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MALAYSIAN JOURNAL OF DERMATOLOGY

ORIGINAL ARTICLE

CASE REPORT

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ORIGINAL ARTICLE

Bringing the Treatment of Atopic Eczema Into a New Era with Janus Kinase Inhibitors: A Position Statement By the Persatuan Dermatologi Malaysia

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Abstract

Atopic eczema (AE) is a complex, chronic and recurrent inflammatory pruritic skin condition that impacts the quality of life and exerts an economic toll on patients and their families. One of the factors contributing to AE is the immune dysregulation of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) inflammatory pathway. This has prompted the conduct of various large clinical trial programs to evaluate the efficacy and safety of Janus kinase inhibitors (JAK-i) for AE. The overall and significant benefit of these drugs from clinical studies resulted in regulatory approvals for JAK-i to treat moderate-to-severe atopic eczema. The objective of this position paper was to evaluate the safety, efficacy and role of upadacitinib, baricitinib and abrocitinib in managing AE and update the current recommended treatment algorithm within the 2018 Malaysian Clinical Practice Guidelines for the Management of Atopic Eczema. The Persatuan Dermatologi Malaysia recommends that these JAK-i can be considered as an option for systemic therapy in severe AE.

Key Words: *Atopic dermatitis, JAK-i, Recommendations*

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Introduction

Atopic eczema (AE), also known as atopic dermatitis, is a complex, chronic and recurrent inflammatory pruritic skin condition that develops in early childhood and can persist into adulthood.

The global prevalence of AE ranges between 15-30% in children[1,2] and 2-10% in adults.[1] In

Malaysia, the prevalence of AE has not been well studied. Malaysia participated in the International Study of Asthma and Allergies in Childhood (ISAAC). The prevalence of childhood AE in 1996 in the 6-7 year and 13–14 year age groups increased from 9.5% and 8.9% in 1996 to 12.6% and 9.9% in 2006, respectively.[3] A more recent cross-sectional survey by Goh YY, *et* al. involving 384 children aged 1-6 years old attending kindergarten in Kuala Lumpur revealed eczema in 13.4%.[4] In a retrospective, cross-sectional study conducted in the Department of Dermatology, Hospital Kuala Lumpur, from the 1st January 2008 to 31st December 2014, eczema was the most common disease (39.07%) treated in the skin clinic, of which 6.9% were AE.[5]

AE, particularly in those with moderate-to-severe disease, significantly impacts the patient's and their family's quality of life (QoL).[2,6-8] The symptoms of AE are significantly associated with the severity of disease. AE symptoms lead to sleep disturbance, anxiety, depression and embarrassment in children and adults.[6,8] The effects of AE on children extend beyond the short-term and have been associated with an increased risk of developing psychosocial, cognitive and functional impairment and behavioural problems.[2] A more recent study demonstrated an increased risk in children with allergic disorders developing attention deficit hyperactivity disorders or autism spectrum disorder.[9]

AE incurs a hefty financial burden on the families of children with AE and adult patients. The direct cost of AE is estimated to range from USD199-USD743[10] and €2242 to €6924.[7] Indirect cost including loss of work and productivity ranges from €7277 to €14,236 in adult AE patients.[7]

The Malaysian Clinical Practice Guideline (CPG) for the management of AE was published in 2018. The objectives are to guide the correct and early diagnosis, and outline effective and safe treatments for AE.[11] It contains evidence-based recommendations for the diagnosis, severity assessment, investigations, and available therapy for AE. The Janus kinase inhibitors (JAK-i), which are small molecule agents for targeted therapy, have been available for use in various diseases such as rheumatoid arthritis and psoriatic arthritis. These drugs have recently been approved by the Ministry of Health, Malaysia for treating moderate-to-severe AE. Baricitinib was approved for moderate-to-severe AE in adults in September 2021,[12] and upadacitinib in adults and adolescents aged 12 years and above in May 2022.[13]

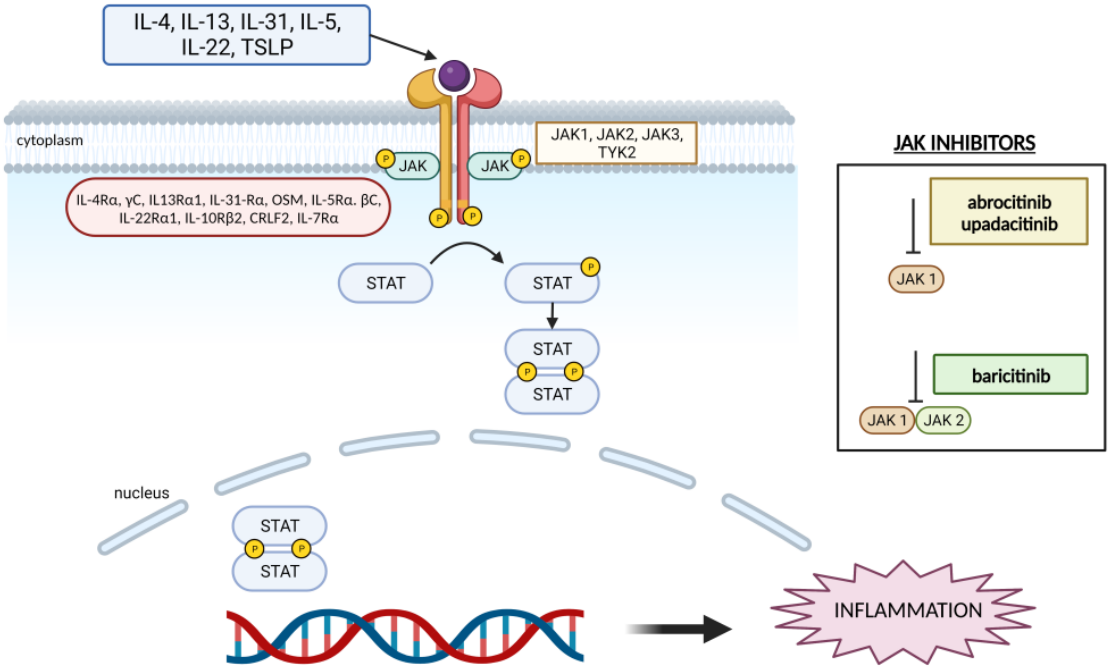
The recent (September 2022) EuroGuiDerm Guideline on Atopic Eczema recommends JAK-i for AE patients who are candidates for systemic treatment.[14] In Asia, the 2021 Japanese guidelines for atopic dermatitis (ADGL) and 2022 Taiwan guidelines for the diagnosis and management of paediatric atopic dermatitis recommend JAK-i as a treatment option for severe AE.[15,16] Hence, the primary objective of this paper is to revisit and update the current AE treatment recommendations with regard to the position of JAK-i for treating AE within the Malaysian context. We examine the role of the Janus kinase (JAK) enzyme in AE pathophysiology and the mechanism of action, safety and efficacy of JAK-i for this purpose.

The role of JAK enzymes in AE

The various pathophysiological factors contributing to AE development are complex and include skin barrier dysfunction, immune dysfunction and altered cutaneous microbiome.[17]

The JAK enzymes constituting JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) are a class of cytoplasmic tyrosine kinases. The skin barrier dysfunction activates T-helper cells (T_H) resulting in different cytokine expressions. After binding to their receptor, these cytokines activate the JAK-STAT signalling pathway to mediate their cytokine response. This contributes to the inflammatory cascade leading to AE. (Figure 1).[18,19]

Figure 1. JAKs attach to the intracellular sections of the cytokine receptor chains to produce functional signalling complexes and regulate the inflammatory process through activating the intracytoplasmic transcription factors (STATS). These STATs move into the nucleus and regulate downstream inflammatory mediators



CRLF2, cytokine receptor-like factor 2; IL, interleukin; JAK, Janus kinase; OSM; oncostatin M; STAT, signal transducer and activator of transcription; TSLP, thymic stromal lymphopoietin; TYK2, tyrosine kinase 2. Adapted from Chovatiya R, et al. J Allergy Clin Immunol 2021.[19]

The mechanism of action of JAK-i in AE

JAK-i are small molecule compounds that target AE-associated cytokine-mediated inflammatory pathways. By inhibiting the JAK enzymes selectively and reversibly, they allow for a targeted approach to treating AE. The three JAK-i currently available for AE are indicated for treating moderate-to-severe disease. Abrocitinib and upadacitinib inhibit JAK1, whilst Baricitinib inhibits both JAK1 and JAK2 enzymes (Figure 1). The inhibition of JAK-dependent cytokines (e.g., interleukin [IL]-6 and IL-31) reduces the inflammation and itch in AE, while the inhibition of the JAK2 appears to reduce the pathological changes.[18,20]

Efficacy and safety of JAK-i in treating AE

Efficacy outcomes compared to placebo

Among the three JAK-i available for treating AE, the BREEZE-AD clinical programme for baricitinib has the most extensive number of clinical trials (BREEZE-AD 1-7). However, all the studies were placebo-controlled. The landmark trials for baricitinib are BREEZE-AD 1 and 2,[21] while BREEZE-7[22] investigated its efficacy in combination with topical corticosteroid (TCS).

The study population involved in the BREEZE-AD were patients aged ≥18 years, who had a diagnosis of AE for ≥12 months before screening and a documented history of an inadequate response to topical therapies and failure to systemic immunosuppressants.[23] Eczema Area and Severity Index (EASI) score of ≥16, a validated Investigator's Global Assessment (vIGA) score of ≥3 and ≥10% body surface area (BSA) involvement were other inclusion criteria. Some important exclusion criteria were a history of eczema herpeticum a year before screening or ≥2 prior episodes of eczema herpeticum and current or recent serious infections, including herpes zoster and tuberculosis (TB).[23]

Upadacitinib (MEASURE UP) and abrocitinib (JADE) efficacy trials were similar. They involved patients who were ≥12 years old with a body weight of ≥40 kg and were placebo-controlled. These trials' inclusion and exclusion criteria were similar to the BREEZE-AD.[24,25] Like in BREEZE-AD 7, the abrocitinib trial involving adolescents (JADE TEEN)[26] investigated its efficacy on a background of TCS use.

The trials all had a fair representation of the Asian population with 20-30% of the total subjects in each treatment and placebo arm. Significantly more patients in the treatment arms for all agents achieved vIGA (0,1) and EASI 75 compared to placebo (Tables 1-3). The efficacies were dose-dependent, with higher doses and concomitant use of TCS eliciting better outcomes.

Table 1. Baricitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Baricitinib 4 mg	Baricitinib 2 mg	Placebo
BREEZE-AD1[21] (N=624)	vIGA (0,1)	16.8***	11.4*	4.8
	EASI 75	24.8***	18.7**	8.8
	Itch NRS	21.5***	12.0	7.2
BREEZE-AD2[21] (N=615)	vIGA (0,1)	13.8***	10.6*	4.5
	EASI 75	21.1***	17.9***	6.1
	Itch NRS	18.7***	15.1**	4.7
BREEZE-AD7[22] (N=329)	vIGA (0,1)	31	24	15
	EASI 75	48***	43	23
	Itch NRS	44***	38	20

*Significance compared with placebo: *P≤0.05; **P≤0.01; ***P≤0.001. The primary outcome was the proportion of patients achieving vIGA (0,1) with 4 mg and 2 mg baricitinib at 16 weeks, and those achieving EASI 75 and Itch NRS were secondary outcomes. Itch NRS referred to patient-rated improvement in itch with a change of ≥4 points.*
BREEZE-AD 7 allowed concomitant TCS during the study, and BREEZE-AD 1,2 allowed TCS as rescue treatment only.
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; NRS, Numeric Rating Scale; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

A network meta-analysis comparing the efficacies of targeted systemic therapies used in treating AE without the addition of topical corticosteroids and/or topical calcineurin was recently published.[27] It included phase 3 and 4 placebo- or active intervention-controlled studies involving JAK, interleukin-4 and interleukin-13 inhibitors in adults and adolescents with moderate to severe AE. Based on 11 clinical trials (N=6254), upadacitinib 30 mg daily demonstrated better and earlier efficacy, followed by abrocitinib 200 mg daily, upadacitinib 15 mg daily, abrocitinib 100 mg daily and baricitinib 4 mg daily. However, caution must be applied as network meta-analyses are susceptible to the methodological quality of the included studies, reporting biases and choices of study eligibility criteria and do not replace comparisons of multiple head-to-head RCTs.[27]

Table 2. Upadacitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Upadacitinib 30 mg	Upadacitinib 15 mg	Placebo
MEASURE UP-1[28] (N=847)	vIGA (0,1)	62***	48***	8
	EASI 75	80***	70***	16
MEASURE UP-2[28] (N=836)	vIGA (0,1)	52***	39***	5
	EASI 75	73***	60***	13

*Significance compared with placebo: ***P≤0.001. The proportion of patients achieving vIGA (0,1) and EASI 75 were the co-primary outcomes for both studies. Concomitant TCS and other medicated topical therapy were prohibited, but rescue therapy was permitted from week 4.*
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

Table 3. Abrocitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Abrocitinib 200 mg	Abrocitinib 100 mg	Placebo
JADE MONO-1[29] (N=387)	IGA (0,1)	44***	24*	8
	EASI 75	63***	40***	12
JADE MONO-2[30] (N=391)	IGA (0,1)	38.1***	28.4***	9.1
	EASI 75	61***	44.5***	10.4
JADE TEEN[26] (N=285)	IGA (0,1)	46.2**	41.6**	24.5
	EASI 75	72**	68.5**	41.5

*Significance compared with placebo: *P=0.0037; **P≤0.05; ***P≤0.001. The proportion of patients achieving vIGA (0,1) and EASI 75 were the co-primary outcomes for all studies.*
In the JADE-MONO 1,2, concomitant use of TCS and other medication topical medications were not allowed, and rescue medications were prohibited. In the JADE-TEEN study, standardised regimens of non-medicated and medicated topical therapy were required, and oral histamines were also permitted.
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

Head-to-head studies with dupilumab

Dupilumab is a human monoclonal immunoglobulin (Ig) G4 antibody that binds to IL-4Rα and inhibits IL-4 and IL-13 signalling. It

has been approved for the treatment of moderate to severe AE in adults and children aged 6 and above.[31]

Head-to-head comparison between JAK-i and dupilumab has been conducted with upadacitinib and abrocitinib.[32,33] Upadacitinib 30 mg daily and abrocitinib 200 mg daily had significantly better primary outcomes (EASI 75 for both and IGA for abrocitinib only) compared with dupilumab 300 mg every other week at week 12 and 16, respectively. The efficacy of abrocitinib 100 mg daily was comparable to dupilumab. Upadacitinib 30 mg and abrocitinib 200 mg demonstrated superiority for improving itch scores as early as the first (mean 31.4% vs 8.8%; $p<0.001$) and second week (difference from dupilumab 22.1%; $p<0.001$), respectively. A longer-term trial, JADE DARE, to determine the efficacy of abrocitinib 200 mg compared to dupilumab is ongoing (treatment duration – 26 weeks).[34]

Long-term efficacy

So far, baricitinib has the longest follow-up data for efficacy at 68 weeks from BREEZE-AD 3. The subjects were derived from the BREEZE-AD 1, 2 trials. The efficacy outcomes [vIGA (0,1), EASI 75 and Itch NRS] remained relatively stable in both responders and partial responders, indicating that baricitinib could be an option for long-term therapy for adult patients with moderate-to-severe AE.[35] Upadacitinib has demonstrated sustained efficacy up to 52 weeks from treatment initiation among the patients from the MEASURE UP 1, 2 studies.[36] The JADE REGIMEN trial evaluated the sustainability of abrocitinib-induced responses over 40 weeks. The primary outcome to determine the probability of a flare during the maintenance period was 18.9%, 42.6% and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg and placebo, respectively.[37]

Safety outcomes

The three JAK-i available for treating AE have good safety and tolerability profiles. The most frequent treatment-emergent adverse events (TEAE) were mild to moderate in severity and included upper respiratory tract infections, nasopharyngitis, gastrointestinal symptoms (e.g., nausea, vomiting and diarrhoea) and headache.[21,28-30] The younger population in the upadacitinib and abrocitinib trials could explain the development of acne in up to 17% of patients.[28] The most frequent biochemical TEAE in all treatment arms was elevated plasma creatine phosphokinase (CPK).

The occurrences of TEAE of eczema herpeticum and herpes zoster were very low for all three JAK-i (none to two cases per study).[21,28-30] However, the proportion of patients developing TEAE of herpes simplex with baricitinib was slightly higher than in the placebo arms (range: 3.3%-7.2%) and was not dose-dependent.[21] There was no reactivation of TB reported in any of the trials. The rate of discontinuation of the drug due to adverse events was low in all studies.

Serious adverse events were uncommon and similar across the treatment and placebo arms in all studies. The serious adverse events were dose-independent and ranged from none to approximately 4%, except for baricitinib 1 mg in the BREEZE-AD2 (7.3%).

Baricitinib's long-term safety profile was derived based on a pooled safety analysis across its clinical programme and included the long-term extension studies (N=2531 with 2247 patient-years). The most common serious adverse events were eczema herpeticum (n=11; incidence rate 0.5), cellulitis and pneumonia.[38] Nasopharyngitis, headache, elevated CPK levels and diarrhoea were the most frequently reported TEAE.

Long-term (52 weeks) safety studies of upadacitinib revealed that treatment discontinuation due to TEAE was low overall. Both upadacitinib doses (15 mg and 30 mg) were well tolerated and did not demonstrate any new safety signals.[36]

Baseline investigations and monitoring

The recent EuroGuiDerm Guideline on Atopic Dermatitis (June 2022) recommends that

the same baseline screening and treatment monitoring investigations should be conducted for all JAK-i (Table 4).

Table 4. Baseline screening and monitoring for all JAK-i[14]

Baseline screening	Monitoring at 4 weeks after initiation and then 3-monthly while on treatment
• Full blood count • Renal and liver function tests • Fasting lipid profile • Serum creatine phosphokinase • Viral hepatitis and TB screening, including a chest radiograph	• Full blood count • Renal and liver function tests • Fasting lipid profile • Serum creatine phosphokinase

Precautions and contraindications

The JAK-i are contraindicated in patients with hypersensitivity to the active substance or any of its excipients and those with active TB or serious infections, severe hepatic impairment and pregnancy.[39-41] In case of latent TB or those with a high risk of TB infection, anti-TB therapy should be considered before starting these agents.

There is a dose-dependent increase in lipid parameters with JAK-i that can be monitored and controlled with statin therapy. If liver enzymes levels increase (alanine transaminase ≥5-times and aspartate transaminase ≥10-times the upper limit of normal) and drug-induced liver injury is suspected, the agents should be temporarily discontinued until liver injury is excluded.[41]

All three JAK-i have been associated with increased serum levels of creatine phosphokinase (CPK) in patients with inflammatory disorders but not in patients with myeloproliferative disease or healthy subjects treated for a limited duration.[42] Most patients do not report myalgia or other symptoms associated with CPK elevation. However, the exact mechanism of JAK-i-associated myalgias has not yet been fully elucidated.[43]

JAK-i should be used with caution in patients with risk factors for venous thromboembolism (e.g., older age, obesity and prior history of venous thromboembolic events) and discontinued if the patients exhibit any features of the condition. A recent meta-analysis of two large cohort studies and 15 RCTs (N=466 993) found no significant association of increased risk of venous thromboembolic events in AE patients treated with JAK-i.[44] Patients with diverticular disease should be prescribed baricitinib with caution.

Temporary discontinuation of these agents should be made if the absolute neutrophil count is <1 x 10^9 cells/L, absolute lymphocyte counts is <0.5 x 10^9 cells/L or haemoglobin is <8 g/dL. Treatment can be resumed once the levels reach above these values.

Women of childbearing age should use effective contraception during and for at least one week after stopping treatment.

The drug-drug interaction profiles relating to metabolization via the CYP450 enzymes also differ between JAK-i (Table 5).[45-47]

Table 5. Summary table for baricitinib, upadacitinib and abrocitinib

JAK-i	Target JAK	Dosing	Common adverse events
Baricitinib[21,41]	JAK 1 and JAK 2 (selective)	4 mg/day 2 mg/day if ≥75 years old or eGFR 30-60 ml/m^3	Nasopharyngitis, headache, increased blood CPK levels, URTI
Upadacitinib[†28,40]	JAK 1 more than JAK 2, JAK 3 or TYK2	15 mg/day Can be increased to 30 mg/day if necessary If ≥65 years old, 15 mg/day is recommended	Acne, URTI, nasopharyngitis, headache, increased CPK levels
Abrocitinib[‡30,39]	JAK 1 (selective)	100 mg/day Can be increased to 200 mg/day if necessary 50 mg/day is recommended if eGFR 30-60 ml/m^3	Nausea, nasopharyngitis, headache, URTI, acne, vomiting, upper abdominal pain, increased CPK levels, folliculitis, thrombocytopenia

CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; JAK, Janus kinase; JAK-i, Janus kinase inhibitors; TYK2, tyrosine kinase 2; URTI, upper respiratory tract infection.

Table 5. Summary of drug-drug interactions of the different JAK-i relating to CYP450 enzymes

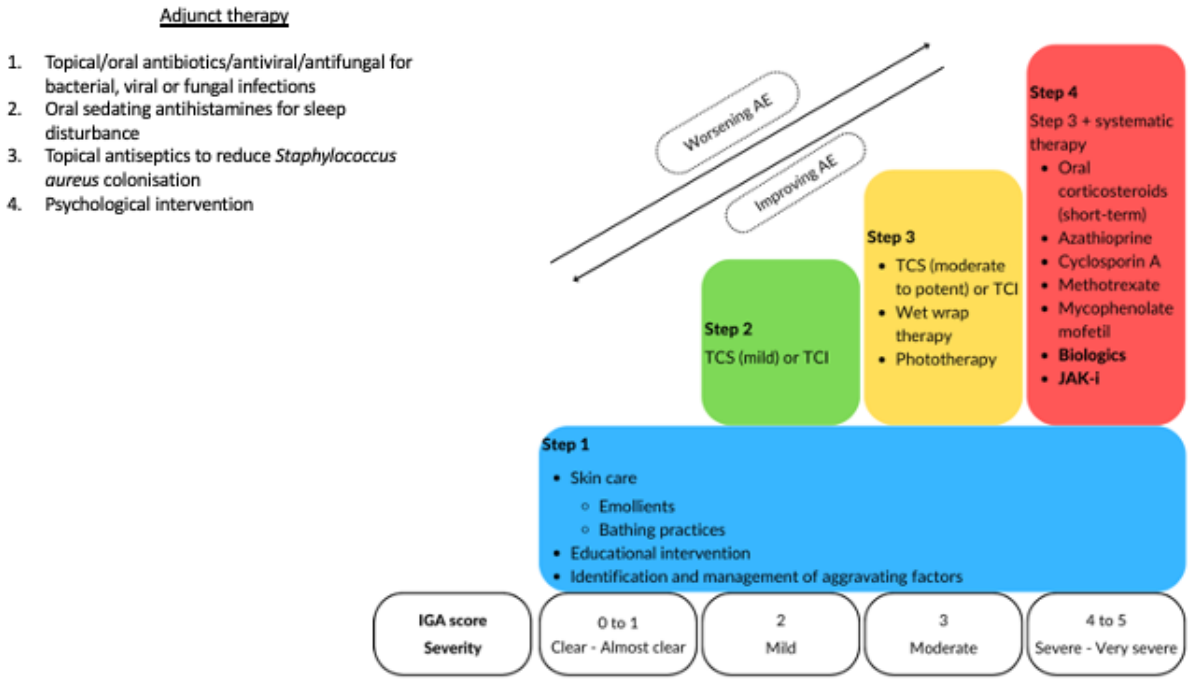
Interaction with CYP450 enzyme	Baricitnib[46]	Upadacitinib[45]	Abrocitinib[47]
Metabolization via CYP450 enzymes	<10% by CYP3A4	Mainly by CYP3A4	~53% by CYP2C19 ~30% by CYP2C9 ~11% by CYP3A4 ~6% by CYP2B6
Relevance for CYP450 drug interactions	None	Yes: CYP3A4 inducers or inhibitors can affect upadacitinib exposure	Yes: CYP2C19 and CYP2C9 inhibitors or inducers can affect abrocitinib exposure
Dosing considerations for CYP450 drug interactions		Upadacitinib 15 mg OD should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g. clarithromycin, erythromycin, diltiazem, verapamil, itraconazole, ketoconazole and ritonavir) Upadacitinib 30 mg OD dose is not recommended for patients with AE receiving chronic treatment with strong CYP3A4 inhibitors Food or drink containing grapefruit should be avoided during treatment with upadacitinib Patients should be monitored for changes in disease activity if upadacitinib is co-administered with strong CYP3A4 inducers	In patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose should be reduced by half to 100 mg or 50 mg once daily Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/ CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin)

OD, once daily.

Important notice: As of September 1st 2021, and based on a review of a large, randomised safety clinical trial, the United States Food and Drug Administration (US FDA) requires a black box warning for all JAK-i for serious infections, malignancy and thrombosis. The US FDA concluded an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots and death with tofacitinib. This warning is to be extended to all JAK-i due to similar mechanisms of action.[47]

Updated AE treatment algorithm

Figure 2. The updated treatment algorithm for AE includes biologics and JAK-i. Biologics and JAK-i have been added as treatment options for severe to very severe AE. IGA, Investigators' Global Assessment; JAK-i, Janus kinase inhibitors; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors. Adapted from the Ministry of Health Malaysia, Persatuan Dermatology Malaysia. Clinical Practice Guidelines for the management of atopic eczema. 2018.[11]



Conclusion

After evaluating the data on the efficacy and safety of baricitinib, upadacitinib and abrocitinib, we recommend that JAK-i can be considered as an option for systemic therapy in severe AE. These newer agents are currently undergoing long-term extension studies, and thus, the recommendation may vary from time to time when more evidence arises.

Conflict of Interest Declaration

Dato' Dr Noor Zalmy Azizan has received honorarium for chairing meetings from Zuellig Pharma Therapeutics, Novartis and Eucerin. She is also the President of the Persatuan Dermatologi Malaysia (2020-2022), which is an unpaid position. Received drug samples from Zuellig Pharma Therapeutics and Abbvie.

Associate Professor Dr Adawiyah Jamil has received sponsorship for the Annual Dermatology Congress Malaysia 2022 from Zuellig Pharma Therapeutics and participated in an advisory board meeting by Boehringer Ingelheim.

Dr Chang Choong Chor has received drug samples from Zuellig Pharma Therapeutics.

Dr Dawn Ambrose, Dr Foong Boon Bee, Henry, Dr Rajalingam Ramalingam, Dr Sharifah Rosniza Binti Syed Nong Chek, Dr Sabeera Begum bt Kader Ibrahim and Dr Wong Hoi Ling have no conflict of interests to declare.

Dr How Kang Nien has received consulting fees from Boehringer Ingelheim and honoraria from Janssen, Beiersdorf and Zuellig Pharma Therapeutics. He has also received support for meeting attendance from Novartis, and is an Executive Committee Member in the Persatuan Dermatologi Malaysia.

Dr Tan Wooi Chiang has participated in advisory board meetings for Zuellig Pharma Therapeutics and Pfizer. He is also the vice president of the Persatuan Dermatologi Malaysia (2022-2024).

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ORIGINAL ARTICLE

Serum Vitamin B12 Level and Dietary intake in Adult Atopic Dermatitis: A Case Control Study

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Abstract

Background

Vitamin B12 is a contributing factor in pruritus and peripheral nerve regeneration. Its role in atopic dermatitis (AD) is still unclear. This study aimed to compare vitamin B12 level between AD patients and healthy controls, determine its correlation with pruritus and AD severity, and evaluate dietary pattern with energy, macro and micronutrient intakes.

Methods

This was a case control study involving adult AD patients and age-, gender-, ethnicity- and body mass index-matched healthy controls. All adult patients who fulfilled UK Working Party AD diagnostic criteria were included. Exclusion criteria include patients on systemic agents, diseases known to affect B12 level and vegan diet. AD severity was determined using SCORing Atopic Dermatitis (SCORAD) index. Serum vitamin B12 level were measured. A three-day 24-hour dietary recall was collected and analyzed.

Results

A total of 42 AD patients and 42 controls were recruited. Mean SCORAD index was 39.2±16.6, and AD duration was 12.7 ± 8.1 years. Vitamin B12 was lower among AD (215.6 ± 110.2 pmol/L) versus control (295.1± 119.9 pmol/L), $p<0.01$ despite similar dietary B12 intake in both groups. There were no significant correlations between AD duration and severity with vitamin B12 level. Energy intake (kcal/day) was significantly lower in AD ($p=0.04$). There were no significant differences in proportion of main food groups consumed and other macronutrient and micronutrient intakes.

Conclusion

Serum vitamin B12 level was significantly lower in AD patients despite similar dietary pattern and nutrient intake with healthy controls. There were no correlations with AD severity or disease duration. Dietary pattern of AD patients should be routinely assessed to ensure adequate nutrition.

Key Words: C*obalamin, B12, Atopic dermatitis, Nutrition*

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory, pruritic skin disorder affecting up to 10% of the adult population.[1] Micronutrients may have an impact on atopic dermatitis as proper nutrition, especially vitamins, minerals,

and trace elements play an active role in immune health. The relationship between nutrition and atopic pathogenesis has been debated for many years.[2] Current knowledge is still not sufficient to discern the exact role of specific vitamins and trace minerals on AD.

Vitamin B12 (cobalamin) is a chemical compound with vitamin properties, that is mainly present in sufficient amount in animal-derived foods.[3] Self-imposed dietary restriction (i.e. red meat, egg, seafood) without consulting a doctor or dietitian is a common practice among AD patients.[4,5] The lack of supervision of these dietary modifications has been associated with risk of nutrient deficiency in both children and adults.[6-8] A local study in toddlers with AD[6] yielded a non-significant lower level of serum vitamin B12 among food restricted group. However, clinical manifestation of B12 deficiency from diminished intake or absorption may not manifest for several years after the depletion of body stores.[9] Furthermore, prevalence of vitamin B12 deficiency is difficult to assess since under-diagnosis is likely and subclinical disease is considered not uncommon.[10]

Vitamin B12 precursor has been shown to have a potent action as a nitric oxide scavenger in inflammatory conditions. The ability of vitamin B12 to regulate inflammatory cytokines suggests that it may have antioxidative properties.[11] Topical vitamin B12 has some efficacy in the treatment of atopic dermatitis.[12]

Hence, the aim of this case control study is to compare serum vitamin B12 level between AD patients and healthy volunteers. Correlations between serum B12 level with AD severity, disease duration and pruritus were determined. Dietary pattern, energy and other macro- and micronutrient intakes were also assessed.

Materials and Methods

A case control study was performed. Patients with AD attending Dermatology clinic Hospital Tengku Ampuan Afzan were screened and recruited from August 2020 until May 2021. Healthy age, gender, ethnicity and body mass index-matched volunteers constituted the control group. We included patients aged 18 years old and older who met the criteria for atopic dermatitis based on the UK Working Party Atopic Dermatitis diagnostic criteria.[13] Exclusion criteria were (i) patients on systemic agents which include azathioprine, methotrexate and cyclosporin (ii) patients with other pruritic conditions including urticaria, (iii) generalized hyperpigmentation, (iv) atrophic glossitis, (v) patients conditions known to affect vitamin B12 level which include pernicious anemia , hypochlorhydria due to atrophic gastritis, partial or total gastrectomy, bariatric surgery, ileal resection of >20 cm, malabsorptive disorders, short bowel syndrome, inflammation of the ileum – eg: Crohn's disease, celiac disease, chronic pancreatitis, small intestine bacterial overgrowth, Whipple's disease, ongoing/ previous history of gastric cancer/gastrectomy, (vi) patients on medications affecting vitamin B12 level which include B12 supplement, proton pump inhibitor, H2 receptor antagonist and metformin, (vii) patients on vegan diet, and (viii) pregnancy.

Demographic data of the participants and their body mass index (BMI; weight [kg]/height m^2) and waist circumference (cm) were recorded, as was the SCORing Atopic Dermatitis (SCORAD),[14] and Dermatology Life Quality Index (DLQI) score[15] for the cases. Severity in the SCORAD index is classified as mild (<25), moderate (25-50), and severe (>50). The maximum score is 103. All participants were asked to recall their 3-day dietary intake which consists of two weekdays and one weekend. Description include the type of food or beverage consumed and portion size and cooking methods. Portion size was determined using a common food guide (cups, bowls, tablespoon, teaspoons, glasses).

Participants are first asked about all the food they consumed within the last 24-hours, followed by a thorough probing whereby they detailed information for each food/beverage, for the

type, amount, any addition to the food/toppings, preparation methods including the type of oil/fat used is obtained. If the food was packaged, the brand name, as well as the amount consumed, was obtained. Finally, the record of foods and the amount consumed was reviewed, to provide the investigator a chance to clarify any unclear information.[16] To understand food preferences, main food groups consumed, meat (chicken, beef, and pork), seafood (fish, crustaceans, and mollusk), vegetables, egg, milk and peanut, cakes and sweets were examined.

Dietary intake was analyzed using Nutritionist Pro™ Software (Axxya Systems, the United States Department of Agriculture (USDA) Standard Reference Database, First DataBank, Inc., San Bruno, California) for macronutrients and micronutrients. The Nutritionist Pro™ software contains Malaysian Food composition databases as well as other international databases such as USDA Food Database, Canadian Food Database, and Mexican Food Database. Schofield's equation was used to determine the basal metabolic rate (BMR). The Energy Intake (EI): BMR ratio was used to identified under reporters. Classification of the EI: BMR ratio into under reporters (EI: BMR<1.2), plausible (EI: BMR 1.2-2.4), and over reporters (EI: BMR>2.4) were used.[17]

Venous blood was obtained for serum B12 levels. Assays for serum B12 level was performed using Access® Immunoassay System Model DxI 800 UniCel®, which use chemiluminescent paramagnetic microparticle immunoassay (assay range 133 – 675 pmol/L) from (Beckman Coulter, USA). Basic hematological profile was measured as well. These tests were conducted in the Pathology Department of Hospital Tengku Ampuan Afzan, Pahang.

This study was approved by Medical Research and Ethical Committee (MREC), Malaysia with research code NMRR-20-1768-55814. The sample size of this study was calculated using the statistical online software OpenEpi Version 3[18] based on the case-control study by Polat, M., et al.[19] Fourty two subjects in each group were needed to be able to reject the null hypothesis with a probability power of 0.9.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Version 24.0, IBM Corp). Most continuous variables were normally distributed and were summarized as mean and standard deviation (SD). Qualitative data were expressed as percentages. The chi-square test and t test were used in analyzing differences between groups. The significance level was set at $p < 0.05$. Correlations between variables were tested with the Pearson correlation analysis. Significance was determined according to the two tailed alternative hypothesis, and results were deemed significant for p values < 0.05.

Results

A total 33 men and 31 women were enrolled in the study. The case and control groups were matched for age, sex, race and body mass index. The mean age of participants was 28.1 ± 7.2 years. Majority of the participants are female (60.7%) and Malays (86.9%). The mean BMI was similar with 25.3 ± 5.9 and 23.8 ±5.1 in the case and control groups, respectively, ($p = 0.2114$). There was significant difference in the proportion with comorbidities between AD patients (45.2%) and controls (16.7%), $p < 0.01$.

Table 3 shows there is lower energy intake among AD patients AD 1589.85 kcal±406.69 versus control 1755.61 kcal±331.12, ($p=0.04$). However despite trend of lower intake of protein, carbohydrate, and fat, these differences were not significant ($p=0.27$, $p=0.06$, $p=0.22$ respectively). No significant differences noted on intake of all other micronutrients.

Serum vitamin B12 levels were within the normal range of 133–675 pmol/L. In the case group, the mean serum vitamin B12 level was lower 215.6±110.2 pmol/L and in the control group it was 295.1±119.9 pg/ml, which was statistically significant (p=0.002179). The mean dietary B12 intake were not statistically difference in both group(AD 3.09 ± 2.07 mcg/

day versus control 3.55±1.78 mcg/day, *p=0.29*).

The mean eosinophil and platelet to lymphocyte ratio were significantly higher (AD 7.6 ±7.3 and 14.4%±7.5%, respectively) compared to control group (*p=0.0002953; p=0.02058* respectively). There is significant correlation of eosinophil with the SCORAD which showed that higher eosinophil percentage correlated with higher SCORAD index score (*p=0.009*, Pearson correlation *r=0.397*).

Mean duration of disease among AD patients were 12.7±8.1 years. The mean SCORAD index scores in the case group was 39.2±16.6. Pearson correlation analysis showed higher SCORAD correlated with higher DLQI (*r=0.457, p=0.002*). However there were no significant correlations between serum vitamin B12 level and disease severity (SCORAD) (*r=0.068, p=0.669*), VAS pruritus (*r=-0.021, p=0.896*), and duration of disease(*r=-0.111, p=0.486*).

Table 1. Demographic data

Demographic data	Total (n=84)		*p – value*
	Case (n=42) Mean±SD or n (%)	Control (n=42) Mean±SD or n (%)	
Age, in years[a]	28.0 ± 7.2	28.2 ± 7.1	0.94
Gender[b]			
Male	16 (38.1%)	17 (40.5%)	0.82
Female	26 (61.9%)	25 (59.5%)	
Race[b]			
Chinese	4 (9.5%)	5 (11.9%)	0.92
Indian	1 (2.4%)	1 (2.4%)	
Malay	37 (88.1%)	36 (85.7%)	
Comorbidities	19 (45.2%)	7 (16.7%)	<0.01
Bronchial asthma	1 0(23.8%)	0	
Allergic Rhinitis	4 (9.5%)	0	
Endometriosis	1 (2.3%)	0	
Hypertension	1 (2.3%)	0	
Acne	7 (16.7%)	7 (16.7%)	
Smoking	5 (11.9%)	5 (11.9%)	1.00
Alcohol	1 (2.4)	1 (2.4)	1.00

[a]Independent t test; [b]Chi Square test

Significant differences were noted among the proportion of AD subjects, there were no significant differences between proportion of food pattern intake among participants (Table 4). There was less proportion (5/42 subjects) among AD subjects who consumed nuts (which include peanut/ groundnut, almond , and cashew) however this was not statistically significant (11.9% in AD subjects versus 28.6% in control, *p=0.06*).

Table 2. Clinical characteristic and laboratory parameters

	Case (n=42) Mean ± SD or n (%)	Control (n=42) Mean ± SD or n (%)	*p value*
Clinical characteristicst[a]			
BMI[1], in kg/m2	25.3 ± 5.9	23.8 ± 5.1	0.21
Waist circumference, in cm	81.1 ± 10.7	79.7 ± 9.7	0.56
SCORAD[2]	39.2 ± 16.6	NA	NA
Severity			
Mild(<25)	11(26.2%)	NA	NA
Moderate (25-50)	20(47.6%)	NA	NA
Severe(>50)	11(26.2%)	NA	NA
VAS pruritus	6.1 ± 1.7	NA	NA
Duration of atopic dermatitis, in years	12.7 ± 8.1	NA	NA
DLQI score[3]	12.9 ± 6.2	NA	NA
Laboratory Parameter[a]			
Serum vitamin B12(pmol/L)	**215.6 ± 110.2**	**295.1 ± 119.9**	**<0.01**
Hemoglobin (g/dl)	13.9 ± 1.5	13.7 ± 1.6	0.55
PCV[4] (%)	41.6 ± 3.9	40.4 ± 4.1	0.16
MCV[5] (fL)	80.1 ± 9.0	81.6 ± 7.1	0.37
MCH[6] (pg)	26.8 ± 3.4	27.8 ± 2.7	0.13
WBC[7] (10^9/L)	9.6 ± 5.7	8.4 ± 4.3	0.31
Neutrophil (%)	57.4 ± 13.3	57.9 ± 9.5	0.84
Lymphocyte (%)	26.6 ± 10.2	30.6 ± 8.4	0.06
Eosinophil (%)	**7.6 ± 7.3**	**3.1 ± 2.6**	**<0.01**
Platelet (10^9/L)	330.3 ± 76.7	316.3 ± 70.7	0.39
Absolute neutrophil count(ANC)	5.2 ± 2.7	4.9 ± 2.8	0.61
Neutrophil to Lymphocyte Ratio (NLR)	2.7 ± 1.9	2.1 ± 1.0	0.10
Platelet to Lymphocyte Ratio (PLR)	**14.4 ± 7.5**	**11.2 ± 4.1**	**0.02**

[a]Independent t test; [b]Chi Square test; [1]Body Mass Index; [2]SCORing Atopic Dermatitis; [3]Dermatology Life Quality Index; [4]Packed Cell Volume; [5]Mean Corpuscular Volume; [6]Mean Corpuscular Hemoglobin; [7]White Blood Cell; NA: Not applicable; VAS: Visual Analogue Score

Table 3. Energy and nutrient intake

Nutrient intake per day	Total (n=84)[a]		*p – value*
	Case (n=42) Mean ± SD	Control (n=42) Mean ± SD	
BMR[1](kcal)	1513.50 ± 234.12	1496.48 ± 280.91	0.76
EI[2] (kcal)	**1589.85 ± 406.69**	**1755.61 ± 331.12**	**0.04**
EI: BMR Ratio	**1.07 ± 0.28**	**1.19 ± 0.23**	**0.02**
Protein (g)	67.94 ± 20.82	72.81 ± 19.45	0.27
Carbohydrate (g)	208.24 ± 64.78	234.16 ± 61.15	0.06
Fat (g)	53.38 ± 19.61	58.17 ± 15.85	0.22
SFA[3] (g)	11.53 ± 6.82	10.44 ± 5.61	0.42
MSFAT[4] (g)	11.70 ± 7.66	11.97 ± 7.62	0.87
PUFAT[5] (g)	9.09 ± 5.29	10.95 ± 7.25	0.18
Vitamin A (IU)	4582.65 ±2571.05	4700.60 ± 3340.15	0.86
Beta Carotene (µg)	954.87 ± 1238.95	1038.39 ±1642.26	0.79
Vitamin C (mg)	34.24 ± 34.48	34.16 ± 33.71	0.99
Vitamin D (IU)	45.85 ± 56.77	48.21 ± 75.46	0.88
Vitamin E (IU)	6.61 ± 3.94	7.82 ± 5.60	0.26
Thiamine (mg)	0.74 ±0.40	0.71 ± 0.30	0.72
Riboflavin (mg)	1.14 ± 0.56	1.07 ± 0.46	0.53
Niacin (mg)	14.43 ± 6.38	15.08 ± 7.33	0.66
Pyridoxine (mg)	0.93 ± 0.54	0.92 ± 0.54	0.93
Pantothenic acid (mg)	1.04 ± 0.78	1.11 ± 1.23	0.75
Folate (µg)	103.71 ± 65.00	100.35 ± 73.99	0.83
Vitamin B12 (µg)	3.09 ± 2.07	3.55 ± 1.78	0.29
Calcium (mg)	353.84 ± 198.35	372.54 ± 182.04	0.65
Phosphorus (mg)	926.17 ± 338.32	913.28 ± 254.88	0.84
Iron (mg)	19.46 ± 9.74	19.77 ± 10.71	0.89
Zinc (mg)	4.41 ± 1.80	4.42 ± 2.31	0.98
Copper (mg)	0.69 ± 0.40	0.64 ± 0.33	0.54
Magnesium (mg)	122.76 ± 57.69	118.79 ± 57.57	0.75
Total dietary fiber (g)	5.07 ± 3.75	3.89 ± 3.32	0.13

[a]Independent t test; [1]Basal Metabolic Rate; [2]Energy intake; [3]Saturated fatty acids; [4]Monounsaturated fat; [5]Polyunsaturated fat

Table 4. Dietary pattern

Dietary Pattern	Total (n=84) [b]		*p – value*
	Case (n=42) n (%)	Control (n=42) n (%)	
Poultry	35 (83.3%)	39(92.9%)	0.18
Beef	10 (23.8%)	14 (33.3%)	0.33
Fish	26 (61.9%)	27 (64.3%)	0.82
Wheat	24 (57.1%)	28 (66.7%)	0.37
Dairy	5 (11.9%)	9 (21.4%)	0.24
Egg	24 (57.1%)	30 (71.4%)	0.17
Nuts	5 (11.9%)	12 (28.6%)	0.06
Shellfish	9 (21.4%)	12 (28.6%)	0.45
Vegetables	31 (73.8%)	28 (66.7%)	0.47
Fruits	9 (21.4%)	10 (23.8%)	0.79
Cakes & sweets	15 (35.7%)	15 (35.7%)	1.00

[b]Chi Square test

There were 32 (38.1%) under reporters (EI:BMR ratio <1.2) and 52 (61.9%) plausible reporters (EI:BMR ratio 1.2-2.4). There was no over reporters (EI: BMR ratio >2.4) among the participants (Table 5).

Table 5. Energy Intake - BMR ratio (EBR)

EI[1]:BMR[2] ratio (EBR)	Participants		Total (%)
	Case	Control	
EBR <1.2 (under reporters)	14	18	32 (38.1)
EBR 1.2-2.4 (Plausible)	28	24	52 (61.9)
EBR >2.4 (over reporters)	0	0	0

Energy intake; Basal Metabolic Rate

Discussion

Vitamin B12 supports myelinization and axonal transport, thus helping regeneration of peripheral nerve cells.[20] Its deficiency plays a role in the etiology of neuropathic itching by causing small-fiber neuropathy.[21] Anti-inflammatory and anti-oxidative properties of vitamin B12 are exerted by downregulation of pro-inflammatory cytokines and reduction of nitric oxide. Low vitamin B12 has been associated with chronic pruritic dermatoses including generalized pruritus[19] and chronic spontaneous urticaria.[22] Robust itch sensations, increased neuronal activity, and hyperinnervation are observed in AD skin.[23] Chesini and Caminati[24] described a patient with severe, refractory AD and low serum vitamin B12. Subsequent correction of his vitamin B12 level with oral supplementation resulted in significant AD improvement. Therefore, assessment of vitamin B12 level in patients with difficult-to-control atopic dermatitis was suggested.[24] Emerging data indicate that a topical vitamin B12 preparation may prevent atopic dermatitis flares due to its high affinity binding to nitric oxide produced by keratinocyte.[25,26]

Our findings showed significantly lower serum vitamin B12 level in AD patients compared to healthy controls despite similar dietary patterns and intake of macronutrients and other micronutrients. Mean serum vitamin B12 levels were within normal limits in both groups. We postulate that long standing utilization of tissue

vitamin B12 in maintaining and regenerating peripheral nerve cells in AD may have resulted in reduction in the level of serum vitamin B12. The historical lower normal value for serum vitamin B12 was 148 pmol/L[27] compared to our reference value of 133 pmol/L with overall coefficient of variation of performance of 5–15% between different assays and inter-method biases of plus 10% or minus 20% from the all-laboratory trimmed mean.[28] However, it is still unknown whether serum B12 correlated with its tissue level. Additionally, level that represent subclinical deficiency, i.e., a low serum vitamin B12 in the absence of clinical symptoms is unclear.[29,30] Raising the lower range to 258 ng/L has been considered, but the benefit of detecting subclinical deficiencies may be limited as there are few associated metabolic abnormalities[31] and a small number of subclinical deficiencies that progress to clinical deficiencies. Low-normal levels with potential effect on patients' health are often ignored by physicians and even genuinely low levels may be ignored if neuropathy or anaemia are not evident. Further testing using a functional test such as methylmalonic acid (MMA) assay is recommended for levels <221 pmol/L.[32]

Subclinical reduction in vitamin B12 due to subclinical malabsorption and increased utilization of proliferating tissue have been postulated to contribute to inflammation in AD (33). Vitamin B12 modulates inflammation cascade by suppressing production of T lymphocytes-derived cytokines, in particular interleukin-6 (IL-6), interferon-gamma (IFN-gamma), and interleukin-1 beta (IL-1 beta).[34] Inverse correlations between chronicity of AD and severity of pruritus with serum vitamin B12 level was demonstrated in our cohort, which supports this postulation. However, our study was not sufficiently powered to determine this relationship.

Dietary pattern and nutrient intake were estimated using 3 days diet recall in our study. Vitamin B12 was slight lower than the recommended nutrient intake (RNI) for Malaysia at 4 microgram per day.[35] This was not a contributing factor to the lower level of serum B12 in our AD cohort as the intake for both cases and control was similar. The validity of 24-hour dietary recall is dependent on the degree of accuracy in which respondents recall their food consumption. Under reporting of energy intake is defined as EI:BMR ratio below 1.2.[36] The prevalence of underreporting in our study was lower than Arumugam et al (77.4%)[37] and Zainuddin et al (61%).[17] Factors associated with underreporting include obesity, age, gender, social status and controlled eating habits.[38,39] Reporting bias may lead to a misinterpretation of the individual's nutritional state and may result in misleading associations between diet and disease.

Apart from that, serum eosinophils levels were also noted to be significantly higher in our cohort and the degree of severity also correlated with eosinophil level. This was consistent with previous studies.[40-42] We also notice a higher platelet to lymphocyte ratio which was in line with previous studies.[43-45] These simple indicators may serve as a potential adjunct markers of ongoing systemic inflammation in atopic dermatitis patients in the future.[43]

In our cohort, AD severity correlated well with the DLQI indicating its effect on patients' quality of life. This has to be emphasized in regards to aiming for optimal disease control to improve patients' daily activity and emotional burden. Patients with subclinical vitamin B12 deficiency are prone to symptoms of depression[46-48] and anxiety,[49] thus exacerbation or worsening of depressive symptoms may occur with a concomitant chronic disease like AD that significantly affects quality of life.

Limitation

Our study is limited by the possibility of recall bias with the 3-days dietary recall. Comprehensive evaluation of other biomarkers like homocysteine and methylmalonic acid were not possible due to unavailability of the assays at our centre. Other micronutrients level including vitamin D, zinc, folate and trace

mineral were beyond the scope of this study. Concurrent parasitic infestation was not tested in this study.

Conclusion

Serum vitamin B12 level was significantly lower in AD patients. There were no differences in dietary pattern, macronutrient and micronutrient intakes between patients with AD and healthy controls. Serum vitamin B12 level did not correlate with AD severity or disease duration. Although the role of vitamin B12 in AD is still unclear, dietary patterns of AD patients should be assessed to ensure adequate nutrient intake.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CASE REPORT

A Case of Eosinophilic Granulomatosis with Polyangiitis Mimicking Cutaneous Tuberculosis and Tuberculous Lymphadenitis

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Summary
Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss Syndrome (CSS) is a rare granulomatous necrotizing vasculitic disease characterized by the presence of asthma, sinusitis, and hypereosinophilia. We describe a patient who was initially diagnosed with tuberculous lymphadenitis and later diagnosed with EGPA.

Key Words: *Churg-Strauss syndrome, Eosinophilic Granulomatosis with Polyangiitis, Tuberculous lymphadenitis, Rituximab*

Introduction
Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome (CSS) is a rare granulomatous necrotizing vasculitic disease characterized by the presence of asthma, sinusitis, and hypereosinophilia.[1-3] EGPA causes vasculitis of small-to-medium blood vessels that affects many organ systems such as the cardiovascular, pulmonary, renal, nervous and vascular systems.[4] Vasculitis of extrapulmonary organs is a major cause of morbidity and mortality in this disease.[3] Corticosteroids are considered the first-line of treatment for EGPA patients to achieve remission.[4] Rituximab is an anti-CD20 monoclonal antibody that is approved for use in the treatment of lymphoid malignancies, rheumatoid arthritis, and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).[5] We report a challenging case of active severe EGPA mimicking cutaneous tuberculosis and tuberculous lymphadenitis who initially responded to intravenous (IV) pulse corticosteroid and Rituximab, relapsed and retreated, but succumbed to Coronavirus disease 2019 (COVID-19) infection.

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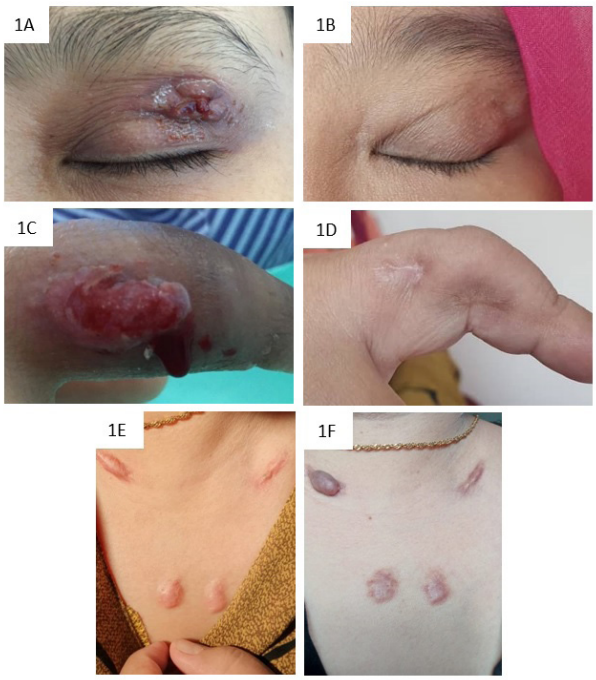
Case Report

A 38-year-old female with underlying bronchial asthma and rhinosinusitis presented to the dermatology clinic with multiple erythematous papules, plaques and ulcerated nodules on her left eye lid (Figure 1A), dorsum of the right index finger (Figure 1C), forearms, and chest (Figure 1E) with intermittent fever for 6 months. Systemic review was otherwise unremarkable. She had been empirically treated for smear-negative tuberculous lymphadenitis by the treating physician for a year but showed no improvement.

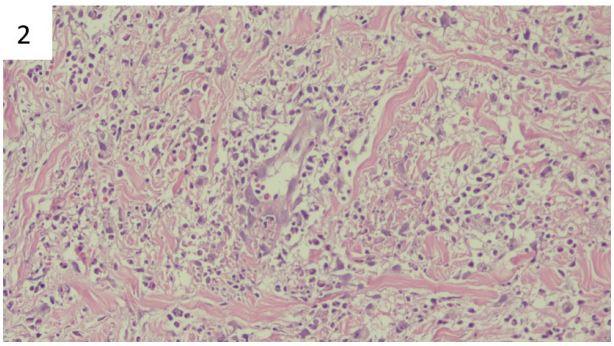
Figure 1. Churg-Strauss syndrome. (A) Erythematous multilobulated plaque with ulcerated haemorrhagic crust on left eye lid; (B) Eye lid post-treatment, resolved lesion; (C) Erythematous juicy ulcerated nodule with contact bleeding on right dorsal index finger; (D) Index finger post-treatment, resolved lesion; (E) Multiple pink elongated papules over anterior chest; (F) Chest post-treatment, resolved lesions with keloid scars.



Laboratory tests revealed leukocytosis (16820/mm^3) with eosinophilia (1050/mm^3). Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), chest radiograph, echocardiograph and Tuberculosis Quantiferon results were normal. Computed tomography (CT) scan of thorax, abdomen and pelvis revealed multiple non-necrotic cervical, mediastinal, inguinal lymphadenopathy with lung, liver and bone nodules. Positron emission tomography (PET) scan showed avid lytic lesions with rims of sclerosis along vertebra, bilateral ileum and right tibia representing chronic granulomatous bone changes. Magnetic resonance imaging and angiography (MRI/MRA) brain showed multiple supratentorial non enhancing hyperintense foci.

Biopsies taken from the lymph node and skin plaque showed a mixture of neutrophils, eosinophils and histiocytes in aggregates, forming granulomas. Blood vessels showed evidence of vasculitis with eosinophils (Figure 2). Immunohistochemical staining for S100 and CD1a were positive, whereas langerin (CD207) staining was negative. Culture and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* from skin biopsy were negative. A diagnosis of EGPA was made based on the clinical manifestations, histopathological findings of eosinophilic granulomas as well as small vessel vasculitis.

Figure 2. Dermal small vessel vasculitis in CSS. Histopathologic findings of infiltrated plaque on chest showing dermal eosinophilic vasculitis and focal granuloma. Hematoxylin-eosin stain, magnification X200.



Induction of remission was achieved with combined pulse IV methylprednisolone 500 mg daily for 3 days and IV Rituximab 375 mg/m^2 weekly for 4 doses. Cyclophosphamide was not used due to type 1 hypersensitivity reaction of urticaria eruption. There was significant improvement in clinical signs, eosinophilia and radiological features in our patient following treatment. Remission was achieved for 6 months, with tapering oral corticosteroid and azathioprine (2 mg/kg/day) as maintenance therapy. Her disease relapsed with hip joint

synovitis confirmed by MRI, multiple areas of hypermetabolic disease involving mediastinal nodes, subcutaneous, bones and joints on PET/CT scan, and raised inflammatory markers. Azathioprine was switched to mycophenolate mofetil (2000 g/day), with a subsequent second cycle of IV Methylprednisolone and Rituximab 15 months after the first cycle. Her symptoms improved significantly whilst maintaining on mycophenolate mofetil, with plans for follow-up scans. Unfortunately, she succumbed to COVID-19 with category 5 severity, complicated with organizing pneumonia and pulmonary embolism 10 weeks after the second cycle of IV Rituximab.

Discussion

EGPA is a rare granulomatous necrotizing vasculitis with a very low incidence of 0.5 to 6.8 new cases per million patients every year.[1,4] It affects both men and women equally and the average age at diagnosis is 48 years.[4] The exact cause of EGPA is unknown.[1] Clinical diagnosis of EGPA is based on the American College of Rheumatology (ACR) Criteria which requires any 4 or more of the following clinical criteria to be present: asthma, eosinophilia > 10%, pulmonary infiltrates, paranasal sinus abnormality, neuropathy, or extravascular eosinophils.[4] Our patient fulfilled the ACR Criteria for EGPA, presenting with peripheral eosinophilia, asthma, paranasal sinus abnormalities and biopsy containing a blood vessel with extravascular eosinophils.[6]

The sequence of pathophysiological events in EGPA includes 3 stages.[4] Firstly, the pre-vasculitic phase can be characterized by asthma and other allergies, along with blood and tissue eosinophila.[4,7] Next, infiltration of eosinophils into tissues occurs in organs such as the lungs, gastrointestinal tract, or heart.[4,7] The last stage is when vasculitis occurs, which can be necrotizing or non-necrotizing, and EGPA is diagnosed.[4] However, this sequence of events may vary in different patients, and multiple manifestations may appear at the same time.[7] The most frequently observed clinical manifestations of EGPA are asthma, allergic rhinitis, peripheral nervous system involvement, gastrointestinal symptoms, cardiac involvement, and renal disease.[7-9] Anti-neutrophil cytoplasmic antibodies (ANCA) have been reported in 6–77% of EGPA patients.[6] In our patient, ANCA was not detected.

Up to 81% of EGPA patients experience cutaneous manifestations, and approximately 14% of cases present such manifestations as a sign of the disease.[7] Palpable purpura of the extremities is the most common cutaneous manifestation, affecting up to 50% of EGPA patients, followed by urticarial lesions and less commonly, livedo reticularis, papules, cutaneous infarctions, Raynaud's phenomenon, vesicles, and pustules.[7,9] The major histopathological features of EGPA include vasculitis, eosinophilic infiltration, and extravascular granuloma.[7]

Our patient was initially treated for smear-negative tuberculous lymphadenitis based on clinical findings of persistent fever, constitutional symptoms and lymphadenopathy. However, there was no clinical improvement upon completion of anti-tuberculosis treatment for a year. Upon suspicion of EGPA, the dermatologist and rheumatologist were consulted, and we proceeded with a skin and lymph node biopsy, culture and PCR, which suggested the diagnosis of EGPA and excluded tuberculosis.

Prior to the use of alkylating agents, survival with this disease was quite poor, current treatment regimens have reversed this poor prognosis, but treatments are still associated with toxicity. Most EGPA patients respond well to immunosuppressive therapy and can achieve long-term remission.[4,9] Generally, corticosteroids act as the first-line therapy for EGPA patients to achieve remission and improve survival.[4] Corticosteroids can either be used alone or in combination with one or more immunosuppressive drugs such as cyclophosphamide or methotrexate, especially in cases where recurrences are more frequent or associated with a severe form of necrotizing

vasculitis in other organs.[4,7] Therapy typically consists of two stages of treatment: remission induction and maintenance of remission.[10]

According to the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of ANCA-associated vasculitis, the recommended treatment for remission induction in patients with active, severe EGPA is pulse glucocorticoids or high-dose oral glucocorticoids with either rituximab or cyclophosphamide.[11] For maintenance, methotrexate, azathioprine, or mycophenolate mofetil or leflunomide is recommended after remission induction.[11]

Our patient had active severe EGPA, she achieved initial clinical remission of 6 months after the first cycle of pulse glucocorticoid steroid and Rituximab, and was maintained with azathioprine. Subsequently, her disease relapsed and required another cycle of pulse glucocorticoid steroid and Rituximab and switching of azathioprine to mycophenolate mofetil, in which she showed improved clinical symptoms. Unfortunately, our patient succumbed to severe COVID-19 infection 10 weeks after the second cycle of Rituximab. Growing evidence has suggested that treatment with anti-CD20 therapy such as Rituximab, increases the risk of developing severe outcomes from COVID-19 (risk ratio: 1.7–5.5).[12] Several studies have demonstrated that humoral immune responses after COVID-19 vaccination are poor in patients receiving anti-CD20 therapy, even after two doses of the vaccine.[12]. Physicians should be aware of such risks and discuss possible alternative treatments with patients who are receiving or would initiate treatment with Rituximab over the remainder of the COVID-19 pandemic.

Conclusion

In summary, we report a case of a patient who was initially treated for tuberculous lymphadenitis and eventually diagnosed with EGPA. In order to establish a diagnosis of EGPA, clinicians must have a high index of suspicion in patients with background of bronchial asthma, rhinosinusitis, persistent eosinophilia and organs involvement that is histologically consistent with an eosinophilic granulomatous reaction. It is essential to diagnose this rare disease early so that effective treatment can be initiated in time to improve the prognosis of EGPA patients. Therapies like Rituximab and other immunosuppressants can be effective in controlling the disease activity. However, the course of the disease and response to therapy is unpredictable. Increased risk of severe COVID-19 infection while on Rituximab may be detrimental, and thus, poses great therapeutic dilemma and challenges to physicians, especially in this era of the COVID-19 pandemic.

Conflict of Interest Declaration

The authors declare that there is no conflict of interest in this work.

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We would like to thank the Director General of Health Malaysia for his permission to publish this article.

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CASE REPORT

Spontaneous Re-pigmentation of Vitiligo Following Excision of Halo Congenital Melanocytic nevi: An Interesting Case Report

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Summary

Halo nevi (HN) are benign skin lesion that represent melanocytic nevi in which an inflammatory infiltrate develops, resulting in zone of depigmentation around nevus. Although Sutton originally described the lesion in 1916 as leukoderma acquista centrifugum, the lesions were noted earlier as evidenced in the painting by Matthias Grunwald cica 1512-1516. The prevalence of HNs in the general population is 1%, and HNs usually appear in childhood or early adulthood. Up to 26% of patients with HN have vitiligo, but in very few instances is there an association of HN around congenital melanocytic nevi (CMN) and vitiligo. The exact mechanisms responsible for the development of vitiligo and HN and its resolution are unknown. One of the most accepted hypotheses considers that both phenomena are a result of a self-limited immunologic response to pigmented cells, either in the "normal" skin or within the melanocytic lesion. Hereby we present a rare case report of a girl with halo CMN and infraorbital vitiligo. The halo CMN was excised which was followed by spontaneous improvement of vitiligo.

Key Words: *Leukoderma acquista centrifugum, Vitiligo, Excision*

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Introduction

Halo nevus, also called Sutton's nevus, is a melanocytic nevus surrounded by a halo of depigmentation, which is usually symmetrically round or oval. Halo nevi affect up to 5% children in the age group of six to fifteen years old.[1,2] in an equal sex distribution. The most common location is the back. HN has been shown to be associated with many autoimmune diseases, of which vitiligo is the most closely related with reported incidence of between 1-48%.[3,4] There are limited reports in the literature, especially with regard to CMN excision.

Case Report

A 11-year-old girl presented to the Dermatology Outpatient department for a congenital

melanocytic nevus (CMN). The lesion had been present since birth and a hypopigmented halo developed around the congenital nevus 3 years ago. She also developed hypopigmented patches developed over left periorbital region, approximately 13 months prior. Her past history and family history were unremarkable. On physical examination, the congenital nevus, measuring 0.5 cm diameter was located on the left side of nape of neck. The nevus was dark brown in colour with a depigmented halo. Examination of other body parts revealed a linear depigmented patch over the left infraorbital area. The clinical diagnosis of halo congenital melanocytic nevus associated with vitiligo was established. **(Figure 1)** The patient's parents were concerned about the appearance of the halo and vitiligo and requested to remove the CMN. Excision of the nevus with punch biopsy was performed. Pathologic examination revealed compound melanocytic nevus with congenital features and minimal lymphocytes and no macrophage infiltration, completely excised. Patient was followed up after a week to reveal a healing wound over the excision site and followed up monthly. At 5 month follow-up, the patient's halo nevus site was in a resolution phase and the vitiligo in the left infraorbital region was noted to be spontaneously repigmented **(Figure 2 & 3).**

Figure 1. Pre-excision: Halo CMN of 0.5cm in diameter with left infraorbital vitiligo

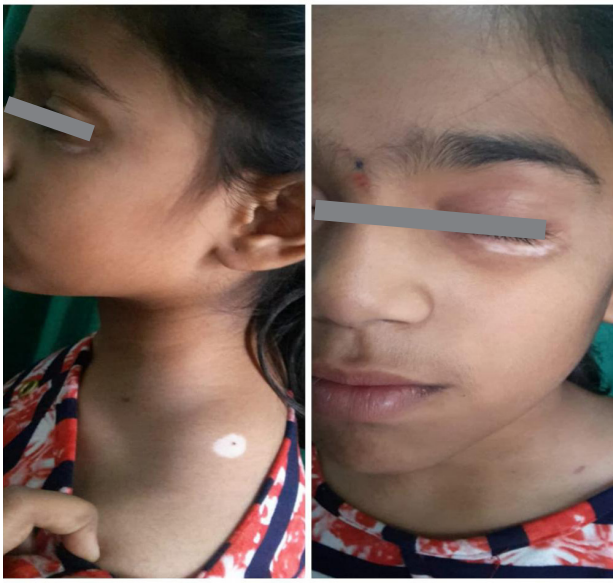


Figure 2. Gradual reduction in the size of nevi post excision in monthly visits

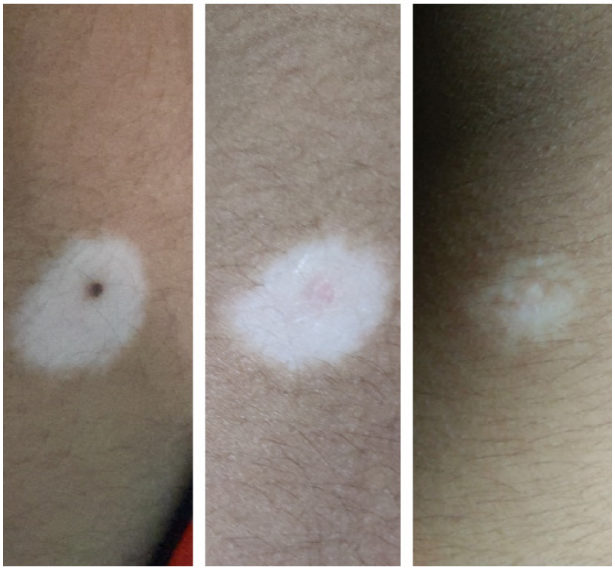
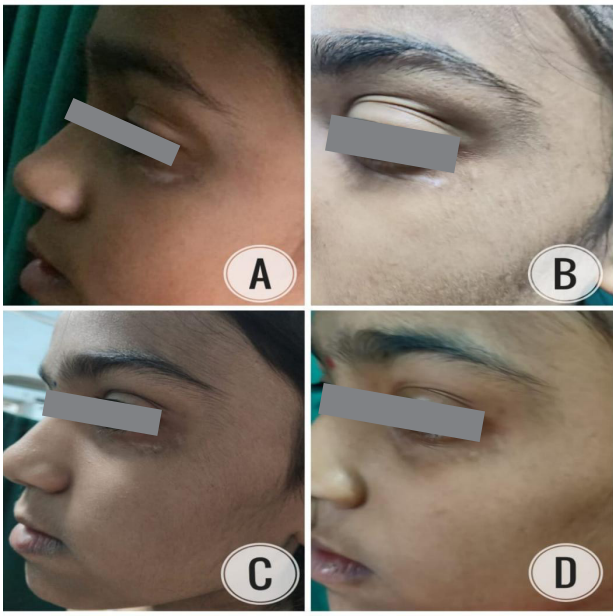


Figure 3. Spontaneous resolution of vitiligo in the left infraorbital area in monthly visits



Discussion

Halo nevi with vitiligo is well described,[5] but halo formation around congenital nevi is much less common.[6] It has been thought that similar autoimmune mechanisms, in which cytotoxic T-lymphocytes and antibodies to melanocytes (specifically IgM) cause depigmentation of the affected skin, cause vitiligo and halo nevi.[6,7] CMN with halo or vitiligo needs to be monitored clinically. The natural history of the lesion varies, because the CMN may remain

stable or undergo complete regression.[8] The risk of malignant transformation of CMN is reported to be between 1% and 5%, depending on size.[10] Surgical excision of CMN is indicated if the lesion is significantly irregular or its appearance is unstable. The resolution of vitiligo after excision is not an expected outcome, with only one prior report of excision of halo CMN with subsequent re-pigmentation of vitiligo.

In this case, excision was indicated based on the request of the patient's parents. To the best of our knowledge, there are only three prior reports of excision of halo CMN with subsequent re-pigmentation of vitiligo[8,9] in the literature. The mechanism is not quite clear. The theory of autoimmune mechanism of vitiligo and halo formation assumed that the removal of the nevus (potent "antigen") resulted in downregulation of melanocytic antibodies, leading to gradual re-pigmentation of the patient's vitiligo without further therapy. According to prior reports, re-pigmentation of the halo area often takes place over months or years, however, it does not always occur. Workman et al reported an incredibly similar case to ours, but they observed reoccurrence of depigmentation around the buttock scar 18 months after surgery. The reported reoccurrence was thought to be due to undetected residual melanocytes or antigen-presenting cells outside the margin of resection.[10]

Conclusion

In our case the rapid recovery could be due to the small size of nevus and vitiliginous area. The outcome was promising. It suggests that when antigens are removed and antibodies are cleaned out of the circulation, vitiligo may be resolved. Removing the inciting agent may be a promising way to control vitiligo.

Conflict of Interest Declaration

The authors have no conflict of interest.

Acknowledgement

Nil

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CASE REPORT

A Report of Staphylococcus Scalded Skin Syndrome in Adult

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Summary
Staphylococcal scalded skin syndrome (SSSS) is typically a clinical diagnosis,[1] affecting primarily neonates and children. It is characterised by a diffuse skin disorder with tenderness, erythema, large wrinkled superficial blistering, and desquamation caused by the hematogenous dissemination of exotoxin-producing strains of staphylococcus aureus to the skin.[4,10] Hospital admission is required for intravenous anti-staphylococcal antibiotic therapy and supportive care.

The rarity of SSSS in adults is best explained by the presence of exotoxins neutralizing antibodies and renal elimination of the toxins.[2] Two major risk factors are kidney failure and immunosuppression. Therefore, SSSS in adults warrants thorough evaluation.[3] Mortality is also greater than 60% in adults, attributed to predisposing comorbid conditions.[1,4]

One of the mimickers of SSSS is toxic epidermal necrolysis (TEN). Here, we report a successful treatment of SSSS in an adult with recreational drug abuse and incidental liver cirrhosis possibly secondary to hepatitis C viral infection, after careful exclusion of TEN.

Key Words: *Staphylococcal scalded skin syndrome, Staphylococcus aureus, Toxic epidermal necrolysis, Immunodeficiency, Penicillin*

Introduction
SSSS commonly spread from a nidus of Staphylococcus aureus infection, with exfoliative toxins A and B cleaving desmoglein-1, leading to epidermal granular layer separation. These toxins are secreted by some 5% of Staphylococcus aureus infection and species.[3,4,8,9] Currently, the overall prevalence of SSSS in adults is approximately 1 case per 1 million adults and increasing incidence has been reported worldwide.[5] The true incidence is also possibly underestimated in Asia, where Staphylococcus aureus is an important nosocomial pathogen for developing countries[14].

Adult SSSS is frequently identified in

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individuals who have renal insufficiency and primary inherited defects in the immune system or secondary immunodeficiencies; heroin addiction, HIV, malnutrition with chronic alcohol abuse, glucocorticoids, immunomodulator drugs, malignancy, and 'immuno-paralysis' during severe sepsis.[7,12-13]

Adult SSSS is commonly misdiagnosed as toxic epidermal necrolysis (TEN).[11] Clinical presentation is as in children with striking skin tenderness, pathognomic Nikolsky sign, and typical mucous membranes sparing mark their distinction, usually. Majority of adult cases are complicated with bacteremia, a result of increased severity and the underlying comorbid conditions.[3] The poor prognostic factors are sepsis, electrolyte imbalance, and dehydration.[1,4]

Case Report

A 50-year-old gentleman an electrical labourer, presented with abrupt onset of fever accompanied by the eruption of tiny vesicles over the face that rapidly devolved into bullae with frank pus and peri-oral 'honey-crusted' erosions over the span of 2 days that subsequently became generalised. The flaccid bullae had accentuated epidermal detachment, exposing extremely tender, erythematous raw areas over flexural and decubitus areas. No enanthema was observed.

He reported dysuria and lower back pain 5 days prior and had taken diclofenac sodium (Olfen™) bought over the counter. There were no history of respiratory symptoms, no burn or trauma, and no topical application to the skin.

His past medical history was significant for chronic mechanical lower back pain, receiving regular short courses of piroxicam (Feixicam), dexamethasone (Dexasone), diclofenac (Voren) almost weekly for the past 3 years. His social history recorded active recreational drug use (heroin, morphine), last taken 2 days prior. There was no family history of any blistering skin diseases.

Vital signs on admission recorded blood pressure 100/66 mmHg, heart rate 100 bpm and temperature 36°C. Physical examination revealed skin lesions covering approximately 30% of the body surface area and Nikolsky sign was positive.

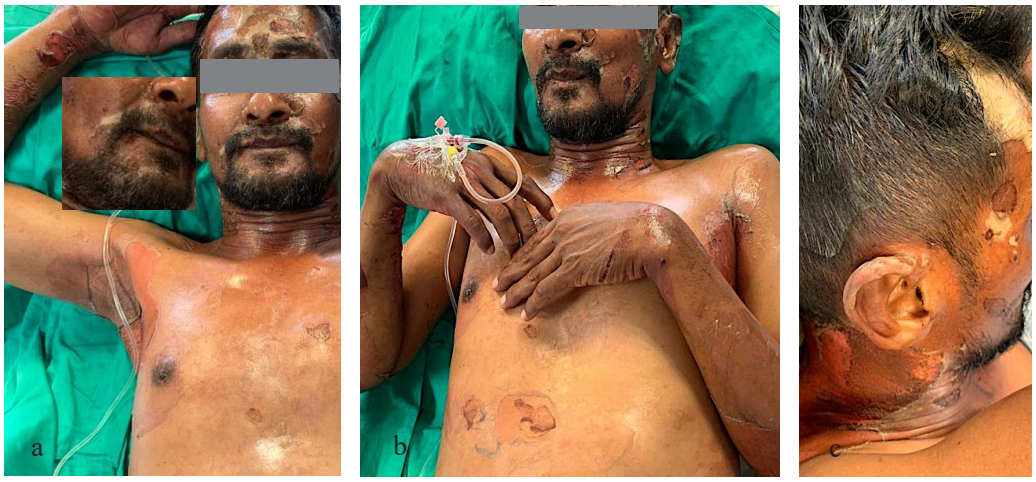
Urinalysis revealed trace leukocyte, negative nitrite, protein 1+ and erythrocyte 3+. Laboratory evaluations showed leukocytosis with left-shifted neutrophils, serum blood urea nitrogen 21.6 mmol/L, serum creatinine 190 micromol/L, serum aspartate aminotransferase 323, serum alanine aminotransferase 88, serum creatinine kinase 417 U/L, C-reactive protein 318 mg/L. Electrolytes were within normal limits. Chest X-ray had heterogeneous opacities over the left lung fields.

At that juncture, the dilemma was on whether this patient had SSSS or drug-induced TEN. However, given the overall clinical picture of urinary tract infection (UTI), pneumonia and sepsis with the lack of mucosal involvement, drug-induced TEN was less favoured. He was diagnosed with SSSS, admitted to the high dependency unit, and intravenous cloxacillin was administered with supportive care.

Microbiologic culture from forehead bullae (pus aspirate) and peripheral blood sent grew methicillin-susceptible *Staphylococcus aureus* (MSSA), resistant to penicillin G. No vegetation was found on echocardiogram. Sputum culture was not available. We had ordered infectious disease screening which was reactive for Hepatitis C Antigen. Ultrasound abdomen revealed multiple hyperechoic liver lesions in the background of liver cirrhosis and features of early bilateral renal parenchymal disease.

These were consistent with the diagnosis of disseminated *Staphylococcus aureus* bacteremia with SSSS. We did not perform staphylococcus aureus phage-typing, as this is not routinely available in our hospital laboratory and a skin biopsy was also unnecessary.

Figure 1 a & b. Superficial pus-filled blisters over face with shallow erosions over the axilla and inner forearm. Inset showed perioral honey crusted lesion. Mucosal surfaces spared. No purpuric macules or targetoid lesions. **c.** Wrinkled superficial blistering extended to nape.



He received intravenous cloxacillin 2 gram 6 hourly and his renal function improved with hydration. He was also given morphine infusion for pain control, emollients and non-adhesive dressings for thermoregulation and to enhance wound healing.

The lesions were superficial and healed without scaring barring areas with previous superimposed bacterial infection after a period of 12 days. No pathogens were isolated on repeated cultures.

Figure 2. Right back lesions healing, re-epithelialization with no significant scarring

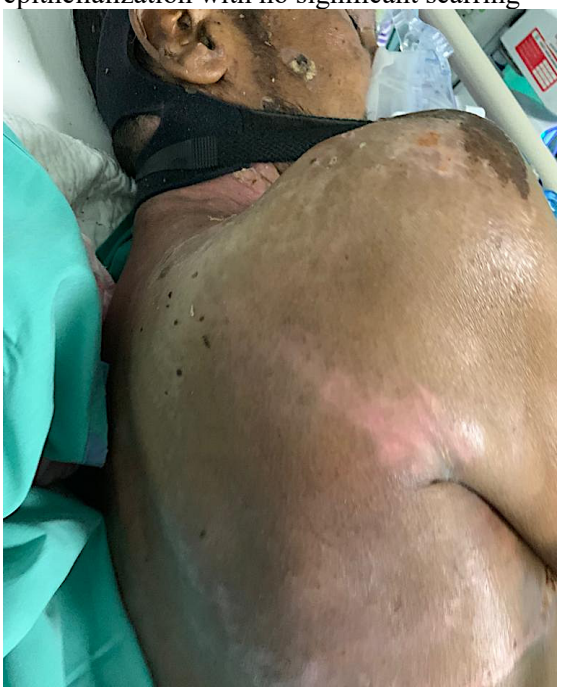


Figure 3. Sheet-like desquamation of the anterior chest wall skin and re-epithelization at axilla

Discussion

Although SSSS is also reported in healthy adults, there clearly appear to be undisputed factors that influence the susceptibility of adult individuals to SSSS. Our patient had recreational drug use, chronic glucocorticoid use, incidental liver cirrhosis and lesions suggestive of hepatocellular carcinoma with possible underlying hepatitis C, which suggest an immunocompromised state. Steroid therapy also significantly increases bacterial burden by facilitating its growth.

He presented with typical features of SSSS in which diffuse tender, erythematous shallow erosions form ruptured flaccid bullae with flexural accentuation and most importantly, without enanthema, thus ruling out the possibility of TEN. Either pneumonia or UTI could be the primary source of infection. Toxins produced could be overwhelming and exceeded what his kidneys could cope with, given the baseline renal parenchymal disease and the severity of illness.

Management of SSSS differs from TEN as systemic glucocorticoid used for TEN is contraindicated irrespective oral or topical administration.[16] Prompt adequate parenteral semisynthetic penicillins are the choice of antimicrobial as *Staphylococcus aureus* strains isolated in SSSS are found to be penicillin-resistant and penicillinase-resistant.[15] Consideration for methicillin-resistant *Staphylococcus aureus* (MRSA) coverage should also be made in endemic areas in which Panton Valentine Leukocidin (PVL) toxin associated *Staphylococcus aureus* is also a particular concern due to its association with more severe infection.

Because the extent of body surface area involved was great, corresponding to severe burns (more than 20%), the supportive management towards the loss of the skin barrier function should be intensified. Patients should remain adequately hydrated and managed like major burn patients; emollients should be applied to eroded skin areas, and antiseptics deployed to impede secondary colonization. We used an antiseptic with broad-spectrum efficacy and most of all, well-tolerated without risk of systemic absorption. Warming blankets were also used to compensate for the change in core body temperature as we had to adhere to strict cool temperature standards in the high dependency unit. Alternating pressure air mattresses are preferred to the seemingly less efficient two-hourly repositioning. This also minimises the risk of mechanical trauma and sleep deprivation.[19]

It is also imperative that pain control in this extremely painful condition is not overlooked as this could potentially cause significant distress to the patients. The World Health Organization pain ladder is used as a guide for the prescription of analgesia and the preferred choice is opiates. The role of non-steroidal anti-inflammatories (NSAIDs) in the development of SSSS remains elusive. However, it should be omitted due to its potential detrimental effect on kidney function, which further complicates the disorder.

Skin lesions heal without significant scarring after prompt and adequate management confirming the diagnosis of SSSS. As desmoglein-1 is mainly expressed in the superficial upper layers of the epidermis, skin lesions usually heal within 14 days without scarring. Mucosal membranes which lack desmoglein-1 are thus spared.[15]

Conclusion

Clinicians should be aware of the clinical spectrum of adult SSSS which is a potentially endemic, life-threatening disorder. Early recognition requires a great deal of clinical finesse for prompt management of this high mortality disease entity. It appears that prudent effort is still required for the prevention and management of SSSS since its first description in 1972 and screening for immediate family members of the diagnosed patients as potential carriers of the ET- A and B producing strains of *Staphylococcus aureus* should be done to prevent outbreaks.

Conflict of Interest Declaration

The authors declare that there is no conflict of interest in this work.

Acknowledgement

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CASE REPORT

Successful Treatment of Recalcitrant Ungual Wart with Tuberculin Purified Protein Derivative Immunotherapy

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Summary
Despite a variety of therapeutic options that is available, treatment of warts remains challenging and rate of recurrence is high. Intralesional immunotherapy is an emerging therapy for warts. Tuberculin purified protein derivative (PPD) is one of the immunotherapeutic antigens used for the treatment of warts. Here we report a case of recalcitrant periungual wart successfully treated with tuberculin immunotherapy.

Key Words: *Immunotherapy; Tuberculin; Purified protein derivative; Periungual wart*

Introduction
Wart is a benign skin tumour caused by Human Papillomavirus.[1] It typically presents as well-circumscribed single or multiple papules with a hyperkeratotic surface.[1] Ungual wart is common and can be painful as it burrows deep and erode the underlying tuft of the distal phalanx. It can also cause fissures, which predisposes the nail to paronychia.[1]

Ungual warts can be difficult to treat. Previous literature has reported various therapies, including topical keratolytic, cryotherapy, electrocautery, or laser therapy.[1-2] However, the expected cure rate ranges from 60 – 70% only.[1] Furthermore, none of the treatments is free from side effects such as blisters, pigmentary changes, ulcers and onychodystrophy.[1-2]

Recurrences are common as warts may be partially visible around the nail. The remaining wart may extend underneath the nail plate, which makes it challenging to deliver effective treatment.[1] Prevalence of recurrence rate of ungual warts range from 6% to 100% in adults.[3] Total or partial nail avulsion may be employed

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to counter this problem. However, it is not the first-line treatment as there is a risk of destroying the nail bed, nail matrix or underlying bone.[1]

Immunotherapy is an emerging modality for the treatmentof ungual warts. It stimulates cell-mediated immunity, which results in wart clearance.[1-4] Here, we report a case of recalcitrant periungual wart, successfully treated with intralesional immunotherapy of tuberculin purified protein derivative (PPD).

Case Report

An 18-year-old immunocompetent male patient presented with a painful periungual growth of the left thumb for 2-years duration. He failed previous therapies, which were a partial nail avulsion and 10 sessions of cryotherapies. The cryotherapy involved liquid nitrogen spray, delivered at 10 -15 seconds with 2 freeze-thaw cycles. On examination, there was a 15 x 10 mm hyperkeratotic, dark brown plaque on the left thumbnail bed. Removal of the surface with a surgical blade revealed thrombosed capillaries. The surrounding nail was dystrophic. A diagnosis of ungual wart was made.

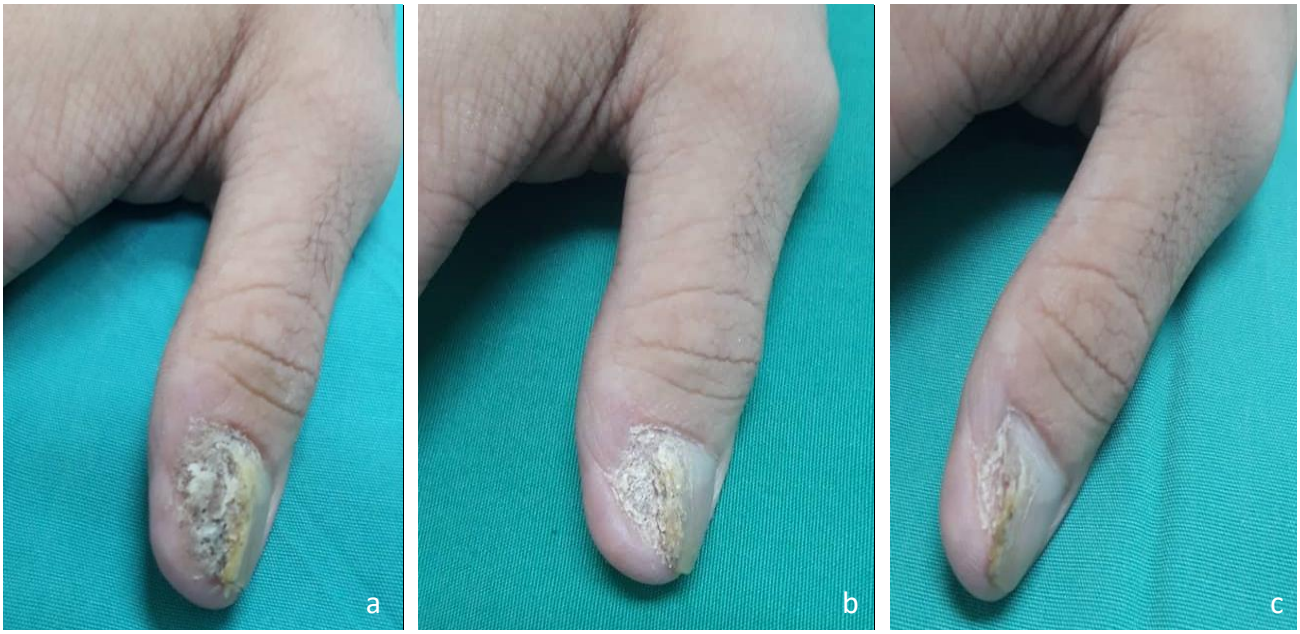
He received an intralesional injection of tuberculin PPD at a dose of 2.5 Tuberculin Unit (0.14ml). The injection was done using a 1 ml-syringe and 26-gauge needle.[5] Two weeks later, the wart's size reduced to almost 50% (8.57x5.22mm). Another tuberculin PPD of the same dose was administered. At 4-week follow up, the wart resolved entirely (***Figure 1***). He reported pain during injection, which resolved spontaneously three to four hours later. There was no erythema, blister or oedema observed at the injection site. There was also no fever, malaise, myalgia or arthralgia.

Discussion

Immunotherapy exerts its effects in treatment of wart by mounting a delayed-type of hypersensitivity reaction[4,6] which involved stimulation of Th1 cytokines.These cytokines then activates cytotoxic and natural killer cells to eradicate the HPV from the epidermis.[6]

Tuberculin is a purified protein derivative extracted from *Mycobacterium* tuberculosis cultures.[7] It is used widely for tuberculosis screening, especially in countries where the disease is endemic, such as in Malaysia. Tuberculin is used across all age groups, including infants, children and pregnant women.[7] As tuberculosis is endemic in our

Figure 1: (a) Pre-treatment; (b) Week 2 post-injection; (c) Week 4 post-injection



country, this therapy may be useful in our population as majority of patients are sensitized to it. We chose tuberculin because it is readily available in our centre.

Previous literature works have reported tuberculin's efficacy rate in treating warts, ranging from 29.4% to 93%.[8-13] A network meta-analysis reported that tuberculin and MMR were the most effective treatments for achieving complete primary and distant wart recovery compared to other immunotherapeutic agents, cryotherapy and imiquimod.[14] Abou-Taleb et al[15] compared intralesional (IL) vitamin D3 vs IL PPD in treatment of multiple warts, and significantly, higher clearance rates for all warts were observed with IL PPD compared to IL vitamin D. In the study by Wan Syazween et al[5], comparing efficacy and safety between Tuberculin PPD and cryotherapy, complete wart clearance rates were higher with immunotherapy than cryotherapy; also immunotherapy has a positive effect on distant, untreated warts.

The most common adverse events reported were local injection site reaction such as pain, erythema and oedema.[14] These side effects were often transient and resolved after a few days. Very rarely, immunotherapy may result in painful digit syndrome. La Pelusa et al and Perman et al reported distal pain, swelling, and purple hue of finger pos-immunotherapy. Both patients, however, recovered with complete resolution of the wart after the event with treatment with oral prednisolone.[17-18]

Conclusion

This case report highlights the efficacy of tuberculin immunotherapy on recalcitrant ungual wart. This treatment should be recommended for treatment of recalcitrant wart particularly in difficult to treat area such as subungal and periungal region. More studies are needed locally to treat recalcitrant warts using intralesional immunotherapy for patients who fail liquid nitrogen cryotherapy.

Conflict of Interest Declaration

The authors have no conflict of interest.

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CASE REPORT

Coevality of Secondary Syphilis with Condyloma Acuminata in a HIV reactive MSM: Rare Triple Sexually Transmitted Infections

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Summary

Secondary syphilis is a rare infectious sexually transmitted disease caused by *Treponema pallidum* in present era. It affects skin as well as other organs of the body. We hereby present a case of an adult male who presented with a one-month history of multiple brownish red maculopapular lesions all over the skin of the body involving the palms, soles, oral cavity and genitalia. His serology was positive for HIV, VDRL and TPHA with a low CD4 count. The patient was treated with three weekly doses of parenteral Benzathine penicillin G, antiretroviral therapy and podophyllin for condyloma acuminata to which he responded well.

Key Words: *Syphilis, Immunocompromised host, Condyloma acuminata, Chancre, Penicillin*

Introduction

Syphilis is a chronic infectious granulomatous disorder caused by *Treponema pallidum*, a spirochete. Transmission occurs chiefly via sexual contact and to some extent by blood transfusion of infected blood, via transplacental route or by accidental exposure to the infectious material. Micro or macroscopic trauma in the squamous or columnar epithelium may allow entry of the organism.[1] Syphilitic chancre on glans penis or rectal mucosa provides a portal of entry for the HIV virus. Once the organism enters the human body it invades all the organs of the body most notably skin.[2] The incidence of secondary syphilis has decreased nowadays, but with the emergence of HIV, syphilis may show an unpredictable course and can present with an unusual clinical picture.[3]

HIV-infected males having history of sex with men should undergo screening for syphilis. This might reduce the incidence of the disease in those who test positive and also its consequences.[4] Genital human papillomavirus (HPV) infection is the most common sexually transmitted disease and is second only to human immunodeficiency virus (HIV) infection in

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causing morbidity and mortality. Perianal HPV infection produces a wide range of disease presentations, from asymptomatic infection to benign genital warts to invasive cancer.[5] Patient herein had secondary syphilis with condyloma acuminata with HIV co-infection rarely reported until now.

Case Report

A 28-year-old unmarried male working as teaching faculty in college presented with multiple brownish red raised lesions all over the skin of the body including palms, soles, genitalia and oral cavity along with a growth in the perianal region since 1 month and a small ulcer over the glans penis since 1 month. He also complained of intermittent fever, redness of eyes, weight loss and loose motions for 1 month. On detailed and persistent enquiry, the patient gave history of unprotected sexual contact with his roommates while pursuing his education. He reported that most of the time he was acting as a passive receptive partner for peno-anal intercourse. There was no history of intravenous drug abuse or blood transfusion or heterosexual contact in past. The patient was of average built and had generalized painless firm lymphadenopathy involving suboccipital, postauricular, submandibular, upper jugular, supraclavicular and superficial inguinal group of lymph nodes. Systemic examination was within normal range.

Cutaneous examination revealed multiple brownish red papulonodular rashes all over the body involving palms and soles and external genitalia ranging in size from 0.5 to 2 cm (***Figure 1-4***). Superficial painless erosions were present over the hard palate. The Buschke-Ollendorff sign was positive. Genital examination showed a whitish pink growth covering the anal opening consistent with condyloma acuminata. A single superficial healing painless ulcer was present over the glans of the penis with an indurated base.

His serology was positive for HIV-1 and syphilis with VDRL (1:128) and TPHA reactivity. CSF analysis showed no biochemical or cellular abnormality. Total CD4 count by flow cytometry was in the low range 312 cells/mm3 (normal values: 500 cells/mm^3 to 1,200 cells/mm^3).

Figure 1. Multiple erythematous maculopapular secondary syphilides present over back

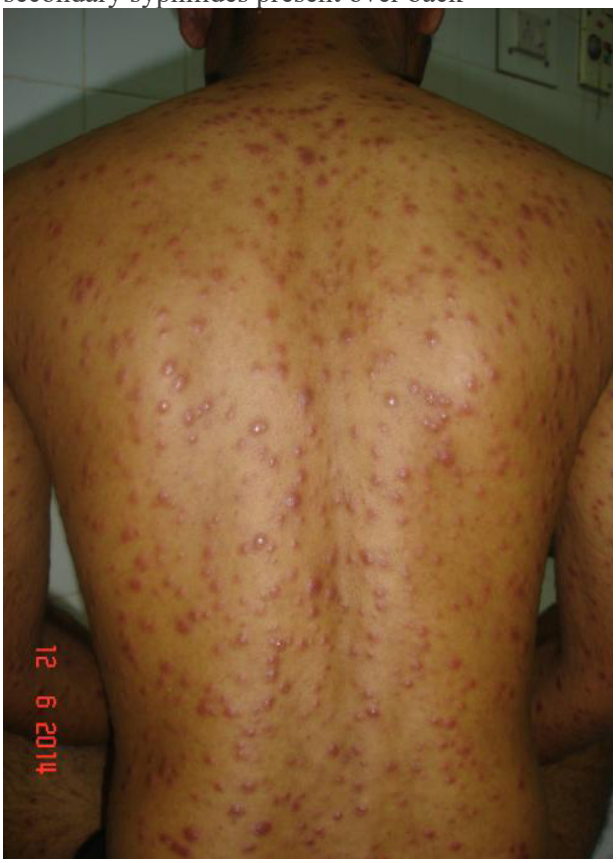


Figure 2. Multiple papular syphilides over both palms

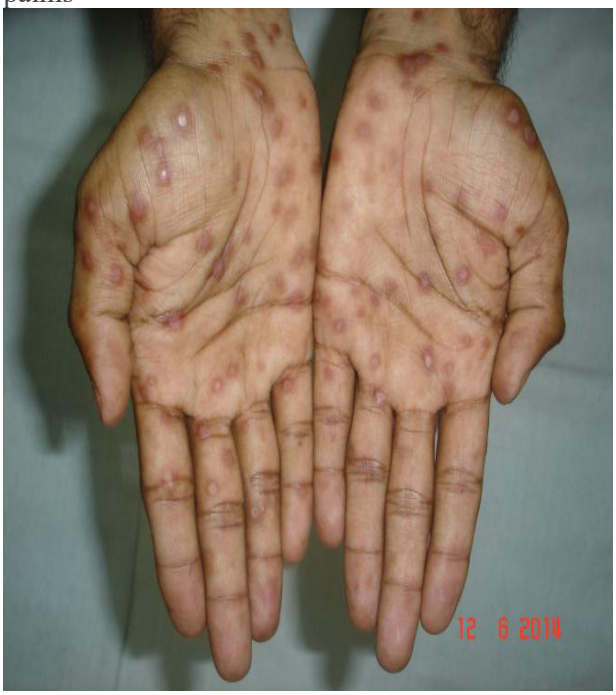
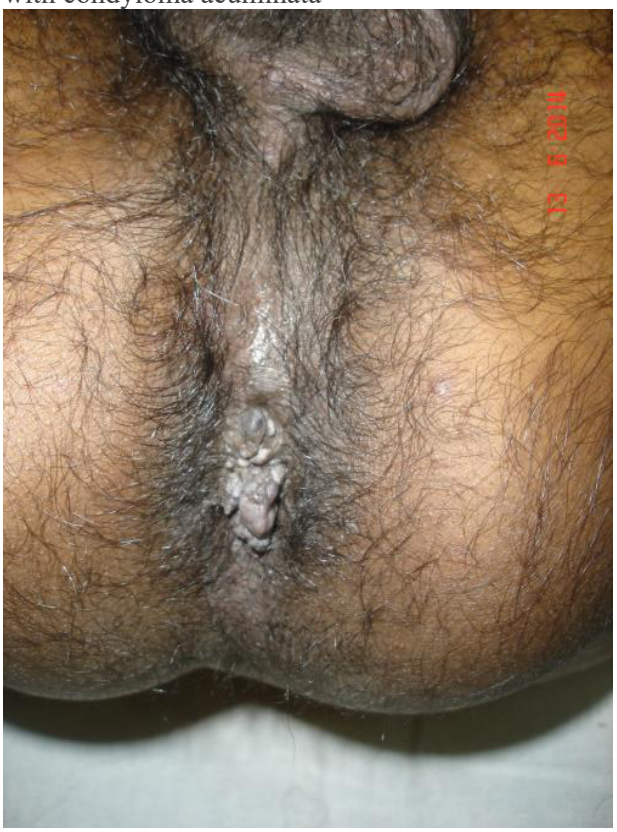


Figure 3. Superficial painless ulcer over glans penis with an indurated base

Figure 4. Warty growth over anal opening consistent with condyloma acuminata



The patient was treated with three doses of parenteral benzathine penicillin 2.4 million units a week apart. The VDRL titre was reduced to 1:32 after treatment in 1 month. In view of co-existing HIV infection and low CD4 count, the patient was started on highly active antiretroviral therapy (ZLN regime), however a week later the patient developed nevirapine-induced maculopapular drug rash. In view of his NVP induced skin rash, his HAART was changed to efavirenz-based regimen. Condyloma acuminata was treated with weekly application of podophyllin resin, which required 5 sittings, 1 week apart for complete clearance of lesions. Partner was called for evaluation but the partner did not come for evaluation and management.

Discussion

The patient reported in our case has coeval three sexually transmitted diseases simultaneously in the form of HIV infection, syphilis and genital condyloma acuminata. Syphilis with HIV infection is extremely rare in today's era due to rampant and injudicious use of antibiotics.[6] But it has been observed in various epidemiologic studies that the incidence of syphilis has increased in homosexual men especially among those who are infected with HIV. Increase in high risk behaviour and decrease in mortality due to HAART can be the cause of this increase.

Syphilis and HIV co-infection may lead to aggravation and early development of tertiary syphilis. It is believed that the sexually transmitted disease including syphilis which produces an ulcerative or warty lesion over the genital organs creates a portal of entry for the HIV virus due to ample availability of inflammatory cells. As a result of co-existing HIV infection, syphilis may rapidly progress to the tertiary stage in a short time period and despite an adequate treatment, relapses or treatment failure may occur. Patients with HIV and syphilis may show a poor response to anti-syphilitic treatment. Serofastness is not observed in patients of syphilis with HIV coinfection.[8]

HPV infection among MSM is highest in those coinfected with HIV.[9] Anal HPV infection, especially high-risk type, is independently associated with HIV acquisition. The mechanisms are not clear yet, but there is a biological plausibility that HPV infection leads to an active cell-mediated immune response through recruitment of macrophages and T

lymphocytes, which are HIV-susceptible cells and may facilitate HIV acquisition.[10] Anogenital disease in the HIV-positive population tends to be more aggressive, multifocal, rapidly progressive, and recalcitrant to standard therapies, compared with disease occurring in HIV-negative patients. HIV-positive patients, therefore, require aggressive screening, treatment, and follow-up.

Our case had coexistence of syphilis and HPV with HIV infection, which has not been reported until now. Also in spite of being immunocompromised our patient responded well to first line treatment for syphilis and condyloma acuminata as opposed to the dictum of lesions recalcitrant to standard therapies. In addition, our patient was a teacher in a rural where in school-based sexual health education and comprehensive approach to promoting sexual health among young people was also undertaken.

Conclusion

In spite of being literate and having awareness about harmful effects of unprotected sexual contact, still he continued with high-risk behavioral activity. Hence, we must rethink our sexual health awareness program.

Conflict of Interest Declaration

The authors have no conflict of interest.

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Nil

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