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De novo or exacerbations of head and neck dermatitis in patients treated with dupilumab for atopic dermatitis

Speaker: S Barbarot
European Task Force on Atopic Dermatitis

Dupilumab is used to treat atopic dermatitis (AD) and its safety in adults has been assessed. The most common side effects were: injection site reactions, nasopharyngitis, conjunctivitis and transient increases in eosinophil counts from baseline. While most of the side effects were well-tolerated, new dermatoses have recently been reported in AD patients treated with dupilumab.

The development of the new regional dermatoses was mainly localised to the head and neck region, mimicking rosacea and erythrodermic presentation of psoriasis. In a study conducted to assess the clinical characteristics in patients treated with dupilumab, 4.2% of 1000 adults patients were found to have head and neck dermatoses. Most of them were middle-aged men of which the onset of AD was during infancy or childhood. The mean days to onset of head and neck dermatitis was 65.4 days after initiation of dupilumab therapy and 48% had concomitant ocular adverse side effects.

Several hypotheses have been suggested to explain the observed head and neck dermatoses:

1. Flare of AD due to topical steroid withdrawal after dupilumab initiation.
2. Modulation of T-helper cell signalling due to IL-4 receptor alpha blockade, unmasking a Th1-driven allergic contact dermatitis.
3. Activation of the TH17 pathway leading to *Malassezia* fungus proliferation.

Learning points:

Development of head and neck dermatitis in patients treated with dupilumab for AD may be a paradoxical, novel or adverse event. The clinical characteristics are different from rosacea or psoriasis and may lead to discontinuation of dupilumab.

Biomarkers in chronic spontaneous urticaria

Speaker: A Gimenez-Arnau
Hospital del Mar

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention. Autoimmune chronic spontaneous urticaria (aiCSU) is an important subtype of chronic spontaneous urticaria (CSU) in which functional IgG autoantibodies to IgE or its high-affinity receptor (Fc ε RI) but has not been fully characterised.

The proposed CSU biomarkers were categorised according to the features of disease activity, response to treatment and disease course. For disease activity, increased levels of D-dimer, C-reactive protein, prothrombin fragment 1+2, interleukin 6 and mean platelet volume were associated with more active disease.

For treatment response to antihistamines, a higher D-dimer level was associated with insufficient clinical response. For treatment response to cyclosporine, positive basophil histamine release and lower levels of D-dimer were associated with satisfactory clinical response. For treatment to omalizumab, low levels of interleukin 31 was associated with satisfactory clinical response, while lower expression of Basophil Fc ε RI receptor, lower total IgE levels at baseline levels and a lower IgE level increase after treatment initiation were associated with insufficient clinical response.

For disease course, the presence of anti-thyroid antibodies was associated with longer disease duration while higher levels of CD63 expression was associated with earlier spontaneous resolution in paediatric CSU.

Learning points:

Chronic spontaneous urticaria results from degranulation of mast cells. IgE to auto-allergens and IgG to Fc ε RI or to IgE are major auto-antibodies. Biomarkers may help in disease monitoring and optimisation of treatment regimen.

Early diagnosis and treatment of dermatomyositis

Speaker: Mirjana V. Milinkovic
Clinic of Dermatovenerology, Clinical Centre of Serbia, University of Belgrade

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) characterised by distinct skin lesions and heterogenous systemic manifestations. The International Myositis Classification Criteria Project (IMCCP) introduced new classification criteria that distinguishes IIM from the other forms of myopathy and classifies the major IIM subsets into 5 types: polymyositis, inclusion body myositis, classic DM, amyopathic DM and Juvenile DM.

According to the new criteria, the diagnostic criteria included: three major cutaneous manifestations, namely heliotrope eruption, Gottron's papules and Gottron's sign; Clinical findings include muscle weakness with history of insidious development of systemic proximal limb, truncal, neck or pharyngeal/oesophageal muscle weakness, while DM without muscle weakness was classified as amyopathic DM regardless of abnormal laboratory findings. Other laboratory findings of elevated serum levels of muscle enzymes (CK, LDH, AST and ALT) were included.

Detection of myositis-specific antibodies (MSA) in an increasing number of these cases identified a subgroup of patients characterised by their clinical or pathological phenotypes, prognosis and response to treatment.

The Anti-synthetase autoantibodies (ASA) target different tRNA synthetases. They are associated with characteristic clinical manifestations of myositis, arthritis and interstitial lung disease (ILD), mechanic's hands and Raynaud's phenomenon. Anti-synthetase autoantibodies are associated with a favourable prognosis.

The Anti-Mi-2 autoantibodies target nuclear DNA helicase which is involved in transcription. They are associated with classical DM clinical features (Gottron's sign, heliotrope rash, V-neck sign, shawl sign and cuticular overgrowth). Anti-Mi-2 autoantibodies are associated with a favourable prognosis and good response to treatment but there is a significant risk of recurrence.

Anti-MDA-5 autoantibodies target RNA-specific helicase and are involved in antiviral immune responses. They are associated with severe myocardial dysfunction and are usually found ILD and DM cutaneous manifestations. Anti-MDA-5 autoantibodies were found to have poor prognosis and rapidly progressive ILD.

The Anti-NXP-2 autoantibodies targeted nuclear matrix protein 2. It is associated with severe muscle weakness and increased risk for internal malignancy. Anti-NXP-2 autoantibodies are associated with a poor prognosis with severe clinical presentation and prognosis.

The Anti-TIF-1γ autoantibodies target TIF-1γ and are a part of transcription intermediary factor family of homologous proteins consisting of regulators of transcription, tumour suppressors, and mediators of DNA damage repair. They are strongly associated with malignancy and severe, chronic cutaneous manifestations. Anti-TIF-1γ autoantibodies were found to have poor prognosis with increased risk of malignancy.

The Anti-SAE1/2 autoantibodies target A and B subunits of a small ubiquitin-like modifier 1 activating enzyme. They are associated with severe dysphagia, severe cutaneous manifestation, persistent cutaneous ulcers. The risk of malignancy was found to be significantly higher in Japan.

Learning points:

The recent discovery of MSA could help distinguish between different DM clinical subtypes and the MSA profile could guide the management of malignancy work-up, ILD and systemic investigations.

Workup and management of patients with livedoid vasculopathy

Speaker: W Piette
John H. Stroger, Jr. Hospital

Livedoid vasculopathy (LV) was a chronic disorder characterised by painful, bilateral, recurrent ulcers, resulting in atrophic porcelain stellate scars with peripherial hyperpigmentation and telangiectasis. However, the classical description of atrophie blanche is not specific for livedoid vasculopathy and is also seen in other skin conditions e.g., systemic lupus erythema,atrophie blanche-like and IgA vasculitis.

A study published in 2006 to look for further evidence of procoagulant pathogenesis of LV. Total 45 patients were recruited and 50% of them were found to have thrombophilic abnormalities: Factor V Leiden, decreases protein C or S activity, prothrombin G 20210A mutation, anticardiolipin antibodies, lupus anticoagulant and elevated homocysteine levels. Another study published in 2010 also found around 52% of LV patients had laboratory

abnormalities indicative of a hypercoagulable condition. However, when given anticoagulation treatment, only 1/3 of patients were successful.

One large study in 2017 to investigate the relationship between the thrombophilia testing and venous thrombosis. Studies showed only a slight, non-significant increase in the risk of recurrence for patients with protein C/S and antithrombin deficiencies as compared with the patients who did not have the thrombophilia. Even if the thrombophilia testing was positive, the patients generally did not require indefinite anticoagulation therapy for the first provoked venous thrombosis event.

Up till now, no validated testing guidelines of inherited thrombophilia had been published and ordering of the thrombophilia testing was controversial. Data also showed that the clinical usefulness and benefits of testing were limited or non-existent. These findings suggest that LV is more complex than previously thought.

With the reference to the Delphi Consensus Review, treatment options were antiplatelet/anticoagulant, fibrinolytics, immuno-modulators, vasoliators and others eg, smoking cessation, compression therapy and hyperbaric oxygen.

Learning points:

Thrombophilia testing in LV was not clearly helpful and it did not appear to guide understanding of disease nor correlate with therapeutic response.