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Journal Watch

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Acral melanoma foot lesions. Part 1: epidemiology, aetiology, and molecular pathology

Desai A, Ugorji R, Khachemoune A
Clin Exp Dermatol 2017;42:845-8.

This review outlines the new updates on epidemiology, aetiology and molecular pathology of acral melanoma foot lesions. Acral melanoma is an uncommon type of cutaneous malignant melanoma that carries a poor prognosis. It is, however, the most common subtype found in patients of African or East Asian descent. Acral melanoma is found on acral skin, usually the soles of the feet, palms of the hands, and the nails.

Compared with the other subtypes of malignant melanoma, acral melanoma is associated with a lower incidence of familial malignant melanoma, and lower number of common and atypical naevi. On the other hand, it is associated with both personal and family history of extra-cutaneous cancers.

Acral melanoma was first described by Richard J. Reed in 1976 and was so named because of its predilection for acral, or distal parts of the body. Many acral melanomas are further characterised by their radial or "lentiginous" growth phase.

Its pathogenesis remains elusive, but genetic mutations in BRAF, NRAS and KIT have been implicated. BRAF mutations are more commonly encountered in malignant melanomas found on skin with intermittent sun exposure than chronic exposure, or those with low to no sun exposure. On the contrary, NRAS mutations are more commonly found in skin with chronic sun damage. The oncogene KIT which encodes a transmembrane tyrosine kinase receptor is present in 10-20% of acral melanomas. The L576P mutation in exon 11 was the mutation most frequently detected. PTEN mutations occur least commonly in acral melanomas. Identification of these mutations has important implications on therapy, particularly relating to targeted therapies.

Effectiveness of surgical treatment of severe macrocheilia in a patient with orofacial granulomatosis

Vassallo C, Rivetti N, Merlino M, Borroni G, Brazzelli V.
Clin Exp Dermatol 2017;42:887-9.

Orofacial granulomatosis is characterised by recurrent or persistent swelling of the soft tissues of the orofacial region. Existing therapies often produce only moderate and temporary control of the condition; and consensus about preferred treatment differs. Systemic and intralesional corticosteroids, oral antibiotics, clofazimine, dapsone and thalidomide have variously been used.

In this report, a surgical approach to its treatment was adopted. Surgical reduction with excision of the excessive tissues was carried out. The Conway surgical method involves a transverse sickle-shaped mucosal and submucosal excision up to the orbicularis oris muscle. Post-operatively, the patient received doxycycline for three months to minimise the risk of infection and level of

inflammatory cells. The patient remained in remission three years later.

In the past, it was advocated that surgery be deferred until the disease has been controlled with medical treatment in order to avoid recurrence. The current report describes a patient on whom surgery was necessitated by severe functional impairment.

The study highlights that surgical management followed by doxycycline remains an option in the treatment of this challenging condition.

Secukinumab is superior to fumaric acid esters in treating patients with moderate-to-severe plaque psoriasis who are naive to systemic treatments: results from the randomized controlled PRIME trial

Sticherling M, Mrowietz U, Augustin M, Thaci D, Melzer N, Hentschke C, et al.
Br J Dermatol 2017;177:1024-32.

Secukinumab (human interleukin 17A monoclonal antibody) is the first biological therapy recommended as first-line systemic treatment for psoriasis by European S3-Guidelines. Its therapeutic response was compared with another first-line systemic psoriasis treatment of European S3-Guidelines: fumaric acid esters (FAEs) in this study. In this randomised, multi-centre, open label study, the therapeutic response of subcutaneous secukinumab 300 mg for moderate-to-severe plaque psoriasis (without prior systemic treatment) was compared to that of oral FAEs using Psoriasis Area and Severity Index score (PASI response) and Dermatology Life Quality Index 0 or 1 response at week 24. More cases achieved PASI 75 and PASI 90 in the secukinumab group (89.5%, 81% respectively) than FAEs group (33.7%, 28.4% respectively) at week 24 ($p<0.001$). Dermatology Life Quality Index 0 or 1 response (i.e. no impairment of health-related quality of life) of secukinumab group (71.4%) was higher than FAEs group (25.3%) at week 24 ($p<0.001$). Secukinumab had a favourable safety profile. More patients in FAEs group developed adverse effects of infection, flushing, upper abdominal pain, diarrhoea and lymphopaenia. No report of death or causal relationship for severe adverse events were found in both groups. In conclusion, secukinumab has superior efficacy and tolerability than FAEs in treatment of moderate-to-severe plaque psoriasis over 24 weeks.

Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study

Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, et al.
Br J Dermatol 2017;177:1014-23.

The interleukin (IL)-23/IL-17 axis is important in the pathogenesis of psoriasis. This multicentre, double-blinded, controlled parallel-group trial compared the therapeutic response for psoriasis between ixekizumab (IXE, IL-17A inhibitor) and ustekinumab (UST, IL-12/23 inhibitor) by using Psoriasis Area and Severity Index (PASI), static Physician's Global Assessment (sPGA) score and Dermatology Life Quality Index (DLQI) score as treatment outcomes over 52 weeks. The IXE treatment regimen was given subcutaneously as: 160 mg at week 0, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks up to 52 weeks. The UST treatment regimen was given subcutaneously as: 45 mg (body weight <100 kg) or 90 mg (body weight >100 kg) at week 0, 4, 16, 28, 40. PASI 90 response rate of IXE group (72.8%) was higher than UST group (42.2%) at week 12 ($p<0.001$). The IXE group also had a significantly higher PASI, sPGA, DLQI response rate than UST group at week 24. The most common adverse effect in both groups was nasopharynitis and other common adverse effects included headache, rhinitis, arthralgia, back pain and hypertension. No difference of incidence rate for adverse events was found between the two

groups and there were no deaths in either group. Both treatments were well tolerated and safe. In conclusion, IXE has a more rapid onset of action and superior efficacy.

Association of immunotherapy with overall survival in elderly patients with melanoma

Perier-Muzet M, Gatt E, Péron J, Falandry C, Amini-Adlé M, Thomas L, et al.
JAMA Dermatol. 2018;154:82-7.

Immunotherapy for metastatic melanoma has been a focus of research for decades. Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Nivolumab is a human programmed death receptor-1 (PD-1)-blocking antibody and pembrolizumab targets the programmed death 1 (PD-1) receptor.

This single centre, cohort analysis included patients with metastatic melanoma treated by immunotherapy between January 2007 and February 2016. Patients with metastatic melanoma treated with ipilimumab, nivolumab or pembrolizumab were retrospectively analysed. The main outcomes measured were overall survival, progression-free survival, and immune-related adverse events.

A total 92 patients were included and a total of 120 lines of treatment was given. There were 54 patients who were 65 years or younger, and 38 patients older than 65 years. Patients were followed up for a mean of 12.5 months after treatment initiation. There was a better mean progression-free survival (4.8 vs 3.4 months; p=0.04) in patients older than 65 years treated with immunotherapy and overall survival (not reached vs. 10.1 months; p=0.009) compared with younger patients. The association between older age and a better prognosis was stronger for those patients treated with anti-programmed cell death protein 1. There was no difference in frequency or grade of immune-related adverse effects between younger and older patients.

This study showed that immune adverse events were not increased in patients older than 65 years treated with immunotherapy. Therefore, the authors concluded age should not be a limiting factor for immunotherapy for metastatic melanoma.

Factors associated with clinical remission of skin disease in dermatomyositis

Paige W, Wolstencroft PW, Chung L, Li SF, Casciola-Rosen L, Fiorentino DF.
JAMA Dermatol 2018;154:44-51.

Dermatomyositis is an autoimmune connective tissue disease characterised by cutaneous findings, e.g. heliotrope rash, Gottron's papules, etc., and muscle weakness.

This was a prospective cohort study which included a total of 74 patients at a dermatology clinic of a tertiary academic referral centre. The main outcomes and measures were the percentage of patients who achieved clinical remission of their cutaneous disease as measured by the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score.

Twenty-eight patients (38%) achieved clinical remission during 3-year follow-up period. The analysis showed that the following were significantly associated with clinical remission of skin disease: (1) increased age (odds ratio [OR], 1.07; 95% CI, 1.02-1.12; p=0.01), (2) dermatomyositis-associated malignancy (OR, 14.46; 95% CI, 2.18-96.07; p=0.01), and (3) treatment with mycophenolate mofetil (OR, 6.00; 95% CI 1.66-21.78; p=0.01). On the other hand, patients with anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibodies were significantly less likely to be in the clinical remission group.

The authors concluded clinical remission of skin disease in dermatomyositis was relatively uncommon in the study population and even less common in patients with anti-MDA5 antibodies, despite the use of aggressive systemic therapy.

Fuckbuddy partnerships among men who have sex with men - a marker of sexually transmitted infection risk

Cornelisse VJ, Fairley CK, Philips T, Walker S, Chow EP.
Int J STD AIDS 2018;29:44-50.

'Fuckbuddies' are considered by men who have sex with men (MSM) as a type of regular partner with whom men have ongoing sexual contact, generally in the absence of romantic attachment. These 'fuckbuddy' partnerships may carry a higher risk than regular partnerships such as boyfriends and husband. The aim of the study was to determine the frequency of fuckbuddy partnerships amongst sexual health clinic attendees and to assess their sexual risk and rate of sexually transmitted infections (STIs).

During 6-month study period in a STI treatment centre, 939 MSM were enrolled with median age 29 years (IQR 25-36). They reported a median of five male sexual partners (IQR 2-9) in the last three months and 764 (81%) claimed on condom use, of whom, 385 (50%) reported consistent condom use for receptive and/or insertive anal sex. Thirty-four participants were HIV positive.

There were 502 MSM (54%; 95% CI 50-57) with at least one current regular sexual partner leading to a total of 1139 regular partnerships. The majority were fuckbuddies (60%, n=686); followed by partners (16%, n=184), boyfriends (16%, n=178) and then husbands (1%, n=13). Of regular partnerships, 7% (n=78) were others in which 46% were undefined, 24% were a variation of friends with benefits, 21% were akin to fuckbuddies (occasional hook-up, fling) and 9% were ex-partners or new regular relationships.

MSM with regular fuckbuddies were more likely to have casual sexual partners than MSM without fuckbuddies (88% vs 57%, OR 5.7, 95% CI 3.6 - 8.9, p<0.001).

MSM with regular fuckbuddies were more likely to have rectal chlamydia than MSM without fuckbuddies. (12.4% vs 5.7%, OR 2.32, p=0.019. There was no significant difference among other STIs such rectal, pharnyngeal, urethral gonorrhoea, urethral chlamydia or syphilis. During the study period, five patients newly acquired HIV of which one reported having a fuckbuddy. However, as the number of new HIV cases was low, a statistical association could not be established.

The authors concluded that their findings suggest MSM with fuckbuddies have a higher risk of STIs.

Cost-effectiveness of microscopy of urethral smears for asymptomatic *Mycoplasma genitalium* urethritis in men in England

Sutton AJ, Roberts TE, Jackson L, Saunders J, White PJ, Birger R, et al.
Int J STD AIDS 2018;29:72-9.

The cost-effectiveness of microscopy of urethral smear for asymptomatic *Mycoplasma genitalum* (MG) in men was still controversial. The aim of this study was to determine whether using urethral microscopy to diagnose asymptomatic non-chlamydial, non-gonococcal urethritis (NCNGU) in men is a cost effective strategy for avoiding pelvic inflammatory disease (PID) in their female partners.

A transmission dynamic model (TDM) describing the transmission of MG in a population of 16-30 year olds in England was constructed to examine changes in the use of urethral microscopy in asymptomatic men in GUM clinics. Three different pathways were compared in terms of their resources use and costs: (1) no microscopy offered for asymptomatic men (No Microscopy); (2) offering 5% of microscopy for asymptomatic men

(5% Microscopy) and (3) offering 100% of microscopy for asymptomatic men (100% Microscopy).

The "5% Microscopy" strategy had a positive impact on PID with lower case numbers and major outcomes including infertility and ectopic pregnancy. Although "5% Microscopy" was more effective than "No Microscopy", it had an incremental cost-effectiveness ratio (ICER) of $15,700 meaning that an investment of $15,700 is required to avoid one case of PID. The ICER was $16,300 in "100% Microscopy". Similarly, "5% Microscopy" was more effective than "No Microscopy" in averting major outcomes. However, it needed an investment of $49,900 to avert one major outcome and $51,900 was needed in "100% Microscopy". When cost was considered, a reduction in major outcomes was insufficient to make "5% Microscopy" or "100% Microscopy" cost saving.

The authors concluded that offering 5% microscopy or offering 100% microscopy for asymptomatic men in MG is not cost-effective. No microscopy is necessary for asymptomatic people.

Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderated-to-severe melasma

Del Rosario E, Florez-Pollack S, Zapata L Jr., Hernandez K, Tovar-Garza A, Rodrigues M, et al.
J Am Acad Dermatol 2018;78:363-9.

Melasma is a common yet difficult to manage pigmentary disorder. Tranexamic acid (TA) is an anti-fibrinolyic originally used for menorrhagia and bleeding diatheses. It was found that TA also decreases tyrosinase activity in melanocytes, and was shown in various studies to be effective in managing melasma. However, most of these were done in Asian patients and in an uncontrolled manner. The authors studied the efficacy of TA in North American women in this randomised, controlled study.

Patients with moderate-to-severe melasma were recruited. Moderate melasma were defined as having modified Melasma Area and Severity Index (mMASI) score of 5.8 to 7.9 while severe with score of eight or higher. Patients who had been recently treated with depigmenting agents, topical steroids, laser or dermabrasion were excluded. Those who had contraindications to TA according to FDA guidelines, severe organ dysfunction or who were pregnant or nursing were excluded. Eligible patients were then randomised to either receiving TA 250 mg BD for three months or placebo capsules. Both group of patients were advised to apply sunscreen every two hours while on active treatment and continue sunscreen alone for three more months. All participants were followed up at month 1, 2, 3 and 6 for assessment of response by mMASI scoring and photography, side effects and compliance.

A total of 44 eligible patients were included and 39 completed study. More than 80% of the participants were Hispanic women and 60% of them had tried some form of treatment for their melasma. After three months of active treatment, those with moderate and severe melasma showed a significant reduction in mMASI score (45% vs 16%, and 51% vs 19% respectively). At 6-month follow-up, ie 3 months after active treatment, there was still 32% reduction in mMASI score in TA group for moderately-affected patients as opposed to 13% in placebo group, whereas in severe patients, 21% vs 24% reduction in mMASI was observed. TA was generally well-tolerated and most commonly reported adverse effects were gastrointestinal discomfort and menstrual disturbance, which was mild and resolved spontaneously. One patient stopped TA due to severe myalgia. However, no thrombotic events reported.

The authors concluded that TA is effective in managing moderate-to-severe melasma and severe patients appeared to respond better. However, the effect was not sustained in these

groups after stopping the treatment. Furthermore, TA and sunscreen did not achieve complete clearance. Further studies are needed to explore whether longer duration of TA in severe melasma and examine whether combination with depigmenting agents can achieve better outcome. Also, studies with longer follow-up are needed to assess the relapse rate.

Risk of infection in patients with atopic dermatitis treated with dupilumab: A meta-analysis of randomized controlled trials

Fleming P, Drucker AM.
J Am Acad Dermatol 2018;78:62-9.

Patients with atopic dermatitis (AD) are prone to cutaneous infections. This may be related to skin barrier disruption, decreased expression of antimicrobial peptides and production of cytokines and overabundance of microbes. Dupilumab, an IL-4 and IL-13 inhibitor, has recently been shown to be effective and safe in treating moderate-to-severe AD. Moreover, the infection rate also appeared to be reduced. In this study, the authors examined the infection rates in patients with moderate-to-severe AD treated with dupilumab.

This meta-analysis included randomised-controlled trials (RCTs) of dupilumab for AD published up to June 2017. The risk of skin, herpes and overall infection were studied. A total of eight RCTs with 2706 moderate-to-severe AD patients were included with follow-up time ranging from four to 52 weeks. A reduction of skin infection (RR = 0.54 (95% CI, 0.42-0.70)) and eczema herpeticum (OR = 0.34 95% CI = 0.14-0.84) was found. However, there was no significant association between dupilumab and overall herpesvirus infection (RR, 1.16; 95% CI, 0.78-1.74) and overall infection rate (RR, 0.98; 95% CI, 0.83-1.16).

The reason for reduction in skin infection and eczema herpeticum remains unknown. Normalisation of skin barrier and microbiome, and treatment of aberrant immune response may have played a role. Other anti-inflammatory treatments which improve skin barrier have also shown reduced infection rates signifying that this reduction in infection may not be specific effect of dupilumab.

The authors concluded that dupilumab reduced skin infection and eczema herpeticum. However, further studies with more patients and longer follow up are required to better delineate the effect on specific infection.