

Journal Watch

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Three patients with orbital xantho-granuloma and non-progressive haematological abnormalities

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The authors reported three elderly Chinese patients with orbital xanthogranuloma. They had symmetrical periorbital yellowish subcutaneous plaques which were firm and not attached to underlying structures. The lesions were asymptomatic, except for mild pruritus in one case. They did not cause any visual impairment. They all had haematological abnormalities such as thrombocytopenia, normochromic normocytic anaemia or eosinophilia. Bone marrow examination was done in two patients and was unremarkable. Skin biopsy showed diffuse histiocytic infiltrate of dermis and subcutaneous tissue. Some large cells with abundant foamy cytoplasm and an incomplete ring of nuclei were present. Other inflammatory cells like eosinophils, plasma cells and lymphocytes were also noted. The cutaneous lesions remained localised and the haematological abnormalities stable during a follow-up period of up to seven years.

Totally 22 cases of orbital xanthogranuloma (including the present three) were reported in the English literature. Haematological abnormalities like lymphopenia, neutrophilia and thrombocytopenia were reported in 12 patients (54.5%) while eosinophilia was found in nine (40.9%). Thus the association with haematological abnormalities was unlikely to be due to chance occurrence. However, their clinical significance remained unknown.

The differential diagnosis of orbital xanthogranuloma includes necrobiotic xanthogranuloma, juvenile xanthogranuloma and Erdheim-Chester disease. Its treatment was largely anecdotal. Oral prednisolone alone or together with radiotherapy or chemotherapy were tried. For the three reported patients, no systemic treatment was given in view of their age, lack of significant symptom and inherent risks of aggressive therapy.

Tacrolimus ointment 0.1% in the treatment of nickel-induced allergic contact dermatitis

Saripalli YV, Gadzia JE, Belsito DV.

J Am Acad Dermatol 2003;49:477-82.

The effectiveness and safety of 0.1% tacrolimus ointment in treating nickel-induced allergic contact dermatitis (ACD) were assessed in a randomised, double-blind, vehicle-controlled, bilateral paired comparison study.

Twenty-two volunteers who had known delayed hypersensitivity to nickel were recruited. They were subjected to patch test challenge with 2.5% nickel sulphate in petrolatum on their upper inner arms bilaterally. Twenty subjects who developed ACD to an approximately equal extent on the test sites bilaterally proceeded to the next phase. Their mean age was 38.5 years and 16 were female. They were randomized to apply vehicle on one arm's test site and 0.1% tacrolimus ointment on the other arm twice daily for two week, starting from day 0. They were also instructed to apply 2.5% nickel sulphate to the test sites for four hours

on days 3, 5, 7, and 10, imitating the recurrent exposure to an allergen in real life. The subjects were evaluated in terms of their signs and symptoms, the investigator's global assessment and occurrence of adverse events.

Nineteen volunteers completed the protocol and one was discontinued on day 7 because of impetigo at the site of tacrolimus application. Significant overall improvement in signs, symptoms and the investigator's global assessment were noted at the tacrolimus-treated sites on day 14, compared to those at the vehicle-treated sites. About 80% of volunteers (n=16) were clear or almost clear of the dermatitis on the tacrolimus-treated sites on day 14. Five patients had increased pruritus or burning as a result of initial tacrolimus application. This event was transient and no subject withdrew because of this.

The authors suggested that topical tacrolimus might be a safe and effective option for nickel-induced ACD. This study was supported by Fujisawa Healthcare Inc.

Oral cyclophosphamide for treatment of pemphigus vulgaris and foliaceus

Cummins DL, Mimouni D, Anhalt GJ, Nousari CH. *J Am Acad Dermatol* 2003;49:276-80.

The authors evaluated the efficacy and safety of daily oral cyclophosphamide in patients with refractory pemphigus vulgaris (PV) or pemphigus foliaceus (PF). Twenty-three patients (20 PV, 3 PF) were selected because of failure to achieve remission with prednisolone and adjuvant immunosuppressive agent(s), significant side effects with prior treatment, or rapidly progressive disease.

Cyclophosphamide was given at a daily dose of 2-2.5 mg/kg of ideal body weight, with subsequent vigorous oral hydration. Prednisone was also given at 1 mg/kg of ideal body weight/day, with tapering of dose two to three months

later. With remission, cyclophosphamide would be maintained for another 9-12 months to produce a durable remission. Complete remission was defined as the absence of lesions for at least four weeks while on cyclophosphamide and a dose of prednisone ≤ 0.15 mg/kg/day. Nineteen patients (17 with PV, 2 with PF) achieved complete remission after a median treatment period of 8.5 months. Cyclophosphamide was given for a median period of 17 months (range: 4-39) and the median follow-up duration was 27 months (range: 6-250). One PF patient achieved partial remission and three PV patients failed to respond. The side effect profile was as follows: infection (26%, n=6), haematuria (22%, n=5), tolerable nausea or abdominal pain (13%, n=3), localised non-melanoma skin cancer (8%, n=2), and bladder cancer (4%, n=1).

The authors suggested that oral cyclophosphamide was an effective adjuvant therapy for severe PV/PF refractory to usual immunosuppressive therapy. However, close monitoring was necessary due to its more significant side effects.

Narrowband ultraviolet B radiation therapy for recalcitrant vitiligo in Asians

Natta R, Somsak T, Wisuttida T, Laor L. *J Am Acad Dermatol* 2003;49:473-6.

This open retrospective study evaluated the effectiveness of narrowband ultraviolet B (NB-UVB) in treating vitiligo not responding to either topical steroid therapy or PUVA in a Thai Hospital. There were 38 women and 22 men, with a mean age of 36 years (range: 11-61) and a mean disease duration of 8.2 years (standard deviation=7.1 years). Vitiligo was generalized in 53 and localized in seven subjects. Their skin types were III in 25, IV in 33, and V in two cases. Thirty-six patients underwent previous oral PUVA, with minimal to moderate response or gastrointestinal intolerance.

NBUVB was started at 100 mJ/cm² twice weekly, with 20% increment/session for the first 10 sessions, then 10% increment/session for the next 10 sessions. Subsequently the increment became 2% to 5% per session till occurrence of 50% repigmentation or persistent erythema. The therapy was continued until maximum repigmentation occurred. A maximum of 50 sessions was tried for patients with no or less than 25% improvement.

With this regimen, more than 50% repigmentation was achieved in 25 patients (42%) over face, trunk, arms and legs. All responders had generalised vitiligo. Nobody had more than 25% repigmentation on hands and feet. The mean dose of NBUVB given was 73 J/cm² (standard deviation=56), with treatment duration ranging from five months to two years. Those who had not been treated with PUVA were more likely to respond than those given prior PUVA (odds ratio=6.00). Most patients (90%) had mild erythema or pruritus while on treatment. This study showed that NBUVB was useful in Asian patients with vitiligo over face, trunk and proximal limbs, resistant to topical therapy.

A randomised trial of amorolfine 5% solution nail lacquer in association with itraconazole pulse therapy compared with itraconazole alone in the treatment of *Candida* fingernail onychomycosis

Rigopoulos D, Katoulis AC, Ioannides D, Georgala S, Kalogeromitros D, Bolbasis I, et al. *Br J Dermatol* 2003;149:151-6.

Twelve percent of onychomycosis is caused by yeasts, with *C. albicans* responsible for 50-83% of those involving fingernails. This study compared two pulses of itraconazole combined with six weeks of 5% amorolfine nail lacquer (Group 1) and three pulses of itraconazole alone (Group 2) in treating *Candida* fingernail onychomycosis. Ninety patients with mycologically confirmed

Candida fingernail onychomycosis were recruited, excluding those receiving topical or systemic antifungal agents in the past four weeks and six months respectively. They were then randomized into two treatment groups. The patients were examined clinically and mycologically each visit (screening, inclusion visit, three months, six months) and at nine months (endpoint). Adverse effects were recorded and cost-effectiveness calculated. Eighty-five patients (73 women) completed the study, with five dropouts (lack of compliance in two, loss to follow-up in two, and abnormal liver function in a subject of Group 2). Their mean age was 44.2±12.9 years. At three months, mycological cure was seen in 74% of the cases in Group 1 and 60% in Group 2 (p>0.1). At nine months, 93.2% of those in Group 1 and 80.9% in Group 2 were mycologically negative and had 20-90% reduction in total disease surface area (p>0.1). The cost per cure ratio was lower for Group 1 (1.63 versus 1.70).

In conclusion, combination therapy with amorolfine and two pulses of itraconazole was at least as safe and effective as three pulses of itraconazole. The small number of cases in this study is a major drawback and may partly account for the lack of statistical significance.

Is topical metronidazole effective in seborrhoeic dermatitis? A double-blind study

Koca R, Altinyazar HC, Estürk E. *Int J Dermatol* 2003;42:632-5.

This randomised double-blind study evaluated the effectiveness and adverse effects of topical metronidazole 0.75% gel versus placebo in treating seborrhoeic dermatitis (SD). It recruited 84 patients (52 males and 32 females; age range: 21-49 years) with clinically mild to moderate facial SD. They were randomised respectively to twice daily topical metronidazole application (metronidazole group) and twice daily vehicle gel application (placebo group) for a maximum of

eight weeks. They were assessed every two weeks and graded numerically from 0, absent; 1, mild; 2, moderate; 3, severe; for erythema, scaling, papules and pruritus on eyebrows, dorsal side of the nose, nasolabial folds and posterior aspect of the ears (maximum severity score: 48). At the end of the study, the final response was graded as excellent (76-100% improvement), good (51-75%), fair (26-50%), or poor (0-25%).

Forty-eight patients in the metronidazole group and 30 in the placebo group completed the study. There was a reduction of the mean severity scores with time in both groups but no statistically significant difference was found between the two ($p > 0.05$). There was also no statistically significant difference in the final response between the two groups. The drug was well tolerated, with mild dryness and erythema in six patients of the metronidazole group. The authors concluded that topical metronidazole was effective in the treatment of SD, but the effect did not reach statistical significance when compared with placebo.

Ciclopirox for the treatment of superficial fungal infections: a review

Gupta AK, Skinner AR.

Int J Dermatol 2003;42(Suppl.1):3-9.

Ciclopirox is a synthetic hydroxypyridone derivative for the treatment of a variety of fungal infections. It inhibits cellular uptake of essential compounds and at high concentrations changes cell permeability in fungi. It blocks transmembrane transport in *C. albicans* and *Saccharomyces cerevisiae*. Chelation with polyvalent metal cations like Fe^{3+} and Al^{3+} leading to an inhibitory action on enzymes involved in fungal cellular processes was also noted. *In vitro* studies show that it is effective against a broad spectrum of fungus, like dermatophytes, yeasts, dimorphic fungi, eumycetes and actinomycetes in a fungistatic or fungicidal manner. It also possesses antibacterial activity, particularly against gram-negative

bacteria, as showed in both *in vitro* and *in vivo* studies. This point is worth noting in treating gram-negative bacterial infection complicating fungal infection. It penetrates the skin rapidly and a portion of the drug also deposits in the stratum corneum creating a reservoir effect. Furthermore, it has anti-inflammatory effects which are mediated via the inhibition of prostaglandin and leukotriene synthesis.

In the United States, topical ciclopirox is approved for the treatment of superficial fungal infections, including tinea pedis, tinea cruris, and tinea corporis due to *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*. It is also indicated for cutaneous candidiasis due to *C. albicans*, pityriasis versicolor due to *M. furfur*, and seborrhoeic dermatitis of the scalp. Side effects like burning sensation and local irritation are reported in less than 5% of the patients in most series. Allergic contact dermatitis has rarely been reported. A twice daily four-week therapy is recommended and clinical improvement should occur in the first week.

Comparison of chronic autoimmune urticaria with chronic idiopathic urticaria

Bakos N, Hillander M.

Int J Dermatol 2003;42:613-5.

This study investigated the association between thyroid autoimmunity and *Helicobacter pylori* infection as a causal factor in chronic autoimmune urticaria and chronic idiopathic urticaria. It recruited 48 patients (30 females and 18 males, mean age: 40.8 ± 16.4 years) suffering from chronic urticaria for two to 240 months (mean duration: 18.4 ± 19.1 months). Autologous serum skin test was performed and 26 patients (54.2%) were found to have chronic autoimmune urticaria and 22 patients (45.8%) had chronic idiopathic urticaria (non-autoimmune group). Thyroid function test, anti-thyroid peroxidase antibody (TPO), gastroscopy, urease testing and *H. pylori*-

specific IgG were performed for all. The mean basophil count was $0.030 \pm 0.012 \times 10^9/L$ for the autoimmune group and $0.046 \pm 0.011 \times 10^9/L$ for the non-autoimmune group ($p=0.001$). The authors did not explain the significance of such difference. IgE level and the prevalence of *H. pylori* infection were not significantly different between the groups. In the autoimmune group, 11 patients (42.3%) were found to have TPO, compared with three patients (13.6%) in the non-autoimmune group ($p=0.03$). In the autoimmune group, 10 of 11 patients with TPO (90.9%) versus seven of 15 without TPO (46.7%) were found to be infected with *H. pylori*. This difference in the prevalence of *H. pylori* infection within the autoimmune group was statistically significant ($p=0.02$). The result might be accounted for by the molecular similarity between human thyroid peroxidase and *H. pylori* peroxidase, which caused immunologic cross-reactivity and led to the development of thyroid autoimmunity and autoimmune urticaria. The authors suggested that *H. pylori* might play a possible role in triggering autoimmune urticaria in some patients.

Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression

Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT.

Arch Dermatol 2003;139:857-66.

A retrospective cohort study of 525 patients with mycosis fungoides (MF) and Sézary syndrome (SS) was performed to identify their outcomes and clinical factors to predict disease progression.

The distribution of patients by T classification was as follows: T1 = 30%, T2 = 37%, T3 = 18%, and T4 = 15%. Their median age was 57 years (range 12-88 years) and the female-to-male ratio was 1:1.7. Most patients (86%) were

white and the median interval from symptom onset to diagnosis was 4.2 years. At the time of study, death occurred in 278 patients (53%) and 120 were due to MF, mainly in those with T3 or T4 disease. The rest were due to other causes like cardio-pulmonary disease and/or malignancy.

The overall median survival was 11.4 years and the relative risk of death (RR) for patients with MF compared with the control population was 2.4. Patients with T1 disease had a good prognosis comparable to that of the general population. Conversely, patients with T3 and T4 disease had a less favourable outcome (10-year survival: T1 88%, RR 0.7; T2 55%, RR 2.3; T3 26%, RR 4.7; T4 24%, RR 4.2). The median survival time also decreased with advancing clinical stage. There was no significant sex-related difference in survival. Univariate analysis showed that age, TNM and B classifications, extracutaneous disease, and overall clinical stage were significant prognostic factors, while subsequent multivariate analysis confirmed that extracutaneous disease, age, and T classification were significant independent predictors. The extent of cutaneous disease (T classification) also correlated with the development of extracutaneous disease.

The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress

Chiu A, Chon SY, Kimball AB.

Arch Dermatol 2003;139:897-900.

The aim of this prospective cohort study was to evaluate the changes in the severity of acne vulgaris in response to examination stress. Twenty-two university students (15 women, 7 men) with a mean age of 22.25 years (range: 18-41 years) were recruited. Their acne severity was evaluated using the Leeds acne score, about one month

before examinations (non-examination period) as well as three days before to seven days after an examination (examination period). Their stress level was assessed with the Perceived Stress Scale questionnaire. Topical or oral acne treatments (except isotretinoin) were continued during the study.

The baseline Leeds acne score ranged from 0.50 to 1.75. The increase in stress correlated with the increase in acne severity ($r=0.61$, $p<0.01$). Photographic review by clinicians who were unaware of the period of assessment gave similar grades for acne severity in most cases. During the examination period, there was a significant increase in mean Leeds acne score to 1.33, compared to a score of 0.97 during non-examination period. A self-perceived, worsened diet (but not worsened sleep quality) was also significantly associated with worsened acne, although the association was weaker ($r=-0.48$, $p=0.02$).

The authors concluded that acne vulgaris might increase in severity during stressful periods like examinations, implying that certain behavioural interventions might be helpful in cases with known stressors. However, the significance of a self-perceived worsened diet in relation to acne severity should be interpreted with caution for methodological reasons and findings of previous studies.

Discoid lupus erythematosus in children: clinical, histopathologic, and follow-up features in 27 cases

Moises-Alfaro C, Berrón-Pérez R, Carrasco-Daza D, Gutiérrez-Castrellón P, Ruiz-Maldonado R. *Pediatr Dermatol* 2003;20:103-7.

A retrospective study of the clinical and histopathologic features of 27 children with discoid lupus erythematosus (DLE) was performed. Twelve were under 10 years of age and fifteen between 10 to 16 years of age. Their mean age

at the time of diagnosis was 10 years 11 months and the female-to-male ratio was 2.4:1. However, in those under 10 years of age, the female-to-male ratio was 5: 1. Lesions were localized in 17 (63%) patients and disseminated in 10 (37%). Although there was no difference between the age groups, pigmented lesions were more common in those below 10 ($p<0.04$). Antinuclear antibody (ANA) was positive in 17 out of 27 patients (63%). Anti-DNA antibody was positive in nine out of 19 patients (47%) and anti-ENA positive in five out of nine patients (55%). There was no significant difference in efficacy among the various treatments (topical corticosteroids, chloroquine, thalidomide). Their mean follow-up time was 36 months (range: 2 years 4 months to 12 years 6 months) during which seven patients (26%) developed systemic lupus erythematosus (SLE). Four of these patients developed DLE before the age of 10. Of the four patients who had a positive family history for rheumatic disease, three developed SLE. The extent of DLE lesions was not associated with the risk of developing SLE.

It was concluded that the chance of progressing to SLE in children with DLE onset before 10 years of age was similar to those with onset between 10 and 16. The extent of lesions was not a predisposing factor but a positive family history for rheumatic disease might be.

Patch testing in children, adults and the elderly: influence of age and sex on sensitisation patterns

Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R. *Pediatr Dermatol* 2003;20:119-23.

In this retrospective study, patch testing with 34 contact allergens was done on 2766 patients suspected to have contact dermatitis in Vienna, Austria. There were 2115 females (76.5%), with a mean age of 40.05 (standard deviation=17.4 years). For the 651 males, their mean age was 38.32 (standard deviation=17.92 years).

The most common allergens were nickel (20.9%), ethylmercuric chloride (13.2%), thimerosal (11.8%), fragrance mix (9.3%), metallic mercury (8.9%), palladium (5.8%), balsam of Peru (3.8%), copper (3.7%), cobalt (3.3%), and chromium (2.3%). About 49% patients had at least one positive reaction. Children under 10 years of age had the highest rate of patch test reactivity (62.0%) while those over 70 years of age had the lowest rate of reactivity (34.9%). A high rate of sensitisation to metals was noted in children under 10 years old, in particular mercury (11.4%) and copper (15.2%), both being present in dental amalgams. Sensitivity to nickel, cobalt, palladium and copper decreased with age, while fragrance

mix sensitivity was similar among the age groups. On the other hand, balsam of Peru sensitivity was more common in the elderly. Thimerosal sensitivity peaked before 30 years of age and then began to decline afterwards. In the elderly, fragrances, metals and preservatives were the most common allergens. There was a higher incidence of sensitivity to nickel, cobalt, and palladium in females. However, there was no such increase for chromium sensitivity.

It was concluded that metals, mercurials and fragrances were the commonest sensitisers in this Austrian series, with the overall sensitisation rate highest in children, decreasing with age.