented 3 challenging cases presenting with chronic and recurrent ulcerative skin diseases. Chronic erythema induratum with ulcer, erythema induratum in a primary Sjogren syndrome patient with renal involvement, and cryoglobulinemic vasculitis were presented.

Extensive mucocutaneous lesions in Behçet disease associated with Aplastic Anemia and other Autoimmune diseases

Next, Dr. Nohemi Trejo Chavira presented a case of extensive mucocutaneous Behcet's disease associated with autoimmune disease in a patient with trisomy 8. The patient had aplastic anemia due to bone marrow failure. There seems to be an association between Behçet disease and bone marrow failure, with an increased autoimmune response and specific proinflammatory cytokines. Trisomy 8 is the most common cytogenetic abnormality reported in around 64–86% cases.