Hong Kong J. Dermatol. Venereol. (2018) **26**, 154-159

Journal Watch

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Cutaneous sarcoidosis: a new subset in the spectrum of paraneoplastic dermatoses

El-Khalawany M, Mosbeh A, Aboeldahab S, Ali S. Clin Exp Dermatol 2018;43:683-91.

Paraneoplastic dermatoses are skin diseases which are associated with the presence of malignancies. The literature on the correlation between sarcoidosis and malignancies is inconclusive. However, sarcoidosis with cutaneous involvement is associated with a higher rate of malignancy, with haematological malignancies being the most frequent neoplasms associated with sarcoidosis.

This observational prospective study recruited all newly diagnosed cases of cutaneous sarcoidosis in three dermatology centres from January 2009 to December 2014. A total of 94 patients were included.

Twelve patients with paraneoplastic sarcoidosis were identified. The paraneoplastic malignancies included Hodgkin lymphoma in six patients, multiple myeloma in five and non-Hodgkin lymphoma in one case. They were more common in older and male patients. Histologically, atypical cells and mitoses were more commonly reported in those with paraneoplastic syndrome. It took four to 25 months for the malignancy to be diagnosed from the diagnosis of cutaneous sarcoidosis. Patients responded poorly to systemic steroid. Those on combination therapy exhibited frequent relapses. Upon treatment of the malignancies, 7 out of 12 patients showed completion resolution of the lesions and five showed moderate improvement.

As previously reported in the literature, in the current study, haematological malignancy was the most common neoplastic condition associated with paraneoplastic sarcoidosis. Patients with sarcoidosis with new or evolving lesions also appeared to be at a high risk of malignancy.

These findings suggest that sarcoidosis is a new subset in the spectrum of paraneoplastic dermatoses and that lymphoproliferative disorders should be considered in those who respond poorly to conventional treatment or in those with a large number of mitoses on skin biopsy.

Association of clinicopathological features of melanoma with total naevus count and a history of dysplastic naevi: a cross-sectional retrospective study within an academic centre

Tan SY, Strazzulla LC, Li X, Park JJ, Lee SJ, Kim CC. Clin Exp Dermatol 2018;43:566-72.

High naevus count (HNC), defined as a nevus count of 50 or more, and the presence of dysplastic naevi (DN) are risk factors for the development of malignant melanoma. It was not known whether there was any difference in clinical or histopathological features between the melanomas which developed in those with a HNC or DN, compared to those without.

The study was a cross-sectional retrospective chart review that examined 281 patient records with melanoma from April 2013 to March 2014 at an academic pigmented lesion clinic.

Patients with low naevus count (LNC) melanoma were older (51 vs 41 years of age), had more aggressive melanoma features in terms of greater Breslow thickness (1.1 vs 0.8 mm), more mitoses (2 vs 1 mitoses/mm^2), lower rate of superficial spreading types (58% vs 78%) and higher melanoma stage, compared to patients with HNC.

Patients with DN exhibited a similar tendency as patients with HNC. Additionally, they were more likely to have a truncal melanoma (55% vs 39%), less ulceration (13% vs 29%). Patients without DN were more likely to have a history of non-melanoma skin cancer (33% vs 21%) and amelanotic melanoma (33% vs 21%).

In conclusion, patients with LNC might develop melanoma with more aggressive features and were older. These were important caveats for diagnosis, screening and education of patients. These findings also supported screening for melanomas at an earlier age on patients with a HNC and DN. Education about clinical signs, such as those of the amelanotic and nodular subtypes could be tailored to those patients with a LNC and those without DN.

Assessment of a Predictive Scoring Model for Dermoscopy of Subungual Melanoma In Situ

Ohn J, Jo G, Cho Y, Sheu SL, Cho KH, Mun JH.
JAMA Dermatol 2018;154:890-6.

In this cohort study, 19 patients with biopsy-proved subungual melanoma-in-situ and 26 patients with benign longitudinal melanonychia were recruited. The aims of this study were to investigate the characteristic dermoscopic findings of subungual melanoma in situ and to establish a predictive scoring model for the diagnosis of subungual melanoma in situ in patients with adult-onset longitudinal melanonychia affecting a single digit.

Among these 45 patients, widths of the pigmentation of at least 3 mm were seen in 17 patients (89%) in the subungual melanoma-in-situ group and in 16 patients (62%) in the benign longitudinal melanonychia group (OR, 5.31; 95% CI, 1.01-28.07). The most commonly observed colour in 19 lesions of subungual melanoma-in-situ was dark brown (16 of 19 lesions [84%]), followed by grey (13 [68%]), light brown (12 [63%]), and black (9 [47%]). Seventeen patients in the subungual melanoma-in-situ group had multicolour pigmentation (OR, 11.59; 95% CI, 2.21-60.89; P=0.004). Asymmetry (OR, 34.00; 95% CI, 3.88-297.70), border fading (OR, 9.33; 95% CI, 2.37-36.70), presence of Hutchinson sign (OR, 18.18; 95% CI, 2.02-163.52) were features of longitudinal melanonychia that were significantly associated with subungual melanoma-in-situ.

A predictive scoring model incorporating the above dermoscopic features of subungual melanoma-in-situ, width of pigmentation, multicolor pigmentation, asymmetry, border fading, as well as Hutchinson sign, was assessed. The model ranged from 0 to 8 points. The cut-off value of 3 points coincided with a sensitivity of 89% and a specificity of 62%.

In conclusion, the authors suggested that clinicians use the predictive scoring model during physical examination to assist in screening for subungual melanoma in situ.

Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults With Atopic Dermatitis

Simpson EL, Guttman-Yassky E, Margolis DJ, Feldman SR, Qureshi A, Hata T, et al.
JAMA Dermatol 2018;154:903-12.

The aim of this cross-sectional study was to characterise the patient-reported burden of atopic dermatitis with regard to impact of disease severity and inadequate control in adults.

Data from six US academic medical centres collected by an Internet-based, self-administered questionnaire were analysed. In this study, 1519 adult patients with atopic dermatitis were stratified as mild or moderate/severe using the Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD). Patients on treatment with systemic immunomodulators/phototherapy were further classified as those with adequate or inadequate disease control. The outcomes assessed included itch, pain, anxiety and depression, health-related quality of life, and sleep.

Among 1519 patients studied, 830 patients (54.6%) had moderate/severe atopic dermatitis. A total of 185 (22.3%) patients with moderate/severe disease received systemic immunomodulators/phototherapy, of whom 103 (55.7%) considered their control to be inadequate.

Compared with patients with mild atopic dermatitis, patients with moderate/severe disease suffered from itching more days per week (5.7 vs 2.7) and there was a higher proportion with an itch duration of over half a day (190 [22.8%] vs 20 [2.9%]). Pain severity was higher among moderate/severe compared with mild group. Patients with moderate/severe atopic dermatitis reported more sleep problems compared with those with mild atopic dermatitis. There was a higher proportion suffering from sleep problems included trouble sleeping (3.9 vs 1.1 on the PO-SCORAD visual analogue scale), sleep disturbances more frequent (2.6 vs 0.4 nights in past week), sleep latency longer (38.8 vs 21.6 minutes), and an increased need for over-the-counter sleep medications (324 [39%] vs 145 [21%]). Symptoms of anxiety or depression were more commonly reported by 417 (50.2%) patients with moderate/severe atopic dermatitis compared with 188 patients with mild disease (27.3%) ($P<0.001$) and mean Dermatology Life Quality Index (DLQI) scores were higher among patients with moderate/severe compared with those with mild disease (9.2 vs 2.9; $P<0.001$), and among patients with inadequately controlled compared with controlled disease (13.4 vs 9.3; $P<0.001$)

This study demonstrated reported a significantly greater burden in patients with moderate/severe atopic dermatitis on all outcomes and that inadequate disease control among patients with moderate/severe atopic dermatitis despite treatment is high. The authors suggested a need for more effective therapies for moderate/severe atopic dermatitis.

Differential effects of secukinumab vs. ustekinumab for treatment of psoriasis on quality of life, work productivity and activity impairment: a structural equation modelling analysis

Stull DE, Griffiths CEM, Gilloteau I, Zhao Y, Guana A, Finlay AY, et al.
Br J Dermatol 2018;178:1297-307.

Psoriasis may cause significant impact on patient's quality of life. This study compared the effects of secukinumab vs ustekinumab through Psoriasis Area and Severity Index (PASI) 50, 75, 90, 100 response and psoriasis-related symptoms (pain, itching, scaling) on Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment (WPAI) questionnaire at week 16 and 52. The CLEAR study (**C**omparison to assess **L**ong-term **E**fficacy, s**A**fety and tole **R**ability of secukinumab vs ustekinumab) was a 52-week, multicentre, randomised, double-blind, head-to-head study between secukinumab and ustekinumab in moderate-to-severe psoriasis. Data from the CLEAR study was used and analysed in this study. At weeks 16 and 52, secukinumab patients were significantly more likely to achieve a PASI 50, 75, 90, 100 response than ustekinumab patients and with an improved DLQI. Secukinumab patients were significantly have better improvements in pain, itching and scaling than ustekinumab patients and hence also improved the DLQI. Both secukinumab group (336 patients) and ustekinumab group (339 patients) showed achievement of PASI 90 response and improvements in itching, pain and scaling results in significantly better DLQI scores and lower WPAI

activity impairment. Both secukinumab and ustekinumab had a comparable safety profile. In conclusion, secukinumab showed a greater improvement in PASI score, psoriasis-related symptoms (pain, itching, scaling), health-related quality of life, and WPAI than ustekinumab.

Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial

Gerbens LAA, Hamann SAS, Brouwer MWD, Roekevisch E, Leeflang MMG, Spuls PI.
Br J Dermatol 2018;178:1288-96.

Systemic immunosuppressants may be indicated for patients with severe atopic dermatitis (AD). This study was a single-blinded 5-year, open-label follow-up of clinical randomised controlled trials to investigate the long-term effectiveness, drug survival and safety of methotrexate (MTX) (10-22.5 mg/week) and azathioprine (AZA) (maximum 2.5 mg/kg) for moderate-to-severe AD. Forty-three patients (MTX:20 patients, AZA: 23 patients) were monitored every 3 months over 5 years. Primary outcomes were mean absolute and relative reduction in SCORing Atopic Dermatitis (SCORAD) index and Investigator's Global Assessment (IGA) compared with baseline. Mean absolute reduction in total SCORAD was similar between MTX group (32.1) and AZA group (32.1). Mean relative reduction in SCORAD index was similar between MTX group (53%) and AZA group (54%). IGA was four in both MTX and AZA groups. Sixty-nine remissions were found over 5 years in the study with similar remissions between MTX group (35%) and AZA group (39%). There was longer median drug survival in MTX group (28.8 months) than AZA group (11.5 months) was found. Longer drug survival period after 5 years was found in MTX group (n=5) than AZA group (n=1) but survival in both groups was low. Reasons for discontinuation were ineffectiveness, adverse effects, controlled AD, wish to conceive, own initiative. The most common side effects in both groups were infections and infestations (common cold, influenza). Most side effects were mild to moderate only. In conclusion, both MTX and AZA are effective and safe treatments for moderate-to-severe AD up to 5 years.

A maintenance 3-day-per-week schedule with the single tablet regimen efavirenz/emtricitabine/tenofovir disoproxil fumerate is effective and decreases sub-clinical toxicity

Rojas J, Blanco JL, Sanchez-Palomino S, Marcos MA, Guardo AC, Gonzalez-Cordon A, et al.
AIDS 2018;32:1633-41.

With the advancement of anti-retroviral therapy (ART), HIV has been transformed from a life-threatening disease to a chronic illness. However, long-term ART may be associated with toxicities. Reducing the daily dose of efavirenz (EFV) from 600 mg to 400 mg and using tenofovir alafenamide (TAF) instead of tenofovir disoproxil fumarate (TDF) are strategies decrease the use EFV and TDF. The authors hypothesised that the viral load suppression can be maintained and less toxic when simplifying Atripla once daily to three days per week.

The inclusion criteria included HIV cases over 18 years old taking Atripla with viral load <37 copies/mL and CD4 count >350 cells/ml for at least two years before the study. Those with prior virological failure to any ART; documented resistance to EFV, tenofovir or emtricitabine (FTC); any psychiatric illness; history of alcohol abuse or illicit drug usage and any other conditions at doctor's discretion that did not allow ensuring a correct adherence were excluded. In women of child-bearing age, a negative pregnant test was required and contraceptive measures were required. The patients were randomised into two groups: a. Atripla daily (Daily arm) and b. 3 days per week on Monday, Wednesday and Friday (3 W arm).

There was no significant difference between the two arms in terms of age, sex, ethnicity, BMI, route of HIV transmission and CDC stage. The baseline laboratory and other tests (creatinine; lipid profile; estimated GFR, 25-OH vitamin D level; CD4 count; CD4/8 ratio; ultrasensitive HIV RNA; efavirenz plasma level; Pittsburg sleep quality index (PSQI); bone density and urine analysis) were also not significantly different between both groups. At 24 weeks, 100% of patients in both arms completed the study. There were no treatment failures and the proportion of cases with plasma HIV-1 RNA below detection threshold was similar between the two groups (70% in the 3W arm vs. 71% in the OD arm, P=0.933). Eleven (36%) patients in the Daily arm and 13 (43%) patients in 3W arm reported at least one adverse effect. However, all were mild and not related to Atripla and no patient discontinued therapy because of adverse effects.

The authors concluded that a 3-day-per-week Atripla in patients for sustained viral suppression was a feasible option.

Highlighting the clinical need for diagnosing Mycoplasma genitalium infection

Ison CA, Fifer H, Gwynn S, Horner P, Muir P, Nicholls J, et al.
Int J STD AIDS;2018;29:680-6.

There is no commercially available Mycoplasma genitalium (MG) assay that is fully approved by the Food and Drug Administration (FDA) even though MG is a well-recognised pathogen of non-gonococcal urethritis (NGU). To prevent the emergence of MG resistance, a robust diagnostic and treatment pathway is needed. The aim of this study was to assess the opinion of clinical professionals involved in the diagnosis and management of conditions associated with MG in order to make appropriate recommendations for best practice.

A panel of experts in GU medicine and microbiology examined the issues involved in the diagnosis and management of MG. A modified Delphi methodology was used in this study in which a questionnaire with 4-point Likert scale consisting of thirty-two consensus statements was circulated to clinicians and laboratory staff. Consensus was measured through written feedback. A consensus was considered to be reached if there was a greater than 75% agreement.

The response rate was 29.8% (60/201). Overall 84.4% of the statements achieved over 75% agreement. There was a strong consensus that MG testing should be performed in urethritis and unexplained vaginal discharge. More evidence was required regarding MG proctitis in MSM. Also, there was strong consensus that MG testing and resistance testing should be available in all tertiary centres.

Clinical and histologic features of Mycoplasma pneumoniae-related erythema multiforme: A single-center series of 33 cases compared with 100 cases induced by other causes

Amode R, Ingen-Housz-Oro S, Ortonne N, Bounfour T, Pereyre S, Schlemmer F, et al.
J Am Acad Dermatol 2018;79:110-7.

Mycoplasma pneumoniae is a well-reported cause of erythema multiforme (EM) and Stevens-Johnson syndrome-toxic epidermal necrosis (SJS-TEN), especially in children and young adults. However, its clinical presentation and histology is poorly described. In this retrospective cohort study, all patients with the diagnosis of erythema multiforme were recruited from a single centre. Cases associated with *M. pneumoniae* were compared to non-*M. pneumoniae* cases in terms of clinical features, histological findings and follow-up sequalae.

A total of 133 cases with EM were identified over a period of 5 years, 33 of them associated with *M. pneumoniae* and the rest were non-*M. pneumoniae*. Among them, more than half of them were related to herpes simplex infection, followed by other infection or drug-related cause. However, one third of them were idiopathic. It was found that *M. pneumoniae*-related EM was more frequent in winter. Clinically, they were significantly less acrally-distributed (32% vs 88%, P<0.0001), fewer typical target lesions (45% vs 74%, P=0.01) , and more frequently presented with mucositis in more than one site, especially ocular and pharyngeal areas (97% vs 60%; P<0.0001). Moreover, *M. pneumoniae* EM cases resulted in significantly longer hospital stay, mainly due to respiratory and mucosal sequalae. In addition, skin biopsies from all cases with *M. pneumoniae* EM showed typical histological finding of TENS, namely apoptosis and pan-epidermolysis, while non-*M. pneumoniae* EM cases typically showed lichenoid inflammatory changes with basal epidermal necrosis.

The authors concluded that *M. pneumoniae* EM represented a distinct entity with less acral involvement, more atypical target lesions, more severe mucositis and respiratory sequalae and specific histological features mimicking TENS.

Ixekizumab treatment shows a neutral impact on cardiovascular parameters in patients with moderate-to-severe plaque psoriasis: Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3

Egeberg A, Wu JJ, Korman N, Solomon JA, Goldblum O, Zhao F, et al.
J Am Acad Dermatol 2018;79:104-9.

Patients with psoriasis are associated with cardiovascular risk factors and co-morbidities as both psoriasis and atherosclerosis are mediated by type 1 and type 17 helper T cells. Ixekizumab, a monoclonal antibody that selectively targets IL-17A has been shown to be highly effective in controlling moderate-to-severe psoriasis. However, its impact on cardiovascular parameters and co-morbidities are unclear. In this study, the authors gathered data from the three randomised, double-blinded, controlled phase III trials on Ixekizumab (UNCOVER-1, UNCOVER-2 and UNCOVER-3) which studied adults with moderate-to-severe psoriasis. During the induction period (week 0-12), patients were randomly assigned to placebo, ixekizumab, or etanercept. After week 12, responders were randomised to receiving either placebo or ixekizumab through week 12-60 as maintenance. The following cardiovascular parameters were measured: fasting lipid profiles, fasting glucose, advanced lipid profiles, electrocardiograms, high-sensitive C-reactive protein(hsCRP), and blood pressure monitoring.

More than 3000 patients were included. Of these, 4-10% were overweight, with type 2 diabetes mellitus and hyperlipidaemia, and around 30% with hypertension. It was found that there were no significant changes in cardiovascular parameters, blood pressure and body weight in patients receiving ixekizumab from baseline to week 60. Also, lipid profile, fasting glucose and apolipoprotein after maintenance were comparable between ixekizumab and placebo groups. There was a significant but transient decrease in hsCRP at week 12 in Ixekizumab group, which was maintained at week 60 though not significantly. This suggested a reduction in systemic inflammation. However, its clinical implication could not be evaluated.

The authors concluded that effect of ixekizumab was neutral on multiple cardiovascular-related parameters. Further long term studies and surveillance are required to further evaluate its efficacy on cardiovascular risk. Hence, patients receiving ixekizumab should still have their cardiovascular parameters monitored, treated and investigated.