Volume 46 | Jun 2021 | ISSN: 1511-5356

Malaysian Journal of Dermatology

JURNAL DERMATOLOGI MALAYSIA

PERSATUAN DERMATOLOGI MALAYSIA | DERMATOLOGICAL SOCIETY OF MALAYSIA

Indexed in: **Western Pacific Research Index Medicus**

www.dermatology.org.my

Notice to Authors

The Malaysian Journal of Dermatology welcome manuscripts on all aspects of cutaneous medicine and surgery in the form of original articles, research papers, case reports and correspondence. Contributions are accepted for publication on condition that they are submitted exclusively to the Malaysian Journal of Dermatology. The Publisher and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the publisher and Editors, neither does the publication of advertisements constitute any endorsement by the publisher.

Manuscripts should be submitted via email to:
tanwooichiang@yahoo.com

Questions regarding the Malaysian Journal of Dermatology can be sent to:
tanwooichiang@yahoo.com

Contributions should be written for one of the following categories:

Case Report*
A report of 400-600 words, illustrated by no more than three illustrations. This category offers a means for rapid communication about a single subject.

Commentary*
An editorial 700-1200 words in length with approximately five references. The author may express his or her opinion without complete documentation.

Clinicopathological Challenge*
A photographic essay that includes both clinical and pathological photographs in color. The diagnosis and legends for the photographs should be listed after the references in the article. The article should be no more than 2-3 pages in length.

Correspondence*
Letters to the editor and short notes. Contributions should not exceed 600 words, 2 figures, and 10 references.

Dermatological Surgery
An article relating to the surgical aspects of treatment. Article types may include Review, Report or Case Report Format.

Original Article
An original article including, whenever possible, an Introduction, Materials and Methods, Results, Discussion, Conclusion and References. A Structured Abstract of not more than 250 words must be included. It should consist of four paragraphs, labelled Background, Methods, Results and Conclusion. It should describe the problem studies, how the study was performed, the main results, and what the author(s) concluded from the results.

Review
By invitation only. A major didactic article that clarifies and summarizes the existing knowledge in a particular field. It should not be an exhaustive review of the literature, and references should not exceed 100 in number. Tables, diagrams, and selected figures are often helpful. The length is left to the judgment of the author, although it generally should not exceed 5000 words. Topics may include updates in clinically relevant basic science and cutaneous biology.

*No abstract required

Manuscripts should include a title page bearing the title of the paper, the author(s)' name(s), degrees, and affiliation(s), the category of the article, the number of figures and tables, and three key words for indexing purposes. The name and full postal address (including a street address), phone and fax numbers and an email address of the corresponding author who will be responsible for reading the proofs must also be given on the title page. The author(s) must also declare any affiliation or significant financial involvement in any organizations or entity with a direct financial interest in the subject matter or materials discussed in the manuscript on this page.

All measurements should be according to the metric system. If confusion could result, please include other measurement systems in parentheses.

Refer to patients by number or letters; names or initials should not be used.

References
References must be listed in the order in which they appear in the manuscript. References from journals should include: (1) name(s) followed by the initials of the author(s), up to six authors: if more than six authors, include the first six authors followed by et al.; (2) title of paper; (3) title of the journal as abbreviated in the Index Medicus; (4) year of publication; (5) volume number; (6) first and final page numbers of the article.

For example:
Ambrose D, Gangaram HB, Hussein SH. Sporotrichosis: A Hospital Kuala Lumpur experience. Malaysian J Dermatol 2006;19:52-5.

References to books should include: (1) author(s) or editor(s); (2) chapter (if any) book titles; (3) edition, volume, etc.; (4) place of publication; (5) publisher; (6) year; (7) page(s) referred to.

For example:
Foong HBB. Transcontinental Dermatology: Virtual Grand Rounds. In: Wootton R and Oakley A, editors. Teledermatology. London. Royal Society of Medicine 2002. p.127-34.

The author is responsible for the accuracy and completeness of all references; incomplete references may result in a delay to publication.

Tables should be typed, double-spaced with a heading, each on a separate sheet, and should only include essential information. Drawings, graphs, and formulas should be submitted on separate pages.

Send illustrations as tiff or jpeg files. In the case of photomicrographs, the stain type and original magnification should be stated. Each figure should bear a reference number corresponding to a similar number in the text.

To minimise the publication time of your manuscript it is important that all electronic artwork is supplied to the Editorial Office in the correct format and resolution.

Disclaimer
The Publisher and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the publisher and Editors, neither does the publication of advertisements constitute any endorsement by the publisher and Editors of the products advertised.

MALAYSIAN JOURNAL OF DERMATOLOGY

REVIEW ARTICLE

2 **Psoriasis Patients with Human Immunodeficiency Virus Infection: Data from the Malaysian Psoriasis Registry**
Teh YC, Robinson S, Tan WC, Kwan ZL, Tang MM

11 **Prevalence and Types of Mucocutaneous Disorders, Their Correlation to CD4 Count and Their Impact on Quality of Life in Adults with HIV Infection**
Lim YT, Tey KE, Choon SE

21 **Prevalence of Atopic Dermatitis Among Primary School Children and Its Impact on Quality of Life in Kuching, Sarawak**
Lee SE, Foo SY, Badaruddin NSF, Bujang MA, Muniandy P

31 **The Association of Skin and Nasal Colonisations of Staphylococcus aureus in Children with Atopic Dermatitis with Disease Severity and Its Impact on Quality of Life**
Lim JH, Mohamad AR, Tey KE

38 **A 5-years Retrospective Study on Narrowband Ultraviolet B (NBUVB) Phototherapy Utilisation Experience in A Tertiary Hospital in East Malaysia**
Teo HG, Kiing JW, Muniandy P

CASE REPORT

43 **Dermoscopy of Dilated Pore of Winer**
Basavapura Madegowda S, Somaiah A Savitha

46 **Calcinosis Cutis Secondary to Trauma in a Patient with Systemic Lupus Erythematosus and Ovarian Cancer**
Mashor M, Azizan NZ, Lee BR

49 **Quinacrine: An Effective Addition to the Treatment of Refractory Cutaneous Lupus Erythematosus**
Ding HJ, Ong SG

52 **Cutaneous Serratia Marcescens Infection - A Rare Case Report**
Yew KM, Ong SSS, Ismail M, Tang JJ

55 **Symmetrical Flexural and Intertriginous Exanthema: A Rare Manifestation Associated with COVID-19 Infection**
Goh JY, Chin HH, Chin PW, Zaid M

ACKNOWLEDGEMENT

Editor-in-Chief
Assoc Prof Dr Tan Wooi Chiang
MRCP, Adv M Derm
Georgetown, Penang

Co-Editor
Dr Tang Min Moon
MRCP, Adv M Derm
Wilayah Persekutuan Kuala Lumpur

Founding Editor
Dr Steven Chow Kim Weng
FRCP
Wilayah Persekutuan Kuala Lumpur

Editorial Office
Department of Dermatology (105)
Hospital Pulau Pinang
Jalan Residensi,
10990 Georgetown, Penang

Editorial Board
Dr Henry Foong Boon Bee *FRCP, FAMM*
Ipoh, Perak

Dr Agnes Heng Yoke Hui *MRCP*
Ipoh, Perak

Dr Chan Lee Chin *MMed*
Georgetown, Penang

Dr Chang Choong Chor *MRCP, Adv M Derm*
Wilayah Persekutuan Kuala Lumpur

Dr Norashikin Shamsudin *FRCP, Adv M Derm*
Serdang, Selangor

Assoc Prof Dr Adawiyah Jamil *MMed, Adv M Derm*
Wilayah Persekutuan Kuala Lumpur

Assoc Prof Dr Felix Yap Boon Bin *MRCP, Adv M Derm*
Wilayah Persekutuan Kuala Lumpur

Dr Tang Jyh Jong *MRCP, Adv M Derm*
Ipoh, Perak

Assoc Prof Dr Tarita Taib *MMed, Adv M Derm*
Selayang, Selangor

Dr Ch'ng Chin Chwen *MRCP, Adv M Derm*
Wilayah Persekutuan Kuala Lumpur

Dermatological Society of Malaysia | *Persatuan Dermatologi Malaysia*

Executive Committee
Dato Dr Noor Zalmy Azizan, Adv M Derm - *President*
Dr Sabeera Begum, MMed - *Vice President*
Dr Tan Wooi Chiang, Adv M Derm - *Secretary*
Dr Sharifah Rosniza Syed Nong Chek, Adv M Derm - *Treasurer*
Dr Chan Lee Chin, MMed - *Past President*
Dr Tang Jyh Jong, Adv M Derm - *Committee Member*
Dr Peter Ch'ng Wee Beng, Adv M Derm - *Committee Member*
Dr Teoh Tze Yuen, Adv M Derm - *Committee Member*
Dr Nazirin Ariffin - *Committee Member*

Dermatological Society of Malaysia
Medical Academics of Malaysia, Unit 1.6, Level 1, Enterprise 3B, Technology Park Malaysia, Jalan Innovasi 1, Lebuhraya Puchong-Sg Besi, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

MALAYSIAN J OF DERMATOLOGY
ISSN 1511-5356

Published by Dermatological Society of Malaysia twice a year from year 2009 (June and December issues)

Printed by Vanda Dynamic Enterprise
723E, 1st Floor, Vanda Business Park, Jalan Sungai Dua, 11700 Penang
Tel : 04-6584515 / 04-6578515 Fax : 04-6584505

®2021 Persatuan Dermatologi Malaysia. All rights reserved.
No part of this journal can be reproduced without the written permission from editorial board.

ORIGINAL ARTICLE

Psoriasis Patients with Human Immunodeficiency Virus Infection: Data from the Malaysian Psoriasis Registry

Yeon Chiat Teh[1], *MRCP*, Suganthy Robinson[1], *AdvMDerm*, Wooi Chiang Tan[2], *AdvMDerm*, Zhenli Kwan[3], *AdvMDerm*, Min Moon Tang[1], *AdvMDerm*

[1]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[2]Department of Dermatology, Hospital Pulau Pinang, Penang, Malaysia
[3]Division of Dermatology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Background

Psoriasis can be a presenting feature of human immunodeficiency virus (HIV) infection. Our objective was to determine the frequency of HIV infection among patients with psoriasis and to describe the clinical features, treatment and quality of life in this population.

Methods

This is a multi-centre retrospective cross-sectional study of psoriasis patients who were registered to the Malaysian Psoriasis Registry (MPR) from January 2007 to December 2018.

Results

Of a total of 21,735 patients registered, 105 (0.5%) had HIV infection. Among these patients, 90 (85.0%) were male, mean age was 40.90 ± 10.85 years, and plaque psoriasis was the most frequently encountered presentation (85.7%). Significantly more patients with HIV had severe psoriasis (61.3% vs 49.9%, p=0.043), face and neck (62.7% vs 51.4%, p=0.022) involvement, and nail disease (69.9% vs 56.2%, p=0.005) compared to those without HIV. Only n patients (8.7%) had psoriatic arthropathy, and only 9 (8.8%) received systemic therapy, namely acitretin and methotrexate. None received a biologic, and only one patient was treated with narrowband ultraviolet-B therapy. The mean Dermatology Life Quality Index (DLQI) score at enrolment was 10.98 ± 7.07 for the HIV cohort compared to 8.68 ± 6.60 for the non-HIV cohort (t=2.190, p=0.029). More patients with HIV reported a DLQI score >10 compared to those without HIV (51.5% vs 40.2%, p=0.021).

Conclusion

The frequency of HIV infection among patients with psoriasis in the MPR was 0.5%. Patients with HIV had more severe disease, more nail, face and neck involvement, and greater impairment of quality of life. Treatment of HIV patients with psoriasis remains conservative in Malaysia.

Key words: *Psoriasis, Human immunodeficiency virus, Acquired immunodeficiency syndrome*

Corresponding Author
Dr Teh Yeon Chiat
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586 Kuala Lumpur, Malaysia.
Email: tehyeonchiat@yahoo.com

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disease, in which the aetiopathogenesis is unclear.[1,2] It can be a presenting feature of human immunodeficiency virus (HIV) infection and disease severity may reflect the state of immune dysfunction.[3] Psoriasis in HIV patients is often more severe and refractory to treatment.[4]

Prevalence of psoriasis among HIV patients ranges from 2-3% in the western cohort,[2,5] similar to the prevalence in the general population.[4,6] Although there are many epidemiological studies on psoriasis, data on HIV-infected psoriasis patients are lacking. The aim of this study was to determine the prevalence of HIV infection among patients with psoriasis in Malaysia, and to describe the clinical features, treatment and quality of life in this population.

Materials and Methods

This was a multicentre retrospective cross-sectional study of psoriasis patients who were entered into to the Malaysian Psoriasis Registry (MPR) from January 2007 to December 2018. Psoriasis patients had to have two positive HIV antibody tests to be diagnosed as having HIV infection. The MPR is a prospective systematic collection of data of psoriasis patients in Malaysia from 32 public hospitals and 2 private hospitals. All psoriasis patients were enrolled at their first visit and those on systemic treatment or phototherapy were seen every 6 months thereafter f. This study was approved by the Malaysian Medical Research and Ethics Committee (MREC) number NMRR-20-802-53706.

Body surface area (BSA) involvement was used to assess disease severity, whereas the Dermatology Life Quality Index (DLQI) was used to assess the impact of psoriasis on quality of life.[7] Severe impact of psoriasis on health-related quality of life (HRQoL) is defined as a DLQI score of more than 10.[8] Body surface area (BSA) involvement of more than 10% with or without a DLQI score of more than 10 is also considered severe psoriasis.[8]

Descriptive analyses were performed for characterizing sociodemographic characteristics, clinical pattern, and treatment modalities of the patients. Data were tabulated and analysed using IBM® Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. Descriptive data were presented as numbers and percentages for categorical variables. Mean with standard deviation (SD) was used for continuous data. Pearson Chi-square test and Fisher's exact test were used to analyse categorical data where applicable. Comparison of means was performed using independent sample T-test. A p value of <0.05 was considered as statistically significant.

Results

There were 105 patients (0.5%) reported to be infected with HIV among a total 21,735 psoriasis patients registered in the MPR between January 2007 and December 2018. Sociodemographic characteristics are presented in Table 1. There was a significantly higher proportion of males in the HIV group compared to those not infected with HIV (86.7% vs 55.3%, $p<0.001$). The mean age for HIV-infected patients was 40.95 ± 10.93 years. Overall, 11.4% of HIV-infected patients had a positive family history of psoriasis, compared to 22.4% in the non-HIV infected group ($p=0.004$). About twenty percent of the HIV-infected psoriasis patients were obese, with a body mass index (BMI) ≥ 25mg/kg^2 (Table 2). Other comorbidities associated with the HIV-infected cohort were dyslipidaemia (13.1%), hypertension (7.8%), diabetes mellitus (4.9%) and ischemic heart disease (2.0%). Six patients had co-infection with either hepatitis B or hepatitis C.

Table 1. Demographic characteristics of study population

Demographic Characteristic		HIV n=105 (%)	Non-HIV n=21630	*p*-value
Age (years)	Mean (SD)	40.95 (10.93)	41.80 (17.48)	*p*=0.621
	Min, Max	19, 82	1, 92	
Gender	Male	91 (86.7)	11967 (55.3)	***p*<0.001**
	Female	14 (13.3)	9663 (44.7)	
*Ethnicity	Malay	39 (37.5)	11762 (54.4)	***p*<0.001**
	Chinese	42 (40.4)	4112 (19.0)	***p*<0.001**
	Indian	13 (12.5)	3537 (16.4)	*p*=0.288
	Others	10 (9.6)	2210 (10.2)	*p*=0.840
Family history of psoriasis		12 (11.4)	4841 (22.4)	***p*=0.004**
Comorbidities	Dyslipidaemia	13 (13.1)	3401 (15.7)	*p*=0.584
	Hypertension	8 (7.8)	4979 (23.0)	***p*<0.05**
	Diabetes mellitus	5 (4.9)	3323 (16.4)	***p*<0.05**
	Ischemic heart disease	2 (2.0)	1015 (4.7)	*p*=0.345
	Cerebrovascular disease	0 (0)	311(1.4)	*p*=0.401

*HIV, human immunodeficiency virus; SD, standard deviation; *HIV n=104, Non-HIV n=21621*

Table 2. Clinical characteristics of study population

Clinical Characteristic		HIV n=98 (%)	Non-HIV n=20355 (%)	*p*-value
Type of psoriasis	Plaque	84 (85.7)	18905 (92.9)	***p*=0.002**
	Guttate	9 (9.2)	729 (3.5)	***p*=0.003**
	Erythrodermic	4 (4.1)	384 (1.9)	*p*=0.116
	Palmoplantar non-pustular	1 (1.0)	85 (0.4)	*p*=0.339
	Inverse	0 (0)	104 (0.5)	*p*=1.000
	Generalised pustular	0 (0)	92 (0.5)	*p*=1.000
	Localised pustular	0 (0)	56 (0.3)	*p*=1.000
[#]Body mass index (BMI) (kg/m2)	<18.5	21 (22.1)	1358 (7.2)	***p*<0.001**
	18.5-22.9	38 (40.0)	4129 (21.9)	***p*<0.001**
	23-24.9	17 (17.9)	2730 (14.5)	*p*=0.348
	>25	19 (20.0)	10616 (56.4)	***p*<0.001**
[b]Body surface area (BSA) (%)	<5	30 (36.6)	7392 (44.8)	*p*=0.134
	5-10	19 (23.2)	5173 (31.4)	*p*=0.110
	11-90	28 (34.1)	3498 (21.2)	***p*=0.004**
	>90	5 (6.1)	422 (2.6)	***p*=0.044**
[c]Face and neck involvement		64 (62.7)	10439 (51.4)	***p*=0.022**
[d]Nail disease		72 (69.9)	11797 (56.2)	***p*=0.005**
[e]Scalp		87 (85.3)	16674 (81.2)	*p*=0.293
[f]Psoriatic arthropathy		9 (8.7)	2747 (13.1)	*p*=0.180
[g]DLQI >10		53 (51.5)	7909 (40.2)	***p*=0.021**
[h]Severe psoriasis (BSA >10 and/ or DLQI >10)		49 (61.3)	7553 (49.9)	***p*=0.043**

HIV, human immunodeficiency virus; BMI, body mass index; BSA, body surface area; DLQI, dermatology life quality index; [#]HIV n=95, non-HIV n=18833; [b]HIV n=82, non-HIV n=16485; [c]HIV n=102, non-HIV n=20301; [d]HIV n=103, non-HIV n=20988; [e]HIV n=102, non-HIV n=20529; [f]HIV n=104, non-HIV n=20973; [g]HIV n=103, non-HIV n=19651; [h]HIV n=80, non-HIV n=15128

The most common type of psoriasis in our HIV cohort was plaque psoriasis (85.7%), followed by guttate psoriasis (9.2%), erythrodermic psoriasis (4.1%) and non-pustular palmoplantar psoriasis (1.0%), as shown in Table 2. Non-plaque forms of psoriasis were significantly more frequently encountered in HIV-infected psoriasis patients (p=0.002), with guttate and erythrodermic psoriasis reported at a higher rate among those with HIV infection. Scalp involvement in the HIV cohort (85.3%) was slightly higher compared to the non-HIV group (81.2%). HIV-infected psoriasis patients reported a higher rate of face and neck involvement (62.7% vs 51.4%) (*p*=0.022) and nail disease (69.9% vs 56.2%) (*p*=0.005) compared to non-HIV psoriasis patients. Psoriatic arthropathy was observed in 8.7% of the HIV cohort, less frequently than in the non-HIV-infected group (13.1%). Oligo-mono-arthropathy was the most common type of psoriatic arthropathy in both groups, followed by distal hand joint involvement and symmetrical rheumatoid-like polyarthropathy.

In terms of disease severity, 40.2% of HIV-infected psoriasis patients had severe disease with a BSA of >10%, compared to 23.8% in the non-HIV infected group (*p*=0.004). The rate of erythroderma was observed to be significantly higher in the HIV cohort (6.1% vs 2.6%, *p*=0.044).

Fifty-three (51.5%) of the HIV-infected psoriasis patients had a DLQI score of more than 10 at enrolment versus 40.2% in the non-HIV group. The mean DLQI score for the HIV cohort was 11.58 ± 7.02, which was significantly higher compared to the non-HIV psoriasis group (9.61 ± 6.75 *p*=0.003). The domains that displayed a significant difference between the two groups were personal relationship (70.0% vs 56.4%, *p*=0.022) and work and school (65.8% vs 46.1%, *p*<0.001) (Table 3). In aggregate, 61.3% of HIV-infected psoriasis patients had severe psoriasis defined by a BSA of more than 10% and/ or a DLQI of more than 10, compared to 49.9% in the non-HIV infected cohort (*p*=0.043).

Similar to the non-HIV cohort, the majority of the HIV patients were prescribed topical treatment with topical corticosteroids and emollients as the mainstays of treatment (Table 4).

Only 9 patients (8.8%) in the HIV-infected category received systemic therapy (7 (6.9%) were prescribed acitretin and 2 (2%) were prescribed methotrexate), compared to 14.3% of the non-HIV-infected psoriasis patients. Only one HIV-infected psoriasis patient underwent narrow band ultra-violet B (NBUVB) phototherapy treatment. None of the HIV-infected patients received a biologic treatment, whereas 0.4% of non-HIV patients were

treated with a biologic agent.

Table 3. Comparison of Dermatology Life Quality Index (DLQI) scores between patients with human immunodeficiency virus infection and those without

Domain	HIV (%)	Non-HIV (%)	*p*-value
[t]Physical symptoms and feeling	96.1	94.8	*p*=0.324
[v]Daily activities	83.3	76.0	*p*=0.402
[w]Leisure	83.3	75.2	*p*=0.318
[x]Work and school	65.8	46.1	***p*<0.001**
[y]Personal relationship	70.0	56.4	***p*=0.022**
[z]Treatment	70.7	60.8	*p*=0.149

HIV, human immunodeficiency virus; DLQI, dermatology life quality index; [t]HIV n=102, non-HIV n=19583; [v]HIV n=96, non-HIV n=18725; [w]HIV n=90, non-HIV n=17122; [x]HIV n=73, non-HIV n=12879; [y]HIV n=70, non-HIV n=14580, [z]HIV n=92, non-HIV n=18590

Table 4. Types of treatment for psoriasis in study population

Treatment Option		HIV n=104 (%)	Non-HIV n=20792 (%)	*p*-value
Treatment	Topical	96 (92.3)	19733 (94.9)	*p*=0.23
	[α]Phototherapy	1 (1.0)	550 (2.7)	*p*=0.282
	[β]Systemic therapy	9 (8.8)	2949 (14.3)	*p*=0.116
	Acitretin	7 (6.9)	574 (2.8)	***p*=0.013**
	Methotrexate	2 (2.0)	2289 (11.1)	***p*=0.003**
	Systemic corticosteroids	0	179 (0.9)	*p*=0.345
	Cyclosporin	0	144 (0.7)	*p*=0.398
	Biologics	0	78 (0.4)	*p*=0.534
	Hydroxyurea	0	23(0.1)	*p*=0.736

HIV, human immunodeficiency virus; [α]HIV n=103, non-HIV n=20461; [β]HIV n=102, non-HIV n=20461

Discussion

The reported prevalence of psoriasis varies in different regions of the world based on different epidemiological studies.[4,6,9,10] In Western countries, it is estimated to affect 2-4% of the general population[1,11] and the prevalence of psoriasis among HIV patients ranges from 2-3%.[2,5,12] A literature search revealed limited studies on the prevalence of HIV in psoriasis patients. It had reported that 1.8% of psoriasis patients in Thailand were infected with HIV,[13] which is slightly higher than the 1.1% prevalence of HIV in the general population there.[14] It was estimated that there were 87,041 people living with HIV in Malaysia with a prevalence of 0.4%.[14] The frequency of HIV infection among individuals with psoriasis in our cohort (0.5%) was comparable to the prevalence of HIV in the general population of Malaysia.[14] The lower rate of HIV infection among psoriasis patients in the MPR (0.5%) compared to Thailand was possibly be due to voluntary notification, non-mandatory HIV testing among psoriasis patients or management of HIV patients with mild psoriasis by primary care doctors who are not registered with the registry. A French survey study revealed that currently health practitioners only screen psoriasis patients for HIV based on risk factors such as high-risk behaviour, clinical severity and assessment prior to systemic and biologic therapy.[15] An updated guideline on the timing to screen for HIV in psoriasis patients is needed to ensure HIV infection is detected early and managed accordingly.

The clinical manifestations of psoriasis observed in HIV-infected patients appear to be similar to those in non-HIV-infected persons in our cohort. Plaque psoriasis is the most common presentation in the HIV psoriasis population in Western countries.[16] However, psoriasis patients with HIV can present with multiple subtypes concurrently.[3,4,17] Several studies from the United States of America, the United Kingdom and South Africa reported that guttate, inverse and erythrodermic psoriasis occur with higher frequency in HIV-infected psoriasis patients.[3,4,16] Similar findings were also evident in our cohort, with the exception of inverse psoriasis as none was reported.

Interestingly, we observed a greater number in the HIV cohort having face and neck involvement. The literature revealed that sebo-psoriasis is a psoriasis variant associated with increased incidence in HIV infection.[17,18] Sebo-psoriasis represents a clinical overlap between seborrheic dermatitis and plaque psoriasis, affecting the flexural areas, scalp and retro- auricular region.[17,18] Lesions tend to be more greasy and less scaly compared to scalp psoriasis.[17] The MPR, however, does not capture this phenotypic variant of psoriasis. Hence, sebo-psoriasis may be labelled as flexural psoriasis or as psoriasis involving the face and neck. It is important to recognise sebo-psoriasis as a separate entity as it can occur in HIV patients with a normal CD4 count and/or those with a suppressed viral load. A high index of suspicion among patients presenting with prominent sebo-psoriasis is therefore paramount as it may act as an indicator of early HIV infection.[18]

As sebo-psoriasis is reported to respond well to topical or systemic antifungal treatment[18], could be overlooked easily.

Up to 50% of psoriasis patient have nail involvement[13,19] and lifetime incidence is up to 90%.[20] Common manifestations include onycholysis (69.6%) and pitting of the nails (62.6%).[13] It has been reported that 32% of HIV-infected psoriasis patients, have nail involvement[21], which may present in a similar manner to nail psoriasis in non-HIV infected patients (i.e. superficial pitting, distal and lateral onycholysis, subungual hyperkeratosis and onychodystrophy).[3,22] Interestingly, in our study, nail disease in the HIV cohort was found to be significantly more prevalent than in the non-HIV infected cohort. Nail changes in psoriasis are strongly associated with arthropathy, which affects 23-50% of HIV-positive psoriasis patients worldwide.[22,23] The prevalence of arthropathy is higher among HIV-infected patients, compared to the general psoriasis population(5.8% to 19%),[2,24,25] and it is associated with more severe types of joint disease.[2,23,25,26] Symmetrical polyarthropathy, enthesopathy and dactylitis represent the most frequently observed types of psoriatic arthropathy in HIV patients.[2,27,28] In contrast, our study revealed a significantly lower rate of arthropathy among patients in the HIV-infected group. The most common type of arthropathy described in our HIV cohort was oligo-arthritis.

Interestingly we did not observe any cases of either localized or generalized pustular psoriasis in our cohort. Pustular psoriasis may be associated with specific variants of the *IL36RN*, *AP1S3* and *CARD14* genes, resulting in different clinical manifestations and treatment response.[29] IL36, which is implicated in the pathogenesis of pustular psoriasis, has not been described in HIV infection.[30,33] Morar *et al.* observed a reactive arthritis-like syndrome in HIV-infected patients; these patients presented with keratoderma blenorrhagica with palmoplantar psoriasiform plaque.[3] Histology of skin lesions from these patients is identical to that seen in pustular psoriasis.[3] Mikhail et al reported successful use of etanercept to treat a case of von Zumbusch pustular psoriasis in a HIV patient on antiretroviral therapy (ART) with a CD4 count of 435/μL.[31]

Psoriasis has a detrimental effect on a person's quality of life comparable to other chronic illnesses.[32] To our knowledge, there are no other published data assessing DLQI among psoriasis patients with HIV. In our study, more than one third of patients at enrolment had a DLQI score of more than 10, which indicates severe impairment in quality of life. The higher mean DLQI among HIV-infected patients could be attributed to their manifesting more severe disease compared to non-HIV infected patients.[4] The DLQI domain most affected was physical symptoms and feelings among both HIV- and non-HIV-infected psoriasis patients. In our study, work and school, and personal relationship were significantly more impaired in the HIV group compared to the non-HIV group. These items could be influenced by other co-morbidities related to HIV infection that could cause disturbances in daily activities as well as social interaction with others.

Management of psoriasis in HIV patients is challenging due to the abnormal immune status of patients at various phases of their disease course.[30,33] Imbalance in the $CD8^+$ to $CD4^+$ ratio in HIV has been associated with the pathogenesis of psoriasis, which is $CD8^+$ T-cell mediated. A low $CD4^+$ T-cell count relative to CD8+ T-cells in the setting of HIV, may lead to a propensity to develop more severe psoriasis.[34,35]

Some reports showed that psoriasis may improve after treatment with ART.[36-39] Case reports from Italy and Chile have reported improvement of erythrodermic psoriasis in HIV patients after ART was initiated.[36,37] ART as a first line therapy has been shown to control the progression of HIV and also effectively treat HIV-associated psoriasis, which commonly occurs when $CD4^+$ T-cell counts fall below 350cells/mm^3.[4,40] Zidovudine, a thymidine analogue and a nucleoside reverse transcriptase inhibitor (NRTI) has also been reported to be beneficial in improving psoriasis in HIV patients.[16,41] Likewise, antiretroviral combinations of protease inhibitors and a non-nucleoside reverse transcriptase inhibitor (NRTI), or two NRTIs plus an entry inhibitor, have demonstrated efficacy in treating HIV-associated psoriasis.[39] However, data on neither $CD4^+$ T-cell counts nor the use of ART was available from our registry.

On the contrary, there have been reports of exacerbation of psoriasis as a manifestation of

immune reconstitution inflammatory syndrome (IRIS) upon commencement of antiretroviral therapy in HIV-infected psoriasis patients.[35] Flare of plaque psoriasis has been reported after commencement of ART.[35,42] Tripathi *et al.* reported a HIV-infected patient who had IRIS with worsening of the pre-existing psoriasis plaques and acral involvement after switching to new ART (elvitegravir, tenofovir, cobicistat and emtricitabine). The patient's condition improved after ART was reintroduced with concurrent phototherapy using psoralen and ultraviolet A therapy together with topical clobetasol.[42] Another case report from Lebanon described the occurrence of psoriasis for the first time in 2 patients after ART was introduced, manifesting as IRIS.[35] However, both patients were not compliant with their ART leading to altered $CD4^+/CD8^+$ T-cell ratios, which further contributed to their psoriasis flare.[35] These two scenarios reveal that worsening of psoriasis in the context of IRIS may occur at commencement or interruption of ART.[35]

HIV-infected patients who have mild psoriasis were generally prescribed topical medications, such as topical corticosteroids, calcipotriene, tar preparations and emollients.[33] Phototherapy with ultraviolet (UV) radiation in combination with antiretroviral therapy is recommended as a first-line treatment for moderate-to-severe psoriasis in patients with HIV.[4] Phototherapy does not induce immunosuppression and low dose ultraviolet light has been shown to be beneficial in HIV-infected patients with skin disease.[43,44] However, it was not prescribed as a preferred modality in our cohort. Reasons for low usage of phototherapy in the HIV-infected cohort could be adherence issues for these patients and the lack of access to phototherapy. Of note, the use of phototherapy in HIV patients with Kaposi's sarcoma is prohibited as it may lead to worsening of Kaposi's sarcoma.[41,45,46]

A majority of dermatologists were most comfortable with prescribing acitretin, followed by phototherapy, for the treatment of psoriasis in HIV-infected patients based on a survey in France.[15] Our data showed that only 10% of HIV-infected patients received systemic therapy despite having more severe disease than patients in the non-HIV cohort. This showed that our dermatologist was cautious in prescribing these agents for fear of the compounded immunosuppressive effect in the HIV cohort or hesitancy of HIV patients on ART to be on numerous medications. Further studies to assess factors contributing to the lack of use of systemic therapy or phototherapy for treating HIV-infected psoriasis patients are needed. Acitretin, an oral retinoid, can improve psoriasis signs and symptoms, and is a preferred systemic treatment option over methotrexate and cyclosporin by virtue of its non-immunosuppressive effect.[4,21] Monitoring of fasting serum lipid levels is important as risk of hypertriglyceridemia and pancreatitis may be increased when oral retinoids are used together with antiretroviral medications.[4]

Treatment of HIV-infected patients with recalcitrant psoriasis who have failed or were unable to tolerate first line therapy is challenging. Use of methotrexate should be avoided in HIV-infected psoriasis patients.[51] A report from Duvic *et al* discouraged the use of methotrexate due to the risk of opportunistic infections.[41] Another case series reported *Pneumocystis carinii* infection in 2 of 4 patients treated with methotrexate.[47] On the other hand, treatment with cyclosporin, a calcineurin inhibitor, had limited reports, though it has been used safely and with good responses in HIV-infected psoriasis patients.[48,49] Of note, monitoring cyclosporin levels may be required as the bioavailability may be increased by the concomitant use of protease inhibitors.[50] Due to the risk of nephrotoxicity and hypertension, short-term use is recommended for up to 12 weeks.[3] Systemic treatment for HIV-infected psoriasis patients should be individualised with close monitoring of the CD4 count and viral load.[51] Although unavailable in Malaysia, apremilast, a phosphodiesterase-4 inhibitor is approved for the treatment of moderate to severe psoriasis.[49] Data on the usage of apremilast in HIV-infected psoriasis patients is scarce. There were a few reports of successful treatment of plaque and palmoplantar psoriasis in HIV-infected psoriasis patients.[53-55] Sacchelli *et al.* had also noted improvement in psoriatic nail disease in their cohort of patients.[56]

There are no guidelines on the usage of biologics in psoriasis patients with HIV. Not with standing, biologic agents are predicted to be safe in HIV-infected psoriasis patients especially for those on ART.[57] Biologic agents such as etanercept, adalimumab, infliximab and ustekinumab have

been used to treat HIV-infected psoriasis patients with good clinical response, safety outcomes and tolerability.[40,57,58] Clinical responses among HIV-infected psoriasis patients treated with a biologic are reported to be comparable to those with non-HIV-infected psoriasis.[31,59,60] Bardazzi *et al.* suggested that biologic agents may be considered in psoriasis patients with stable HIV infection, and with close monitoring of CD4 counts and HIV viral load levels.[57] The use of biologic agents for the treatment of psoriasis in our cohort study was low among non-HIV-infected patients, and no patients in the HIV-infected group were treated with a biologic. Many factors such as budget constraints and policies may have contributed to this.

Limitations

The registry database does not discern whether more than one type of psoriasis occurred in the same patient, as only the predominant type is documented. Data on antiretroviral therapy, CD4 counts and whether a diagnosis of psoriasis preceded HIV infection, or vice versa, are also not available. As with all retrospective studies, missing data may not be accounted for and causal relationships could not be determined.

Recommendations

A prospective study focusing on the evolution of psoriasis throughout the different stages of HIV/AIDS would be valuable. Research assessing systemic and biological treatments for psoriasis patients with HIV infection is needed. Registries dedicated to studying HIV-infected psoriasis patients should be established to allow for more comprehensive data collection.

Conclusion

The prevalence of HIV infection among psoriasis patients in the MPR was 0.5%. Most of the HIV-infected psoriasis patients in this cohort had plaque psoriasis. Higher proportion of HIV-infected patients had more nail, face and neck involvement, and more severe disease, which significantly affected quality of life. Treatment of psoriasis in patients with HIV infection was comparatively less aggressive compared to treatment of non-HIV-infected psoriasis patients in the MPR cohort.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

We would like to acknowledge all contributors for providing MPR data and thank the Director General of Health Malaysia for permission to publish this article.

References

1. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377-85.
2. Mallon E, Bunker CB. HIV-associated psoriasis. AIDS Patient Care STDS 2000;14:239-46.
3. Morar N, Willis-Owen SA, Maurer T, Bunker CB. HIV-associated psoriasis: pathogenesis, clinical features, and management. Lancet Infect Dis 2010;10:470-8.
4. Menon K, Van Voorhees AS, Bebo BF, Gladman DG, Hsu S, Kalb RE et al. Psoriasis in patients with HIV infection: from the Medical Board of the National Psoriasis Foundation. J Am Acad of Dermatol 2010;62:291-9.
5. Lebrun D, Hentzien M, Cuzin L, Rey D, Joly V, Cotte L et al. Epidemiology of autoimmune and inflammatory diseases in a French nationwide HIV cohort: AIDS 2017;31:2159-66.
6. Tsai T-F, Wang T-S, Hung S-T, Tsai P-I, Schenkel B, Zhang M et al. Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. J Dermatol Sci 2011;63:40-6.
7. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
8. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol 2006;132:236-44.
9. Ding X, Wang T, Shen Y, Wang X, Zhou C, Tian S et al. Prevalence of psoriasis in China: a population-based study in six cities. Eur J Dermatol 2012;22:663-7.
10. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol 2014;70:512-6.
11. Ceccarelli M, Venanzi Rullo E, Vaccaro M, Facciola A, d'Aleo F, Paolucci IA et al. HIV-associated psoriasis: epidemiology, pathogenesis, and management. Dermatol Ther 2019;32:e12806.
12. Hentzien M, Cuzin L, Raffi F, Jacomet C, Reynes J, Rey D et al. Factors associated with psoriasis in a French Nationwide HIV cohort: the independent role of HLA-B*57. AIDS 2020;34:1057-63.
13. Jiamton S, Suthipinittharm P, Kulthanan K, Chularojamamontri L, Wongpraparut C, Silpa-archa N et al. Clinical characteristics of Thai patients with psoriasis. J Med Assoc Thai 2012;95:795-801.
14. United Nation. UNAIDS country factsheets Malaysia 2018. Available at: https://www.unaids.org/en/regionscountries/countries/malaysia. (Last accessed 5 April 2020).
15. Guignant M, Mahé E, Duval-Modeste A-B, Vermersch-Langlin A, Resopso GEM. Psoriasis and HIV infection, what do French Dermatologist do? Ann Dermatol Venereol 2019;146:265-72.
16. Obuch ML, Maurer TA, Becker B, Berger TG. Psoriasis and human immunodeficiency virus infection. J Am Acad of Dermatol 1992;27:667-73.
17. Alpalhão M, Borges-Costa J, Filipe P. Psoriasis in HIV

infection: an update. Int J STD AIDS 2019;30:596-604.
18. Tull TJ, Noy M, Bunker CB, Morar N. Sebopsoriasis in patients with HIV: a case series of 20 patients. Br J Dermatol 2017;176:813-5.
19. Baran. The burden of nail psoriasis: an introduction. Dermatology 2010;221:1-5.
20. Asil K, Yaldiz M. Diagnostic role of ultrasound elastography for nail bed involvement in psoriasis. Medicine 2019;98:1-5.
21. Fernandes S, Pinto GM, Cardoso J. Particular clinical presentations of psoriasis in HIV patients. Int J STD AIDS 2011;22:653-4.
22. Montazeri A, Kanitakis J, Bazex J. Psoriasis and HIV infection. Int J Dermatol 1996;35:475-9.
23. Yang Q, Qu L, Tian H, Hu Y, Peng J, Yu X et al. Prevalence and characteristics of psoriatic arthritis in Chinese patients with psoriasis: prevalence and characteristics of psoriatic arthritis. J Eur Acad Dermatol Venereol 2011;25:1409-14.
24. Lawson E, Walker-Bone K. The changing spectrum of rheumatic disease in HIV infection. Br Med Bull 2012;103:203-21.
25. Radtke M, Reich K, Blome C, Rustenback S, Augustin M. Prevalence and clinical features of psoriatic arthritis and joint complaints in 2009 patients with psoriasis: Results of a German national survey. J Euro Acad Dermatol Venereol 2009;23:683-91.
26. Plachouri K-M, Georgiou S. Challenges in the treatment of psoriasis with biologics: vaccination, history of malignancy, human immunodeficiency virus (HIV) infection, and paediatric psoriasis. Int J Dermatol 2019;58:1008-13.
27. Rodrıguez FM. Rheumatic manifestations of human immunodeficiency virus infection. Rheum Dis Clin North Am 2003;29:145-61.
28. Espinoza LR, Berman A, Vasey FB, Cahalin C, Nelson R, German BF. Psoriatic arthritis and acquired immunodeficiency syndrome. Arthritis Rheum 1988;31:1034-40.
29. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Köks S et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017;31:1792-9.
30. Tasca KI, Calvi SA, de Souza LDR. Immunovirological and cytokines in HIV infection. Rev Soc Bras Med Trop 2012;45:663-9.
31. Mikhail M, Weinberg JM, Smith BL. Successful treatment with Etanercept of von zumbusch pustular psoriasis in a patient with human immunodeficiency virus. Arch Dermatol 2008;144:453-6.
32. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41:401-7.
33. Queirós N, Torres T. HIV-associated psoriasis. Actas Dermosfiliogr 2018;109:303-11.
34. Yen YF, Jen IA, Chen M, Lan YC, Lee CY, Chuang PH et al. HIV infection increases the risk of incident psoriasis: A nationwide population-based cohort study in Taiwan. J Acquir Immune Defic Syndr 2017;75:493-9.
35. Cheaito MA, Khalifeh M, Jaafar B, Rizk N. Immune reconstitution inflammatory syndrome presenting as psoriasis after initiating antiretroviral therapy: A case-report. J Infect Dis Ther 2018;6:1-4.
36. Chiricozzi A, Saraceno R, Cannizzaro MV, Nisticò SP, Chimenti S, Giunta A. Complete resolution of erythrodermic psoriasis in an HIV and HCV patient unresponsive to antipsoriatic treatments after highly active antiretroviral therapy (Ritonavir, Atazanavir, Emtricitabine, Tenofovir). Dermatology 2012;225:333-7.
37. Valenzuela F, Fernández J, Sánchez M, Zamudio A. Erythrodermic psoriasis and human immunodeficiency virus: association and therapeutic challenges. An Bras Dermatol 2018;93:438-40.
38. Mahajan V, Sharma N, Sarin S, Bansal A, Sud N. Triple antiretroviral therapy improves psoriasis associated with human immunodeficiency virus infection: a clinico-therapeutic experience. J Euro Acad Dermatol Venereol 2008;22:1017-8.
39. Socio G, Simonetti S, Stagni G. Clinical improvement of psoriasis in an AIDS patient effectively treated with combination antiretroviral therapy. Scand J Infect Dis 2006;38:74-5.
40. Mamkin I, Mamkin A, Ramanan SV. HIV-associated psoriasis. Lancet Infect Dis 2007;7:496.
41. Duvic M, Johnson TM, Rapini RP, Freese T, Brewton G, Rios A. Acquired immunodeficiency syndrome-associated psoriasis and reiter's syndrome. Arch Dermatol 1987;123:1622-32.
42. Tripathi SV, Leslie KS, Maurer TA, Amerson EH. Psoriasis as a manifestation of HIV-related immune reconstitution inflammatory syndrome. J Am Acad Dermatol 2015;72:e35-6.
43. Breuer-McHam J, Marshall G, Adu-Oppong A, Goller M, Mays S, Berger T et al. Alterations in HIV expression in AIDS patients with psoriasis or pruritus treated with phototherapy. J Am Acad Dermatol 1999;40:48-60.
44. Arisi M, Gelmetti A, Focà E, Rossi MT, Rovati C, Clazavara-Pinton P et al. UVA1 phototherapy as a treatment option for plaque psoriasis in HIV-positive patients. Photodermatol Photoimmunol Photomed 2020;36:478-80.
45. Meola T, Soter NA, Ostreicher R, Sanchez M, Moy JA. The safety of UVB phototherapy in patients with HIV infection. J Am Acad Dermatol 1993;29:216-20.
46. Gelfand JM, Rudkoff D, Lebwohl M, Klotman ME. Effect of UV-B Phototherapy on Plasma HIV Type 1 RNA level: A self-controlled prospective study. Arch Dermatol 1998;134:940-5.
47. Maurer TA, Zackheim HS, Tuffanelli L, Berger TG. The use of methotrexate for treatment of psoriasis in patients with HIV infection. J Am Acad Dermatol 1994;31:372-5.
48. Allen BR. Use of cyclosporin for psoriasis in HIV-positive patient. Lancet 1992;339:686.
49. Tourne L, Durez P, Van Vooren J-P, Farber CM, Lisnard C, Heenen M et al. Alleviation of HIV-associated psoriasis and psoriatic arthritis with cyclosporine. J Am Acad Dermatol 1997;37:501-2.
50. Frassetto L, Baluom M, Jacobsen W, Christians U, Roland ME, Stock PG et al. Cyclosporine Pharmacokinetics and Dosing Modifications in Human Immunodeficiency Virus-Infected Liver and Kidney Transplant Recipients. Transplantation 2005;80:13-7.
51. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient. J Am Acad Dermatol 2019;80:43-53.
52. Manfreda V, Esposito M, Campione E, Bianci L, Giunta A. Apremilast efficacy and safety in a psoriatic arthritis patient affected by HIV and HBV virus infections. Postgrad Med 2019;131:239-40.
53. Sahuquillo-Torralba A, de Unamuno Bustos B, Serna RM, Boquet EM, Estrada RB. Treatment Persistence and Safety of Apremilast in Psoriasis: Experience With 30 Patients in Routine Clinical Practice. Actas Dermo-Sifiliográficas (English Edition) 2020;111:415-8.
54. Reddy SP, Shah VV, Wu JJ. Apremilast for a psoriasis patient with HIV and hepatitis C. J Eur Acad Dermatol

Venereol 2017;31:e481-2.
55. Zarbafian M, Cote B, Richer V. Treatment of moderate to severe psoriasis with apremilast over 2 years in the context of long-term treated HIV infection: A case report. SAGE Open Med Case Rep 2019;7:1-2.
56. Sacchelli L, Patrizi A, Ferrara F, Bardazzi F. Apremilast as therapeutic option in a HIV positive patient with severe psoriasis. Dermatol Ther 2018;31:e12719.
57. Bardazzi F, Magnano M, Campanati A, Loconsole F, Carpentieri A, Potenza C et al. Biologic Therapies in HIV-infected Patients with Psoriasis: An Italian Experience. Acta Derm Venerol 2017;97:989-90.
58. Paparizos V, Rallis E, Kirsten L, Kyriakis K. Ustekinumab for the treatment of HIV psoriasis. J Dermatolog Treat 2012;23:398-9.
59. Fink DL, Hedley L, Miller RF. Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals. Int J STD AIDS 2017;28:110-9.
60. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis 2008;67:710-2.

ORIGINAL ARTICLE

Prevalence and Types of Mucocutaneous Disorders, Their Correlation to CD4 Count and Their Impact on Quality of Life in Adults with HIV Infection

Yee Ting Lim[1], *MRCP*, Kwee Eng Tey[1], *MRCP*, Siew Eng Choon[2], *FRCP*

[1]Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia
[2]Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Healthy Sciences, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Abstract

Background

Data on prevalence and type of mucocutaneous diseases in HIV-positive patients and their impact on quality of life (QoL) are sparse. We aim to determine prevalence and type of mucocutaneous disorders, their correlation to $CD4^+$ counts and impact on QoL for adults with HIV, using the Dermatology Life Quality Index (DLQI).

Methods

A cross-sectional study of HIV-infected adults seen in HIV and Dermatology Clinic.

Results

The majority (90%) of 174 participants recruited was male. Median age at diagnosis of HIV infection was 29 years (IQR 10). Mucocutaneous disorders were present in 90.2%, out of which 58.6% had two or more mucocutaneous disorders. Mean $CD4^+$ count was significantly lower in patients with, compared to those without mucocutaneous disorders (363 vs 548 cells/μL; p=0.030). Infections accounted for 67.2% of all mucocutaneous disorders seen, followed by inflammatory dermatoses (51.7%), cutaneous adverse drug reactions (17.8%) and neoplasm (2.3%). The five most frequent manifestations were eczema (22.4%), anogenital warts (21.2%), candidiasis (16.7%), dermatophytosis (15.5%) and secondary syphilis (12.0%). Oral candidiasis, pruritic papular eruption, drug-induced maculopapular eruption and drug rash with eosinophilia and systemic symptoms were significantly more prevalent in patients with $CD4^+$ counts <200 cells/μL but anogenital warts were more prevalent in patients with $CD4^+$ counts ≥200 cells/μL. The mean DLQI score was 8.39 (SD ± 6.83). QoL was severely impaired (DLQI >10) in 34.4%.

Conclusion

Mucocutaneous disorders were common in HIV patients causing significant impairment in quality of life. Prevalence co-related with low $CD4^+$ counts. Adequate management of HIV may reduce the prevalence of mucocutaneous disorders and improve QoL.

Key words: *Mucocutaneous manifestations, Human immunodeficiency virus infection, $CD4^+$ T-cell counts, Quality of life*

Introduction

Human immunodeficiency virus (HIV) is a retrovirus that cripples immunity by the destruction of $CD4^+$ T-lymphocytes.[1] The underlying immunodeficiency predisposes the HIV-infected patient to a variety

of mucocutaneous disorders.[2,3] Furthermore, the incidence and severity of these disorders increases as the HIV infection worsens.[2,3] Although mucocutaneous diseases are rarely life-threatening, they can severely impair the patients' quality of life.[4] The use of combination antiretroviral therapy (ART) may prolong the patient's life but drug-induced adverse reaction is a problem[5] because they may cause disfiguring facial lipoatrophy.[5,6,7]

Interestingly, skin diseases may be the first manifestations of HIV infection.[8] Hence, knowledge of the prevalence of these mucocutaneous disorders, the types and their impact on the HIV-infected patients' life are important aspects for their optimal management. We set out to study the prevalence of mucocutaneous manifestations in these patients, their types and their impact on patients' quality of life (QoL). We also explored the relationship between these disorders and $CD4^+$ T-cell counts, a known indicator of disease progression.

Materials and Methods

This was a cross-sectional study involving adults (18 years and above) who were diagnosed with HIV infection based on ICD-10-CM code B20. Study subjects were approached when they attended their scheduled HIV or Dermatology Clinic, Hospital Sultanah Aminah Johor Bahru (HSAJB), a tertiary referral centre in southern Malaysia. All confirmed HIV patients seen consecutively between 1st May 2019 to 31st July 2019 were recruited into the study which was approved by the Malaysian Ministry of Health Institutional Review Board and Medical Research Ethnics Committee (NMRR-19-92-46001). Written consents were given by all patients.

Study Procedures

After consent, patients underwent a thorough interview and full physical examination. $CD4^+$ T-cell counts and other relevant blood tests and procedures such as skin biopsies, skin scrapings and cultures were performed based on clinical findings. All findings were recorded in a standard Case Report Form (CRF).

Patients with mucocutaneous disorders were asked to fill up the DLQI questionnaire. DLQI is a 10-item dermatology-specific questionnaire that assesses the impact of skin disease and its treatment on the patient's life such as their symptoms of

Corresponding Author
Dr Lim Yee Ting
Department of Dermatology,
Hospital Sultanah Aminah,
Jalan Persiaran Abu Bakar Sultan,
80100 Johor Bahru, Malaysia.
Email: yeeting8899@yahoo.com

itch, embarrassment, interferences with their daily activities, leisure, work and study, personal relationships and problems in taking the treatment. Each question is scored from 0 to 3; 0 for not at all or not relevant, 1 for a little, 2 for a lot, 3 for very much. Questions 3 to 10 offered a "not relevant" response (NRR) option that was scored as an item that had no impact on study participants' life. A composite score is then calculated by summing the score of each question. It could range from a minimum of 0 to a maximum of 30. A DLQI score of 0 to 1 means the skin disease has no effect on the patient's life; 2-5 a small effect, 6-10 a moderate effect, 11-20 a very large effect and 21-30 an extremely large effect on patient's life.[9]

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables. Means and standard deviation (SD) was used for normally distributed data while median with an interquartile range (IQR) was used for data which were not normally distributed. Chi-square test, Fisher's exact test or Kruskal-Wallis test are used for univariate analysis depending on data distribution. Statistical significance was set at $p < 0.05$. Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) (version 23; SPSS Inc., Chicago, IL. USA).

Results

Demographic Characteristics

A total of 174 HIV-infected individuals participated in this study. The male to female ratio was 11.4:1. The median age at diagnosis was 29 (IQR: 10) years. In the racial distribution, 48.3% were Malays, 43.1% Chinese, 8.0% Indian and 0.6% others. About 88% of the study participants completed at least secondary school education level. Most of the participants were currently single and employed (Table 1).

Risk Profile, $CD4^+$ T-cell Counts and Treatment Status of 174 HIV-positive Patients

The main mode of HIV transmission was through sexual intercourse with 85% of participants having multiple sexual partners. Forty-five percent of them were homosexual.

Twenty-seven participants (15.5%) were intravenous drug users, five of them being active users and nineteen of them (70.4%) had multiple sexual partners. Twenty-two participants (12.6%) were either using or had a history of using stimulants either in the form of inhalational drugs or pills during engagement of sexual activities (Table 2).

The median duration of HIV infection was 172 (IQR:287) weeks. The median $CD4^+$ T-cell counts were 335 (IQR:508) cells/μL. Most of the study participants had already commenced on antiretroviral treatment.

Mucocutaneous Manifestations of the Study Participants

Close to 90% of the participants had at least one mucocutaneous manifestation (Table 3). Furthermore, the $CD4^+$ T-cell counts were significantly lower in patients with mucocutaneous manifestations when compared to those without (363 ± 338 cells/μL vs 548 ± 229 cells/μL; $p=0.030$).

Common mucocutaneous disorders were infections (67.2%), followed by inflammatory dermatoses (51.7%), cutaneous Adverse Drug Reactions (cADR) (17.8%) and neoplasm (2.3%). Participants with $CD4^+$ T-cell counts <200 cells/μL were significantly more likely to develop cADR. Most of the drug eruption in our study were secondary to sulfamethoxazole/trimethoprim (54.8%), followed by antiretroviral therapy (35.5%), anti-tuberculous drugs (6.5%) and antibiotics (3.2%).

Relationship between $CD4^+$ T-cell Counts and Mucocutaneous Manifestations

For study participants with $CD4^+$ T-cell counts of <200 cells/μL, there were 38% of them who had mucocutaneous manifestations compared to only 6% of them without any manifestations ($p=0.008$) (Table 4).

Several dermatoses were noted to be significantly higher among participants with $CD4^+$ T-cell counts <200 cells/μL when compared to those higher than 200 cells/μL (Table 5). These were candidiasis ($p=0.001$), pruritic papular eruption ($p=0.037$), drug-induced maculopapular eruption ($p=0.001$) and drug rash with eosinophilia and systemic symptoms (DRESS) ($p=0.001$).

However, anogenital warts were noted to be

significantly higher in those with CD4+ T-cell counts of ≥200 cells/μL (p=0.006). No differences in CD4+ T-cell counts was observed for other mucocutaneous manifestations.

Effect of Mucocutaneous Manifestations on Participants' DLQI Scores

The mean (± SD) of the total DLQI score was 8.39 ± 6.83 (range:0-27) (Table 6). When further analysed, the mean (± SD) DLQI score for participants who had ≥3 mucocutaneous disorders was not significantly higher, scoring 8.73 ± 6.54 (p=0.858). In all, 54 participants (34.4%) with mucocutaneous manifestations experienced severely impaired quality of life, having DLQI score >10. Thirty-five participants (22.3%) had moderate effect while 42 participants (26.8%) had a small effect. No effect was seen in 26 participants (16.6%) (Figure 1).

In the questionnaire, Questions 3 to 10 had a "not relevant response" (NRR) option. About two-thirds of participants chose this option at least once from questions 3 to 10. A higher proportion was recorded for questions on sexual difficulties (38.9%), sports (36.3%) and working or studying (22.9%).

Table 1. Demographic characteristics of 174 study participants with HIV infection

Variables		n (%)
Age category in years	18-30 31-40 41-50 51-60 61-70	94 (53.7) 44 (25.1) 26 (14.9) 8 (4.6) 2 (1.1)
Gender	Male Female	160 (92.0) 14 (8.0)
Ethnicity	Malay Chinese Indian Others	84 (48.3) 75 (43.1) 14 (8.0) 1 (0.6)
Education level	Primary Secondary Tertiary	21 (12.1) 86 (49.4) 67 (38.5)
Marital status	Single Married Divorced Widow / Widower	127 (73.0) 21 (12.1) 19 (10.9) 7 (4.0)
Occupation	Self-employed Employee Unemployed	33 (19.0) 90 (51.7) 51 (29.3)

Table 2. Risk profile, CD4+ T-cell counts and treatment status of 174 HIV-positive patients

Variables		n (%)
Sexual orientation	Homosexual Heterosexual Bisexual	79 (45.4) 61 (35.1) 33 (19.5)
Number of sexual partners	Multiple Single	147 (84.5) 26 (14.9)
Risk factors of HIV transmission	Sexual transmission Sexual transmission & Intravenous drug user Intravenous drug user	147 (84.5%) 26 (14.9%) 1 (0.6%)
CD4+ T-cell counts	<200 cells/μL 200-349 cells/μL 350-499 cells/μL >500 cells/μL	61 (35.1) 30 (17.2) 28 (16.1) 55 (31.6)
Participants on antiretroviral treatment (ART)	Yes No	129 (74.1) 45 (25.9)

Table 3. Comparison of mean CD4+ T-cell counts in 174 HIV-positive patients with and without Mucocutaneous Disorders

Variables	n (%)	Mean CD4+ T-cell Counts (cells/μL ± SD)		p-value[a]
		Presence of Disorders (n=157)	Absence of Disorders (n=17)	
All mucocutaneous manifestations	157 (90.2)	363 ± 338	548 ± 229	0.030
1 Disorder	65 (37.3)	378 ± 280		
2 Disorders	43 (24.7)	364 ± 362		
≥3 Disorders	49 (28.2)	342 ± 388		
Infection*	117 (67.2)	381 ± 360	381 ± 270	0.991
Inflammatory dermatoses*	90 (51.7)	361 ± 329	403 ± 337	0.406
Cutaneous adverse drug reactions (cADR)*	31 (17.8)	194 ± 249	422 ± 335	<0.001
Neoplasm*	4 (2.3)	404 ± 323	381 ± 334	0.891

SD = Standard deviation; [a]independent samples T-Test

**One patient may have multiple mucocutaneous manifestations; the percentage reported is based on total patients in each group*

Table 4. The effect of CD4+ T-cell counts on Mucocutaneous Manifestations

CD4+ T-cell Counts	Mucocutaneous Manifestations		p-value[b]
	Yes (%)	No (%)	
<200 cells/μL	60 (34.5)	1 (0.6)	0.008
≥200 cells/μL	97 (55.7)	16 (9.2)	

[b]Chi-Square test

Table 5. Relationship between type of Mucocutaneous Manifestations and $CD4^+$ T-cell counts

Variables		n (%)	Participants with $CD4^+$ T-cell Counts (cells/µL) <200 {n=60 (%)}	Participants with $CD4^+$ T-cell Counts (cells/µL) ≥200 {n=97 (%)}	*p*-value[b]
All mucocutaneous manifestations		157 (90.2)			0.248
	1 Disorder	65 (37.3)	24 (40.0)	41 (42.3)	
	2 Disorders	43 (24.7)	13 (21.7)	30 (30.9)	
	≥3 Disorders	49 (28.2)	23 (38.3)	26 (26.8)	
Infection*					
Viral					
Human papillomavirus	Anogenital warts	37 (21.2)	7 (11.7)	30 (30.9)	0.006
	Palmoplantar warts	6 (3.4)	3 (5.0)	3 (3.1)	0.675[c]
	Herpes simplex virus	10 (5.7)	6 (10.0)	4 (4.1)	0.183[c]
	Molluscum contagiosum	6 (3.4)	3 (5.0)	3 (3.1)	0.675[c]
	Varicella and Herpes zoster virus infection	5 (2.9)	3 (5.0)	2 (2.1)	0.371[c]
	Oral hairy leukoplakia	3 (1.7)	3 (5.0)	0 (0)	0.054c
Fungal	Candidiasis	29 (16.7)	20 (33.3)	9 (9.3)	0.000
	Dermatophytes	27 (15.5)	9 (15.0)	18 (18.6)	0.566
	Deep fungal infection	3 (1.7)	3 (5.0)	0 (0)	0.054[c]
Bacterial	Syphilis	21 (12.0)	7 (11.7)	14 (14.4)	0.621
	Cellulitis	12 (6.9)	3 (5.0)	9 (9.3)	0.375[c]
	Impetigo	5 (2.9)	0 (0)	5 (5.2)	0.157[c]
	Abscesses / Carbuncle	1 (0.6)	0 (0)	1 (1.0)	1.000[c]
Parasitic	Scabies	1 (0.6)	1 (1.7)	0 (0)	0.382[c]
	Pediculosis capitis	1 (0.6)	0 (0)	1 (1.0)	1.000[c]
Inflammatory dermatosis*	Eczema	39 (22.4)	12 (20.0)	27 (27.8)	0.270
	Pruritic papular eruption	14 (8.0)	9 (15.0)	5 (5.2)	0.035[c]
	Acne vulgaris	11 (6.3)	2 (3.3)	9 (9.3)	0.207[c]
	Psoriasis	10 (5.7)	2 (3.3)	8 (8.2)	0.320[c]
	Prurigo nodularis	8 (4.6)	4 (6.7)	4 (4.1)	0.482[c]
	Seborrheic dermatitis	7 (4.0)	3 (5.0)	4 (4.1)	1.000[c]
	Urticaria	5 (2.9)	2 (3.3)	3 (3.1)	1.000[c]
	Hidradenitis suppurativa	4 (2.3)	1 (1.7)	3 (3.1)	1.000[c]
	Ichthyosis	3 (1.7)	2 (3.3)	1 (1.0)	0.558[c]
	Xerosis	2 (1.1)	2 (3.3)	0 (0)	0.145[c]
	Cutaneous vasculitis	1 (0.6)	1 (1.7)	0 (0)	0.382[c]
	Photodermatitis	1 (0.6)	0 (0)	1 (1.0)	1.000[c]
	Other inflammatory dermatosis	5 (2.9)	0 (0)	5 (5.2)	0.157[c]
Cutaneous Adverse Drug Reactions (cADR)*	Maculopapular eruption	16 (9.2)	12 (20.0)	4 (4.1)	0.001
	Drug rash with Eosinophilia and Systemic symptoms	8 (4.6)	8 (13.3)	0 (0)	0.000[c]
	Lipodystrophy	5 (2.9)	0 (0)	5 (5.2)	0.157[c]
	Toxic epidermal necrolysis	2 (1.1)	2 (3.3)	0 (0)	0.145[c]
	Erythema multiforme	1 (0.6)	1 (1.7)	0 (0)	0.382[c]
	Other cADRs	2 (1.1)	1 (1.7)	1 (1.0)	1.000[c]
Neoplasm*	Cutaneous lymphoma	2 (1.1)	1 (1.7)	1 (1.0)	1.000[c]
	Kaposi's sarcoma	1 (0.6)	0 (0)	1 (1.0)	1.000[c]
	Bowen's disease	1 (0.6)	0 (0)	1 (1.0)	1.000[c]

[b]Chi-Square test; [c]Fisher's exact test

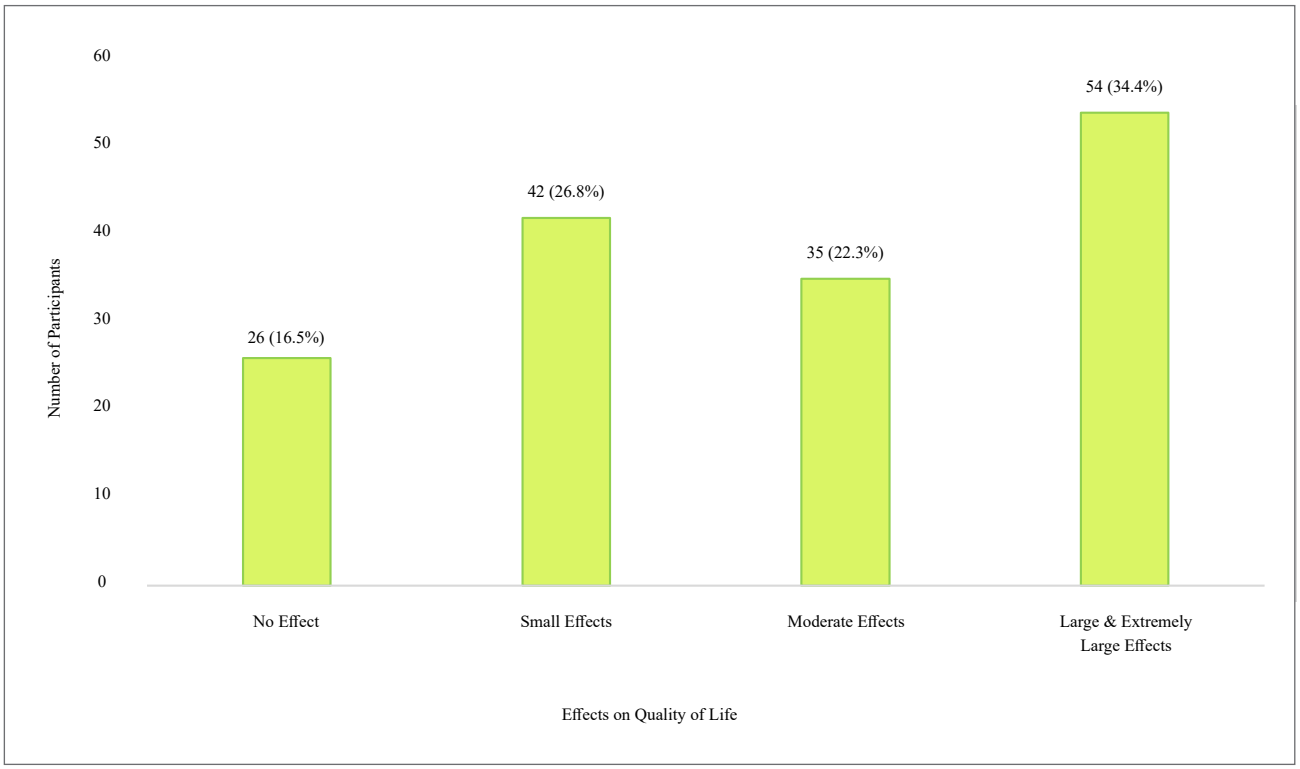
**One patient may have multiple mucocutaneous manifestations; the percentage reported is based on total patients in each group*

Table 6. The effect of Mucocutaneous Manifestations on participants' mean DLQI scores

Variables		Mean DLQI Scores (SD)	*p*-value[a]
General effect of Mucocutaneous Manifestations	Yes No	8.39 (6.83)	
Infection	Yes No	8.65 (6.95) 6.05 (6.10)	0.017
Inflammatory dermatoses	Yes No	7.87 (5.84) 7.73 (7.69)	0.892
Neoplasm	Yes No	6.25 (9.85) 7.84 (6.73)	0.645
Cutaneous adverse drug reactions (cADR)	Yes No	8.71 (6.34) 7.60 (6.87)	0.411
DLQI components			
Symptoms and Feeling	Yes No	2.38 (1.81) 0.82 (0.95)	0.001
Daily activities	Yes No	1.50 (1.89) 0.06 (0.24)	0.002
Leisure	Yes No	1.24 (1.76) 0.12 (0.49)	0.009
Daily activities	Yes No	0.65 (1.15) 0.12 (0.49)	0.009
Daily activities	Yes No	0.65 (1.15) 0.12 (0.49)	0.009
Treatment	Yes No	0.65 (1.15) 0.12 (0.49)	0.009

[a]*Independent samples T-Test*

Figure 1. Effects of Mucocutaneous Manifestations on participants' DLQI



Discussion

Ever since its recognition in 1981, HIV has become a major global public health issue. In 2019, there were 1.7 million newly infected people of whom 690,000 people died from its related causes.[10] Malaysia is no different; by the end of 2018 it is estimated that 87,041 people would have lived with HIV in Malaysia and 55% of these will be receiving antiretroviral treatment (ART).[11] Close to 80% of our study participants were below 40 years old of

which, 92% were of males. These figures are similar to those reported by Wang Jing in 2000 in Malaysia who showed that 75% of his study participants were less than 40 years old and with a male preponderance of 87%.[12]

Homosexual contact was the most common mode of transmission in our patients. However, two previous studies from Singapore and Malaysia showed that most of their study participants were heterosexuals.[12,13] Furthermore, Kanter *et al.*[14] in 2011 screened 517 men who had sex with men in Kuala Lumpur and found that 3.9% of them tested positive for HIV infection. This study shows a change in risk factor for HIV transmission and therefore, targeted interventions should be offered to prevent and control HIV transmission.[15]

Mucocutaneous manifestations are common in patients of HIV. They may occur anytime during the course of the disease. Ninety percent of our patients displayed at least one type of dermatological manifestation whereby more than half had 2 or more mucocutaneous disorders. This high prevalence is likely attributed to recruitment of patients done in a tertiary referral centre of HIV and Dermatology Clinic. Consistent with observation documented by Li *et al.*[16], our study showed that patients with mucocutaneous disorders had significantly lower $CD4^+$ T-cell counts. However, no significant difference in $CD4^+$ T-cell counts was observed between patients with one and more than one mucocutaneous disorders. This contradicted findings by Li *et al.*[16] who showed that significant reduction in $CD4^+$ T-cell count occurred with increasing number of mucocutaneous manifestations.

Infections

Human papillomavirus (HPV) infection in the form of anogenital warts was noted to occur frequently among our participants, especially those with $CD4^+$ T-cell counts >200 cells/μL. In contrast to our findings, Chikandiwa *et al.*[17] showed that anogenital warts were more prevalent among those with lower $CD4^+$ T-cell counts (<200 cells/μL). HIV infection may have altered the natural history of HPV infection and thus were more common among individuals with HIV infection, regardless of their $CD4^+$ T-cell counts.[19] Furthermore, our findings might be related to the fact that 84.5% of our study participants had multiple sexual partners and 45.4% of them were homosexual. This finding is supported by other workers. Dareng *et al.*[18] showed that anogenital warts were more prevalent among his study participants who had multiple sexual partners. Similarly, Sonnenberg *et al.*[19] found that the diagnosis of anogenital warts were more frequent in men who had sex with men.

On the other hand, candidiasis seemed to be predominant among our participants with $CD4^+$ T-cell counts of less than 200 cells/μL. Altuntas *et al.*[20] and Kore *et al.*[21] showed similar results. Interestingly, in our study, there was a significant lower prevalence of candidiasis in patients who were on ART treatment. This is in line with the study by Hengge *et al.*[22] in which they found a decrease in the prevalence of oral candidiasis after ART administration. This implies that candidiasis infection is related to low immune function. Candidiasis may therefore be an important indicator of progression of the HIV infection and starting ART could decline its prevalence.

Secondary syphilis was present in 12% of study participants, it being the most common bacterial infection with 71.4% occurring among the homosexuals. This finding is not surprising as syphilis is associated with high-risk sexual behaviours and infection substantially increases in association with HIV transmission and acquisition.[23] In Canada, the incidence of syphilis was 300-fold greater among male who had sex with male positive for HIV than the reported case rate in the general male population.[24]

Inflammatory Dermatoses

Of the inflammatory dermatoses, the most common manifestations were eczema (22.4%), followed by pruritic papular eruption (PPE) (8.0%), psoriasis (6.3%) and acne vulgaris (6.3%). However, of these only pruritic papular eruption was significantly associated with $CD4^+$ T-cell counts of less than 200 cells/μL. A similar observation was reported by Resnick *et al.*[25] and Farsani *et al.*[26] and they postulated that PPE reflects an altered and exaggerated immune response to arthropod antigens among HIV-infected individuals.

Eczema was present in 22.4% of our participants. Similar percentage was reported in a group of patients from Thailand.[27] It is known that both

eczema and HIV share a similar Th2 cytokine profile characterized by elevated IgE, eosinophils, IL-4 and IL-5 levels. This may explain the relationship between the two diseases.[28, 29]

Psoriasis was seen in 6.3% of our patients, an incidence much higher than that reported (2.9%) by others from Iran.[30] We also found that in about 50% of our patients' psoriasis were aggravated soon after the diagnosis of HIV infection. This may be related to the fact that the HIV, in attacking $CD4^+$ T-cells increases the proportion of $CD8^+$ T-cells which in turn secrete IFN-γ and aggravates psoriasis.[31]

Cutaneous Adverse Drug Reactions

HIV-infected individuals have both an immunologic dysfunction and do take a diverse set of drugs. A higher incidence of drug eruption among these individuals may therefore be expected.[32] Cutaneous Adverse Drug Reactions (cADR) affected 17.8% of the study participants and this was positively correlated with those patients with $CD4^+$ T-cell counts of less than 200 cells/μL, especially in those with maculopapular eruption and drug rash with eosinophilia and systemic symptoms (DRESS). This shows that drug eruptions are strongly related to the patient's immune function.[33]

Most of the cADR were secondary to sulfamethoxazole/trimethoprim, followed by antiretroviral therapy, anti-tuberculous drugs and antibiotics, which was also portrayed in other studies.[34,35] The frequent occurrence of opportunistic infections among HIV patients[36] often leads to concurrent use of sulfamethoxazole/trimethoprim for *Pneumocystis jirovecii* pneumonia prophylaxis and anti-tuberculous therapy, both of which are well-documented instigators of mild to severe cADR. These reactions can seriously impede effective management of HIV and opportunistic infections among HIV-infected individuals.

Dermatology Life Quality Index

HIV patients with mucocutaneous manifestations had a mean (± SD) DLQI score of 8.39 ± 6.83. More than one-third of HIV-infected individuals felt that having mucocutaneous manifestations severely affected their quality of life. This finding was similarly reported by Shittu *et al.*[37] Severe impairment of QoL (DLQI >10) was clearly shown affecting our patients presenting with mucocutaneous disorders regardless of the numbers of manifestations experienced by them.

Not with standing, the mean DLQI scores in our patients may have been underestimated because, about 67% of them chose the "not relevant response". These were in the areas of sexual difficulties (38.9%), sports (36.3%) and working or studying (22.9%). Abstaining from these activities on account of their mucocutaneous diseases might have been the reason for them choosing the NRR option. Rencz *et al.*[38] noted similar findings whereby, their participants with psoriasis also picked NRR options for sexual difficulties, sports and working or studying.

The presence of mucocutaneous manifestations also caused significant discomfort in terms of itchiness, pain and embarrassment in our participants. A similar finding was seen in newly diagnosed HIV/AIDS-infected patients in a study from Nigeria.[37] Daily and leisure activities were also impaired in our patients with mucocutaneous manifestations as opposed to those with none. In addition, they found it burdensome to seek treatment on account of their mucocutaneous manifestations.

Limitations

This study involved only single centre and had a relatively short study duration of three months. In using convenience sampling, the participants may not have been representative of the target population.

Conclusion

Mucocutaneous disorders were common and diverse among patients with HIV infection. More than one-third of patients with mucocutaneous manifestations had severely impaired quality of life. Hence, early and adequate treatment of HIV patients may reduce the prevalence of mucocutaneous disorders and their impact on patients' QoL. Cutaneous ADR including potentially life-threatening DRESS were significantly higher in patients with $CD4^+$ T-cell counts <200 cells/μL. This highlights the need for caution in prescribing only absolutely necessary medication for HIV patients with low $CD4^+$ T-cell counts.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

The authors would like to thank the Director General of Health, Malaysia for permission to publish this article.

References

1. de Goede AL, Vulto AG, Osterhaus AD, Gruters RA. Understanding HIV infection for the design of a therapeutic vaccine. Part I: Epidemiology and pathogenesis of HIV infection. Ann Pharm Fr 2015;73:87-99.
2. Chandrakala C, Parimalam K, Wahab AJ, Anand N. Correlating CD4 count with mucocutaneous manifestations in HIV-positive patients: A prospective study. Indian J Sex Transm Dis AIDS 2017;38:128-35.
3. Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. Int J Dermatol 2005;44:646-9.
4. Kanmani CI, Udayashankar C, Nath AK. Dermatology life quality index in patients infected with HIV: A comparative study. Egypt Dermatol Online J 2013;9:3.
5. Masuka JT, Chipangura P, Nyambayo PP, Stergachis A, Khoza S. A Comparison of Adverse Drug Reaction Profiles in Patients on Antiretroviral and Antitubercular Treatment in Zimbabwe. Clin Drug Investig 2018;38:9-17.
6. Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. J Am Acad Dermatol 2002;46:284-93.
7. Birbal S, Dheda M, Ojewole E, Oosthuizen F. Adverse drug reactions associated with antiretroviral therapy in South Africa. Afr J AIDS Res 2016;15:243-8.
8. Mirnezami M, Zarinfar N, Sofian M, Botlani Yadegar B, Rahimi H. Mucocutaneous Manifestations in HIV-Infected Patients and Their Relationship to CD4 Lymphocyte Counts. Scientifica (Cairo) 2020;2020:7503756.
9. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
10. Joint United Nations Programme on HIV/AIDS (2020). Global HIV & AIDS statistics - 2019 fact sheet. Available online:http://www.unaids.org/en/resources/fact-sheet. Assessed on 19 February 2021.
11. Ministry of Health Malaysia. Country Progress Report on HIV/AIDS 2019 Malaysia. Available online: http://www.moh.gov.my › Umum › Report_GAM_2019_(Final). Assessed on 19 February 2021.
12. Jing W. A Retrospective Survey of Mucocutaneous Manifestations of HIV Infection in Malaysia: Analysis of 182 Cases. J Dermatol 2000;27:225-32.
13. Goh BK, Chan RKW, Sen P, Theng CTS, Tan HH, Wu YJ et al. Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. Int J Dermatol 2007;46:695-9.
14. Kanter J, Koh C, Razali K, Tai R, Izenberg J, Rajan L et al. Risk behaviour and HIV prevalence among men who have sex with men in a multiethnic society: a venue-based study in Kuala Lumpur, Malaysia. Int J STD AIDS 2011;22:30-7.
15. Ramakrishnan L, Ramanathan S, Chakrapani V, Goswami P, Deshpande S, Yadav D et al. Comparison of Sexual Risk, HIV/STI Prevalence and Intervention Exposure Among Men Who Have Sex with Men and Women (MSMW) and Men Who Have Sex with Men Only (MSMO) in India: Implications for HIV Prevention. AIDS Behav 2015;19:2255-69.
16. Li YY, Yang SH, Wang RR, Tang JT, Wang HM, Kuang YQ. Effects of CD4 cell count and antiretroviral therapy on mucocutaneous manifestations among HIV/AIDS patients in Yunnan China. Int J Dermatol 2020;59:308-13.
17. Chikandiwa A, Kelly H, Sawadogo B, Ngou J, Pisa PT, Gibson L et al. Prevalence, incidence and correlates of low risk HPV infection and anogenital warts in a cohort of women living with HIV in Burkina Faso and South Africa. PLoS One 2018;13:e0196018.
18. Dareng EO, Adebamowo SN, Famooto A, Olawande O, Odutola MK, Olaniyan Y et al. Prevalence and incidence of genital warts and cervical Human Papillomavirus infections in Nigerian women. BMC Infect Dis 2019;19:27:1-10.
19. Sonnenberg P, Tanton C, Mesher D, King E, Beddows S, Field N et al. Epidemiology of genital warts in the British population: implications for HPV. Sex Transm Infect 2019;95:386-90.
20. Altuntas Aydin Ö, Kumbasar Karaosmanoglu H, Korkusuz R, Özeren M, Özcan N. Mucocutaneous manifestations and the relationship to CD4 lymphocyte counts among Turkish HIV/AIDS patients in Istanbul, Turkey. Turk J Med Sci 2015;45:89-92.
21. Kore SD, Kanwar AJ, Vinay K, Wanchu A. Pattern of mucocutaneous manifestations in human immunodeficiency virus-positive patients in North India. Indian J Sex Transm Dis AIDS 2013;34:19-24.
22. Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviral therapy. AIDS 2000;14:1069-70.
23. Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers 2017;3:17073.
24. Burchell AN, Allen VG, Gardner SL, Moravan V, Tan DH, Grewal R et al. High incidence of diagnosis with syphilis co-infection among men who have sex with men in an HIV cohort in Ontario, Canada. BMC Infect Dis 2015;15:356.
25. Resneck JS Jr, Van Beek M, Furmanski L, Oyugi J, LeBoit PE, Katabira E et al. Etiology of pruritic papular eruption with HIV infection in Uganda. JAMA 2004;292:2614-21.
26. Farsani TT, Kore S, Nadol P, Ramam M, Thierman SJ, Leslie K et al. Aetiology and risk factors associated with a pruritic papular eruption in people living with HIV in India. J Int AIDS Soc 2013;16:17325.
27. Punyaratabandhu P, Prasithsirikul W, Jirachanakul P. Skin manifestation of Thai HIV infected patients in HAART era. J Med Assoc Thai 2012;95:497-504.
28. Rudikoff D. The relationship between HIV infection and atopic dermatitis. Curr Allergy Asthma Rep 2002;2:275-81.
29. Garg T, Sanke S. Inflammatory dermatoses in human immunodeficiency virus. Indian J Sex Transm Dis AIDS 2017;38:113-10.
30. Davarpanah MA, Motazedian N, Jowkar F. Dermatological manifestations of HIV/AIDS individuals in Shiraz, South of Iran. J Glob Infect Dis 2018;10:80-3.
31. Patel RV, Weinberg JM. Psoriasis in the patient with human immunodeficiency virus, part 1: review of pathogenesis. Cutis 2008;82:117-22.
32. Tzung TY, Yang CY, Chao SC, Lee YJ. Cutaneous Manifestations of Human Immunodeficiency Virus Infection in Taiwan. Kaohsiung J Med Sci 2004;20:216-24.
33. Huang XJ, Li HY, Chen DX, Wang XC, Li ZC, Wu YS et al. Clinical analysis of skin lesions in 796 Chinese HIV-positive patients. Acta Derm Venereol 2011;91:552-6.

34. Hoosen K, Mosam A, Dlova NC, Grayson W. An Update on Adverse Cutaneous Drug Reactions in HIV/AIDS. Dermatopathology (Basel) 2019;6:111-25.
35. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med 1993;328:1670-4.
36. Lee CY, Wu PH, Lu PL, Tsai HC. Changing Spectrum of Opportunistic Illnesses among HIV-Infected Taiwanese Patients in Response to a 10-Year National Anti-TB Programme. J Clin Med 2019;8:163.
37. Shittu RO, Odeigah LO, Mahmoud AO, Sani MA, Bolarinwa OA. Dermatology Quality of Life Impairments among Newly Diagnosed HIV/AIDS-Infected Patients in the University of Ilorin Teaching Hospital (Uith), Ilorin, Nigeria. J Int Assoc Provid AIDS Care 2013; doi: 10.1177/2325957413488207.
38. Rencz F, Poór AK, Péntek M, Holló P, Kárpáti S, Gulácsi L et al. A detailed analysis of "not relevant" responses on the DLQI in psoriasis: potential biases in treatment decisions. J Eur Acad Dermatol Venereol 2018;32:783-90.

ORIGINAL ARTICLE

Prevalence of Atopic Dermatitis Among Primary School Children and Its Impact on Quality of Life in Kuching, Sarawak

Sut Enn Lee[1], *MRCP,* Sze Ying Foo[1], *MD*, Nur Shairah Fatin Binti Badaruddin[1], *MD*, Mohamad Adam Bujang[2], *BSc*, Pubalan Muniandy[1], *FRCP*

[1]Department of Dermatology, Sarawak General Hospital, Kuching, Sarawak, Malaysia
[2]Clinical Research Centre, Sarawak General Hospital, Kuching, Sarawak, Malaysia

Abstract

Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder that significantly burdens both children and caregivers' quality of life. This study aimed to investigate the prevalence and socio-demography of AD and determine its impact on the quality of life among AD children and their families in Sarawak.

Methods

This was a cross-sectional, observational population-based epidemiological study of primary school children in Kuching. The U.K. Working Party's Diagnostic (UKWPD) criteria was utilized to diagnose atopic dermatitis. Disease impact on quality of life was assessed via standardized questionnaires. Skin examination was performed.

Results

A total of 968 children aged 7 to 12 years were recruited. The prevalence of AD was 7.0%. Malays were the commonest affected ethnic group. Most of the AD children had other associated atopies. Majority of children with AD had mild to moderate severity based on IGA with mean EASI score (standard deviation) of 1.50 (2.0). The mean Children's Dermatology Quality Life Index (CDQLI) and Dermatitis Family Impact (DFI) were 7.26 (5.53) and 7.74 (6.12), respectively. "Symptoms of itch, sore or pain" was the most affected domain in children, whereas "Treatment impact" most affected in families. There was significant association between disease severity and children's quality of life.

Conclusion

Atopic Dermatitis is common in Kuching school children. Children with AD and their families had a significant impact on quality of life, although most were mild diseases.

Key words: *Atopic dermatitis, Eczema, Epidemiology, Quality of life, School children*

Introduction

Atopic dermatitis (AD) is a complex, chronic, and recurrent inflammatory itchy skin disorder that often develops in early childhood and may persist into adulthood.[1] It is characterized by poorly demarcated erythema with oedema, vesicles, and weeping in the acute stage. Recurrent episodes of flares eventually lead to lichenification.[2,3] To date, AD remains a clinical diagnosis. Hanifin and Rajka criteria, the first validated diagnostic tool for

Corresponding Author
Dr Lee Sut Enn
Department of Dermatology,
Hospital Umum Sarawak,
Jalan Hospital,
93586 Kuching, Sarawak.
Email: sutenn0601@yahoo.com

AD comprised of 4 major and 23 minor features.[4] The United Kingdom Working Party (UKWPD) refined and proposed new criteria in the '90s to improve practical applicability.[5] This has become a major advantage as its simplicity is favoured among researchers, particularly in population-based epidemiology studies.[5,6]

The prevalence of AD among children was reported between 5 to 25%. The International Study of Asthma and Allergies in Childhood (ISAAC) revealed that the prevalence of AD among Malaysian children in 2003 was 9.9% to 12.6%.7 The impact on the quality of life among affected children and families was significant with the increase in AD. While the existing local literature on AD was West Malaysia based,[7-14] lesser was known about the disease burden and sociodemography in East Malaysia. The prevalence of AD in the East could differ from the West Malaysia due to the distinctive racial diversity, cultural background and urbanisation. Our study aimed to establish and analyze the epidemiological background, risk factors, and treatment modalities of AD and its impact on the quality of life among the affected children and their families in Kuching, Sarawak.

Materials and Methods

This was a cross-sectional and observational population-based study of primary school children in Kuching, the capital city of Sarawak. Four out of 61 public national primary schools were selected by simple random selection to fulfil the calculated sample size of 954 students at 95% confidence interval. The 4 schools were SK Jalan Ong Tiang Swee, SK Batu Lintang, SK James Quop, and SK Chung Hua Pangkalan Baru. All Malaysian children attending the selected schools, from standard one to six, aged between 7 to 12 years were included.

The data collection commenced from January to December 2020 upon approval from the medical ethics committee. Questionnaire was utilized as research investigation tool and printed in multi-lingual hard copy format (Bahasa, English and Chinese). Written consent was obtained from parents. The respondents were the parents or guardians, and the children.

Clinical skin examination and collection of questionnaires were then conducted at the school premises 2 weeks later. Questionnaires were checked to ensure completeness. Parents or guardians were contacted for incomplete questionnaires. Students who were absent or unconsented during the day were given another date for examination.

Data analysis was done using IBM SPSS Statistics Version 22.0. Descriptive statistics such as mean with standard deviation or frequency with percentage were used to determine the characteristic of the students and the prevalence of AD. Univariate analysis Pearson's Chi-square test was applied to determine the association of the risk factors towards AD and the factors affecting AD children's quality of life. Logistic regression was used in multivariate analysis. $P \leq 0.05$ was considered significant.

Questionnaire

The questionnaire was composed of 3 sections and translated in 3 languages (English, Malay and Chinese). The questionnaire was completed by the parents, or guardians together with their children (except question 6 of section 2 was filled by research team). Section 1 assessed the basic socioeconomic background of the children and their families. Age, sex, ethnicity, number of siblings, order in family, anthropometric measurement, parents' education and occupation, family history of atopy (based on doctor's diagnosis), aggravating factor, treatments used and choice of medical advice were collected.

Section 2 was for the diagnosis of AD through a validated UKWPD criteria.[5] (1) A child must have an itchy skin condition, plus 3 or more of: (2) history of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck; (3) onset under the age of 2 (4) a personal history of asthma or allergic rhinitis; (5) a history of general dry skin in the last year; (6) visible flexural eczema noted by the research team.

Section 3 measured the quality of life in AD children and their family using validated questionnaires, Children's Dermatology Quality Life Index (CDLQI) and Dermatitis Family Impact (DFI).[15,16] CDLQI consisted of 10 subjects and 7 domains related to the week before assessment. The domains are Symptoms (Itchy, sore or pain); Emotion (Embarrassment, sadness, or self-conscious); Leisure (Clothing, going out and play, or hobbies, swimming or other sports); Personal relationships

(Friendships, bully or teasing); School or holidays; Sleep; and Treatment problem. DFI consisted of 10 subjects to measure how much having a child with AD affected the quality of life of the other (adult) members of the family in a one week recall period. For both questionnaires, each question is given a score based on the choice of the respondent, 0 points for "not at all", 1 point for "a little", 2 points for "a lot" and 3 points for "very much". The sum of all 10 questions gives a total score range of 0 to 30.

Clinical Examination

All the consented children were examined at the selected school by the clinical team, consisting of the investigator, medical officers, medical assistant, and staff nurses from Sarawak General Hospital's dermatology clinic. Clinical features of AD and its severity were determined during the examination. Two standardised AD severity scores were used-Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA) scale.[17,18]

EASI score is a tool to measure the extent and severity of AD. The assessment is based on 4 body regions-head & neck, trunk, upper and lower extremities. Extent and severity of eczema signs are evaluated for each body region. The extent is based on percentage of skin affected by eczema and charted on a score from 0 to 6. The severity of eczema signs, including erythema, oedema or papulation, excoriation, and lichenification are charted as none (0 points), mild (1 point), moderate (2 points) or severe (3 points). The final score is the sum of the 4 region scores, which ranges from 0 to 72. A higher score denotes greater AD severity. The 5-point IGA scale categorises the AD severity as clear, almost clear, mild, moderate and severe. The gradings are based on inflammatory signs like the degree of erythema, population or induration, lichenification, and oozing or crusting.

Results

Primary School Children's Demography

A total of 968 from 1133 school children were enrolled in the study, giving a response rate of 85.4%. SK Jalan Ong Tiang Swee contributed 491 students to the study (97.8% response rate). This was followed by 194 students from SK Batu Lintang (60.6%), 159 students from SK James Quop (88.8%), and 124 students from SK Chung Hua Pangkalan Baru (93.9%). Of the 165 students who were not included, they were either absent during the clinical examination or given no consent. Refer to Table 1 for the overall school children's sociodemography.

Children with Atopic Dermatitis

The prevalence of atopic dermatitis in school children was 7.0%. There were 68 students with atopic dermatitis, 38 were girls and 30 were boys, giving a slight predilection for girls with a M:F ratio of 1:1.27. Most of the children with AD were 7 to 9 years old (54.4%).

In this study, AD was more common among Malays (29.4%) and Chinese (25.0%) when compared to the Dayaks [Bidayuh (17.6%) and Iban (20.6%)]. Other ethnicities accounted for 7.3%. The finding was relatively similar to Kuching's racial distribution. The 10 Indians in this study had no atopic dermatitis. The Malay children were mostly in the elder age group, especially 12 years old (35.0%). On the other hand, Dayak children with AD were younger, between 7 to 9 years (61.5%).

Children with AD also had concomitant bronchial asthma (36.8%) or allergic rhinitis (61.2%). One-quarter of the children had AD only (25.0%). Sixteen children (23.5%) had all the 3 diseases. Asthma was more common among Ibans and Bidayuh (56.0%), while more Malays and Chinese (51.4%) had allergic rhinitis. Around 80% of the children with AD had at least one first degree family member with atopy. Those affected family members were either one or both parents (50.0%), especially mother. The remaining half was a combination of siblings and parents. Mother was the most common family member to have atopic dermatitis (46.3%), asthma (48.2%) and allergic rhinitis (72.4%). There were 14 AD children with no family history of atopy. In contrast, family history of atopy was significantly less in children without AD, accounted for 29.6%. Most of the children had less than 4 siblings (73.5%). Thirty- seven were the firstborn in the family, either the only child (37.8%) or eldest among siblings (62.2%).

The two most common aggravating factors were dust and hot weather. Most seek professional medical help as their first choice (85.3%). Those parents who seek consultation from a doctor preferred private

practitioners or dermatologists (71.8%) over public polyclinic practitioners (23.5%). Neither ethnicity nor the parents' education level had influenced the choice of consultation. We found that 67.6% of AD children used moisturisers as part of the treatment. Half of them took antihistamines and applied topical corticosteroids (Table 2).

Although Pearson Chi-Square showed seven variables (only child, order in family, concurrent atopy and family history of atopy) were associated with AD (Table 1), a subsequent binary logistic regression revealed 4 variables remained statistically significant ($p<0.05$). Eldest in the family was 2.6 times (95% CI 1.4, 4.6) more likely to have AD than non-firstborn. The risk of having AD tripled in children with existing allergic rhinitis (95% CI 2.0, 6.9) and doubled in asthma (95% CI 1.3, 5.1). Meanwhile, children with family history of eczema were 7 times (95% CI 3.9, 13.6) more likely to have AD than non-family history. Refer Table 3.

UKWPD Criteria and Atopic Dermatitis Severity (EASI and IGA)

Pruritus is a mandatory feature for diagnosis of AD. Thirty-eight (55.9%) school children fulfilled 4 criteria, 16 (23.5%) met 5 criteria, 7 (10.3%) met 6 criteria, and 7 (10.3%) had all 7 criteria. Half of them had dry skin (51.5%). Majority of the parents reported that the disease affected skin creases (89.7%) in the past, and approximately 80% of the children with AD had visible flexural dermatitis during clinical examination. For the AD children with onset below the age of two, 52.9% had asthma, 58.8% had allergic rhinitis and one third had all the 3 atopic diseases. (Table 2).

Overall, school children with AD were mild with a mean EASI score (SD) of 1.50 (2.0). Majority of the AD children (98.5%) had EASI score less than 7. Scores were higher on limbs compared to head, neck and trunk. Similarly, IGA based assessment showed that more than half (54.4%) of the school children had almost clear to clear disease, 35.3% had mild disease, and 10.3% had moderate disease. None of the children had severe or very severe disease. Children with IGA-based moderate disease had a mean EASI score (SD) of 5.1 (3.75); whereas mean EASI score (SD) for children with IGA-based mild disease was 1.5 (0.76) and IGA-based almost-clear to clear disease was 0.56 (0.61). (Table 4).

CDQLI and DFI in Quality of Life

In our series, CDLQI revealed that 90% of school children's quality of life was affected by AD to varying degrees; more than half (52.9%) experienced moderate to large effect on daily living. We had 19 (27.9%) children whose AD significantly affected their quality of life with CDLQI score of more than 10. Two out of them (2.9%) had scored the highest 19 points. (Table 5) The most affected domain was "Symptoms" [1.35 (0.69)], followed by "School or holiday" [0.97 (1.41)], "Embarrassment" [0.96 (0.89)], "Treatment problem" [0.76 (0.85)] and "Go out & Play" [0.75 (0.82)]. Girls were slightly more affected than boys in all the domains. Looking into the those 19 children's family aspect, 13 families were severely affected with DFI score more than 10 (68.4%). The families of two children who scored highest in CLDQI also had higher DFI scores, 14 and 29. The other 6 families (31.6%) were moderately affected, and the scores were in the range of 6 to 10. The affected domains in DFI were treatment impact [0.97 (1.17)], household expenditures [0.87 (0.91)], and housework [0.74 (0.84)]. Parents had to take more effort and time to prepare the children's meals [0.62 (0.79)]. (Table 6).

We used logistic regression to appraise the relationship between severity of AD to children and family's quality of life. The univariate analysis showed that both the IGA and EASI scores negatively impacted children's quality of life. IGA severity was statistically significant to the domains of CDQLI ($p=0.002$). This relationship remained significant ($p=0.002$) after controlled for selected covariates such as gender, ethnicity and BMI. Post-hoc analysis showed strong association between moderate disease vs clear ($p=0.012$), moderate disease vs almost clear ($p=0.004$) and moderate disease vs mild disease ($p<0.001$). Likewise, statistical significance was seen between EASI severity and CDQLI in one-way ANCOVA ($p=0.025$). Higher EASI scores were associated with a greater impact on children's quality of life. Univariate and multivariate analysis showed no statistical significance between the severity scores and DFI. (Table 7).

Table 1. Demography of primary school children in Kuching

Category		AD	No AD	Total	*p*-value
		n (%)	n (%)	n (%)	
Sex	Male	30 (44.1)	482 (53.6)	512 (52.9)	0.133
	Female	38 (55.9)	418 (46.4)	456 (47.1)	
Age	7-8	23 (33.8)	307 (34.1)	330 (34.1)	0.863
	9-10	26 (38.2)	318 (35.3)	344 (35.5)	
	11-12	19 (27.9)	275 (30.6)	294 (30.4)	
Race	Iban	14 (20.6)	194 (21.6)	208 (21.5)	0.556
	Malay	20 (29.4)	223 (24.8)	243 (25.2)	
	Chinese	17 (25.0)	174 (19.4)	191 (19.8)	
	Bidayuh	12 (17.6)	214 (26.8)	253 (26.2)	
	Melanau	2 (2.9)	18 (2.0)	20 (2.1)	
	Indian		10 (1.1)	10 (1.0)	
	Others	3 (4.4)	38 (4.2)	41 (4.2)	
Order in family	Only child	14 (20.6)	91 (10.7)	105 (11.4)	0.014
	Siblings	54 (79.4)	759 (89.3)	813 (88.6)	
	Eldest	23 (42.6)	220 (29.1)	243 (30.0)	0.037
	Non-firstborn	31 (57.4)	536 (70.9)	567 (70.0)	
BMI	Normal	40 (58.8)	592 (65.9)	632 (65.4)	0.295
	Overweight	9 (13.2)	127 (14.1)	136 (14.1)	
	Obese	19 (27.9)	180 (20.0)	199 (20.6)	
Other atopic diseases	Asthma				<0.05
	Yes	25 (36.8)	67 (7.8)	92 (9.9)	
	No	43 (63.2)	791 (92.2)	834 (90.1)	
	Allergic rhinitis				<0.05
	Yes	42 (61.8)	153 (17.8)	195 (21.1)	
	No	26 (38.2)	705 (82.2)	731 (78.9)	
Family history	Atopy				<0.05
	Yes	54 (79.4)	266 (29.6)	320 (33.1)	
	No	14 (20.6)	634 (71.4)	648 (66.9)	
	Asthma				<0.05
	Yes	29 (42.6)	158 (17.6)	187 (19.3)	
	No	39 (57.4)	742 (82.4)	781 (80.7)	
	Allergic rhinitis				<0.05
	Yes	29 (42.6)	124 (13.8)	153 (15.8)	
	No	39 (57.4)	776 (86.2)	815 (84.2)	
	Eczema				<0.05
	Yes	41 (60.3)	113 (12.6)	154 (15.9)	
	No	27 (39.7)	787 (87.4)	814 (84.1)	
Parents education	None	3 (2.2)	13 (0.8)	16 (0.9)	0.017
	Primary	1 (0.8)	108 (6.9)	109 (6.4)	
	Secondary	53 (40.2)	879 (56.4)	932 (55.1)	
	University / College	75 (56.8)	558 (35.8)	633 (37.5)	
Household [mean (SD)]	Size	4.63 (1.40)	4.91 (1.28)	4.89 (1.29)	
	Birth order	1.76 (1.00)	2.14 (1.22)	2.11 (1.21)	
	Siblings no.	2.75 (1.31)	3.00 (1.28)	2.90 (1.28)	

Table 2. AD diagnosis, aggravating factors, choice of consultation and treatment pattern

	Parents / Guardian's Response, n (%)	
	Yes	No
UKWPD Questions for AD diagnosis		
Q1 - Itchy	68 (100.0)	0
Q2 - Age onset		
Under 2	34 (50.0)	
2 to 5	15 (22.1)	
5 to 10	16 (23.5)	
Over 10	3 (4.4)	
Q3 - Skin creases	61 (89.7)	7 (10.3)
Q4a - Asthma	25 (36.8)	43 (63.2)
Q4b - Allergic rhinitis	42 (61.8)	26 (38.2)
Q5 - Dry skin	35 (51.5)	33 (48.5)
Q6 - Visible flexural dermatitis	55 (80.9)	13 (19.1)
Aggravating factors		
Dust	50 (73.5)	18 (26.5)
Hot weather	47 (69.1)	21 (30.9)
Food	28 (41.2)	40 (58.8)
Grass intolerance	24 (35.3)	44 (64.7)
Furry pets	23 (33.8)	45 (66.2)
Physical exercise	16 (23.5)	52 (67.5)
School stress	7 (10.3)	61 (89.7)
Preferred healthcare provider		
Doctor	58 (85.3)	10 (14.7)
Private general practitioner	31 (36.5)	
Dermatologist	30 (35.3)	
Public polyclinic doctor	20 (23.5)	
Emergency department	4 (4.7)	
Pharmacist	40 (58.8)	28 (41.2)
Family or friends	10 (14.7)	58 (85.3)
Traditional healer / Alternative medicine	8 (11.8)	60 (88.2)
Treatment modalities		
Moisturisers or Emollients	46 (67.6)	22 (32.4)
Antihistamines	36 (52.9)	32 (47.1)
Steroids		
Oral	6 (8.8)	62 (91.2)
Topical	34 (50.0)	34 (50.0)
Antibiotics	19 (27.9)	49 (72.1)
Traditional herbs	9 (13.2)	59 (86.8)

Table 3. The risk factors of atopic dermatitis

Factors	OR	95% CI		*p*-value
Eldest among siblings	2.57	1.43	4.62	0.002
Concomitant asthma	2.54	1.28	5.06	0.008
Concomitant allergic rhinitis	3.75	2.05	6.87	0.000
Family history of asthma	1.23	0.65	2.29	0.526
Family history of allergic rhinitis	1.24	0.64	2.41	0.528
Family history of atopic dermatitis	7.24	3.86	13.58	0.000

Table 4. Severity of AD by EASI and IGA

EASI (Total scores)#	n (%)	IGA	n (%)
Clear (0)	10 (14.7)	Clear	11 (16.2)
Almost clear (0.1-1.0)	28 (41.2)	Almost clear	26 (38.2)
Mild (1.1-7.0)	28 (41.2)	Mild disease	24 (35.3)
Moderate (7.1-21.0)	2 (2.9)	Moderate diseases	7 (10.3)
Severe (21.1-50.0)	0	Severe diseases	0
Very severe (50.1-72.0)	0	Very severe diseases	0

#Mean total EASI score (SD)=1.50 (2.0). Mean EASI score (SD) for each section-head & neck 0.03 (0.14); trunk 0.20 (0.44); upper limb 0.44 (0.53); and lower limb 0.83 (1.11)

Table 5. The scores for CDQLI and DFI

	n (%)				
Scores*	0 to 1	2 to 5	6 to 10	11 to 20	21 to 30
CDLQI	10 (14.7)	22 (32.4)	17 (25.0)	19 (27.9)	0
DFI	17 (25.0)	25 (36.8)	11 (16.2)	14 (20.6)	1 (1.5)

**Scores interpretation: 0-1=no effect; 2-6=small effect; 7-12=moderate effect; 13-18=very large effect; 19-30=extremely large effect*

Table 6. Mean score and standard deviation of each domains in CDLQI and DFI

	Mean Score (SD)			
CDLQI (n=68)	**Total**	**Boys**	**Girls**	***p*-value**
Q1 - Itchy, Sore or Pain	1.35 (0.69)	1.40 (0.81)	1.32 (0.57)	0.633
Q2 - Embarrassed	0.96 (0.89)	0.90 (1.00)	1.00 (0.81)	0.156
Q3 - Friendship	0.26 (0.61)	0.27 (0.69)	0.26 (0.55)	0.788
Q4 - Clothes	0.65 (0.75)	0.83 (0.83)	0.50 (0.65)	0.350
Q5 - Go out & Play	0.75 (0.82)	0.67 (0.84)	0.82 (0.80)	0.812
Q6 - Swimming or Sports	0.63 (0.95)	0.57 (0.86)	0.68 (1.02)	0.270
Q7 - School or Holiday	0.97 (1.41)	0.70 (1.29)	1.18 (1.49)	0.162
Q8 - Bully	0.29 (0.69)	0.30 (0.65)	0.29 (0.73)	0.950
Q9 - Sleep	0.63 (0.85)	0.57 (0.86)	0.68 (0.84)	0.769
Q10 - Treatment problem	0.76 (0.85)	0.70 (0.88)	0.82 (0.83)	0.589
Total score	**7.26 (5.53)**	**6.90 (5.85)**	**7.55 (5.33)**	**0.931**
DFI (n=68)				
Q1 - Housework	0.74 (0.84)	0.60 (0.77)	0.84 (0.89)	0.791
Q2 - Feeding	0.62 (0.79)	0.57 (0.82)	0.66 (0.78)	0.830
Q3 - Sleep	0.56 (0.80)	0.50 (0.78)	0.61 (0.82)	0.728
Q4 - Family activity	0.44 (0.70)	0.27 (0.52)	0.58 (0.79)	0.055
Q5 - Shopping	0.34 (0.66)	0.23 (0.43)	0.42 (0.79)	0.218
Q6 - Expenditure	0.87 (0.91)	0.73 (0.91)	0.97 (0.92)	0.387
Q7 - Tiredness	0.47 (0.78)	0.47 (0.78)	0.47 (0.80)	0.785
Q8 - Emotion	0.49 (0.74)	0.40 (0.56)	0.55 (0.86)	0.052
Q9 - Relationship	0.25 (0.56)	0.20 (0.41)	0.29 ± 0.65	0.146
Q10 - Treatment impact	0.97 (1.17)	1.03 (1.27)	0.92 (1.10)	0.187
Total score	**5.74 (6.12)**	**5.00 (5.32)**	**6.32 (6.70)**	**0.241**

Table 7. Relationship between AD severity (by IGA or EASI) and Quality of life (by CDQLI or DFI)

	Univariate		Multivariate	
Factors	**CDLQI**	**DFI**	**CDLQI**	**DFI**
IGA	0.002[a]	0.242[a]	0.002+	nil
EASI	0.023[c]	0.248[c]	0.025[b]	nil

The p-value for multivariate analysis were derived after controlled for gender, ethnicity and BMI category.
[a]p-value was derived from one-way ANOVA; [b]p-value was derived from ANCOVA; [c]p-value was derived from linear regression

Discussions

Prevalence and Risk Factors

AD is one of the most common skin disorders affecting up to 20% of children in some countries.[7] Approximately 28% of the Malaysian population are children.[19] The ISAAC study published our national prevalence of AD as 11.0% (6-7 years old) and 9.3% (13-14 years old) in 2008, based on population study in cities of West Malaysia (WM).[7,20] The urbanization of Malaysia's cities over the decades has led to the rise of AD prevalence by nearly 4 folds.[7]

This is the first population-based study of AD among school children in Kuching, in the age group of 7 to 12. Based on the UKWPD criteria questionnaire and clinical examination, the overall prevalence of AD was 7% and girls (8.3%) were more prevalent than boys (5.9%). This was comparable to the 7.6% of AD prevalence among secondary school children in Kota Kinabalu, the capital city in another state in East Malaysia, Sabah.[21]

However, the age-specific prevalence of AD in our study was lower than that in WM. The discrepancy might have been attributed to many studies done in WM that were either clinic or hospital-based.[8,9,10,11] There were two population-based studies from WM that reported a higher prevalence, 13.7% (5 to 7 years old) and 13.5% (Preschool age, less than 6 years old).[12-14] This could be due the difference in ethnic mix of children, age and environmental factors. It was also well recognised that AD prevalence varied between rural and urban areas. WM developed at a pace greater than EM due to geographical and logistic differences. Several studies reported a higher prevalence in specific races.[20,22,23] ISAAC study showed a significant difference in the prevalence of both within countries and between geographical areas.[5,20] Scandinavia, Western Europe, Australasia, and urban areas in Africa have a higher prevalence rate than China, the Middle East, Central Asia and Eastern Europe.[24] Children in our cohort were of diversified racial background while other studies from WM were predominantly Malays (80-90%) and Chinese. The prevalence of AD in Iban (6.7%) and Bidayuh (4.7%) children were slightly lower when compared to Malays (8.2%) or Chinese (8.9%). Nonetheless, these data showed that AD is common among school children in Malaysia.

The prevalence of AD is known to decrease with age;[25] however, we found no difference in the prevalence of AD between 7 to 12 years old. A stable trend was noticed at a range of 6.4% to 8.0%. Prevalence was highest in 12 years old (8.4%) and lowest in 11 years old (4.6%).

AD is a known disease of infancy and childhood, in which more than 80% had onset before the age of 7 years.[26] Half of children with AD in our series had onset before the age of 2 years. Only 3 of the children had onset after the age of 10 (4.4%). The finding corresponded to a study in preschool children in Kuala Lumpur, 70% of children had AD onset less than 2 years old.[14] A population-based study in Singapore also recorded similar results.[27] A clinic-based study at the paediatric institute reported early onset of disease with a median age of diagnosis of 22 months.[28] Late-onset of AD is otherwise not uncommon. A study from the National University of Malaysia showed that 22.6% of patients had late onset of AD between 11 to 30 years old.[10] Another cohort also reported that 32.2% of children had disease onset after the age of 7 years.[29]

AD was more common in girls, despite there being more boys in this study. The M:F ratio was the most apparent amongst 12-year-olds (1:2). One population-based study in Australia also found higher prevalence in girls, either by clinical examination (17.7%) or UKWPD criteria (12.3%) than boys, 14.8% and 9.2% respectively.[30] The female preponderance is similar to the ISAAC study and another clinic-based local study.[5,11] On the other hand, other local studies showed more males affected with M:F ratio of 1.7:1.[10,14,28] A Korean review article mentioned that boys were more likely to develop AD than girls during infancy, but there was a girls predominance in adolescence.[31]

Family history of atopy was the single most

critical risk factor for atopy among children.[32] We found similar association in our cohort with a sevenfold increase risk of getting AD. Children with concomitant asthma or allergic rhinitis had doubled to a tripled risk of developing AD. Approximately three-quarter of the school children in this series had at least one concomitant atopic disease. A study in Taiwan also showed increased risk of AD development by two folds among atopy children.[33] The local study had shown significant association between AD and concomitant atopic diseases.14 Our study also showed that the eldest in the family had tripled AD development risk. Studies on siblings suggested a diminished risk of atopy in younger siblings due to the protective effect of early-life viral infections.[34]

Quality of Life among AD Children

AD's chronic and recurrent nature incurred significant negative impact on both affected children and their families.[35] In our study, AD had influenced the children's quality of life in various aspects, even though most had mild course of disease. This was also true in a factor analysis study done in Hong Kong.[36] The most affected domains were "Symptoms", "Emotions" and "School or holiday". Literature had shown consistent results in many studies worldwide.[28,36-41] Constant itch, sore or pain was the most significantly affected psychosocial domains among children with AD. The biggest challenge in AD is the management of itch. Itch had disturbed half of the children's sleep and 50% of them responded "very much" and "quite a lot". Sleep deprivation would affect a child's behavioural development and school performance in longterm.[35,42]

Feeling of embarrassment, self-conscious, upset and sad among the AD children, particularly girls, had indirectly taken a toll on school work and holiday enjoyment. Children with AD often shy away from their peers due to chronic and visible skin lesions.[43] It also affected the domain "Go out & play and swimming or sports". The stigmatization and negative changes of self-perception would gradually drain the children emotionally to mental distress. Although the disease did not affect the domain "friendship' and "bully", careful attention must be emphasized to keep the social stigma of AD at minimal level in schools. The social relations with peers in this age group grow significantly.[44]

Almost a quarter of the AD children also felt that "Treatment" had bothered them at certain extend. A Thai study reported that taking oral medications, especially number of medications could significantly affect quality of life of the children and caretakers.[37] Parental admonitions may further stigmatize the AD children to additional isolation.[43] In our study, children between 10 to 12 years were more affected than juniors (7 to 9 years) in most domains, particularly physical symptoms, school work or holiday enjoyment and emotions. Pre-adolescent children are more self-aware and have a better cognitive, psychosocial and emotional development.[45] They are in transition between childhood and adulthood to gain independence and establish a secure identity. This group of children's self-expression and concern on AD, including emotion and treatment, must be addressed during clinic consultation.

Quality of Life among Families of AD Children

AD affects the social and emotional aspects of families of AD children. A study showed that restrictions of everyday family life and limitations with stringent treatment regimes have led to parental exhaustion, hopelessness, guilt, anger and depression.46 Caring for a child with AD requires adjustments to family lifestyles and incurs financial costs.[47]

Domains that were affected were "Treatment impact", "Expenditure", "Housework", and "Feeding". About a quarter of the family felt "A lot" and "Very much" affected by the "Treatment impact". The family of children with clear to mild disease responded to "Treatment impact" with a mean score (SD) of 0.84 (1.07), compared to those with a moderate disease which was significantly higher, 2.57 (1.13). This was in accordance with other studies.[28,37,48] Parents had spent more time and effort helping the children deal with the disease and its treatment, in addition to the chores in the house, especially to keep the linens clean and environment dust-free. Some of the parents believed that certain foods could aggravate the disease and were meticulous with meal preparation for the family. Consequently, adaptations to family lifestyles have expectedly increased the overall household expenses. The treatment of AD could be costly if parents self-purchased medications, seek consultation from private clinics and alternative

treatment practitioners.

Co-sleeping is a common habit in Malaysia. The mean score (SD) of domain "Sleep" in family members was 0.56 (0.80). There were 16% of them responded to sleep disturbances as "A lot" and "Very much", of which half of the children had mild to moderate disease. This negative effect on parental sleep pattern was also reported in a Thai study.[37]
In our study, majority of the primary caregivers were working parents. Twenty AD children's mothers were housewives. Nevertheless, the domains like "Relationship", "Emotion" and "Tiredness" were less affected. Less than 10% of families regarded those as "very much" or "A lot". This could be explained by the fact that approximately one-third of mothers had atopy. Their personal experience helped in coping and understanding the disease. Mothers were able to cope with emotional distress and exhaustion despite feeling more occupied with childcare. Our cohort of school children was predominantly mild in disease severity. Literature showed that parents of children with more severe AD had more impact on emotional distress.48 We found that those families that responded with profound impact on "Relationship", "Emotion" and "Tiredness" were in the younger age group (7 to 9 years), about 10% had moderate disease. More than 90% had no family history of atopy.

Intervention in AD School Children

The clinical assessment had given the study a great advantage to understand the AD disease burden among school children. We noticed that 33% of children with AD were not using moisturizers, which is the main therapy that improves skin barrier and reduces pruritus.[49] Emollient therapy has proven to enhance topical corticosteroids' efficacy, thus reducing its steroid usage and dependency.[50] The research findings enable our team to plan and organize educational programs for the children and parents, which encompasses disease knowledge, prevention of triggers, practical skincare, treatment and wholesome AD's management. School children with moderate disease or frequent flares were given appointment to be managed and followed up at Sarawak General Hospital's dermatology clinic.

Conclusion

Atopic dermatitis is common among school children in Kuching. This study gave insight into AD in school children and acknowledged that AD had a significant physical, emotional and social impact on the affected children and their families, although the majority were mild in severity. The association between AD and other atopic diseases vis-à-vis asthma, allergic rhinitis is demonstrated, as is the association with genetic tendencies of AD's development. Clinicians should incorporate measurement of quality of life to accurately assess AD severity to improve long term management of AD.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

References

1. Development group of Ministry of Health and Ministry of Education. Malaysia Clinical Practice Guidelines: Management of atopic eczema, 1st ed. Putrajaya. Malaysian Health Technology Assessment Section (MaHTAS) 2008:1-2.
2. Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med 2005;352:2314-24.
3. Simpson EL, Leung DYM, Eichenfield LF, Boguniewicz M. Atopic dermatitis. In Fitzpatrick's dermatology (Volume 1) 9th Ed. New York. McGraw-Hill Education 2019:363-456.
4. Hanifin JM, Rajka G. Dianostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;59:44-7.
5. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol 1994;131:406-16.
6. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol 2008;158:754-65.
7. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multi country cross-sectional surveys. Lancet 2006;368:733-43.
8. Pettit JHS. Perspectives in dermatology: Malaysia. Int J Dermatol 1976;15:505-12.
9. Low SG. Pattern of skin diseases in Alor Setar skin clinic. Malaysian J Dermatol 1988;2:20-8.
10. Jaafar RB, Pettit JH. Atopic eczema in a multiracial country (Malaysia). Clin Exp Dermatol 1993;18:496-9.
11. Kwan Z, Wong SM, Robinson S, Tan LL, Ismail R. Pattern of skin diseases among patients attending an outpatient dermatology clinic in a tertiary hospital in urban Malaysia. Australas J Dermatol 2017;58:e267-8.
12. Quah BS, Razak AR, Hassan MH. Prevalence of asthma, rhinitis and eczema among schoolchildren in Kelantan,

Malaysia. Acta Paediatr Jpn 1997;39:329-35.
13. Quah BS, Wan-Pauzi I, Ariffin N, Mazidah AR. Prevalence of asthma, eczema and allergic rhinitis: two surveys, 6 years apart, in Kota Bharu, Malaysia. Respirology 2005;10:244-9.
14. Goh YY, Keshavarzi F, Chew YL. Prevalence of atopic dermatitis and pattern of drug therapy in Malaysian children. Dermatitis 2018;29:151-61.
15. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol 1995;132:942-9.
16. Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: The Dermatitis Family Impact Questionnaire. Br J Dermatol 1998;138:107-13.
17. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10:11-8.
18. Simpson E, Bissonnette R, Eichenfield LF, Guttman-Yassky E, King B, Silverberg JI et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. J Am Acad Dermatol 2020;83:839-46.
19. Department of Statistics Malaysia. Press release: Children statistics, Malaysia, 2019. [Accessed in Nov 2019] Available from: https://www.dosm.gov.my/v1/index.php?r=column/pdfPrev&id=c3I4eitkb1RZTlMvUjNLZVRBMExVQT09
20. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. J Allergy Clin Immunol 1999;103:125-38.
21. Leung R, Ho P. Asthma, allergy, and atopy in three south-east Asian populations. Thorax 1994;49:1205-10.
22. Janumpally SR, Feldman SR, Gupta AK. In the United States, blacks and Asian/Pacific Islanders are more likely than whites to seek medical care for atopic dermatitis. Arch Dermatol 2002;138:634-7.
23. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol 2011;131:67-73.
24. Yong AMY, Tay YK. Atopic dermatitis: Racial and ethnic differences. Dermatol Clin 2017;35:395-402.
25. Chidwick K, Busingye D, Pollack A, Osman R, Yoo J, Blogg S et al. Prevalence, incidence and management of atopic dermatitis in Australian general practice using routinely collected data from Medicine Insight. Australas J Dermatol 2020;61:e319-27.
26. Rajka G. Essential Aspects of Atopic Dermatitis, 1st ed. Berlin. Springer-verlag 1989:4-55.
27. Tay YK, Kong KH, Khoo L, Goh CL, Giam YC. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. Br J Dermatol 2002;146:101-6.
28. Aziah MS, Rosnah T, Mardziah A, Norzila MZ. Childhood atopic dermatitis: a measurement of quality of life and family impact. Med J Malaysia. 2002;57:329-39.
29. Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. Br J Dermatol 1998;139:834-9.
30. Marks R, Kilkenny M, Plunkett A, Merlin K. The prevalence of common skin conditions in Australian school students: 2. Atopic dermatitis. Br J Dermatol 1999;140:468-73.
31. Pyun BY. Natural history and risk factors of atopic dermatitis in children. Allergy Asthma Immunol Res 2015;7:101-5.
32. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 1998;101:587-93.
33. Ho CL, Chang LI, Wu WF. The prevalence and risk factors of atopic dermatitis in 6-8 year-old first graders in Taipei. Pediatr Neonatol 2019;60:166-71.
34. Von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. BMJ 1994;308:692-5.
35. Ng MS, Tan S, Chan NH, Foong AY, Koh MJ. Effect of atopic dermatitis on quality of life and its psychosocial impact in Asian adolescents. Australas J Dermatol 2018;59:e114-7.
36. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? Clin Exp Dermatol 2008;33:705-9.
37. Wisuthsarewong W, Nitiyarom R, Boonpuen N. Childhood atopic dermatitis: Impact on quality of life in Thai children and their families. Astrocyte 2017;4:144-8.
38. Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. Pediatrics 2004;114:607-11.
39. Finlay AY. Quality of life in atopic dermatitis. J Am Acad Dermatol 2001;45:S64-6.
40. Xu X, van Galen LS, Koh MJA, Bajpai R, Thng S, Yew YW et al. Factors influencing quality of life in children with atopic dermatitis and their caregivers: a cross-sectional study. Sci Rep 2019;9:15990.
41. Ražnatović Đurović M, Janković J, Tomić Spirić V, Relić M, Sojević Timotijević Z, Ćirković A et al. Does age influence the quality of life in children with atopic dermatitis? PLoS One 2019;14:e0224618.
42. Fishbein AB, Vitaterna O, Haugh IM, Bavishi AA, Zee PC, Turek FW et al. Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. J Allergy Clin Immunol 2015;136:1170-7.
43. Chernyshov Stigmatization and self-perception in children with atopic dermatitis. Clin Cosmet Investig Dermatol 2016;9:159-66.
44. Eccles JS. The development of children ages 6 to 14. Future Child 1999;9:30-44.
45. Sanders RA. Adolescent psychosocial, social, and cognitive development. Pediatr Rev 2013;34:354-8.
46. Pustišek N, Vurnek Živković M, Šitum M. Quality of Life in Families with Children with Atopic Dermatitis. Pediatr Dermatol 2016;33:28-32.
47. Al Shobaili HA. The impact of childhood atopic dermatitis on the patients' family. Pediatr Dermatol 2010;27:618-23.
48. Monti F, Agostini F, Gobbi F, Neri E, Schianchi S, Arcangeli F. Quality of life measures in Italian children with atopic dermatitis and their families. Ital J Pediatr 2011;37:59.
49. Van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. Cochrane Database Syst Rev 2017;2:CD012119.
50. Grimalt R, Mengeaud V, Cambazard F; Study Investigators' Group. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. Dermatology 2007;214:61-7.

ORIGINAL ARTICLE

The Association of Skin and Nasal Colonisations of *Staphylococcus aureus* in Children with Atopic Dermatitis with Disease Severity and Its Impact on Quality of Life

Jin Huang Lim[1], *MRCP*, Anis Roziana Mohamad[2], *MPath*, Kwee Eng Tey[1], *MRCP*

[1]Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia
[2]Department of Microbiology, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia

Abstract

Background

Atopic dermatitis (AD) is a chronic, recurrent, pruritic inflammatory skin disease that causes significant burden to affected children. *Staphylococcus aureus* plays a vital role in AD, and its resistance to current topical antibiotics is worrying. This study aims to determine the frequency of *Staphylococcus aureus* colonisation and its resistance pattern. It further assesses the association between *Staphylococcus aureus* colonisation and disease severity; as well as its impact on quality of life.

Methods

A cross-sectional study was conducted among 153 children with AD. Skin and nasal swabs were collected. Antibiotic sensitivity to penicillin, cefoxitin, erythromycin, methicillin, clindamycin, gentamicin, trimethoprim/sulfamethoxazole, tetracycline, rifampicin, fusidic acid and linezolid were tested. Clinical evaluation was performed using the SCORing Atopic Dermatitis index (SCORAD). Quality of life was assessed with the Dermatological Life Quality Index (DLQI).

Results

Twenty-nine patients had positive skin swab results. One patient had methicillin-resistant *Staphylococcus aureus* isolated from nasal swab. Skin colonisation with *Staphylococcus aureus* (p=0.03) and DLQI (p<0.01) were significantly associated with disease severity. The resistant rate is highest in penicillin, followed by fusidic acid, tetracycline, and erythromycin.

Conclusion

Skin colonisation with *Staphylococcus aureus* is an indicator of disease severity in children with AD. Patients with severe disease have lower quality of life. Clinicians need to be aware of high resistance rates towards penicillin and fusidic acid and be prudent in the choice of antibiotics. Antiseptic wash can be considered in patients with *Staphylococcus aureus* colonisation.

Key words: *Staphylococcus aureus, Atopic dermatitis, Dermatological life quality index*

Corresponding Author
Dr Lim Jin Huang
Department of Dermatology,
Hospital Sultanah Aminah,
Jalan Persiaran Abu Bakar Sultan,
80100 Johor Bahru, Johor, Malaysia.
Email: jesling2001@yahoo.com

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, pruritic inflammatory skin disease with estimated prevalence of 10-30% in children and up to 2-5% in adults.[1,2] The incidence of AD appears to be increasing. A systematic review of epidemiologic studies performed between 1990 and 2010 in several regions found increasing trends in incidence

and prevalence of AD.[2] In addition, AD is the most significant contributor to the global burden of disease among skin diseases.[3]

Severe AD causes significant distress to the affected children and their parents.[4,5,6,7] Children with AD often have behavioural problems such as increased dependency, fearfulness, and sleep difficulties.[8] A holistic approach to patient care can be developed after recognising the impact of the disease. Clinicians will be more confident in judging the benefits of therapeutic interventions and ensuring compliance with therapy.

Skin is the biggest organ of the body and it interfaces with the environment. It has a complex ecosystem colonised by many microorganisms (that are either pathogen or mutualist), coexisting in a balance. Atopic dermatitis is well known to be associated with altered skin microbiota, with high prevalence of *Staphylococcus aureus* colonisation and superinfection. The AD skin has a favourable environment for colonisation and proliferation of *Staphylococcus aureus*. The bacteria is frequently found on the skin of AD patients (carriage rates of 30% to 100% depending on the study methodology), whereas in healthy subjects, the prevalence is about 10 to 20%.[9] The prevalence of nasal colonisation by *S. aureus* varies between 10 and 30%.[10,11]

Staphylococci can be mutualist or pathogen depending on its species. The dominant group of skin colonists is the coagulase-negatives, the most prominent of which, is *S. epidermidis*. The bacteria can be an opportunistic pathogen in the context of immunosuppression; it functions predominantly as a mutualist.

Skin-resident *Staphylococcus* species engage in microbe-microbe interactions that are beneficial to the host.[9,12] For example, *S. epidermidis* and *S. hominis* have been shown to secrete antimicrobial peptides that kill *S. aureus*, and transplantation of these species onto the skin of patients with atopic dermatitis led to decreased colonisation by *S. aureus*.[13] However, an association between *S. aureus* colonisation and AD severity is still inconclusive.[14,15,16]

It is not uncommon for children who present with AD to be treated with antibiotics and antiseptic, as this could lead to increased antibiotic resistance.[17] Many studies were done to establish the current antimicrobial resistances and susceptibilities to first-line antibiotic therapy.[18,19,20] With the rapid emergence of resistant bacteria worldwide, rationale use of antibiotics needs to be advocated.

The objectives of this study are to evaluate the frequency of skin and nasal colonisation by *Staphylococcus aureus* in children with atopic dermatitis. In addition, it aims to identify antimicrobial sensitivity, as well as establish the association between colonisation of *S. aureus* and disease severity, and its impact on psychosocial wellbeing of the children.

Materials and Methods

A cross-sectional study was conducted. A total number of 153 children (age below 18 years old) with confirmed diagnosis of atopic dermatitis by dermatologists were recruited between January 2020 and April 2020 from the Dermatology outpatient clinic of Hospital Sultanah Aminah, Johor Bahru, a tertiary hospital in Malaysia.

The estimated sample size was based on a study by Rezaei M, *et al*.[21] Sample size estimation was calculated using two population proportion formulae.[22] A minimum sample size of 153 samples per group is needed to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Pearson's Chi-square test for independence will be used to evaluate this null hypothesis. Exclusion criteria were patients who received oral or topical antibiotic four weeks before the study, patients who have coexisting inflammatory skin diseases, clinical evidence of cutaneous bacterial, viral or fungal infection and upper respiratory infection within four weeks.

A predesigned clinical research form for recording demographic data, medical history, clinical examination, and disease severity using SCORing Atopic Dermatitis (SCORAD) index was completed during the visit. By using the SCORAD index, the severity of eczema was scored in each patient as mild (<25), moderate (25-50) or severe (>50).[23,24] All patients and their parents were required to fill up a validated and licensed Dermatological Life Quality Index (DLQI) form according to the children's age

group. The DLQI stratifies the quality of life into five categories: no effect at all on patient's life (0-1), a small effect on patient's life (2-5), moderate effect on patient's life (6-10), very large effect on patient's life (11-20) and extremely large effect on patient's life (21-30).[25,26]

Skin and nasal swabs were collected from subjects using Micro Science Microbiology Transport Swab with Medium Amies with Charcoal. The skin swab was taken from an eczematous lesion. Levine method was used for obtaining the skin swab. Nasal swab was taken from both nostrils by using the same swab. Specimens were sent to the Department of Microbiology of Hospital Sultanah Aminah within 24 hours for processing.

The nasal sample was inoculated onto 10% sheep blood agar plates, whereas the skin sample was inoculated onto 10% sheep blood agar and MacConkey's medium. After 24 hours inoculation at 37°C, the agars were reviewed. *S. aureus* isolates were identified by a coagulase test (to differentiate *S. aureus* and *Staph spp.*) and catalase test (to differentiate *Strep spp.* and *Staph spp.*). *S. aureus* colony was cultured on the *Staphylococcus* panel including Cefoxitin disk (FOX-disk) for another 24 hours to test for methicillin resistance. The antibiotic sensitivity test is done according to the Clinical and Laboratory Standards Institute (CLSI, 2019). The tested antibiotics included penicillin, cefoxitin, erythromycin, methicillin, clindamycin, gentamicin, trimethoprim/sulfamethoxazole, tetracycline, rifampicin, fusidic acid and linezolid. The interpretation of the susceptibility was given as sensitive (S), intermediate susceptible (IS), or resistant (R) following standard recommendation.

The data analysis was done using the Statistical Package of the Social Science (SPSS) version 22 (IBM Corporation, CA). Descriptive analysis was performed and was presented as frequency and percentage. Association was analysed using Chi-square or Fisher's exact test. A value of $p<0.05$ is considered statistically significant. A graphical presentation was used to illustrate the antibiotic susceptibility. Ethics approval was obtained from the National Medical Research Registry, Malaysia (NMRR-19-3254-53344).

Results

From January 2020 through April 2020, a total of 153 patients with Atopic Dermatitis were screened and all were recruited. There were 111 preschool children (72.5%), 26 primary school children (17%) and 16 secondary school participants (10.5%). Eighty two participants (53.6%) were male. A hundred and twenty participants (78.4%) were Malay, 25 participants (16.3%) were Chinese and seven participants (4.6%) were Indian. Ninety six participants (62.8%) had normal body mass index (BMI), 25 participants (16.3%) were underweight, nine participants (5.9%) were overweight and 23 participants (15%) were obese. A hundred and thirty eight participants (90%) had family history of atopy. Seventy one participants (46%) had personal history of another atopy (Table 1). The SCORAD Index showed 30.7% mild, 53.6% moderate and 15.7% severe. For quality of life, six participants (3%) reported no effect at all, 40 participants (26.2%) reported a small effect, 51 participants (33%) reported moderate effect, 46 participants (30%) reported very large effect and ten participants (6%) reported extremely large effect (Table 2).

Out of 153 patients, 29 of them had positive skin swab. All of those with positive yield cultured methicillin susceptible *Staphyloccocus aureus* (MSSA). One patient had *Streptococcus dysgalactiae* in addition to MSSA. No patient had methicillin-resistant *Staphyloccocus aureus* (MRSA) from the skin swab. Only one patient was a MRSA carrier from the nasal swab. This patient's skin swab had no growth (Table 3).

There was a significant association between positive skin swab and disease severity ($p=0.03$) (Table 4). Out of the 29 patients with positive skin swab, 89.7% with positive skin swab had moderate to severe disease. Three participants (10.3%) had mild SCORAD index, 20 participants (69%) had moderate SCORAD index and six participants (20.7%) had severe SCORAD index. Majority of patients with mild SCORAD index had negative skin swab. Of those with mild SCORAD index, 44 patients had negative skin swab and only three had positive skin swab. Of those with negative skin swab, 44 participants (35.5%) had mild SCORAD index, 62 (50%) had moderate SCORAD index and 18 (14.5%) had severe SCORAD index. There is no significant association between nasal swab

colonisation and disease severity. Only one patient with moderate disease was an MRSA carrier.

There was a highly significant association between disease severity and quality of life (p<0.001). Among patients with DLQI score >20 (extremely large effect), six patients (60%) had severe disease, three patients (30%) had moderate disease and only one patient (10%) had mild disease. All patients who reported no effect at all on DLQI assessment had mild disease. The DLQI score for most of the patients with mild disease were in small effect (44.7%) and moderate effect (25.5%) categories. The DLQI score for most of the patients with moderate disease were in moderate effect (36.6%) and very large effect (36.6%) categories. The DLQI score for most of the patients with severe disease were in moderate effect (37.5%) and very large effect (37.5%) categories. The mean DLQI score for patients with had no effect at all was 2; for patients with small effect was 13.3; for patients with moderate effect was 17; for patients with very large effect was 15.3 and for patients with extremely large effect was 3.3. Majority of participants had moderate disease (53.6%), resulting in higher mean DLQI score from small effect to very large effect categories.

Penicillin (86.2%) was found to have the highest resistant rate followed by fusidic acid (34.5%), tetracycline (17.2%), erythromycin (3.4%) and gentamycin (3.4%) (Figure 1). The most susceptible antibiotics (100% sensitivity) were cefoxitin, methicillin, trimethoprim/sulfamethoxazole, and rifampicin.

Table 1. Demographic characteristics

Demographic		n (%)
Age (years)	Preschool (less than 7) Primary school (7 to 12) Secondary school (13 to 17)	111 (72.5) 26 (17.0) 16 (10.5)
Gender	Male Female	82 (53.6) 71 (46.4)
Ethnicity	Malay Chinese Indian Others	120 (78.4) 25 (16.3) 7 (4.6) 1 (0.7)
BMI	Underweight (≤5th percentile) Normal (5th to ≤ 85th percentile)) Overweight (85th to ≤95th percentile) Obese (≥95th percentile)	25 (16.3) 96 (62.8) 9 (5.9) 23 (15.0)
Age at diagnosed	Preschooler (less than 7) Primary school (7 to 12) Secondary school (13 to 17)	136 (88.9) 15 (9.8) 2 (1.3)
Family history of atopy	Yes No	138 (90.2) 15 (9.8)
Personal history of another atopy	Yes No	71 (46.4) 82 (53.6)

BMI, Body mass index

Table 2. DLQI and SCORAD index

DLQI and SCORAD Index		n (%)
DLQI	No effect Small effect Moderate effect Very large effect Extremely large effect	6 (3.9) 40 (26.2) 51 (33.3) 46 (30.1) 10 (6.5)
SCORAD index	Mild Moderate Severe	47 (30.7) 82 (53.6) 24 (15.7)

DLQI, Dermatological life quality index; SCORAD, SCORing Atopic dermatitis

Table 3. Skin (lesional) and nasal (non-lesional) swab yields for *Staphylococcus aureus*

Skin Swab Result	n (%)
No growth MSSA MSSA + Streptococcus dysgalactiae	124 (81) 28 (18.3) 1 (0.7)
Nasal Swab Result	**n (%)**
No MRSA MRSA	152 (99.3) 1 (0.7)

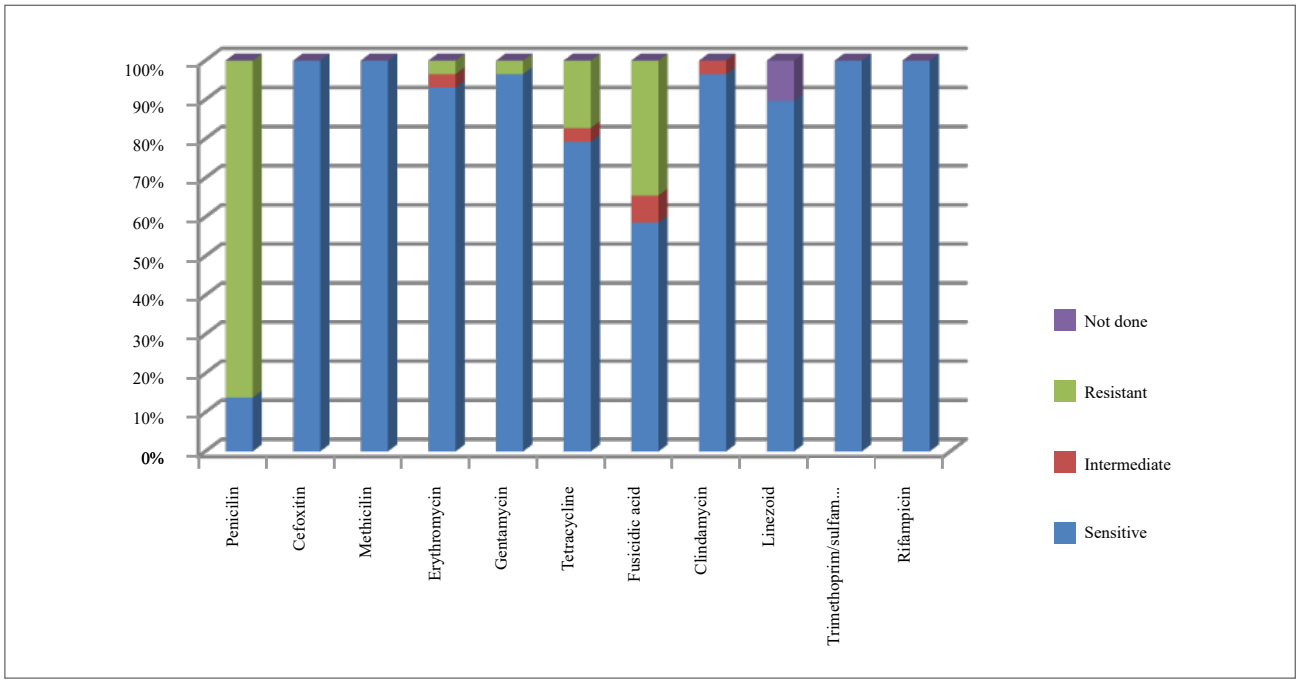
MSSA, methicillin susceptible Staphyloccocus aureus; MRSA, methicillin-resistant Staphyloccocus aureus

Table 4. Association between disease severity (SCORAD) and growth (skin and nasal) and quality of life (DLQI)

	SCORAD Index n (%)			*p*-value
	Mild	Moderate	Severe	
Skin swab				0.030[a]
Growth No growth	3 (10.3) 44 (35.5)	20 (69) 62 (50)	6 (20.7) 18 (14.5)	
Nasal swab				1.000[b]
MRSA No MRSA	0 (0) 47(30.9)	1 (100) 81 (53.3)	0 (0) 24 (15.8)	
DLQI				<0.001[b]
No effect Small effect Moderate effect Very large effect Extremely large effect	6 (100) 21 (52.5) 12 (23.5) 7 (15.2) 1 (10)	0 (0) 19 (47.5) 30 (58.9) 30 (65.2) 3 (30)	0 (0) 0 (0) 9 (17.6) 9 (19.6) 6 (60)	

[a]Chi-square tests; [b]Fisher's exact tests; SCORAD, SCORing Atopic dermatitis; MRSA, methicillin-resistant Staphyloccocus aureus; DLQI, Dermatological life quality index

Figure 1. Antibiotic sensitivities of *Staphylococcus aureus*



Discussion

The sample in this study was mainly preschoolers, followed by primary school children and secondary school children. Similar trends were observed for age when AD was first diagnosed. This was in line with the natural course of childhood eczema which mostly manifests AD before the age of two.[27] Most of the affected children have family history of atopy which indicates the genetic role in the pathogenesis of atopic dermatitis. However, it was observed that less than half of the patients have other atopy histories. This could be due to the initial stage of atopic march which begins with atopic dermatitis, and followed by IgE-mediated food allergy, asthma, and allergic rhinitis.[28]

In this study, the percentage of skin (lesional) colonisation by *S. aureus* was only 19%, whereas nasal (non-lesional) colonisation was 0.7%. This was lower than other studies where skin carriage rates among AD patients were reported between 30% and 100%, while the percentage of nasal colonisation by *S. aureus* varies between 10 and 30%.[9,10,11] This discrepancy might be attributed to the significant variation in AD clinical severity in each study. Most of the patients were found to have mild to moderate AD. Other possibilities for such variations are intermittent colonisation by *S.*

aureus resulting in negative detection at the time of examination, hygienic status of patients, sampling technique, and sampling area of skin lesion.[9,29]

From our study, we found that severity of disease was associated with quality of life ($p<0.01$). About 70 % of the patients with mild disease reported small or moderate effect during the DLQI assessment. On the other hand, 73.2% of patients with moderate disease and 75% of patients with severe disease reported moderate to very large effect during the DLQI assessment. The result showed that higher SCORAD index seemed to be associated with worse DLQI. Although most skin diseases are not life-threatening, it could still lead to a significant disability burden. This result was consistent with the study by Holm et al., where AD had a negative impact on the QoL, and was proportional to the disease severity.[30] Children with AD often have behavioural problems such as increased dependency, fearfulness and sleep difficulties.[34] These findings should draw our attention to the long-term effect on children's behaviour and development.

The resistance rate to fusidic acid in this population was found to be higher compared with other studies. Tang (2011) found that fusidic acid resistance was lower than penicillin, erythromycin, clindamycin, tetramycin and gentamycin.[31] Likewise, Hoeger (2004) and Niebuhr (2008) also had lower fusidic acid resistance rate in their findings.[32,20] However more current studies by Jung (2015) and Lee (2016) found that fusidic acid is the second highest resistant antibiotic after penicillin.[11,33] Higher resistance rates towards fusidic acid in recent studies could be due to increased use of topical fusidic acid in treating the patient with infective or inflammatory skin diseases in recent years. In view of this finding, the use of fusidic acid should not be advocated. Besides that, the use of neomycin and bacitracin were not advised as they were nominated as an allergen in 2003 and 2010, respectively.[34] Moreover, the resistance rates to neomycin and bacitracin were high in Bessa *et al.*'s report.[35] Sulphur-based topical treatments have a high risk of hypersensitivity, leading to physicians' hesitancy to use these in the paediatric group. Therefore, mupirocin and retapamulin are the choice of antibiotics if clinically indicated. With the concern of developing resistance to the newer antibiotic, continuous surveillance of antibiotic susceptibility patterns are important.

From our study, we found that 26 patients (89.7%) with *Staphylococus aureus* colonisation and 105 patients (69.1%) with negative skin swab had moderate to severe disease. As patients with *Staphylococcus aureus* colonisation tends to have more severe disease, decolonisation with antiseptic wash such as a diluted bleach bath should be considered. It helps in relieving symptoms of AD and it is better tolerated than topical antibiotics. This approach could potentially reduce antibiotic resistance.[36,37] Decolonisation of MSSA with a topical antibiotic is not recommended as quick recolonisation occurs after discontinuing the antibiotic.[38,39]

Conclusion

Staphylococcus aureus skin colonisation among AD patients is associated with increased disease severity. The severity of the disease has an impact on patient's quality of life. Antiseptic wash should be considered instead of topical antibiotics for *Staphylococcus aureus* decolonisation. Antiseptic wash is better tolerated and can potentially reduce antibiotic resistance.

Conflict of Interest Declaration

The authors declare no conflict of interest.

Acknowledgment

We would like to thank the Director-General of Health Malaysia for his permission to publish this study. This study was funded with a research grant from the Dermatological Society of Malaysia.

References

1. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL et al. Epidemiolofy of atopic dermatitis in adults: Results from an international survey. Allergy 2018;73:1284-93.
2. Deckers IAG, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One 2012;7:e39803.
3. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Lagan SM et al. Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA Dermatology 2017;153:406-12.
4. Al Shobaili HA. The impact of childhood atopic dermatitis on the patients' family. Pediatr Dermatol 2010;27:618-23.
5. Ho RCM, Giam YC, Ng TP, Mak A, Goh D, Zhang MWB et al. The influence of childhood atopic dermatitis on health of mothers, and its impact on Asian families. Pediatr Allergy Immunol 2010;21:501-7.
6. Aziah MSN, Rosnah T, Mardziah A, Norzila MZ.

Childhood atopic dermatitis: a measurement of quality of life and family impact. Med J Malaysia 2002;57:329-39.
7. Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. Pediatrics 2004;114:607-11.
8. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatr Dermatol 2005;22:192-9.
9. Paller AS, Kong HH, Seed P, Naik S, Scharschmidt TC, Gallo RL et al. The microbiome in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143:26-35.
10. Jagadeesan S, Kurien G, Divakaran MV, Sadanandan SM, Sobhanakumari K, Sarin A. Methicilin-resistent Staphylococcus aureus colonization and disease severity in atopic dermatitis: A cross-sectional study from South India. Indian J Dermatol Venereol Leprol 2014;80:229-34.
11. Jung MY, Chung JY, Lee HY, Park J, Lee DY, Yang JM. Antibiotic Susceptibility of *Staphylococcus aureus* in Atopic Dermatitis: Current Prevalence of Methicillin-Resistant Staphylococcus aureus in Korea and Treatment Strategies. Ann Dermatol 2015;27:398-403.
12. Chen YE, Fischbach MA, Belkaid Y. Skin microbiota-host interactions. Nature 2018;553:427-36.
13. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. Sci Transl Med 2017;9:eaah4680.
14. Narayan V, Sarkar R, Barman KD, Prakash SK. Clinicoepidemiologic profile and the cutaneous and nasal colonization with methicillin-resistant *Staphylococcus aureus* in children with atopic dermatitis from North India. Indian Dermatol Online J 2019;10:406-12.
15. Samosir CT, Ruslie RH, Rusli RE. Bacterial pattern and antibiotic sensitivity in children and adolescents with infected atopic dermatitis. IOP Conf Ser Earth Environ Sci 2018;125:012054.
16. Totté JEE, Pardo LM, Fieten KB, Vos MC, Van Den Broek TJ, Schuren FHJ et al. Nasal and skin microbiomes are associated with disease severity in paediatric atopic dermatitis. Br J Dermatol 2019;181:796-804.
17. Kedzierska A, Kapińska-Mrowiecka M, Czubak-Macugowska M, Wójcik K, Kedzierska J. Susceptibility testing and resistance phenotype detection in *Staphylococcus aureus* strains isolated from patients with atopic dermatitis, with apparent and recurrent skin colonization. Br J Dermatol 2008;159:1290-9.
18. Briscoe CC, Reich P, Fritz S, Coughlin CC. S*taphylococcus aureus* antibiotic susceptibility patterns in pediatric atopic dermatitis. Pediatr Dermatol 2019;36:482-5.
19. Wróbel J, Tomczak H, Jenerowicz D, Czarnecka-Operacz M. Skin and nasal vestibule colonisation by *Staphylococcus aureus* and its susceptibility to drugs in atopic dermatitis patients. Ann Agric Environ Med 2018;25:334-7.
20. Niebuhr M, Mai U, Kapp A, Werfel T. Antibiotic treatment of cutaneous infections with *Staphylococcus aureus* in patients with atopic dermatitis: current antimicrobial resistances and susceptibilities. Exp Dermatol 2008;17:953-7.
21. Suh L, Coffin S, Leckerman KH, Gelfand JM, Honig PJ, Yan AC. Methicillin-resistant Staphylococcus aureus colonization in children with atopic dermatitis. Pediatr Dermatol 2008;25:528-34.
22. Lemeshow S, Hosmer DW, Klar J, Lwanga SK, Organization WH. Adequacy of sample size in health studies. Wiley: Chichester, UK. 1990.
23. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
24. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997;195:10-9.
25. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
26. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol 2005;125:659-64.
27. Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am 2010;30:269-80.
28. Hill DA, Spergel JM. The atopic march: Critical evidence and clinical relevance. Ann Allergy, Asthma Immunol 2018;120:131-7.
29. Alenizi DA. Prevalence of *Staphylococcus aureus* and antibiotic resistance in children with atopic dermatitis in Arar, Saudi Arabia. J Dermatology Dermatologic Surg 2014;18:22-6.
30. Holm JG, Agner T, Clausen ML, Thomsen SF. Quality of life and disease severity in patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2016;30:1760-7.
31. Tang CS, Wang CC, Huang CF, Chen SJ, Tseng MH, Lo WT. Antimicrobial susceptibility of *Staphylococcus aureus* in children with atopic dermatitis. Pediatr Int 2011;53:363-7.
32. Hoeger PH. Antimicrobial susceptibility of skin-colonizing S. aureus strains in children with atopic dermatitis. Pediatr Allergy Immunol 2004;15:474-7.
33. Lee CK, Yusof MY, Lee YY, Tan ESS, Wong SM, Ch'ng CC et al. *Staphylococcus aureus* antibiotic resistance in Atopic eczema. Malaysian J Dermatol 2016;36:5-10.
34. Vazirnia A. Review ACDS' Allergen of the Year 2000-2015. The Dermatologist. 22(II). http://www.the-dermatologist.com/content/review-acds'-allergen-of-year-2000-2015.
35. Bessa GR, Quinto VP, Machado DC, Lipnharski C, Weber MB, Bonamigo RR et al. *Staphylococcus aureus* resistance to topical antimicrobials in atopic dermatitis. An Bras Dermatol 2016;91:604-10.
36. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116-32.
37. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. Pediatrics 2009;123:e808-14.
38. Błażewicz I, Jaśkiewicz M, Bauer M, Piechowics L, Nowicki RJ, Kamysz W et al. Decolonization of *Staphylococcus aureus* in patients with atopic dermatitis: a reason for increasing resistance to antibiotics? Postepy Dermatol Alergol 2017;34:553-60.
39. Gilani, Gonzalez M, Hussain I, Finlay AY, Patel GK. *Staphylococcus aureus* re-colonization in atopic dermatitis: beyond the skin. Clin Exp Dermatol 2005;30:10-3.

ORIGINAL ARTICLE

A 5-years Retrospective Study on Narrowband Ultraviolet B (NBUVB) Phototherapy Utilisation Experience in A Tertiary Hospital in East Malaysia

Teo Hock Gin, *MRCP*, Kiing Jiu Wen, *AdvMDerm*, Pubalan Muniandy, *FRCP*

Department of Dermatology, Hospital Umum Sarawak, Kuching, Sarawak, Malaysia

Abstract

Background

Phototherapy had been a less favourable treatment in recent years. Our study aims to audit the usage of NB-UVB phototherapy service in a tertiary hospital in East Malaysia.

Methods

This is a retrospective study. Phototherapy file of patients who underwent NB-UVB phototherapy between year 2016 and 8 March 2021 were reviewed. Demographic data, treatment history, and acute side effects were analysed.

Results

Forty eight subjects were recruited in this study. The majority (33.3%) of the subjects were in 20-29 age group. There was an equal number of male and female subjects. About 66.7% of the subjects had psoriasis and 18.8% of them had vitiligo. Nearly 36.6% of the subjects had 26-50% body surface area involved at initial phototherapy. Almost 54.2% of the subjects had <50 sessions of NB-UVB phototherapy. About 52.1% of the subjects had a cumulative dose of NB-UVB <25 J/cm^2 while 26.7% of subjects had a cumulative dose >200 J/cm^2. Acute side effects including burning (17.8%), pruritus (4.4%) and flare of psoriasis (2.2%).

Discussion

Low utilization rate of NB-UVB phototherapy was likely due to logistical and transportation factors. Psoriasis was the commonest indication for NB-UVB in our study followed by vitiligo. Annual skin malignancy surveillance should be done especially on patients received NB-UVB >350 sessions even after the discontinuation of treatment. Most patients tolerate NB-UVB phototherapy well with no major side effects.

Conclusion

In conclusion, NB-UVB phototherapy is a relatively safe yet underutilised treatment in our centre.

Key words: *Phototherapy, Narrowband ultraviolet B (nb-UVB), Ultraviolet A, Psoriasis, Vitiligo*

Corresponding Author

Dr Teo Hock Gin

Department of Dermatology,
Hospital Umum Sarawak,
Jalan Hospital,
93586 Kuching, Sarawak, Malaysia.

Email: hgteo86@hotmail.com

Introduction

Phototherapy is a type of light therapy which had been used in various dermatological diseases such as atopic eczema, psoriasis, vitiligo, morphea and so on. In 1925, Goeckerman was the first person who brought in the advancement in phototherapy as part of important treatment in psoriasis by combining

ultraviolet B (UVB) and crude coal tar.[1] Since then many modern phototherapies had been developed ranging from narrowband UVB (NB-UVB) in 1988, psoralen and UVA (PUVA) in 1974 to targeted phototherapy with excimer lamp in 1997.[2,3] In the era of biology, however, with the development of systemic treatment including biology therapy since 2000, phototherapy therapy becomes less favourable.

According to a 5 year report in 2002 from the United States, patients visit for phototherapy, in general, was reduced by more than 90%.[4] The objective of this study is to audit the usage of NB-UVB phototherapy service in Sarawak General Hospital (SGH) for the past five years including phototherapy usage trend, common indications of phototherapy, characteristics of the patients, and side effects of phototherapy. SGH located in East Malaysia. It is a tertiary hospital in the state of Sarawak, Malaysia and it is the only hospital with resident dermatologists in this state.

Materials and Methods

This is a retrospective study carried out at the phototherapy unit Sarawak General Hospital. We recruited patients who had received phototherapy treatment at our phototherapy unit between 2016 and 8 March 2021. Our centre is currently using a Daavlin cabin (UVB) and a hands and feet unit. No UVA phototherapy available at our unit. We excluded subjects on hands and feet phototherapy as data was not complete. Patients' phototherapy folders were reviewed. Data such as demographics, indications, treatment sessions, cumulative dose of the phototherapy, and acute side effects were extracted and analysed by using SPSS.

Results

A total number of 48 subjects received NB-UVB phototherapy between 2016 and 8 March 2021. The demography data of the subjects were shown in Figure 1 & 2. The majority of the patients were in the 20-29 age group. The mean age was 38.7 years old and ranged from 13 to 77 years old. There was an equal number of male and female subjects in the study populations. More than half (n=26, 54.2%) of the subjects were Chinese, followed by Malay (n=12, 25%), Bidayuh (n=5, 10.4%), and Iban (n=3, 6.3%).

Figure 1. Age distribution at the time of first nbUVB Phototherapy

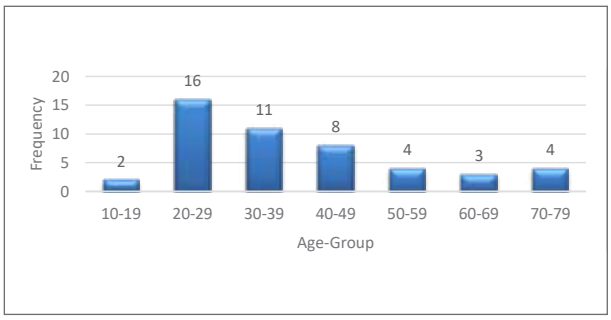
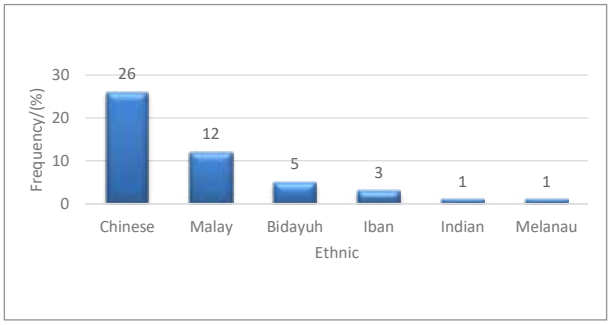
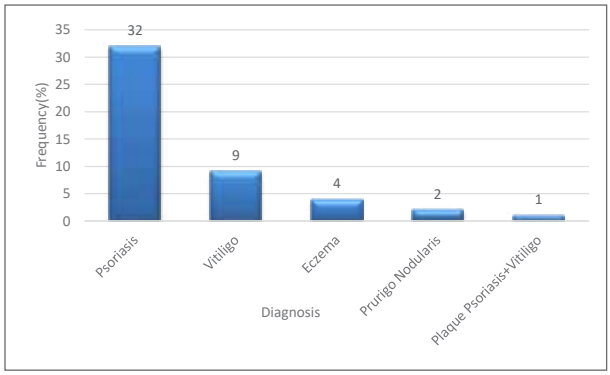


Figure 2. Ethnic groups of the nbUVB Phototherapy subjects



For the indication of NB-UVB phototherapy, 66.7% (n=32) of the subjects were started on nb-UVB phototherapy for their underlying psoriasis in which 2 (4.2%) of the subjects had erythrodermic psoriasis while the remaining of them had plaque psoriasis. This was followed by vitiligo in 18.8% (n=9) of the subjects, while eczema and prurigo nodularis were diagnosed in 8.3% (n=4) and 4.2% (n=2) of the study populations, respectively. One subject (2.1%) was started on NB-UVB phototherapy for both psoriasis and vitiligo. (Figure 3)

Figure 3. Diagnosis of subjects receiving nbUVB



Body surface area (BSA) involved, total number of phototherapy sessions, cumulative dose, and acute side effect were summarised in Table 1.

Among the 41 subjects with complete data on BSA involved, 36.6% (n=15) of them had BSA of 26-50%, followed by subjects with 6-10% BSA (n= 8, 19.5%) and 11-25% BSA involvement (n=5, 12.2%). 3 (7.3%) of them had BSA of >95%, which included 2 erythrodermic psoriasis subjects and one patient with erythroderma secondary to eczema.

Table 1. Baseline BSA and treatments and side effects of the study populations

		Frequency (n)	Percentage (%)
Body surface area/BSA (n=41) *	1-5	2	4.9
	6-10	8	19.5
	11-25	5	12.2
	26-50	15	36.6
	51-75	4	9.8
	76-95	4	9.8
	>95	3	7.3
	Total	41	100.0
Total NB-UVB sessions (n=48)	0-50	26	54.2
	51-100	11	22.9
	101-150	1	2.1
	151-200	1	2.1
	201-250	2	4.2
	251-300	2	4.2
	>300	5	10.4
	Total	48	100.0
Cumulative dose (J/cm ^{2}) (n=48)	1-25	25	52.1
	>25-50	4	8.3
	>50-75	8	16.7
	>100-125	1	2.1
	>125-150	1	2.1
	>150-175	1	2.1
	>200	8	16.7
	Total	48	100.0
Acute side effect (n=45) #	No side effects	34	75.6
	Burning	8	17.8
	Itching	2	4.4
	Flare of disease	1	2.2
	Total	45	100.0

**7 vitiligo subjects were not documented regarding their BSA finding in their phototherapy folders*

#3 subjects had missing data regarding phototherapy side effects as they defaulted our clinic follow up

Fifty-four percent (n=26) of the study populations had less than 50 sessions of NB-UVB phototherapy. Around twenty three percent (n=11) of them had 51-100 sessions of the same phototherapy treatment. Of note, there were 5 (10.4%) subjects who received more than 300 sessions of NB-UVB phototherapy in their lifetime, with the highest record of 963 sessions in 1 subject. All the 5 subjects were diagnosed with vitiligo, and until the closure of the study, there was no evidence of skin malignancy in all the 5 subjects.

The study populations had a wide range of cumulative UVB exposure dosage, which range from 0.15 to 924 J/cm^2 with a median dose of 21 J/cm^2. 52.1% (n=25) of them had a cumulative dose of UVB of 1-25 J/cm^2 followed by >50-75 J/cm^2 group and >200 J/cm^2 group, which consisted of 16.7% (n=8) of the study population respectively.

With regards to acute side effects after the NB-UVB phototherapy, there were 3 subjects who defaulted the phototherapy during the first few sessions, and no clinical records of acute side effects were documented. Among 45 of the remaining subjects, 75.6% (n=34) of them tolerate NB-UVB without significant side effects, while 17.8% (n=8) and 4.4% (n=2) of them complained of burning sensation and pruritus, respectively. 1 (2.2%) subject documented flare of underlying psoriasis. 3 (6.7%) of subjects stopped the NB-UVB phototherapy due to not tolerating acute side effects.

Discussion

Our study showed that in the past 5 years, we have only 48 subjects who received treatment of NB-UVB phototherapy for their underlying skin diseases. There were a few possible reasons for the low prescribing rate of NB-UVB in our centre. The most important reason is the logistical and transportation factors as many of our subjects stay far from Kuching city and some even come from different divisions. They have difficulties to go to hospital 2 to 3 times a week for the phototherapy treatments. The COVID-19 pandemic has an impact on this as well. Dermatologists try to minimise patients' visit to the hospital to reduce the risk of COVID-19 transmission. Therefore, phototherapy was avoided if alternative treatments were available.

Most of our subjects who received NB-UVB phototherapy were in the age group of 20-29, with a mean age of 38.7 years old. This finding was similar to another study done in Hospital Kuala Lumpur, Malaysia during 2011-2015 in which the mean age of the study was 38.8 years old.[5] Another study by Park et al. in Korea showed a similar finding with the majority of the subjects receiving UVA or UVB in their study were in the age of 20-29 years old.[6]

Table 2. Indications for phototherapy in different studies

Study	Country	Treatment	Diagnosis (%)					
			Psoriasis	Atopic Dermatitis	Vitiligo	CTCL	Prurigo Nodularis	Others
Park *et al*, 1996	Korea	UVB	94.8	2.4	-	-	0.5	2.4
Vaani *et al*, 2018	Malaysia	UVA	28.0	0.5	70.2	0.5	-	0.7
		Oral PUVA	17.4	4.3	21.7	47.8	-	8.6
		Topical PUVA	2.8	1.4	85.1	0.7	--	9.8
		nbUVB	57.2	11.4	15.4	3.2	-	12.8
Current study	Malaysia	nbUVB	66.7	8.3	18.8	-	4.2	2.1

In term of indication for NB-UVB treatment, our study finding was consistent with other studies in Korea and Malaysia in which psoriasis was the commonest indication for UVB/NBUVB (Table 2).[5,6] Duarte *et al*. reported, in their study on prescribing behaviour for 67 psoriasis subjects in Sao Paolo, Brazil, that 76% of the subjects received NB-UVB phototherapy with only 34 % was given PUVA.[7] However, in our study, vitiligo is the second commonest indication for NB-UVB phototherapy. This is in contrast with the above studies in which Park *et al*. and Vaani *et al*. reported atopic dermatitis as the second commonest indication for UVB/NB-UVB. In their study, UVA is the preferred mode of phototherapy for vitiligo. PUVA or topical UVA was not available in our centre, and this can explain the difference between the studies. Unlike the other centre, we did not have subjects with cutaneous T cell lymphoma in our study.

The total number of NB-UVB sessions in our study ranged from 1 to 963 sessions, while Vaani *et al*. reported that subjects who underwent NB-UVB phototherapy in their study ranged from 1-252 sessions. More than half of our subjects underwent NB-UVB phototherapy for less than 50 sessions. Another 22.9% underwent 51-100 sessions of NB-UVB phototherapy. This finding is similar to the study by Park *et al*. in Korea.[6] However, from our study, there were 5 (10.4%) subjects who had NB-UVB phototherapy of more than 300 sessions (963,922,818,547,324 sessions respectively). All 5 subjects had vitiligo. Although NB-UVB is effective in vitiligo from several studies done previously, our subjects seem to require long-term phototherapy to maintain their disease.[8,9]

Although they had undergone an extremely high number of phototherapy sessions, there was no skin malignancies reported in our subjects. Although NB-UVB phototherapy increases lifetime exposure to UVB, there is no evidence of increased risk of skin malignancies from the previous studies.[10] Therefore, based on currently available data, the number of allowable UVB treatments can't be defined, although Malaysia Clinical Practical Guideline on the management of psoriasis Vulgaris recommends UVB treatments of not more than 350 sessions.[11] Nevertheless, close monitoring of the side effects and annual skin examinations is important to monitor any skin tumours even after the discontinuation of phototherapy.[12] Subjects who received >350 sessions should be reassessed on the risk and benefit of continue phototherapy.

In our centre, all patients with different skin types were initiated with a low dose NB-UVB of 150m J/cm^2. This was followed by a 20% increment during subsequent treatments if subjects tolerate the previous dose. Parlak *et al*. did a study on the different regimes of NB-UVB phototherapy treatments.13 Group 1 subjects were started with 50% of the minimal erythema dose followed by 20% increment in the next sessions as practised in our center, while group 2 subjects were given the starting dose and dose increment based on the skin types and applied with fixed doses. They concluded that there was no significant difference in terms of cumulative dose, side effect profiles, and improvement in PASI score between the 2 groups.

Among 45 of the subjects with complete data, 75.6% of them tolerate NB-UVB without significant side effects, while 17.8% of them experienced burning sensation after phototherapy, and 4.4% of them complained of pruritus. Most of the side effects resolved with time or after dosage adjustment. One (2.2%) of the subjects documented flare of underlying psoriasis and phototherapy. However, the patient had only received 4 sessions of NB-UVB phototherapy with a cumulative dose of 896m J/cm^2, which is less likely the cause of flare in this

case. Two (4.4%) of them stopped the NB-UVB phototherapy and opted for other systemic therapy as they couldn't tolerate the phototherapy due to the burning sensation.

Our study revealed lower rate of side effects from NB-UVB phototherapy compared to Vaani *et al*., who reported a 30% rate of adverse reactions. On the other hand, their study reported that 17% and 14% of the subjects reported pruritus and erythema, respectively. In our study population, commonest side effects reported were burning sensation (17.8%) followed by pruritus (4.4%). These data may be underreported as there was no standard protocol to report any adverse reaction to NB-UVB treatment and the data was taken from documentation in clinical record and phototherapy folders and subjected to bias.

Conclusion

Our study concluded that NB-UVB phototherapy is underutilised at least in our centre. Psoriasis subjects with a moderate disease or failed topical treatments should be offered phototherapy if transportation is not an issue before we add in other systemic treatments which bring more side effects or biologic treatments which are costly. Lastly, well-designed prospective studies in the future on the effectiveness of NB-UVB phototherapy and their common side effects will give a clearer picture of the NB-UVB phototherapy treatment in different cutaneous diseases and to identify the factors affecting the utilisation of NB-UVB in our centre.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

References

1. Honigsmann H. History of phototherapy in dermatology. Photochem Photoiol Sci 2013;12:16-21.
2. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. N Eng J Med 1974;291:1207-11.
3. Ly K, Smith MP, Thibodeaux QG, Beck KM, Liao W, Bhutani T. Beyond the booth: excimer laser for cutaneous conditions. Dermatol Clin 2020;38:157-63.
4. Torres AE, Lyons AB, Hamzavi IH, Lim HW. Role of phototherapy in the era of biologics. J Am Acad Dermatol 2021;84:479-85.
5. Park SH, Hann SK, Park YK. Ten-year experience of phototherapy in Yonsei Medical Center. Yonsei Med J 1996;37:392-6.
6. Vaani VV, Tang MM, Tan LL, Asmah J. The utilization of phototherapy in the department of dermatology, Hospital Kuala Lumpur: A 5-year audit. Med J Malaysia 2018;73:125-30.
7. Duarte I, Cunha JA, Bedrikow RB, Lazzarini R. What is the most common phototherapy prescription for psoriasis: NB-UVB or PUVA? Prescription behavior. An Bras Dermatol 2009;84:244-8.
8. Adawiyah J, Suraiya HH. A retrospective study of narrowband-UVB phototherapy for treatment of vitiligo in Malaysian subjects. Med J Malaysia 2010;65:297-9.
9. Chen GY, Hsu MM, Tai HK, Chou TC, Tseng CL, Chang HY. Narrow-band UVB treatment of vitiligo in Chinese. J Dermatol 2005;32:793-800.
10. Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. Int J Dermatol 2005;44:355-60.
11. Malaysia Clinical Practice Guideline on Management of Psoriasis Vulgaris. June 2013.
12. Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maître M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol 2012;26:22-31.
13. Parlak N, Kundakci N, Parlak A, Akay BN. Narrowband ultraviolet B phototherapy starting and incremental dose in subjects with psoriasis: comparison of percentage dose and fixed dose protocols. Photodermatol Photoimmunol Photomed 2015;31:90-7.

CASE REPORT

Dermoscopy of Dilated Pore of Winer

Shashikumar Basavapura Madegowda[1], *MD(DVL)*, Savitha Somiiah Allaranda[2], *MD(DVL)*

[1]Department of Dermatology, Sparsha Skin Care Clinic, Mandya, Karnataka, India
[2]Department of Dermatology, Sapthagiri Institute of Medical Sciences and Research Center, Bengaluru, Karnataka, India

Summary

Dilated pore of Winer is a benign adnexal tumour of follicular differentiation. It has typical clinical feature of asymptomatic, solitary enlarged pore with a keratin plug. Dermoscopy offers further assistance in diagnosis. In this case on dermoscopy, well defined lamellated central blackish area arranged in concentric circles, surrounded by a bluish grey halo was seen with a rim of hyperpigmentation.

Key words: *Dilated pore, Dermoscopy, Adnexal tumour*

Introduction

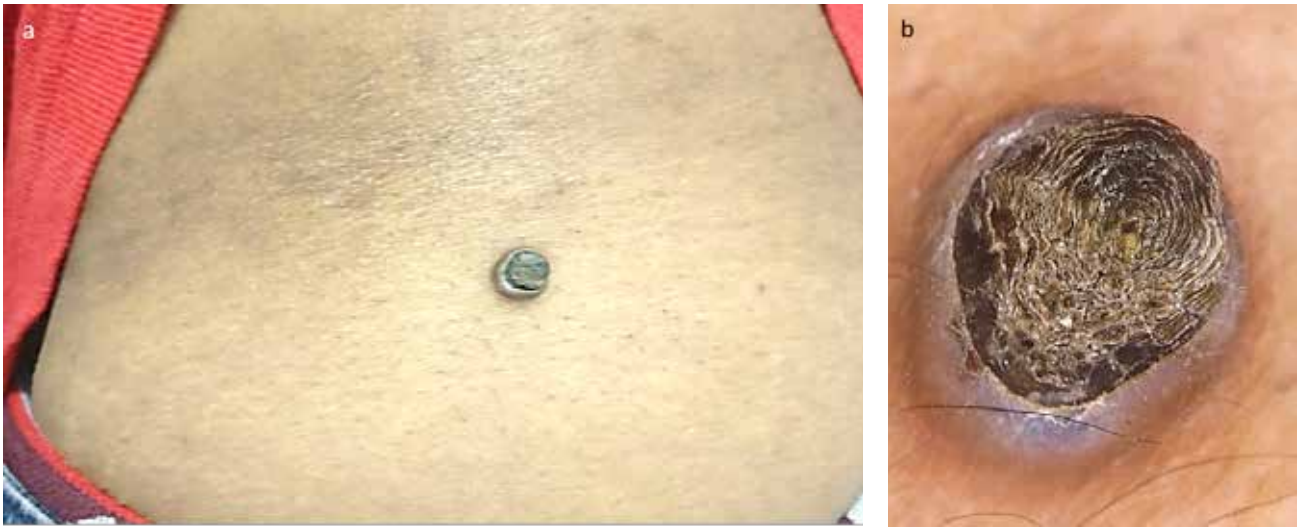
Dilated pore of Winer was first described by Louis H Winer in 1954.[1] Though it is commonly located over the head and neck areas, it is usually found on the trunk also. This frequently occurs in middle aged and elderly individuals. It is an adnexal neoplasm of the follicular infundibulum.[2] The clinical features are characteristic with a solitary dilated pore filled with a black keratin plug. The lesion is benign and asymptomatic and treatment is advised only for cosmetic purposes. Histopathologic examination is advised in doubtful cases to confirm the diagnosis. Dermoscopy can now be used as an additional tool to confirm the diagnosis and thus help to avoid biopsy.

Case Report

A 38-year-old male presented with an asymptomatic slowly enlarging lesion over the trunk for 6 months. On examination, an elevated lesion measuring 5mm x 5mm with central black plug like open comedone was noted (Figure 1a). The surrounding skin was normal. On dermoscopy lamellated central black area in concentric circles, surrounded by a bluish grey zone was noted and peripheral rim of hyperpigmentation was also seen. Biopsy was not performed as the features were classical of dilated pore of Winer (Figure 1b).

Corresponding Author
Dr Shashikumar BM
Sparsha Skin Care Clinic,
#1301, 2nd Cross,
Nehru Nagar, Mandya,
57140n1 Karnataka, India.
Email: shashikumarbm@gmail.com

Figure 1. (a) Papule woth central keratin plug; (b) Concentric areas in the centre, with bluish grey margins and rim of hyperpigmentation on dermoscopy



Discussion

Dilated pore of Winer is a common benign condition. Some reports have considered it to be epidermal inclusion cyst with reactive hyperplasia of its epithelial lining and others proposed it to be a variant of nevus comedonicus.[3] Now it is said to be an adnexal neoplasm of the follicular infundibulum. The exact etiology and pathophysiology is unknown. It is commonly located over the head and neck areas, and also frequently found on the trunk of middle age to elderly individuals. It usually presents as an asymptomatic solitary lesion without any perilesional inflammatory changes.[4]

Biopsy and histopathological examination is advised only in uncertain cases. On histopathology, single or multiple contiguous enormously dilated follicular infundibula is seen extending deep into dermis. It is lined by an acanthotic infundibular epithelium projecting several finger-like projections into the adjacent dermis. These finger-like projections do not contain keratin cysts, ducts, or hair shafts.[3] The cavity is filled with lamellar keratin material. Excessive melanization of this epithelium and/or the central keratin plug may also be observed.

On dermoscopy with Dermlite 4, lamellated central black area with concentric circles, surrounded by a bluish grey zone and peripheral rim of hyperpigmentation was noted. Previous reports on Dermoscopy of Dilated pore of Winer describes a central homogenous bluish black material.[4] In this case the central keratin was organised in concentric layers. The greyish margins correspond to epidermal hyperplasia around the follicular infundibulum.[4]

Differential diagnoses are solitary lesion of nevus sebaceous, pilar sheath acanthoma, epidermal inclusion cyst with punctum and large pore Basal cell carcinoma.

For these lesions, prognosis is excellent as they are benign and do not involve further testing or work-up. Treatment is advised only for cosmetic purposes and excision is the best choice. It is possible to simply remove the keratin content using a comedone extractor. However soon there will be reaccumulation of keratin. Due to the deeply located base of the invagination, destructive methods like electrodesiccation, electrocautery, laser surgery, dermabrasion, and cryotherapy are less efficient.[1]

Conclusion

Dilated pore of Winer is a benign adnexal tumour of follicular differentiation. There are very few reports on the Dermoscopy of dilated pore of Winer and previous reports described a homogenous central area. Hence, we report this dermoscopic finding of central keratin arranged in concentric layers.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

Nil.

References

1. Winer L H. The dilated pore, a tricho-epithelioma. J Invest Dermatol 1954;23:181-8.
2. Steffen C. Winer's dilated pore: the infundibuloma. Am J Dermatopathol 2001;23:246-53.
3. Tellechea O, Cardoso JC, Reis JP, Ramos L, Gameiro AR, Coutinho I et al. Benign follicular tumors. An Bras Dermatol 2015;90:780-96.
4. Adya KA, Inamadar AC, Palit A. Dermoscopic characterization of dilated pore of Winer: Report of two cases. Clin Dermatol Rev 2019;3:96-8.

CASE REPORT

Calcinosis Cutis Secondary to Trauma in a Patient with Systemic Lupus Erythematosus and Ovarian Cancer

Mazliha Mashor[1], *Adv M Derm*, Noor Zalmy Azizan[1], *Adv M Derm*, Bang Rom Lee[2], *MPath*

[1]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[2]Pantai Premier Pathology, Gleneagles Kuala Lumpur, Kuala Lumpur, Malaysia

Summary

Calcinosis cutis is characterized by the accumulation of insoluble calcium salts in the cutaneous and subcutaneous tissue. This condition is classified into four subtypes of calcification: dystrophic, metastatic, idiopathic and iatrogenic. Here, we describe a case of calcinosis cutis in a patient with systemic lupus erythematosus (SLE) who was recently diagnosed with ovarian cancer. Following total hysterectomy with bilateral salphingo-oophorectomy, she developed a painful erythematous plaque over the anterior aspect of the left forearm which turned into single thin yellowish plaque over the following days. Multiple attempts of intravenous cannulation for intravenous fluids occurred at the site. Skin biopsy revealed calcification in the dermis and subcutaneous fat associated with altered dermal collagen. Von Kossa stain demonstrated the presence of calcium deposition. She responded to topical calcineurin inhibitor which resulted in a complete resolution of the skin lesion.

Key words: *Calcinosis cutis, Systemic lupus erythematosus, Ovarian cancer*

Introduction

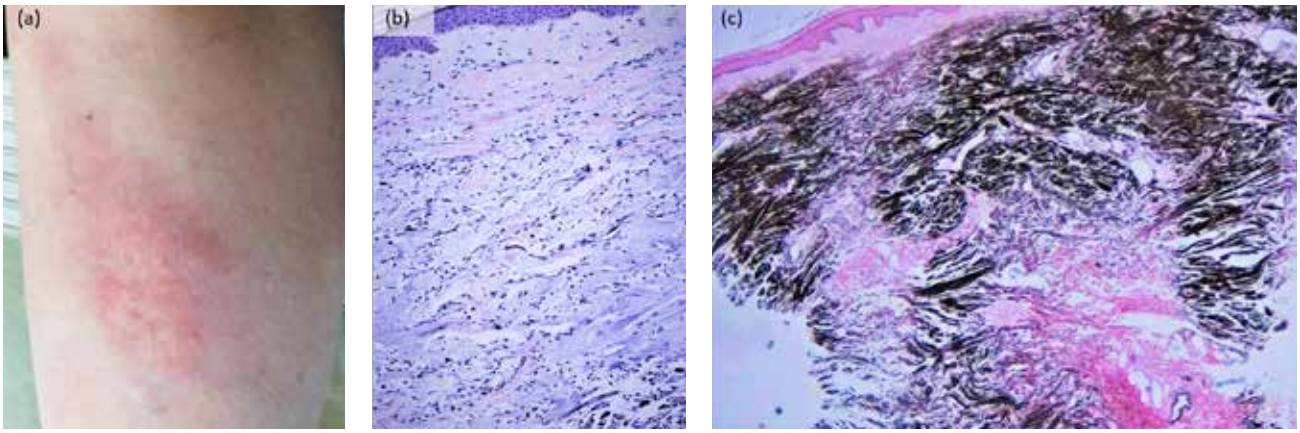
Calcinosis cutis is characterized by the accumulation of insoluble calcium salts in the cutaneous and subcutaneous tissue. This condition is classified into four subtypes of calcification: dystrophic, metastatic, idiopathic and iatrogenic.[1-3] Dystrophic type is closely linked to autoimmune connective tissue diseases. Here, we describe a case of calcinosis cutis in a patient with systemic lupus erythematosus (SLE) who was recently diagnosed with ovarian cancer.

Case Report

A 58-year-old lady presented with a 2-week history of a single plaque on her left forearm. This patient was diagnosed with SLE since 2007 and is currently in remission. Her treatment included prednisolone 5mg daily and hydroxychloroquine 200mg daily. She was also taking calcium carbonate and vitamin D supplement for more than 10 years. Recently, she was diagnosed with ovarian clear cell carcinoma and a total hysterectomy with bilateral salphingo-oophorectomy was performed. Post-operatively, she developed a painful erythematous plaque over the anterior aspect of the left forearm. This was the site where multiple attempts of intravenous cannulation

Corresponding Author
Dr Mazliha Mashor
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586 Kuala Lumpur, Malaysia.
Email: ammz83@yahoo.com

Figure 1. (a) Single thin yellowish plaque over the left forearm; (b) Histopathology shows calcification in the dermis and subcutaneous fat (H&E x 100); (c) Calsium deposits in the dermis using Von Kossa stain x 20)



for intravenous fluids occurred, however there was no drug administered intravenously.

Over the following few days, a single thin yellowish plaque appeared at the same site with an ill-defined border and surrounding erythema (Figure 1a). The plaque was tender and not associated with any blister, ulcer or discharge. Patient was otherwise well with no similar lesion elsewhere on her body. Plane xanthoma and necrobiosis lipoidica were considered as differential diagnoses.

Histopathological examination of the skin lesion revealed calcification in the dermis and subcutaneous fat associated with altered dermal collagen (Figure 1b). Von Kossa stain demonstrated the presence of calcium deposition. Hence, the diagnosis of calcinosis cutis was made (Figure 1c). Serum calcium, phosphate and lipid levels were within normal limits. Our patient was prescribed topical calcineurin inhibitor to reduce the inflammation. She had completed systemic chemotherapy post operatively for her ovarian carcinoma. During her last clinic visit, there was a complete resolution of the skin lesion with no recurrence noted.

Discussion

Calcinosis cutis is more frequently manifested as chalky white subcutaneous nodules. In this case the clinical appearance of a yellowish plaque could be misleading and may look similar to xanthoma, as previously reported by Ankad *et al*.[4] Von kossa stain would be helpful to confirm the diagnosis of calcinosis cutis.

The exact pathophysiology of calcinosis cutis is still unclear. Some studies hypothesized that local inflammation following tissue injury might lead to tissue calcification.[2,3] At the site of trauma, increased cell permeability and damaged proteins of necrotic cells may further attract calcium deposition.[1,2] In our case, local skin microtrauma caused by repeated cannulation might promote the development of calcinosis cutis as suggested in past studies.[5-7]

SLE-associated calcinosis cutis is usually localised with the tendency to develop over the limbs and buttocks.[1,8] Typically, calcinosis cutis presents in patients with a long history of established SLE.[2,8] Similarly, our patient had SLE for more than 10 years before developing calcinosis cutis, despite her SLE currently being in remission.

Elevated level of calcium or phosphate metabolism is usually found in metastatic calcification and calciphylaxis.[1] Normal level of serum calcium and phosphate is observed in idiopathic and dystrophic calcification (as reflected in our case). The patient is unlikely to have idiopathic calcification due to the presence of tissue damage. Other type such as iatrogenic calcification mostly occurs following an intravenous calcium treatment.[1] Whether the oral calcium and vitamin D supplement intake contributed to cutaneous calcification in our patient is unproven.

The treatment of calcinosis cutis in SLE is variable with no standardised algorithm.[8,9] Several medical treatments which are reported to be beneficial include diltiazem, colchicine, minocycline. Surgical treatment is generally considered for large localised and symptomatic lesions.[9]

Conclusion

When encountering a patient with long-standing SLE, normal serum calcium and phosphate levels, and following trauma especially at intravenous cannulation sites, the presence of yellowish plaque should prompt the clinician to consider dystrophic calcinosis cutis as a differential diagnosis.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

References

1. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: Part I. Diagnostic pathway. J Am Acad Dermatol 2011;65:1-12.
2. Kim MS, Choi KC, Kim HS, Song IG, Shin BS. Calcinosis cutis in systemic lupus erythematosus: A case report and review of the published work. J Dermatol 2010;37:815-8.
3. Ammouri W, Harmouche H, Ahrikat O, Maamar M, Tazi MZ, Adanaoui M. Extensive calcinosis cutis in a patient with systemic lupus erythematosus: An exceptional complication. Press Med 2018;47:410-1.
4. Ankad BS, Miskin AT, Math MK, Sakhare PS. Calcinosis cutis mimicking xanthoma: A case report. Our Dermatol Online J 2018;9:95-6.
5. Larralde M, Giachetti A, Cáceres MR, Rodríguez M, Casas J. Calcinosis cutis following trauma. Pediatr Dermatol 2005;22:227-9.
6. Kanda A, Uchimiya H, Ohtake N, Setoyama M, Kanzaki T. Two Cases of Gigantic Dystrophic Calcinosis Cutis Caused by Subcutaneous and/or Intramuscular Injections. J Dermatol 1999;26:371-4.
7. Chung EH, Kim YH. Iatrogenic calcinosis cutis of the upper limb arising from the extravasation of intravenous anticancer drugs in a patient with acute Lymphoblastic leukemia. Arch Plast Surg 2016;43:214-6.
8. Gutierrez Jr A, Wetter DA. Calcinosis cutis in autoimmune connective tissue diseases. Dermatol Ther 2012;25:195-206.
9. Balin SJ, Wetter DA, Andersen LK, Davis MDP. Calcinosis cutis occurring in association with autoimmune connective tissue disease: The Mayo Clinic experience with 78 patients, 1996-2009. Arch Dermatol 2012;148:455-62.

CASE REPORT

Quinacrine: An Effective Addition to the Treatment of Refractory Cutaneous Lupus Erythematosus

Hui Jen Ding, *MRCP*, Swee Gaik Ong, *MRCP*

Rheumatology Unit, Department of Medicine, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Summary

Treatment of refractory cutaneous lupus is challenging. When conventional therapy, including hydroxychloroquine (HCQ), corticosteroids and immunosuppressants, has failed, the addition of quinacrine may be a promising option. We describe a case of refractory chronic cutaneous lupus erythematosus (CCLE) who responded well to quinacrine.

Key words: *Quinacrine, Refractory cutaneous lupus erythematosus, Hydroxychloroquine*

Introduction

Quinacrine, also known as mepacrine, is a synthetic quinine derivative which has been shown to be efficacious in the treatment of discoid lupus erythematosus (DLE) as early as in the 1940s.[1-3] However, its use was superseded by hydroxychloroquine (HCQ) because of quinacrine's purported side effects. Nevertheless, the use of quinacrine has seen a resurgence of late. We report a case of refractory chronic cutaneous lupus erythematosus (CCLE) who responded favourably to quinacrine.

Case Report

Our patient is a 49-year-old man who was diagnosed with systemic lupus erythematosus 22 years ago based on the American College of Rheumatology (ACR) 1997 revised classification criteria for SLE.[4] He is anti-nuclear antibody positive but anti-double-stranded DNA and extractable nuclear antigen negative. His complement levels (C3/C4) were never low. He had mild cytopenias (leukopenia and lymphopenia) in the past but no major organ involvement. His manifestations are predominantly cutaneous: he has disfiguring DLE rashes on the scalp, face and both upper arms and forearms.

His rashes (Figure 1a) are refractory to almost all immunosuppressants that he has tried: multiple rounds of intravenous immunoglobulin and IV methylprednisolone, cyclosporine, azathioprine, colchicine, dapsone, methotrexate and mycophenolate mofetil. These were all used

Corresponding Author
Dr Ding Hui Jen
Rheumatology Unit,
Department of Medicine,
Hospital Kuala Lumpur,
Jalan Pahang,
50586 Kuala Lumpur, Malaysia.
Email: hjding1@gmail.com

on a background of HCQ and topical and systemic corticosteroids. He is steroid-dependent, often flaring when his prednisolone dose is reduced to less than 20mg daily. He is on HCQ 400mg daily, the maximum recommended dose. He developed avascular necrosis of both femoral heads and recurrent serious infections as a result of prolonged high-dose corticosteroid use.

He is an ex-smoker who stopped in 2018 because of the development of peripheral vascular disease and ischemic heart disease. However, despite stopping smoking, his rashes remained active. In late 2019, we applied for special permission to purchase and use quinacrine through the Ministry of Health, as it is not licensed for use in Malaysia. Quinacrine 100mg daily was added to HCQ and prednisolone. He reported progressive improvements in his rashes in the first 6 months. CLASI activity scoring improved from 15 to 2. His prednisolone dose was reduced gradually to 5mg daily. He has now been on quinacrine for 15 months: his lesions have remained inactive and his prednisolone use has not required dose escalation. He has not developed any untoward side effects to quinacrine. Figure 1b shows his cutaneous lesions 6 months after initiation of quinacrine.

Figure 1. Side profile of the patient's face showing DLE rashes; (a) Pre-treatment; (b) Post

Discussion

Antimalarials, together with non-pharmacological methods like smoking cessation and sunscreen usage, are recommended as first-line treatment for cutaneous lupus erythematosus (CLE). Quinacrine is added when there is poor response, where quinacrine has been shown to work synergistically with HCQ or chloroquine.[5]

Antimalarials have been used to treat CLE for years but their mechanism of action is not completely understood. Recent studies have implicated toll-like receptors (TLRs) in the pathogenesis of CLE in producing pro-inflammatory cytokines like interferon-α (IFN-α).[6-7] Antimalarials are able to inhibit TLRs, hence dampening production of IFN-α.[8] Quinacrine and HCQ were shown in a study to decrease the production of IFN-α.[9] Other postulated mechanisms of action of antimalarials include immunomodulatory, anti-proliferative, anti-inflammatory and photoprotective properties.[10]

Quinacrine is a safe drug with relatively few side effects. Notably, it has no retinal toxicity[11-12] and does not potentiate the side-effects of HCQ or CQ when used in combination.[13] However, the commonest side effect is a yellowish discolouration of the skin, which reverses upon cessation of the drug. Other side effects which could occur include headache and gastrointestinal symptoms.[13] Rare side effects include aplastic anaemia[14] and acute hepatitis,[15] although these occurred in conjunction with the use of other drugs and concomitant Hepatitis C infection.

Quinacrine appears to be more efficacious in patients with acute cutaneous lupus and discoid lupus, with response rates ranging from 55-80%.[15-18] However, it is still not widely available in the United States of America, Europe or Asia.[11,17,19] thus limiting its use. Nonetheless, we hope this experience would encourage the use of quinacrine in refractory cutaneous lupus in Malaysia and help reduce the incidence of adverse effects with other immunosuppressants.

Conclusion

Several case series have supported quinacrine's efficacy and safety. It can be considered in patients with DLE who do not show adequate response despite maximal HCQ therapy and corticosteroid therapy.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

References

1. Wallace DJ. The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. Semin Arthritis Rheum 1989;18:282-96.
2. Dubois EL. Antimalarials in the management of discoid and systemic lupus erythematosus. Semin Arthritis Rheum 1978;8:33-51.
3. Page F. Treatment of lupus erythematosus with mepacrine. Lancet 1951;2:755-8.
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
5. Kuhn A, Aberer E, Bata-Csörgő Z, Caproni M, Dreher A, Frances C et al. S2k guideline for treatment of cutaneous lupus erythematosus - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2017;31:389-404.
6. Aringer M, Günther C, Lee-Kirsch MA. Innate immune processes in lupus erythematosus. Clin Immunol 2013;147:216-22.
7. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol 2003;21:335-76.
8. Willis R, Seif AM, McGwin G Jr, Martinez-Martinez LA, González EB, Dang N et al. Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: data from LUMINA (LXXV), a multiethnic US cohort. Lupus 2012;21:830-5.
9. Alves P, Bashir MM, Wysocka M, Zeidi M, Feng R, Werth VP. Quinacrine Suppresses Tumor Necrosis Factor-α and IFN-α in Dermatomyositis and Cutaneous Lupus Erythematosus. J Investig Dermatol Symp Proc 2017;18:S57-63.
10. Rodriguez-Caruncho C, Bielsa Marsol I. Antimalarials in dermatology: mechanism of action, indications, and side effects. Actas Dermosifiliogr 2014;105:243-52.
11. McCune WJ, Gonzalez-Rivera T. Should very low doses of hydroxychloroquine and quinacrine be employed in combination for long-term maintenance of remission in systemic lupus to reduce the risk of ocular toxicity? Curr Opin Rheumatol 2015;27:213-5.
12. Zuehlke RL, Lillis PJ, Tice A. Antimalarial therapy for lupus erythematosus: an apparent advantage of quinacrine. Int J Dermatol 1981;20:57-61.
13. Mittal L, Zhang L, Feng R, Werth VP. Antimalarial drug toxicities in patients with cutaneous lupus and dermatomyositis: A retrospective cohort study. J Am Acad Dermatol 2018;78:100-6.e1.
14. Wallace DJ. Antimalarial agents and lupus. Rheum Dis Clin North Am 1994;20:243-63.
15. Cavazzana I, Sala R, Bazzani C, Ceribelli A, Zane C, Cattaneo R et al. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. Lupus 2009;18:735-9.
16. Benoit S, Goebeler M. Mepacrine in Recalcitrant Cutaneous Lupus Erythematosus: Old-fashioned or Still Useful? Acta Derm Venereol 2015;95:596-9.
17. Chang AY, Piette EW, Foering KP, Tenhave TR, Okawa J, Werth VP. Response to antimalarial agents in cutaneous lupus erythematosus: a prospective analysis. Arch Dermatol 2011;147:1261-7.
18. González-Sixto B, García-Doval I, Oliveira R, Posada C, García-Cruz MA, Cruces M. Aspectos prácticos de la quinacrina como tratamiento del lupus eritematoso cutáneo: serie de casos [Quinacrine in the treatment of cutaneous lupus erythematosus: practical aspects and a case series]. Actas Dermosifiliogr 2010;101:54-8. Spanish.
19. Mittal L, Werth VP. The quinacrine experience in a population of patients with cutaneous lupus erythematosus and dermatomyositis. J Am Acad Dermatol 2017;77:374-7.

CASE REPORT

Cutaneous *Serratia Marcescens* Infection - A Rare Case Report

Kwang Meng Yew[1], *MMed*, Stephanie Sue San Ong[1], *MD*, Mazita Ismail[2], *MPath*, Jyh Jong Tang[1], *AdvMDerm*

[1]Department of Dermatology, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia
[2]Department of Pathology, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

Summary

Cutaneous *serratia marcescens (S. marcescens)* infection is very rare and most cases had history of skin trauma or cutaneous procedure done before. It presents in various forms like non-healing ulcers, abscess formation, nodules with an intermittent course or as granulomatous lesions, thus mimicking non-infective lesions. Antibiotic choice is challenging due to multiple antibiotic resistant strains. We are reporting a case of cutaneous *S. marcescens* in a 70-year old lady with diabetes mellitus presented with non-healing ulcers over the dorsum of left hand for 6 months.

Key words: *Cutaneous, Serratia marcescens, Community acquired*

Introduction

Serratia marcescens, an opportunistic, Gram-negative, facultative anaerobe bacterium, is commonly associated with nosocomial infection and rarely community acquired.[1] Skin infections by *S. marcescens* are extremely rare and usually occur in patients with underlying disease or immunocompromised and almost never in immunocompetent patients.[2,3] It can present in acute or chronic form, with sporotrichoid spread or chronic granulomatous infections, thus mimicking certain types of skin pathology such as sporothricosis, cutaneous tuberculosis, nocardiosis and histoplasmosis.[2,3,7] Worldwide, only a few cases of community acquired infection had been reported involving healthy individuals with no co-morbids.[2-6]

Case Report

A 70-year old Chinese lady with underlying diabetes mellitus on a single oral hypoglycemic agent for more than 10 years, presented with multiple non-healing ulcers over the dorsum surface of left hand past 6 months. She had history of developing solitary, erythematous swelling with ulceration over the left arm, right elbow and leg, which appeared one after another past 1 year. A new swelling would appear after the previous one was removed and resolved. She went to orthopaedic surgeon a few times to have the swellings excised. Tissue and blood cultures done were normal. She was completely free from any swelling after that. She denied any history of

Corresponding Author
Dr Yew Kwang Meng
Department of Dermatology,
Hospital Raja Permaisuri Bainun,
Jalan Raja Ashman Shah,
30450 Ipoh, Perak, Malaysia.
Email: eastdragonkm@yahoo.com

skin trauma or animal bite prior to onset of above lesion. There was no contact with tuberculosis (TB) patient.

4 months ago, she developed another swelling with ulceration over dorsum of left hand, which again being excised by orthopaedic surgeon but this time, the ulcer persisted and developed a few more on the same site. She sought treatment from private dermatologist and skin biopsy done showed acute abscess with vague granuloma infective, suppurative granulomatous lesion. Swab culture and sensitivity (C + S) grew *S. Marcescens*, sensitive to Ceftazidime, Ciprofloxacin, Gentamicin, Ceftriaxone, Ertapenam, Levofloxacin and Co-Trimoxazole. She was empirically started on oral Doxycycline for 3 months but no improvement noted.

Subsequently she was referred to us and her wound had multiple, sloughy ulcers with raised surrounding border and erythematous surrounding. Incisional skin biopsy showed acute on chronic inflammation, no granuloma, fungal body or malignancy (Figure 1). Bacterial C + S was repeated twice which showed *S. Marcescens*, susceptible to Cefepime and Trimethoprim/Sulfamethoxazole. TB work ups comprising chest x-ray, mantoux test, skin sample for TB polymerase chain reaction and fungal culture were negative.

She was treated with oral sulfamethoxazole and trimethoprim 2 tablets BD for 2 weeks and potassium permanganat 1:10,000 plus bactigrass dressing daily, which showed slight improvement, thus sulfamethoxazole and trimethoprim was increased to 3 tablets BD. After 2 weeks, the wounds improved significantly (Figure 3). Oral sulfamethoxazole and trimethoprim was continued for another 2 months and her skin lesion resolved completely after that.

Figure 1. The dermis show moderate to dense lymphoplasma cells and neutrophils infiltrate, vascular congestion and areas of hemorrhage. a. H&E at low power b. H&E at x40

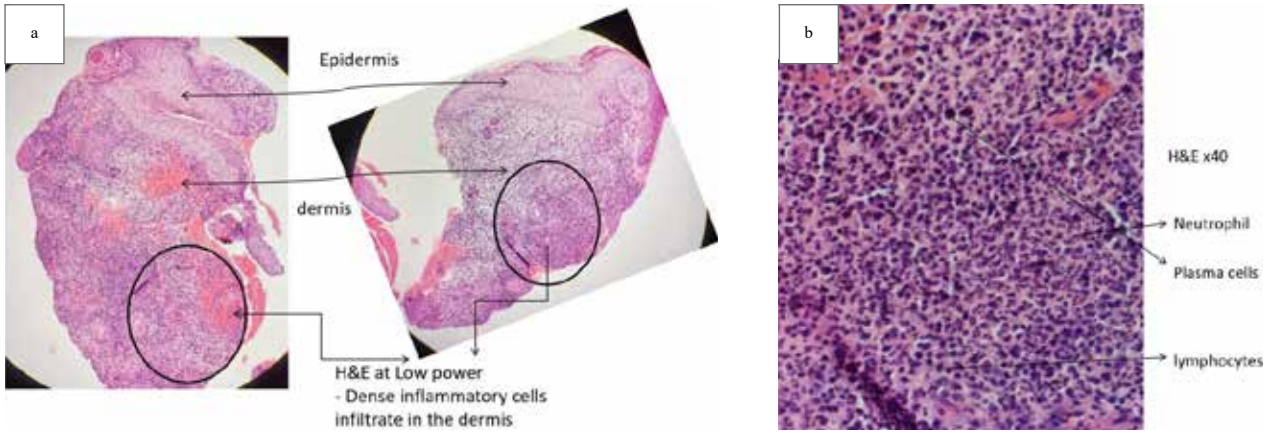
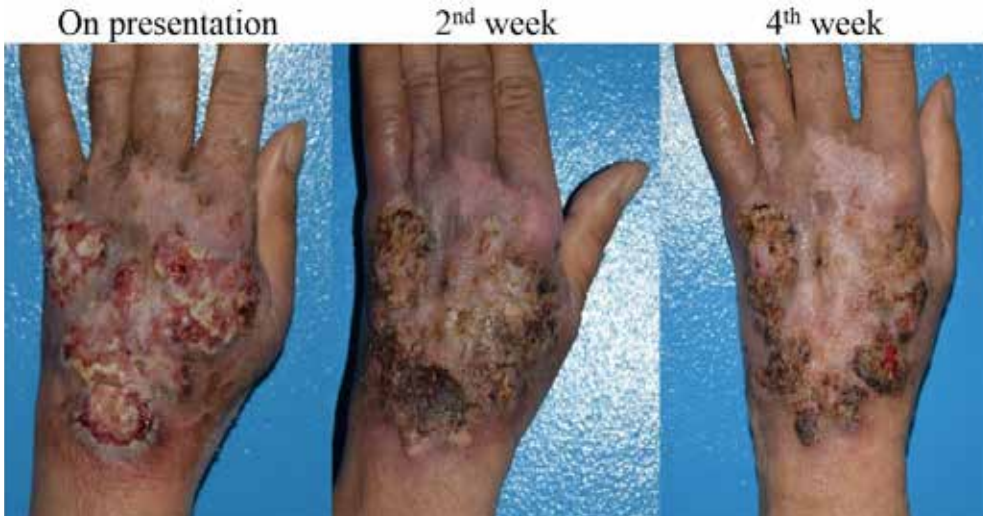


Figure 2. Improvement of the wound over dorsum of left hand lesion with oral Bactrim



Discussion

Community acquired *S. marcescens* infections commonly occur in immunocompromised individuals,[8] in association with contaminated depot, parenteral solutions and illicit drug usage.[9-12] Most skin infection occurred after sustaining trauma or undergoing cutaneous procedures.[2,3,5,6] However, there are some reports where no portal of entry or immunosuppression were identified in infected individuals.[4,13]

Cutaneous infection has various forms ranging from acute type like cellulitis, abscess, ulcers and necrotizing fasciitis or chronic forms such as fluctuant nodules with an intermittent course or granulomatous lesions.[2,4] Our patient has multiple non-healing, with sloughy ulcers over the dorsum of left hand.

It is crucial to rule out differential diagnosis such as chronic granulomatous infections and causes of non-healing ulcers such as subcutaneous fungal infection like sporotrichosis, Tuberculosis, Non-tuberculous mycobacterium (*Mycobacterium ulcerans*), Nocardiosis and others; due to variability in the clinical presentation.[2,6,7,8] Skin biopsy is important to confirm the underlying cause of any non-healing ulcers. Histopathologically, there will be presence of granulomatous reaction and special stain, example, Ziehl Nelson & Periodic Acid-Schiff (PAS) are important to rule out other differential diagnosis, example subcutaneous fungal and mycobacterium infection. Skin biopsy for culture is still the gold standard to confirm the diagnosis of *Serratia marcenscen*. It is through pus and tissue biopsy sample culture of the ulcer, that we managed to identify the infective etiology in our patient.

S. marcescens has multiple antibiotic resistant strains, including those resistant towards broad spectrum antibiotics.[1] Therefore, antibiotic choice has to be guided by culture sensitivity test. Among the antibiotics used successfully to treat *S. marcescens* are ciprofloxacin, sulfamethoxazole and trimethoprim and ertapenem.[2,3,5,6] Our patient was started on oral sulfamethoxazole and trimethoprim and showed significant improvement clinically.

Conclusion

S. marcescens infection should be taken into consideration when a patient presented with non-healing cutaneous lesion. Culture and antibiotic sensitivity test are crucial in identifying the organism and Trimethoprim-sulfamethoxazole is an effective choice of treatment for *S. marcescens* but this has to be guided by sensitivity pattern.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

The authors would like to thank the Director General of Health, Malaysia for permission to publish this paper.

References

1. Herra C, Falkiner FR. *Serratia marcescens*. Antimicrobial Therapy and Vaccines. Vol. 1. New York: Apple Trees Production; 2002.
2. Giráldez P, Mayo E, Pavón P, Losada A. Skin infection due to *Serratia marcescens* in an immunocompetent patient. Actas Dermosifiliogr 2011;102:236-7.
3. Diranzo García J, Villodre Jiménez J, Zarzuela Sánchez V, Castillo Ruiperez L, Bru Pomer A. Skin abscess due to *Serratia marcescens* in an immunocompetent patient after receiving a tattoo. Case Rep Infect Dis 2015;2015:626917.
4. García FR, Paz RC, González RS, Ruiz ES, Martín-Neda FG, Rodríguez MS et al. Cutaneous infection caused by *Serratia marcescens* in a child. J Am Acad Dermatol 2006;55:357-8.
5. Grim KD, Doherty C, Rosen T. Cutaneous *Serratia marcescens* infection in an immunocompetent patient after filler injection. Acta Derm Venereol 2013;93:191-2.
6. Grim KD, Doherty C, Rosen T. S*erratia marcescens* bullous cellulitis after iguana bites. J Am Acad Dermatol 2010;62:1075-6.
7. João AM, Serrano PN, Cachão MP, Bártolo EA, Brandão FM. Recurrent *Serratia marcescens* cutaneous infection manifesting as painful nodules and ulcers. J Am Acad Dermatol 2008;58:55-7.
8. Zhu S, Anil S, Nina R, Stephen P, Neil H. Community Acquired Severe Soft Tissue Infection Due to S*erratia marcescens* in an Immunocompetent Host. Chest 2014;146:141A.

CASE REPORT

Symmetrical Flexural and Intertriginous Exanthema: A Rare Manifestation Associated with COVID-19 Infection

Jin Yi Goh[1], *MRCP*, Huang Hin Chin[2], *MRCP*, Pek Woon Chin[2], *MRCP*, Masliza Zaid[3], *MMED*

[1]Department of Medicine, Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia
[2]Department of Medicine, Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor, Malaysia
[3]Department of Medicine, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia

Summary

Cutaneous manifestations of Coronavirus disease (COVID-19) are variable. We present a case of non-drug related symmetrical flexural and intertriginous exanthema in a patient with COVID-19 infection. A 58-year-old Chinese male who was diagnosed to have COVID-19 infection, developed maculopapular erythematous rashes at bilateral axillary and inguinal folds on the fourth day of illness. He was treated symptomatically with anti-histamine and topical corticosteroid. The skin condition improved and he was discharged well on tenth day of illness. Although symmetrical flexural intertriginous exanthema is classically caused by drug reaction, this case demonstrated the possibility of the rash being directly associated with COVID-19 infection. More cohorts should be evaluated to fully describe the full spectrum of dermatological manifestation in COVID-19.

Key words: *Cutaneous, Rashes, Exanthema, COVID-19*

Introduction

Coronavirus disease (COVID-19) infection, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic in 2020. It was first reported in December 2019 in Wuhan, China.[1] The typical symptoms of COVID-19 infections are fever, dry cough, anosmia, fatigue, and dyspnea. Serious complications include acute respiratory distress syndrome, secondary infection, thrombotic events, and multiorgan failure leading to death. Besides, cutaneous manifestations have been increasingly reported in COVID-19 patients.

A nationwide consensus study in Spain has classified the cutaneous lesions into five clinical patterns, which are acral areas of erythema with vesicles or pustules (19%), vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%).[2] Wollina *et al*. have also suggested other possible cutaneous findings such as symmetrical flexural and intertriginous exanthema, purpuric rash, erythema multiforme-like rash, and Kawasaki like disease/Multisystemic inflammatory syndrome in children.[3]

Corresponding Author
Dr Goh Jin Yi
Department of Medicine,
Hospital Sultanah Nora Ismail,
Jalan Korma, Taman Soga,
83000 Batu Pahat, Johor.
Email: jinyigoh1988@yahoo.com

COVID-19 infection related skin manifestations were more commonly reported in United State and Europe countries compared to Asian cohort.4 Indeed, a systemic review of total 1211 patients with COVID-19 related skin manifestations, 39 (3.1%) patients were from Asian populations and 1172 (96.9%) patients were from Europe and the United States.[4] Here, we would like to present a case of non-drug-related symmetrical flexural and intertriginous Exanthema in a patient with COVID-19 infection.

Case Report

A 58-year-old Chinese male presented with fever and cough for the past three days, followed by an alleged fall at home which he sustained a small laceration wound over the scalp. He attributed the fall to an alleged slippery floor with no obvious neurological deficits. He underwent wound suturing at a private hospital, uneventfully. Incidentally, pre-procedure nasopharyngeal swab showed SARS-CoV RNA PCR detected. (Ct value; E gene = 18.41, RdRp gene = 21.09). He was then transferred to a designated COVID 19 hospital for further management while the local health authorities performed contact tracing amongst his family members and friends. His fever and cough were resolved in the ward.

However, on the fourth day of illness, he developed blanchable maculopapular erythematous rashes at bilateral axillary and inguinal folds. The distribution of rash rapidly involved nape of the neck, forearm, anterior thigh, lower abdomen, and buttock symmetrically over the following days. (Figure 1 (a-d)) These lesions were mildly pruritic with no obvious discharges, vesicles, plaques or bullae noted. Notably, the face, trunk, palm, and sole were spared. He denied taking any medications before the onset of the rash. There was no prior incident of food allergies or documented family history of skin diseases.

His chest radiograph on admission was normal. Laboratory examination showed haemoglobin 15.6 g/dL, white cell counts 6.5 x 10^3 /uL (neutrophil 72.9%, lymphocyte 11.7%, absolute lymphocyte counts 0.76 x 10^3 /uL, monocyte 12.9%, eosinophil 2.0%, absolute eosinophil counts 0.13 x 10^3 /uL, basophil 0.5%), platelet 197, 000. Renal profile and liver function test were normal. C-reactive protein was 5.7 ng/L (<5.0). Dengue IgM/IgG were negative. Skin biopsy was not performed due to patient's consent not granted. He was treated symptomatically with Tablet Loratadine 10mg once daily and topical 0.1% Betamethasone -17-valerate.

Figure 1 (a-f). Maculopapular exanthema over the nape of the neck, axilla and inguinal region

On the tenth day of his hospital stay, the skin lesions showed improvement and he was subsequently discharged well.

Discussion

This case described a patient who developed skin rashes in the early phase of COVID-19 illness. The differential diagnosis that needs to be considered includes viral exanthem, drug-related, and systemic infection. The distribution of rashes was predominantly at the flexural region, which resembles symmetrical intertriginous and flexural exanthema, often due to exposure to the drug such as Beta-lactam antibiotic. However, in this case, the patient did not receive any antibiotics or other medications before or during hospitalization. He also denied having any history of atopy. The normal eosinophil count indicates the rash is less likely to be allergen related. In view that the skin condition appeared on Day 4 of illness with no other attributable factors, we concluded that this rash was due to post-viral infection, likely the COVID-19 virus.

Given various cutaneous manifestations in adult patients with COVID-19, histopathological examination via skin biopsy would provide additional information. Ahouach et al reported the presence of basal cell vacuolation and mild perivascular lymphocytic infiltrate in the skin biopsy obtained from a patient with similar skin condition.[3] Unfortunately, skin biopsy was not performed as condition was improved and patient's consent was not granted.

Conclusion

In conclusion, various morphologies of cutaneous manifestations are associated with COVID-19. This case demonstrated an association between symmetrical flexural and intertriginous exanthema with COVID-19 infection. More cohorts should be evaluated to fully describe the full spectrum of dermatological manifestation in COVID-19.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 2020;183:71-7.
3. Ahouach B, Harent S, Ullmer A, Martres P, Bégon E, Blum L et al. Cutaneous lesions in a patient with COVID-19: are they related? Br J Dermatol 2020;183:e31.
4. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. J Am Acad Dermatol Int 2021;2:119-33.
5. Mawhirt SL, Frankel D, Diaz AM. Cutaneous Manifestations in Adult Patients with COVID-19 and Dermatologic Conditions Related to the COVID-19 Pandemic in Health Care Workers. Curr Allergy Asthma Rep 2020;20:75.

ACKNOWLEDGEMENT
Jun Issue 2021

The Editorial Board of The Malaysian Journal of Dermatology gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Assoc Professor Dr Adawiyah Jamil
2. Dr Agnes Heng Yoke Hui
3. Dr Ch'ng Chin Chwen
4. Dr Chan Lee Chin
5. Dr Chang Choong Chor
6. Dr Chong Yew Thong
7. Dr Dawn Ambrose
8. Assoc Professor Dr Felix Yap Boon Bin
9. Dr Henry Foong Boon Bee
10. Dr Khor Yek Huan
11. Dr Kwan Zhenli
12. Dr Lo Kang Shang Chit
13. Dr Mazlin bt Mohd Baseri
14. Dr Ng Ting Guan
15. Dato' Dr Noor Zalmy Azizan
16. Dr Norashikin Bt Shamsudin
17. Dr Rajalingam Ramalingam
18. Dr Tang Jyh Jong
19. Dr Tang Min Moon