29th Congress of the European Academy of Dermatology and Venereology

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Date: 29-31 Octoter, 2020
Venue: Virtual
Organiser: European Academy of Dermatology and Venereology

SARS-CoV-2 associated acro-syndromes and cutaneous vasculitis

Speaker: C Galvan
Hospital Universitario de Móstoles, Madrid, Spain

Case series from an international registry from the American Academy of Dermatology and International League of Dermatological Societies (published October 2020) collected 716 cases of new-onset dermatological symptoms in patients with confirmed/suspected COVID-19. Of the 171 patients in the registry with laboratory-confirmed COVID-19, the most common morphologies were morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%). Pernio-like lesions were common in patients with mild disease, whereas retiform purpura presented exclusively in ill, hospitalised patients.

Pernio-like lesions (Pseudo-chilblain) mostly occur among children or young adults, usually after the onset of other symptoms, and were associated with a good prognosis. The affected digits present in the forms of erythema with oedema, vesicles or pustules and purpura. These may be asymmetrical and occur in the hands or feet. Pain and itch are common and occur in around 30% of patients. Investigations such as PCR and serology are usually negative.

Retiform purpura and acro-ischaemia tend to occur in older patients and present in the form of acral cyanosis with bulla formation or dry gangrene. It is associated with a worse prognosis and a mortality rate of about 10%.

Biopsies of COVID-19-associated perniosis exhibited vasocentric and eccrinotropic T-cell- and monocyte-derived $CD11c^+$, $CD14^+$ and $CD123^+$ dendritic cell infiltrates. Both COVID-associated and idiopathic perniosis showed striking expression of the type I interferon-inducible myxovirus resistance protein A (MXA), an established marker for type I interferon signalling in tissue. SARS-CoV-2 RNA, interleukin-6 and caspase 3 were minimally expressed and confined to mononuclear inflammatory cells. The biopsies from livedo/retiform purpura showed pauci-inflammatory vascular thrombosis without any MXA decoration. Blood vessels exhibited extensive complement deposition with endothelial cell localisation of SARS-CoV-2 protein, interleukin-6 and caspase 3; SARS-CoV-2 RNA was not seen.

From the aforementioned immunohistochemistry findings, COVID-19-associated perniosis could represent a virally triggered exaggerated immune

reaction with significant type I interferon signalling. This is important in SARS-CoV-2 eradication and indicates a generalised strong inflammatory response and a better prognosis.

In contrast to the thrombotic retiform purpura of critically ill patients with COVID-19, vascular thrombosis in the skin and other organ systems is associated with a minimal interferon response. This allows excessive viral replication with release of viral proteins that localise to extrapulmonary endothelium and trigger extensive complement activation. This could explain the grave prognosis in these patients.

Learning points:

The cutaneous manifestations in patients infected with SARS-COVID-19 are variable. These clinical presentations could be the result of different underlying pathophysiologies and are of prognostic significance.

Molecular and genetic basis of psoriasis phenotypes

Speaker: J Barker
St John's Institute of Dermatology, Division of Genetics and Molecular Medicine, King's College London, London, UK

In psoriasis, genetic factors may affect disease susceptibility, age of onset, severity, co-morbidity and response to biologic treatment.

Heritability accounts for 60-70% risk of psoriasis. Current associations explain around 30% heritability and approximately 60 loci were found associated with psoriasis with genome-wide scan. Most of these genes are involved in innate and adaptive immune responses. Among these, HLA-C*06.02 produces a greater genetic effect than all other loci combined with a heritability odds ratio of ~4-5. It is also associated with type I early-onset psoriasis. However, HLA-C*06.02 is neither necessary nor sufficient to cause psoriasis.

Biological pathways implicated in psoriasis pathogenesis include

i) Skin barrier function e.g. LCE3, KLF4, CDSN
ii) Antigen presentation e.g. HLA-C, ERAPT
iii) Type I interferon signaling e.g. IFIH1, DDX 58
iv) NF-KB signaling e.g. TNP1, TNIP1
v) IL-23/IL-17 axis e.g. IL23R, TYK2

Genetic study with Mendelian Randomisation (MR) confirms that obesity contributes to the pathogenesis of psoriasis but not vice versa. The odds ratio of developing psoriasis increases as BMI increases i.e. ~50% when BMI increase from 25 to 30. However, there is no evidence that psoriasis increases BMI.

Recently it was found that generalised pustular psoriasis (GPP) is associated with mutations in IL36RN. IL36RN mutations were observed in 25% cases of GPP (and acrodermatitis of Hallopeau). There was sustained activation of IL-36 in GPP. On the other hand, IL36RN mutations are not associated with psoriasis. Furthermore, the inhibition of interleukin-36 receptor may reduce the severity of GPP.

HLA-C*06.02 predicts patient's response to biologic therapy. HLA-C*06:02-negative patients were significantly more likely to respond to adalimumab than ustekinumab at all time points (most strongly at 6 months: odds ratio [OR], 2.95; $P=5.85\times10^{-7}$), and the difference was greater in HLA-C*06:02-negative patients with psoriatic arthritis (OR, 5.98; $P=6.89\times10^{-5}$). Biologic-naive patients who were HLA-C*06:02 positive and psoriatic arthritis negative demonstrated a significantly poorer response to adalimumab at 12 months (OR, 0.31; $P=3.42\times10^{-4}$). Results from HLA-wide analyses were consistent with HLA-C*06:02 itself being the primary effect allele.

Learning points:

Genetic factors play an important role in disease susceptibility, age of onset, disease severity, co-morbidity and response to biologic treatment in psoriasis. With a better understanding of the genetic basis of psoriasis, genotyping may promote personalised management.

Ocular rosacea

Speaker: J Cabete
Hospital de Santo Antonio dos Capuchos, Central Lisbon Hospital Center, EPE - Lisbon, Portugal

Rosacea is a chronic disease with variable presentation and severity. It may be present in up to 58-72% of patients with rosacea. However, as the symptoms may be subtle, the disease is commonly overlooked. Nevertheless, ocular rosacea reduces the life quality and is potentially sight-threatening.

Both males and females are equally affected and the condition is more prevalent among fair-skinned patients. It may occur in early childhood with a peak incidence at 40 to 60 years of age. There is no correlation between the severity of ocular disease and the severity of facial rosacea.

The pathophysiology is not fully elucidated. It involves inflammatory changes, altered immune system response (increase cathelicidin peptides and TLR2 and increases serine proteases) and vascular dysregulation.

Clinically patients may present with foreign body sensation, pain or burning eyes, photophobia, itchy and watery eyes, crusting of the eyelids and scales. Physical examination may reveal blepharitis, telangiectasia and erythema of the lid margin; oedema, erythema, and desquamation in collarettes around the eyelashes. There may also be Meibomian gland dysfunction (excess turbid secretions from the Meibomian glands plugging their own orifices, resulting in recurrent chalazion), as well as dry eyes, conjunctival hyperaemia and telangiectasia, keratitis, episcleritis and scleritis.

Treatment include eyelid hygiene and lubricants, topical anti-inflammatory and / or systemic medications and finally laser and surgery in difficult cases.

Warm compresses applied to eyelid margins help to liquefy the thick Meibomian gland secretions and facilitate gland function and cleaning with diluted neutral baby shampoo is also helpful. Non-preserved artificial tears and other lubricants can be applied liberally throughout the day. Topical antibiotic ointments at bedtime may decrease eyelid flora and soften collarettes.

Topical anti-inflammatory medications like topical cyclosporine is used for symptomatic eyelid, conjunctival and / or corneal changes such as keratitis, episcleritis and scleritis. Severe cases with persistent inflammation may require the use of short-term topical corticosteroids. Azithromycin preparation two to three time a day for 2-4 weeks can improve blepharitis and Meibomian gland dysfunction.

Systemic agents like doxycycline have anti-inflammatory, anti-angiogenic effects and decrease eyelid bacterial flora and lipases produced by *Staphylococci*. In paediatric patients, macrolides can be substituted. For refractory cases, oral low dose isotretinion can be used.

Finally, Intense Pulse Laser (IPL) minimises the impact of dry eyes in ocular rosacea and surgery may be required for severe dry eyes, persistent chalazion, corneal thinning and perforation.

Learning points:

Dermatologists should be familiar with the symptoms and signs of ocular rosacea. Collaboration with ophthalmologists is required for the management of patients with ocular rosacea.

Recognizing systemic drug photosensitivity

Speaker: SH Ibbotson
Ninewells Hospital & Medical School, Dundee, Scotland

Drug photosensitivity is the third commonest cutaneous adverse effect caused by drugs. It has exogenous (such as drugs & chemicals) and endogenous (such as porphyrins) causes and can be induced by systemic or topical medications or by therapeutic measures such as PUVA and PDT.

Systemic photosensitisers include psoralens, diuretics, antibiotics, antifungals, antipsychotics and oncologic targeted therapeutic agents such as BRAD inhibitors and EGFR & Tyrosine Kinase inhibitors. The action spectra for drug photosensitivity extends from UVB to visible light but UVA is most relevant for drug photosensitivity.

The mechanisms of drug photosensitivity include phototoxicity (non-immunological), photoallergy and others e.g. drug induced lupus and pellagra. The culprit drug dispersed in the skin tissue interacts with the corresponding waveband absorbed to produce the tissue effects. Phototoxicity, which is the most common cause of systemic drug photosensitivity, manifests clinically as i) immediate prickly feeling, erythema, urticarial, delayed erythema, and pigmentation; ii) exaggerated sunburn; iii) light-exposed sites telangiectasia; iv) delayed erythema at 3-5 days with pigmentation and; v) skin fragility at light-exposed sites (pseudoporphyria). On the other hand, photoallergy mainly manifests as eczematous eruptions.

Laboratory investigations in suspected systemic drug photosensitivity is mainly with monochromator phototesting. Narrow wavebands are tested across the solar spectrum to determine whether there is photosensitivity and if positive, which wavebands are involved. While photopatch testing can be used for suspected topical photoallergy (such as sunscreen chemicals and topical non-steroidals), it is unreliable for systemic drugs. Tests for porphyrin and autoimmune diseases are based on the clinical history.

There are regulatory photo-safety requirements for drugs that absorb wavelengths between 290-700 nm in Scotland. In vitro, ex vivo and controlled trials in human volunteers are required. Volunteers are photo-tested while they are on the drug and again after stopping the drug in order to determine the duration for the photosensitivity.

There is some concern as to whether photosensitisers can be photocarcinogenic as it is well-known that photochemotherapy with psoralens may induce skin cancer. Also, some fluoroquinolones have been found to be carcinogenic in mice. There could be distinct mechanisms for phototoxicity and carcinogenesis. So far, there is conflicting evidence and the possibility of genetic factors involved cannot be excluded. Further studies are needed in this area.

Learning points:

Drug photosensitivity is not uncommon. Dermatologists should aware of potential photosensitisers and the possibility of systemic drug toxicity in patients presenting with a photo-distributed rash and the corresponding symptoms.