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Journal Watch

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Spectrum of mucocutaneous manifestations in human immunodeficiency virus-infected patients and its correction with CD4 lymphocytes count

Fernandes MS, Bhat RM.
Int J STD AIDS 2015;26:414-9.

Skin manifestations are common in human immunodeficiency virus (HIV) infected patients and are found in up to 86-96% of these patients. Different levels of CD4 count, which reflects the immunity of the patient, are associated with different skin manifestations. This study was done to investigate the different mucocutaneous lesions seen in the HIV population and correlate their severity with declining immunity. One hundred HIV seropositive outpatients with skin findings were recruited. The mean CD4 count was 253 cells/mm^3. There were a total of 235 dermatological manifestations with an average of 2.3 conditions per patient. They were divided into three groups according to the CD4 count: (1) <200 cells/mm^3; (2) 200-500 cells/mm^3 and (3) >500 cells/mm^3. In general, lower CD4 counts were associated with more skin manifestations. Fungal infections including dermatophytosis and candidiasis were the commonest infectious dermatoses whereas nail changes was the commonest non-infectious skin condition, followed by xerosis and papular pruritic dermatosis.

Skin conditions association with CD4 count (cells/mm^3):

Conditions	CD4 <200	CD4 200-500	CD4 >500
Dermatophytosis	6	9	0
Candidiasis	14	6	1
Herpes zoster	2	6	0
HSV infection	5	2	1
HPV infection	3	2	0
Nail changes	21	10	1
Xerosis	8	5	3
Papular pruritic dermatosis	13	5	2
Seborrhoeic dermatitis	8	5	3
Adverse drug reaction	8	4	2
Others	28	13	3

The authors concluded that the skin is the most commonly affected organ in HIV patients. It is an important clinical prognostic marker and may even be an indicator for HIV infection.

Microscopy outperformed in a comparison of five methods for detecting *Trichomonas vaginalis* in symptomatic women

Nathan B, Appiah J, Saunders P, Heron D, Nichols T, Brun R, et al.
Int J STD AIDS 2015;26:251-6.

Trichomonas vaginalis (TV) is a common protozoan sexually transmitted infection (STI), mainly diagnosed by wet mount microscopy. However, this method is of low sensitivity with variable results. Recently, nucleic acid amplification tests (NAATs) for TV have become available commercially and have been shown to have a high sensitivity and specificity. The aim of this study was to evaluate five different methods (1) Real-time in-house PCR targeting TV-specific repeats; (2) Aptima TV molecular test; (3) OSOM® Trichomonas Rapid Test which is a point-of-care test (POCT); (4) Culture to diagnose TV infection in symptomatic women and compare these to the current main method of diagnosis: (5) Wet mount microscopy. All symptomatic women aged over 18 years except those diagnosed to have TV in recent six weeks or those who had taken metronidazole within two weeks were recruited.

A total of 250 women were recruited over a six-month period; one culture was lost and three samples were excluded due to incomplete data. Results were negative in 220/246 samples in all five tests. In the remaining 26 positive samples, two or more tests were positive in 24 samples which were used as the reference. Seven samples were positive for all five tests and 11 samples were positive for four tests except TV wet mount microscopy. None of the samples were positive on wet mount alone. The prevalence of TV infection if diagnosed by wet mount alone was 3.66% whereas it was 9.75% if two positive results were used as a reference standard. This study showed that the sensitivity of in-house real-time PCR (88%), the Aptima TV test (92%), POCT (92%), culture (88%) was higher than wet mount (38%) in detecting TV in symptomatic women. The authors concluded that as wet mount microscopy was of poor sensitivity even in symptomatic women, either PCR, Aptima or OSOM® Trichomonas rapid test are recommended over microscopy in high-risk patients.

Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis

Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrel D, Paul C.
J Am Acad Dermatol 2015;72:992-1002.

There has been a controversy about the increased risk of lymphoma in patients with atopic dermatitis (AD) and the use of topical calcineurin inhibitors (TCIs) has also raised the concern of lymphoma risk. This systematic review aimed at assessing the risk of lymphoma and the role of TCIs in AD patients.

The authors retrieved original studies with the Medical Subject Headings (MeSH) "atopic dermatitis" or "eczema" and "lymphoma" or "neoplasm" published between 1980 and 2014. A total of 2046 references met the criteria and 23 articles were selected (5 cohort studies and 18 case control studies). Meta-analysis of the four cohort studies showed an increased risk of lymphoma in AD patients with a relative risk (RR) of 1.43 (95% CI 1.12-1.81). However, no such risk was found in case control studies, with an odds ratio (OR) of 1.18 (95% CI 0.94-1.47). The severity of AD was shown to be a significant risk factor, OR varied from 2.4(95%CI 1.5-3.8) to 3.72 (95%CI 1.4-9.87) in two case control studies and RR 1.95 (95%CI 1.15-3.12). Moreover, potent topical steroid treatment was shown in meta-analysis to increase lymphoma risk in case control studies, OR 1.73 (95%CI 1.52-1.97) but not for low potency steroid. Concerning the use of TCIs and lymphoma, a significant increased risk of lymphoma with topical tacrolimus use, mostly cutaneous lymphoma, was shown in only one cohort study with RR 6.56 (95%CI 3.03-14.19), with a follow-up period of 1.7 years.

The authors concluded that there is a modest increased risk of lymphoma in AD patients and the severity of AD appeared to be a significant risk factor. However, the role of potent topical steroid or TCIs is unlikely to be significant.

These results have to be interpreted with caution as the study was limited by the high degree of heterogeneity in study design, population, the

definition of AD and lymphomas, treatment and follow-up protocol. Also, the possible misdiagnosis of cutaneous T-cell lymphoma as AD may be a potential bias in these studies. Finally, the role of other systemic immunosuppressants used was not assessed in these studies.

Psoriasis and risk of diabetes-associated microvascular and macrovascular complications

Armstrong AW, Guérin A, Sundaram M, Wu EQ, Faust ES, Ionescu-Ittu R, et al.
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Patients with psoriasis are known to be at higher risk of developing diabetes. However, little is known about its effect on the course of diabetes. In this observational study, the authors aimed at comparing the risk of developing microvascular and macrovascular complications in diabetic patients with or without psoriasis.

The authors collected data from Truven Health Market Scan Research Databases, which is a large, nationally representative database that included approximately 25 million individuals annually, between 2000 and 2006. Patients with two or more diagnoses of diabetes were enrolled and they were then divided into two cohorts with or without psoriasis. Only those with a diagnosis of diabetes made prior to that of psoriasis for at least six months were included. Patients with both psoriasis and diabetes were matched with their diabetic counterparts using age, sex, gender, duration of diabetes, use of diabetic medication and prior microvascular and macrovascular events. The severity of psoriasis was categorised based on the use of systemic agents.

In 6164 patients with psoriasis, the risk of microvasular complications was significantly higher than those without psoriasis, hazard ratio (HR) 1.14 ($p<0.01$) and the risk was higher in those with moderate to severe psoriasis than those with mild disease (HR 1.16 vs HR 1.13). A similar increase in risk was also observed with macrovascular complications (HR 1.13, $p=0.001$). However, when stratified according to psoriasis severity, higher risk was not observed in those patients with severe psoriasis (mild case: HR=1.15, $p=0.003$ vs severe case: HR=1.10, $p=0.21$). The authors explained that this was because the use of systemic agents, which had been shown in previous studies of being able to lower the risk of the macrovascular complications, had been used as a proxy for the measurement of disease severity.

The authors concluded that diabetic patients with psoriasis were more likely to develop both micro- and macrovascular complications. But further studies are needed to delineate the underlying pathogenic inflammatory pathways and the possible psoriasis-diabetes synergism. Hence, more aggressive screening for complications, and more targeted treatment might be needed for this group of patients.

This study was limited by the lack of clinical measurements on disease severity and the possible inaccurate coding of diagnoses in this nation-wide database.

Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial

Taieb A, Ortonne JP, Ruzicka T, Roszkiewicz J, Berth-Jones J, Peirone MH, et al.
Br J Dermatol 2015;172:1103-10.

Papulopustular rosacea (PPR) is difficult to treat with only few choices of drugs. The authors conducted an investigator-blinded, randomised, parallel-group study aiming to compare the efficacy of once-daily ivermectin 1% cream (IVM 1%) against twice-daily metronidazole (MTZ 0.75%) cream, on the percentage reduction of inflammatory lesions in subjects with moderate to severe PPR over 16 weeks.

The severity of rosacea was determined by counting the inflammatory lesions and Investigator's Global Assessment (IGA). The incidence of adverse events (AEs) and local tolerance parameters were recorded. Subjects rated their disease by a 5 grade scale and completed questionnaires.

In this study, a total of 962 subjects were randomised to receiving IVM 1% (n=478) or MTZ 0.75% (n=484). At week 16, IVM 1% was significantly better than MTZ 0.75% in terms of

decrease in inflammatory lesions (83.0% vs. 73.7%; p<0.001), which was noted as early as week 3. IGA showed that (subjects 'clear' or 'almost clear') IVM 1% was better (84.9% vs. 75.4%, respectively (p<0.001). The incidence of AEs was similar between the two groups. However, IVM 1% was better tolerated than MTZ 0.75%. There were more subjects receiving IVM 1% who rated their global improvement assessment as 'excellent' or 'good'.

In summary, the authors concluded that ivermectin 1% cream was significantly superior to metronidazole 0.75% cream.

Evidence-based topical treatments for tinea cruris and tinea corporis: a summary of a Cochrane systematic review

van Zuuren EJ, Fedorowicz Z, El-Gohary M.
Br J Dermatol 2015;172:616-41.

Tinea cruris and tinea corporis are two common fungal infections that can be treated with different topical antifungal creams. The authors reviewed the evidence for the effectiveness and safety of topical treatments for tinea cruris and tinea corporis. The authors searched the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library, Medline, Embase, LILACS and ongoing trials registries. There were one hundred and twenty-nine randomised controlled trials (RCTs) with 18 086 participants evaluating a range of interventions and most of these were topical azoles.

The authors noted in five studies that terbinafine showed a statistically significant higher clinical cure rate compared to placebo [risk ratio (RR) 4.51, 95% confidence interval (CI) 3.10-6.56]. There was a substantial heterogeneity in the data for mycological cure and therefore could not be pooled for analysis. In three studies, mycological cure rates were shown to be better with naftifine (1%) compared with placebo (RR 2.38, 95% CI 1.80-3.14), however, the quality of the evidence was low.

Azoles mixed with corticosteroids were noted to be slightly more effective than azoles alone for clinical cure, but the mycological cure rate could not demonstrate a statistically significant difference. The design of most studies were suboptimal and poorly reported. Most active interventions demonstrated adequate therapeutic effects.

In conclusion, this review found that there was a need for further, high-quality, adequately powered RCTs to assess the effects of different topical antifungal creams in treating skin fungal infections, in order to produce reliable evidence in guiding the clinicians.

A multicentre randomized trial of the treatment of patients with pemphigus vulgaris with infliximab and prednisone compared with prednisone alone

Hall RP, Fairley J, Woodley D, Werth VP, Hannah D, Streilein RD, et al.
Br J Dermatol 2015;172:760-8.

Tumour necrosis factor (TNF) is well-known to be an important factor in the pathogenesis of pemphigus vulgaris (PV). The authors of this study aimed to assess the safety profile of infliximab (IFX), a TNF inhibitor, with prednisone compared with prednisone alone in the treatment of PV. Treatment response was measured and mechanistic studies were done.

In this study, subjects with PV who had active disease while being maintained on prednisone were randomised to receive either IFX or placebo besides prednisone. The authors assessed the response rate and immunoglobulin (Ig) G anti-desmoglein (Dsg)1 and Dsg3 antibodies at 18 and 26 weeks. Ten subjects were randomised to each group. All patients tolerated IFX and none had severe adverse effects during the study. One subject in each group responded at week 18 and at week 26, three IFX-treated subjects compared to none in the placebo group responded (p=0.21). At weeks 18 and 26, the median IgG anti-Dsg1 and anti-Dsg3 levels were lower in the IFX-treated patients [IgG anti-Dsg-1 (week 18, p=0.035; week 26, p=0.022); IgG anti-Dsg3 (week 18, p=0.035; week 26, p=0.05)].

The authors concluded that there was no significant difference between the study arms in the percentage of subjects with treatment-related adverse events. IFX therapy failed to demonstrate

superior efficacy in the treatment of patients with PV in this randomised, placebo controlled trial. IFX treatment might be associated with a reduction in anti-Dsg1 and Dsg3 antibodies. However, this study was limited by its small sample size.

Risk of serious infection with biologic and systemic treatment of psoriasis. Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)

Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al.
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Biologic therapies have immunomodulatory or immunosuppressive effects that may predispose patients to potential adverse events. Understanding the long-term safety profile of such therapy, particularly with regard to events such as serious infections, is crucial.

This was a multicentre, longitudinal, disease-based registry (Psoriasis Longitudinal Assessment and Registry [PSOLAR]) at dermatology centres. This study evaluated the incidence of serious infections among patients with psoriasis exposed to different biologic therapies and compares the risk with these individual therapies to the risk with non-biologic treatments. A serious infection was defined as any infection that results in death, is life-threatening, requires inpatient hospitalisation or prolongs existing hospitalisation, causes persistent or significant disability or incapacitation, or may jeopardise the patient or require intervention to prevent one of these outcomes.

A total of 11,466 patients with psoriasis from 2007 to 2013 were enrolled in the study. The cumulative incidence rate of serious infections across treatment cohorts was 1.45 per 100 patient-years (n=323). In the ustekinumab, etanercept, adalimumab, and infliximab cohort, the rates of serious infection were 0.83, 1.47, 1.97, and 2.49 per 100 patient-years respectively, and 1.05 and 1.28 per 100 patient-years in the nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts, respectively. The most commonly reported serious infections across the registry were cellulitis and pneumonia. The following were associated with an increased risk of serious infection: advanced age, diabetes mellitus, smoking, significant infection history, infliximab exposure and adalimumab exposure.

It was discovered that adalimumab and infliximab appeared to carry a higher risk of serious infection compared with nonmethotrexate and nonbiologic therapies, whereas etanercept and ustekinumab did not. These findings can provide guidance to dermatologists when considering different treatment modalities for patients with psoriasis.

Long-term management of adult vulvar lichen sclerosus. A prospective cohort study of 507 women

Lee A, Bradford J, Fischer G.
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The use of superpotent topical corticosteroids (TCS) is the accepted first-line treatment for vulval lichen sclerosus (VLS). However, there is a lack of evidence regarding the optimum measures for maintaining remission, the ideal duration of follow-up and whether long-term management can prevent complications. The following aspects of long-term preventive TCS treatment of VLS were studied: target outcome of induction and maintenance of normal skin texture and colour, whether the risk of vulvar carcinoma is decreased, relief of symptoms, improvement in function, and preservation of vulval architecture, as well as to evaluate the adverse effects of treatment.

This was a prospective, single-centre cohort study of 507 women with biopsy-proven VLS who were treated with TCSs from 2008 to 2014 in Australia. Once disease and symptom suppression had been achieved, a long-term preventive management was initiated. Gradual reduction of TCS potency, titrated to the clinical response was attempted in all patients. A total of 150 patients (29.6%) did not carry out the advised treatment and were considered partially compliant while a total of 357 patients (70.4%) were compliant and adhered to treatment instructions. None of the compliant patients developed biopsy-proven squamous cell carcinoma or vulvar intraepithelial neoplasia during the follow-up period while 7 (4.7%) of the partially compliant patients ($p<0.001$) developed malignant changes. Symptoms were suppressed in 333 (93.3%) compliant patients compared to

87 (58.0%) partially compliant patients (p<0.001). Adhesions and scarring were present during follow-up in 12 (3.4%) compliant patients and 60 (40.0%) partially compliant patients (p<0.001). There was reversible TCS-induced cutaneous atrophy in four (1.1%) and three (2.0%) of compliant patients and partially compliant patients respectively.

This study demonstrated that preventive long-term treatment not only improved function and relieved symptoms but also reduced the development or progression of scarring and the risk of cancer. Significant adverse effects were not seen although there were a few cases of reversible cutaneous atrophy.

Granulysin expression increases with increasing clinical severity of psoriasis

Elgarhy LH, Shareef MM, Moustafa SM.
Clin Exp Dermatol 2015;40:361-6.

Psoriasis is a chronic, systemic inflammatory skin condition linked with arthropathy and systemic complications. The disease is typically associated with strong expression of antimicrobial peptides (AMPs), which renders the condition less susceptible to local skin infections. Granulysin has cytolytic properties and belongs to a family of saposin-like, lipid-binding AMPs. Increased lesional level of granulysin, a pro-inflammatory AMP, may be interpreted as a feature of an activated innate immune system. This study investigated the granulysin expression in patients with psoriasis. Granulysin levels were determined in the lesions of thirty psoriatic patients by immunohistochemical staining of skin biopsy specimens. The granulysin levels of the skin biopsy specimens from ten age- and gender-matched controls taken from similar body locations were also determined. High levels of granulysin were observed in 37% of the patients (n=11), while a moderate level was found in 33.3% (n=10) and low in 30% (n=9) of the patients. There was a significantly higher level of granulysin in psoriatic patients as compared to the healthy controls (p=0.001). The authors also observed a significant difference in the granulysin expression between patients with mild (PASI ≤10) versus moderate to severe disease (PASI >10) (p=0.001). A higher level of granulysin was similarly observed in patients with early-onset psoriasis (<40 years old) when compared to the late-onset patients (>40 years old). The authors concluded that there was a potential role of increased granulysin expression in the pathogenesis of psoriasis, and a possible trigger by infection was hypothesised. Further large-scale studies are required to support such findings and granulysin may represent a future therapeutic target.

Are normolipidaemic patients with xanthelasma prone to atherosclerosis?

Esmat S, Abdel-Halim MR, Fawzy MM, Nassef S, Esmat S, Ramzy T, et al.
Clin Exp Dermatol 2015;40:373-8.

Xanthelasma is a common finding on clinical examination. The occurrence of xanthelasma is not necessarily related to underlying hyperlipidaemia. Nevertheless, evidence does exist that the risk of cardiovascular disease in normolipidaemic patients with xanthelasma is comparable to hyperlipidaemic patients with xanthelasma. The present study compared the risk of atherosclerosis between normo- (NPx) and hyper-lipidaemic (HPx) patients with xanthelasma in the Egyptian population. The investigators enrolled 20 NPx, 20 HPx and 40 healthy controls (normolipidaemic and without xanthelasma) into the trial. The subjects enrolled were age-and gender-matched. Patients with diabetes mellitus were excluded to minimise the confounding effect. The blood pressure, presence of obesity and smoking status were recorded and investigated. Atherosclerotic markers including the total leucocytic count (TLC), C-reactive protein and lipoprotein A were also measured serologically. The carotid intima-media thickness (IMT) of all subjects were measured by ultrasonography. The total serum cholesterol and triglycerides level were significantly higher in the NPx group when compared to the healthy controls. As expected, IMT was higher in the HPx group than in the NPx group and among healthy controls. IMT was significantly higher in the NPx group when compared to the healthy controls. A higher body mass index and TLC level were observed in the NPx group. The higher IMT in the NPx was independent of the other studied risk factors and markers for atherosclerosis. The authors concluded that the presence of xanthelasma among normo-lipidaemic patients may represent an independent risk of atherosclerotic disease despite the normal serum lipid concentrations. These cases should therefore be investigated accordingly.