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REVIEW

Consensus Guidelines in Usage of Biologics in Dermatology during COVID-19 Pandemic: Biologic Advisory Group Malaysia

Steven Kim Weng Chow[1], *FRCP*, Siew Eng Choon[2], *FRCP*, Chan Lee Chin[3], *MMED*, Noor Zalmy Azizan[4], *AdvMDerm*, Pubalan Muniandy[5], *FRCP*, Henry Boon Bee Foong[6], *FRCP*, Agnes Yoke Hui Heng[7], *MRCP*, Benji Tze Yuen Teoh[8], *AdvMDerm*, Felix Boon Bin Yap[9], *AdvMDerm*, Wooi Chiang Tan[10], *AdvMDerm,* Peter Wee Beng Ch'ng[11], *AdvMDerm*, Kwee Eng Tey[12], *MRCP*, Latha Selvarajah[13], *AdvMDerm*, Suganthi Thevarajah[4], *MMed*

[1]KL Skin Centre, Kuala Lumpur, Malaysia
[2]Jeffrey Cheah School of Medicine & Health Sciences, Johor Bahru, Johor, Malaysia
[3]Northern Skin Specialist Clinic, Penang, Malaysia
[4]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[5]Department of Dermatology, Hospital Umum Sarawak, Kuching, Sarawak, Malaysia
[6]Foong Skin Specialist Clinic, Ipoh, Perak, Malaysia
[7]Agnes Heng Dermatology, Ipoh, Perak, Malaysia
[8]Department of Dermatology, Selayang Hospital, Selangor, Malaysia
[9]Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Sungai Long Campus, Selangor, Malaysia
[10]Department of Dermatology, Hospital Pulau Pinang, Pulau Pinang, Malaysia
[11]Gleneagles Kuala Lumpur, Kuala Lumpur, Malaysia
[12]Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia
[13]Department of Dermatology, Hospital Sultan Ismail, Johor Bahru, Johor, Malaysia

Objective

The aim of this Biologic Advisory Group (BAG) Malaysia consensus guideline is to provide clinicians managing cutaneous diseases with biologics relevant parameters to consider prior to initiating or stopping or continuing any biologic treatment in the current landscape of the COVID-19 pandemic. Besides reviewing the medical literatures on COVID-19 and evidences related to other human coronavirus or influenza, expert opinions and clinical experiences are shared and debated in formulation of this biologic consensus guideline.

Preamble

The emergence of the 2019 novel coronavirus SARS-CoV-2 in December 2019 in Wuhan, China and subsequently the pandemic outbreak of COVID-19 worldwide; is a great concern for public health around the world. There is a significant global concern on this COVID-19 pandemic due to its widespread of transmission and its effects in significant proportion of vulnerable patients.

Patients on immunomodulators, in particular biologics and small molecules for cutaneous diseases represent one of the vulnerable populations who require special consideration with regard to their treatment during this COVID-19 pandemic period.

Corresponding Author
Dr Steven Chow Kim Weng
The KL Skin Centre,
323, Ground Floor, Jalan Pudu,
55100 Kuala Lumpur, Malaysia.
Email: drstevenchow@gmail.com

Currently, the Centre for Disease Control Prevention (CDC) and World Health Organization (WHO) have no specific guidelines on the use of biologics during the pandemic.

Treating patients in this COVID-19 pandemic situation, individual clinicians would need to base on their knowledge and experience to weigh the risks versus benefits to decide whether biologics should be initiated or continued in their patients. There are some who cautioned the use of biologics during COVID-19 pandemic, while others cautioned against discontinuation of biologics which can result in loss of response when reinitiated later or formation of auto-antibodies upon discontinuation of biologics.[1-4]

There are several guidance documents published recently by the American Academy of Dermatology (AAD),[5] International League of Dermatological Societies (ILDS)[6] and International Psoriasis Council[7] with regard to the use of biologics on psoriasis patients during COVID-19 pandemic offering some general guidance to clinicians on the management of psoriasis patients with biologics during this COVID-19 pandemic.

In addition, there are some data on the risk of COVID-19 infection with biologic therapy, with recent publication of 2 studies suggesting the usage of biologics in immune-mediated inflammatory diseases is not associated with worse COVID-19 outcomes or at higher risk of being infected with COVID-19 virus.[8-9] In addition, a paper from China analysed 107 psoriasis patients on IL-17 and anti-TNF-α in pandemic epicentre Wuhan has found that patients receiving biologics do not have an increased risk of contracting COVID-19 or developing complications to COVID-19.[10] Emerging data from PsoProtect registries evaluating factors associated with adverse COVID-19 outcomes in patients with psoriasis across 25 countries also found that biologic use in moderate to severe psoriasis patients was associated with lower risk of COVID-19 related hospitalization than non-biologic systemic therapies.[11]

In Malaysia, biologic therapies have also gained acceptance and is currently playing an important role in psoriasis treatment. According to Malaysian Psoriasis Registry 2007-2018 annual report, a total of 136 adult patients received biologic treatment. The biologic therapy that are most frequently used include TNF α inhibitor [Adalimumab (36%), Etanercept (11%), Infliximab (3.6%), Golimumab (0.7%), Certolizumab (0.7%)], followed by Anti IL 12/23 Ustekinumab (34%) others (2.9%).

SARS-Cov-2 Virus and COVID-19 Disease

In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology, which were supposedly epidemiologically linked to a seafood and wet animal market in Wuhan, China[12]. This unknown virus is initially being termed "2019-nCoV" and later changed to "SARS-CoV-2" (officially known as COVID-19 disease now), a beta coronavirus closely linked to SARS-CoV (2003 SARS disease) and MERS-CoV (2011 MERs disease). On 11 Mar 2020, the WHO declared Covid-19 as a global pandemic. As of 2nd Oct 2020, 34 million confirmed cases and around 1 million deaths (3%) have been reported to WHO.[13]

The initial animal reservoir for this virus is believed to be from bats, with the intermediate hosts suspected to be pangolins.[14] Human to human transmission of COVID-19, via respiratory droplets or close contact has been detected.[15] COVID-19 has a probable asymptomatic incubation period of 2-14 days during which the virus can be transmitted.16 The rapid spread of COVID-19 virus has occurred with the basic *R0* of 2.2-2.6, meaning that on average, each individual has the potential to spread the infection to 2.2 other people.[17]

Based on the hospitalized patients data, the majority of COVID-19 cases (about 80-90%) presented with asymptomatic or with mild symptoms while the remainder are severe or critical.[18,19] The most common symptoms of COVID-19 are fever, fatigue and respiratory symptoms including cough, sore throat and shortness of breath, while intestinal symptoms were occasionally reported.[15,18] Most patients developed lymphopenia and pneumonia with characteristics pulmonary ground glass opacity changes on chest CT.[15,18]

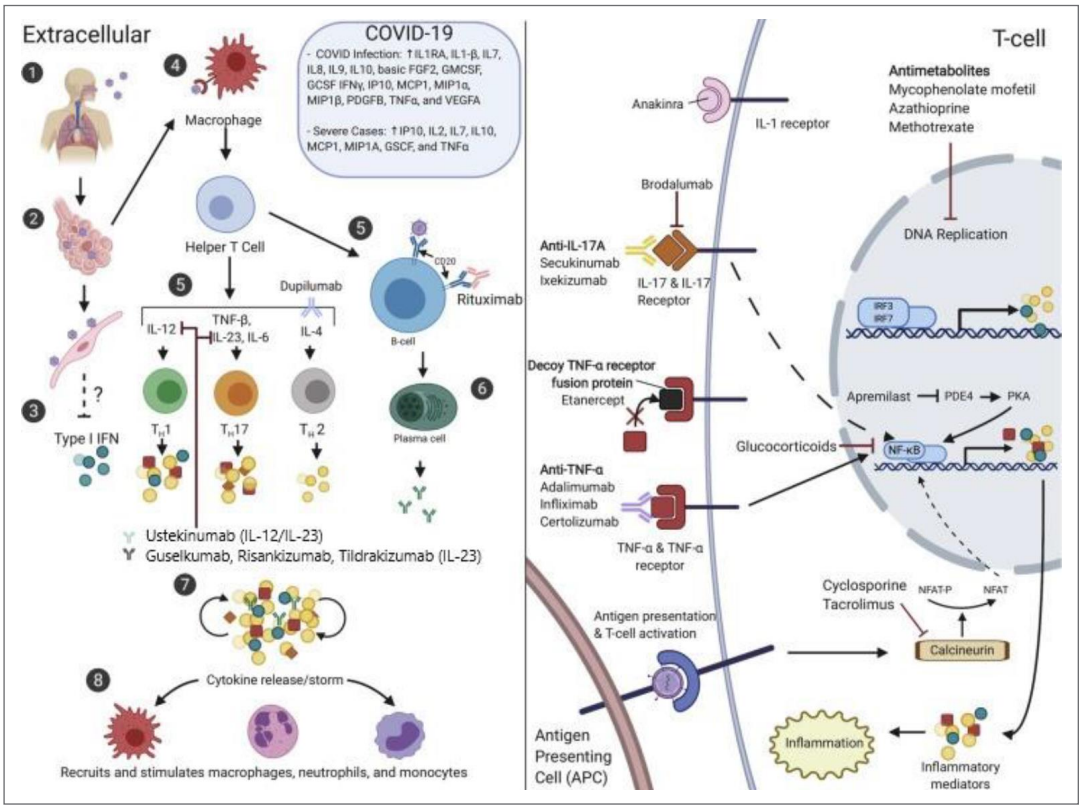
Immune Response in COVID-19 Patients

In addition, significantly high blood levels of cytokines and chemokines (inflammatory mediators) were noted in patients with COVID-19 infection. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α and TNFα that are reasoned to promote disease severity.[18] Inflammatory

mediators can become hyperactivated, resulting in a "cytokine storm" which is the primary cause of death in severe disease.[20]

Theoretical data from previous coronavirus outbreaks has also suggested a prominent role for type 1 interferon, B-cell released antibodies, tumour necrosis factor-α (TNFα) and other cytokines in the viral immune response (Figure 1).[21]

Figure 1. COVID-19 viral immune response and target of common dermatologic immunomodulators and immunosuppressants. (Adapted from Price KN et al[21])



(Left) (1) Person-to-person transmission of COVID-19 occurs through direct contact with respiratory secretions of infected individuals. The virus invades host cells by binding to their receptors and fusing with the cell membrane. (2) It is hypothesized that once inside the body, the lung epithelial cells become the primary target, where the receptor binding domain of the virus spikes bind to angiotensin-converting enzyme (ACE2) receptors of ACE2-expressing target cells. (3) Although not confirmed, it is believed the virus dampens the initial type 1 interferon (IFN) responses, which contributes to uncontrolled viral replication. (4) Once the virus is identified, macrophages present viral components to activate and induce (5) differentiation of T cells and B cells. (6) Activated B cells differentiate into plasma cells that produce antibodies important for neutralizing viruses. (7) The resulting inflammatory cytokines and antibodies continue to stimulate the production of additional cytokines and antibodies, which may contribute to the ''cytokine storm'' noted in those with severe disease. (8) The inflammatory cytokines and antibodies also promote the influx of neutrophils, monocytes, and macrophages along with additional inflammatory cytokines.

(Right) The drug targets for common dermatologic immunomodulators and immunosuppressants have also been included in this diagram. FGF, Basic fibroblast growth factor; GCSF, granulocyte-colony stimulating factor; GMCSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; IP10, interferon-induced protein 10; IRF, interferon regulatory factor; MCP1, monocyte chemoattractant protein 1; MIP1A, macrophage inflammatory protein 1-A; NFAT, nuclear factor of activated T cells; NF-B, nuclear factor-B; PDE4, phosphodiesterase 4; PDGF, platelet-derived growth factor; PKA, protein kinase A; TH, T-helper cell; TNF, tumour necrosis factor; VEGFA, vascular endothelial growth factor A.

Interleukin (IL) 1 promotes fever and the differentiation of T-helper cells to IL-17-producing T-cells. Interleukin (IL) 17 cytokines are important for immune cell recruitment to infection sites to promote clearance, while also activating downstream cascades of cytokines and chemokines. Tumour necrosis factor-α promotes dendritic cell differentiation, leukocyte recruitment, and mediates fever.[22] Antibodies produced by plasma cells help to neutralize the virus, limit infection, and prevent future infections. Disruption of B-cell differentiation into plasma cells could limit antibody production.

While normal immune response is essential to control and eliminate coronavirus infections, however, maladjusted immune responses may result

in immunopathology and impaired pulmonary gas exchange.[22]

Thus, it is currently being hypothesized that possibility of inhibiting these pro-inflammatory mediators through targeted therapy may actually improve clinical outcomes and reduce mortality in severe COVID-19 patients experiencing cytokine storm.[23,24,25,26] Two trials on tocilizumab (IL-6) in France[24] and Italy,[25] have shown clinical improvement, reduced number of ICU admissions and/or mortality in patients with severe COVID-19 pneumonia. An open label controlled trial on adalimumab (TNF-α inhibitor) for the use in treating severe COVID-19 pneumonia has also been initiated in Shanghai, China.[26]

Parameters for Consideration

In this guideline, seven (7) parameters have been considered when drafting this guideline to assess the suitability of patients to be initiated or continued with biologics during this COVID-19 pandemic. Traffic light system has been used to determine "Go" (Green); "Wait, assess other parameters" (Yellow) or "No Go" (Red) in the decision making process for this guideline. The parameters are:

1. COVID-19 Antigen (Ag) viral positivity
2. COVID-19 Antibody (IgM & IgG) seropositivity
3. Clinical signs & symptoms suggestive of COVID-19 infection or any acute respiratory infection
4. Exposure to COVID-19 positive patients
5. Underlying cutaneous disease severity
6. Patient's age
7. Underlying comorbid diseases

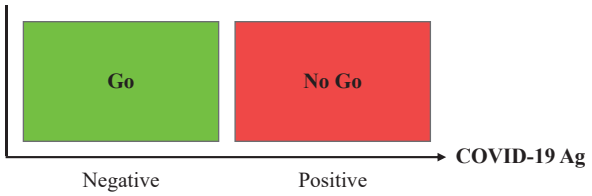
COVID-19 Antigen (Ag) Viral Positivity

This is the most important parameter to be considered in potential biologics or continuing biologics patients.

In Malaysia, there is currently no existing directive or requirement to screen all patients with COVID-19 Ag test before initiating or continuing biologics. However, for patients living in or coming from high-risk area (red zone) or suspected COVID-19 symptomatic patients, a COVID-19 Ag test is recommended.[18,19] COVID-19 RT-PCR according to the Ministry of Health should be used to establish COVID-19 infection status of the patients.

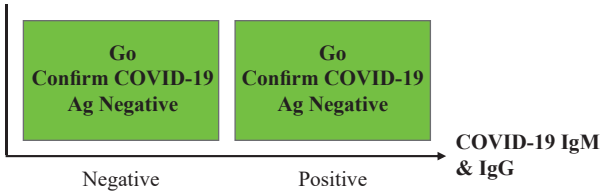
COVID-19 Ag positivity indicates current on-going infection with COVID-19 virus. Inflammatory response and mediators are needed for viral clearance.[22] Thus, it is advisable to stop patients from biologic treatment or defer initiation of biologic treatment for at least 30 days, or until patients have completely recovered and tested COVID-19 Ag negative indicating no viral shedding.[5,27]

For patients where COVID-19 Ag test is unavailable, clinicians will need to rule out COVID-19 infection in their patients through the clinical evaluation of signs & symptoms based on respective local COVID-19 practice guidelines.



COVID-19 Antibody (IgM & IgG) Seropositivity

COVID-19 Antibody test may or may not be done on the patients, as its value is limited in understanding the current infection status of the patients. Seropositivity of COVID-19 Antibody test signifies that the patient has been exposed to COVID-19 virus prior, but it does not confirm that the patient is currently still having the COVID-19 infection. Thus, we recommend those patients with either COVID-19 Antibody seropositive or seronegative to undergo COVID-19 Ag test to confirm the current status of COVID-19 infection prior to biologics initiation or continuation of therapy. If covid-19 seropositive, should WAIT and check COVID-19 Ag.



Clinical Signs & Symptoms Suggestive of COVID-19 Infection or Any Other Acute Respiratory Infection

Cold/flu-like Symptoms or Signs & Symptoms Suggestive of Any Other Acute Respiratory Infection

Patients with more severe skin disorders (e.g severe psoriasis) are inherently at increased risk of developing pneumonias of any cause.[28] While a number of clinical trials of newer biologics used in dermatology patients indicate a slight increased risk of developing upper respiratory tract infections (URTI), there does not appear to be a significant

increase risk of developing influenza (flu).

For patients with cold/flu-like symptoms, it is advisable to stop or defer biologics treatment and refer patients for COVID-19 Ag test.

For patients with cold/flu-like symptoms who are COVID-19 Ag negative, it is also advisable to screen for non-COVID-19 pathogens such as influenza, respiratory syncytial virus (RSV), Streptococcus pneumoniae so that appropriate treatment can be given. Patients with cold/flu like symptoms will still require their active immune system and inflammatory mediators for non-COVID-19 bacterial/viral clearance, thus we advised biologics treatment to be restarted after 14 days or after cold/flu-like symptoms resolves or completion of a course of antibiotics/antivirals.[29]

Diarrhoea

As the COVID-19 virus may directly or indirectly affect the enteric mucosa,[30] diarrhoea and other gastrointestinal findings should raise clinical suspicion for COVID-19 infection, with or without the presence of fever, cough and other respiratory and non-respiratory manifestation. The WHO defines diarrhoea as 3 or more loose/liquid stools per day or an increase in the number of evacuations compared with the usual.[33] A few meta-analysis conducted found that pooled prevalence among patients reporting diarrhoea ranges from 6.1% to 10.4%.[30, 31, 32]

Although the prevalence is rather low, the COVID-19 pandemic has affected millions of people worldwide, translating to a few hundred thousands of diarrhoea-associated case worldwide due to COVID-19. Thus, we recommend that patients with diarrhoea of unknown origin should have COVID-19 infection excluded before initiating or continuing biologics treatment.

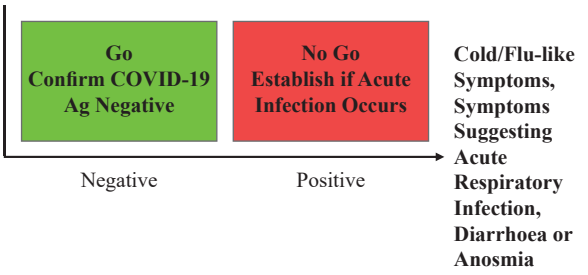
Loss of Smell (Anosmia)

There is an increasing evidence that olfactory dysfunction can present in COVID-19 patients. Anosmia can occur alone or can be accompanied by other symptoms of COVID-19, such as dry cough. However, the pathogenic mechanism of olfactory dysfunction and its clinical characteristics in patients with COVID-19 remains unclear.

There is a variability of data on anosmia among different population of patients. While it has a high incidence rate (47-70%) in COVID-19 patients in Europe[34,35] and American countries, it rarely occurs in Chinese patients (pooled data of 5%).[36]

A recent retrospective study investigating 949 patients with COVID-19 has found that 20% of the patients reported loss of smell during their initial evaluation of COVID-19. This study also found that smell loss is an independent positive prognostic factor of a less severe COVID-19 infection; significantly associated with decreased hospitalization, intensive care unit admission, intubation and acute respiratory distress syndrome rates.[37]

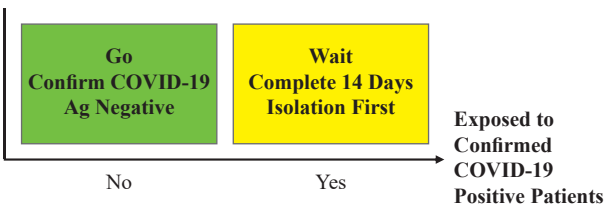
We recommend that also patients with recent onset anosmia should also have COVID-19 infection excluded before initiating or continuing biologic treatment.



Exposure to COVID-19 Positive Patients

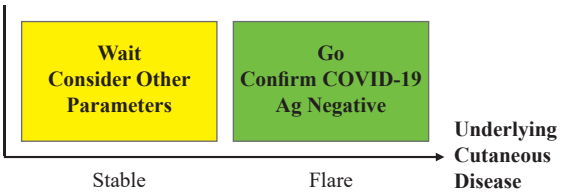
This group of patients with high risk of exposure to COVID-19 include patients living in or traveling frequently to endemic areas, healthcare worker, nursing home resident, household member or co-worker with COVID-19 infection.

These patients are of very high risk of contracting COVID-19 virus from others with close contact with them. Due to their high susceptibility in contracting the COVID-19 anytime throughout this COVID-19 pandemic, we recommend for this group of patients, a 14 days isolation or quarantine if they have been in contact with a COVID-19 positive patient. We recommend COVID-19 infection should be excluded from patients before initiation or continuation of biologics.



Underlying Cutaneous Disease Severity

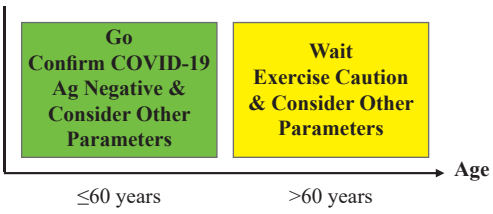
The severity of underlying cutaneous disease is also another parameter that is needed to consider when initiating or continuing biologic therapy. Disease's flare is one factor that clearly indicates benefits outweigh the risk of initiation or continuation of biologic therapy during COVID-19 pandemic. We recommend patients with a flare of underlying cutaneous disease to have the COVID-19 infection excluded before initiating or continuing biologics treatment.



Patient's Age

Patients of the older age group (>60 years old) is a known major risk factor contributing to the mortality of patients with COVID-19 disease. Death is most commonly reported among patients aged >80 years (28.7%), followed by 70-79 years (16.6%) and 60-69 years (6.7%).[19,38,39,41]

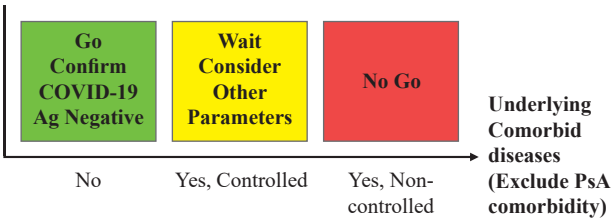
In view of this, we recommend that in patients over 60 years of age, caution need to be exercised and to take in consideration of other parameters in making a decision.



Underlying Comorbid Diseases

Data from US and China found that severe outcomes were more commonly reported for patients with reported underlying conditions (cardiovascular diseases, respiratory diseases, diabetes, liver, kidney diseases or cancer patients or on transplant patients).[24,40,41] Deaths were 12 times higher among patients with underlying conditions compared to those without reported underlying conditions.[38] As such, caution will need to be exercised considering other parameters in this group of comorbid patients.

However, for psoriasis patients with co-existing psoriatic arthritis disease, the use of biologics in these concomitant diseases are much warranted, as both diseases respond well to biologics. Thus, exception to the recommendation above for underlying comorbid disease shall be made for co-existing psoriatic arthritis disease



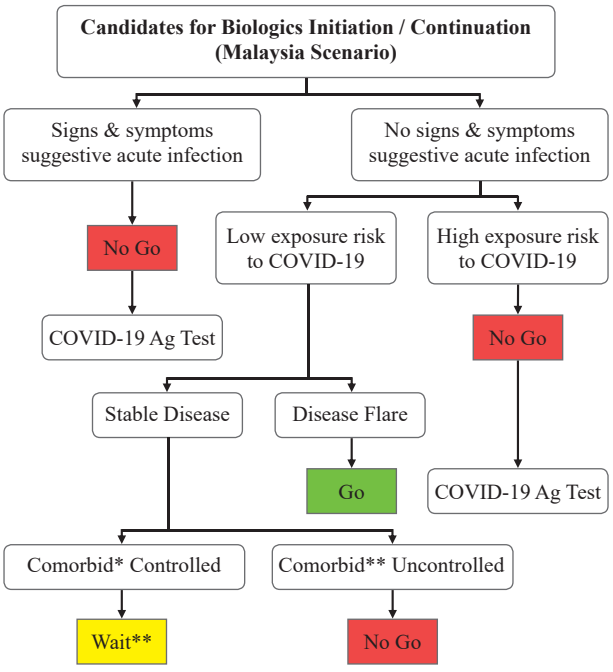
The Algorithm for The Parameters Discussed Above is Summarized in Figure 2

It is important to remember that COVID-19 is a novel, rapidly changing virus. Thus, when more data is available, this BAG Malaysia consensus guideline will need to be updated.

General Measures

Patients who have been initiated or continued with biologics treatment need to be monitored closely and advised appropriately, while those were deferred or discontinued biologics treatment will need to be monitored closely on their disease severity. In addition, all patients should be reminded to practice good infection prevention measures[10] such as frequent hand washing, wear a face mask in public places and practise social distancing.

Figure 2. Algorithm for the initiation/continuation of biologics treatment during COVID-19 Pandemic period (Malaysia Scenario)



**Including, but not limited to cardiovascular disease, respiratory disease, diabetes mellitus, liver disease, kidney disease, cancer and organ transplant patient.*

***Caution needs to be exercised, considering other parameters before initiation of biologics.*

COVID-19 Vaccination in Patients on Biologic Treatment

As of 2nd Oct 2020, there are 42 COVID-19 candidate vaccines in the clinical evaluation phase, while 151 candidate vaccines in the pre-clinical evaluation phase.[42] With vaccines companies all over the world working relentlessly to find a safe and efficacious vaccine to halt the spread of this COVID-19 infection, it is a matter of time that the right candidate vaccine will be available commercially.

COVID-19 vaccines under development include virus vaccines (inactivated or weakened), viral vector vaccines (replicating or non-replicating), nucleic acid vaccine (DNA or RNA) and protein-based vaccine (protein subunit or virus like particles).

Patients on biologic should not be given a virus vaccine. Other vaccines are not contraindicated. It is advisable for those undergoing or planning to have biologic therapy to be recommended a COVID-19 vaccination.

Key Recommendations

	BAG MY Position Statement	Level of Evidence	Strength of Recommendation
8.1	The concurrent use of biologics during the COVID-19 pandemic does not increase the risk of COVID-19 infection	II-2	B
8.2	The concurrent use of biologics during the COVID-19 pandemic does not increase the severity of COVID-19 infection	II-2	B
8.3	Patients with active COVID-19 infection as proven by positive COVID-19 Ag test or with COVID-19 clinical symptoms (without positive virology) should postpone/ defer biologic treatment for a period of at least 30 days and until being tested negative at the end of the period of postponement	III	C
8.4	Patients with other active respiratory infection (other than COVID-19 infection) or with a history of close contact with a proven active COVID-19 patient should postpone/defer biologic treatment for a period of at least 14 days and until being tested negative at the end of the period of postponement	III	C
8.5	Patients with positive serology (IgM/IgG) for COVID-19 infection with negative antigen status can proceed with biologic treatment	III	C
8.6	All patients with increased risk from co-morbid diseases should be assessed on a case-by-case basis by attending physician before commencing use of biologic agents	III	C
8.7	All patients on biologics should be recommended vaccination with a COVID-19 vaccine, should it be available in the near future	III	C

Level of Evidence

Level	Study Design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferable from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic result on uncontrolled experiments (such as the results from the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case report; or reports of expert committees

Source: US/Canada Preventive Services Task Force

Strengths of Recommendation

A	At least one meta-analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

Source: Modified from the Scottish Intercollegiate Guidelines Network (SIGN)

Note: The strength of recommendations related to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Disclaimer

The recommendations stated in this guideline are based on the currently available and/or published information related to the COVID-19 and biologics usage in psoriasis disease, as well as acts as a general guide only. Individual clinicians will need to evaluate each patient based on individualized need and discuss with their patients on their diseases and consequences before initiating or continuing biologics treatment.

Members of BAG MY Panels

a. Dr Steven Chow Kim Weng, Senior Consultant Dermatologist, KL Skin Centre, Kuala Lumpur; President, ALDS; Secretary-General, AADV.
b. Dr Suganthi Thevarajah, Head of Dermatology service, Ministry of Health, Malaysia.
c. Dato' Dr Noor Zalmy Azizan, Current President Persatuan Dermatologi Malaysia (PDM); Senior Consultant Dermatologist, Hospital Kuala Lumpur.
d. Assoc Prof Dr Choon Siew Eng, Senior Consultant Dermatologist, Hospital Sultanah Aminah, Johor Bahru; Associate Professor (Clinical), Jeffrey Cheah School of Medicine & Health Sciences, Johor Bahru.
e. Dr Chan Lee Chin, Past President Persatuan Dermatologi Malaysia (PDM); Consultant Dermatologist, Northern Skin Specialist Clinic, Penang.
f. Dr Pubalan Muniandy, Senior Consultant Dermatologist & Head of Dermatology Department, Hospital Umum Sarawak.
g. Dr Henry Foong Boon Bee, Senior Consultant Dermatologist, Foong Skin Specialist Clinic, Ipoh, Perak.
h. Dr Agnes Heng Yoke Hui, Consultant Dermatologist, Agnes Heng Dermatology, Ipoh, Perak.
i. Dr Benji Teoh Tze Yuen, Consultant Dermatologist & Head of Dermatology Department, Selayang Hospital, Selangor.
j. Associate Prof Dr Felix Yap Boon Bin, Consultant Dermatologist, Sunway Medical Centre, Selangor; Associate Professor, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Sungai Long Campus, Kajang, Selangor.
k. Dr Tan Wooi Chiang, Consultant Dermatologist & Head of Dermatology Department, Hospital Pulau Pinang, Pulau Pinang.
l. Dr Peter Ch'ng Wee Beng, Consultant Dermatologist, Gleneagles Kuala Lumpur, Kuala Lumpur.
m. Dr Tey Kwee Eng, Consultant Dermatologist & Head of Dermatology Department, Hospital Sultanah Aminah, Johor Bahru, Johor.
n. Dr Latha Selvarajah, Consultant Dermatologist & Head of Dermatology Department, Hospital Sultan Ismail, Johor Bahru, Johor.

Conflict of Interest Declaration

All panel members do not have direct conflict of interest.

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ORIGINAL ARTICLE

Cutaneous Manifestations in Patients Infected with Human Immunodeficiency Virus: An Audit in the Department of Dermatology Hospital Kuala Lumpur

Gin Peng Chan, *MRCP*, Meena Nithianandan, *MBBS*, Suganthi Thevarajah, *MMed,* Min Moon Tang, *AdvMDerm*

Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Abstract

Introduction

Patients with human immunodeficiency virus (HIV) may have significant cutaneous morbidities which can potentially affect their quality of life or be life-threatening. This study aimed to describe the demographic data and the pattern of cutaneous manifestations of patients infected with HIV.

Methods

This is a retrospective study on all HIV-infected patients who were referred to the Department of Dermatology Hospital Kuala Lumpur between 2016 and 2019. Patients' medical records were retrieved and reviewed.

Results

There were 424 patients infected with HIV referred to us between 2016 and 2019. The mean age was 31.74 years. The majority of them (50.4%) were in the age group of 20-29 years. About 96.0% (407 patients) were male. Homosexuality was the most common (52.3%) mode of HIV transmission in these patients. Two-hundred-and-ninety-six patients (69.8%) had their CD4 count available for analysis. Of these, about 39.5% of them had a CD4 count less than 200/mm^3. Less than half of the patients (189, 44.6%) were taking anti-retroviral therapy (ART) upon referral to us. There were a total of 638 cutaneous diagnoses made in this cohort with 152 patients had more than one cutaneous diagnosis. Ninety-four patients (22.2%) underwent skin biopsy with a total 98 biopsies performed. The most frequently encountered dermatosis was cutaneous infections (74.0%). These include genital warts, syphilis, genital herpes, talaromycosis and molluscum contagiosum. The most frequent non-infective inflammatory dermatoses observed in our cohort was eczematous dermatoses including papular eczema, seborrheic dermatitis, photodermatitis, contact dermatitis, nodular prurigo, discoid eczema and stasis eczema, contributing 8.4%. Cutaneous adverse drug reaction was diagnosed in 31 patients (7.3%). Fifteen patients (3.5%) had Kaposi sarcoma.

Conclusion

Our data showed that individuals with HIV infection may present with wide variety of skin disorders which included infective dermatoses, non-infective inflammatory dermatoses, cutaneous adverse drug reactions and tumours. About 35% of them had more than 1 dermatoses in our cohort. The most frequent dermatoses observed was cutaneous infections.

Key words: *Human immunodeficiency virus, retroviral disease, acquired immunodeficiency syndrome, Kaposi sarcoma, talaromycosis*

Introduction

Human immunodeficiency virus (HIV) is a retrovirus that causes immunosuppressive state,

which was first described in 1981 in Los Angeles and New York in homosexual men.[1] Based on World Health Organization (WHO) data, since the beginning of the epidemic, 75 million people have been infected with HIV virus and about 37.9 millions of people were living with HIV at the end of 2018.[2] About 0.8% of adults aged between 15 and 49 years worldwide were living with HIV.[2] In 2016, there were 115,263 cases reported to be infected with HIV in Malaysia[3], with an average of 3400 cases per year between 2010-2017.

HIV infection carries significant morbidity, reduces quality of life and causes mortality. With the development of antiviral therapy (ART) it has now significantly changed the perception of HIV/ Acquired immunodeficiency syndrome (AIDS) from a fatal to a chronic potentially manageable disease.[4] In 2018, 23.3 million people were receiving antiretroviral therapy worldwide.[2]

Individuals infected with HIV may present with various cutaneous manifestations, which may result from HIV infection or opportunistic disorders. Recognizing HIV-related skin changes may enable early diagnosis of HIV, thus allowing early initiation of ART. Since the advancement of ART, the incidence of drug reactions and non-infectious skin eruptions has also been enhanced.[5]

This study aimed to describe the demographic data and pattern of cutaneous manifestations of patients infected with HIV who were referred to the Department of Dermatology, Hospital Kuala Lumpur between 2016 and 2019.

Materials and Methods

This is a retrospective study on all newly referred HIV-infected patients to the Department of Dermatology in Hospital Kuala Lumpur between 2016 and 2019. Patients' case notes were retrieved and reviewed. Data collected included demographics, types of referrals, CD4 counts, treatment durations, types of mucocutaneous manifestations, numbers of skin biopsies done, co-morbidities and co-infections.

Results

There were a total of 424 patients infected with HIV referred to the department between 2016 and 2019. Their demographic characteristics are showed in Table 1. The youngest patient referred to us was 15 years old and the oldest was 74 years old. The mean age was 31.74 years old. More than half of the total

Corresponding Author
Dr Chan Gin Peng
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586, Kuala Lumpur, Malaysia.
Email: gpncamel@gmail.com

patients, 214 (50.4%) referred were in the age group of 20 to 29 years, and a quarter of them were in the age group of 30 and 39 years (115, 27.1%). Among the Malaysian patients, Malays contributed to 65.7% of the referrals, followed by Chinese, 25.4%, Indians 7.2% and others, 1.7%. Seven (1.6%) of were foreigners, which includes Indonesians (2, 0.5%), Myanmarese (2, 0.5%), followed by Pakistani (1, 0.2%) and American (1,0.2%). Majority of patients referred were male, 407(96.0%).

Homosexuality was among the most common mode of transmission of HIV in these patients, (222, 52.3%), followed by heterosexual transmission (63,14.9%). As shown in Table 2, a third of the patients (143, 33.7%) had other concomitant medical illnesses which include extracutaneous tuberculosis (TB) (36.4%), extracutaneous fungal infection (11.2%), both extracutaneous tuberculosis and fungal infection occurring concurrently (2.8%), Hepatitis C infection (12.6%), Hepatitis B infection (7.7%), Pneumocystis jiroveci pneumonia (4.9%) etc. Excluding 128 patients whom their CD4 counts were unavailable upon referral, 39.5% (117 of 296 patients) had CD4 count less than 200/mm3. About a quarter (27.4%) had CD4 counts more than 500/mm3. Less than half of our cohort (189, 44.6%) were on ART. Of these, 72 patients (38.1%) received ART within 12 months before they were referred to the Department of Dermatology and most of them has CD4 counts less than 200/mm^3.

A total of 638 cutaneous diagnoses were made for the 424 patients as shown in Table 4. About 36% of the 424 patients had more than one dermatosis diagnosed after dermatology review. Ninety-four patients (22.2%) underwent skin biopsy with a total 98 biopsies performed. As shown in Table 4, the most common dermatoses encountered by our HIV infected patients was cutaneous viral infections, reported to occur in 263 of them (62.0%). These include genital warts, herpes labialis, extra genital wart, viral exanthem, oral leukoplakia, and genital herpes. About 31% of patients (n=131) had bacterial infection, and syphilis was the most common bacterial infection in this cohort (94 patients). This was followed by gonorrhea (15 patients), folliculitis (7 patients), and others such as abscess, cellulitis, furuncles, chancroid, carbuncle and rectal ulcers (Table 4). Seventy-two patients (17%) presented with cutaneous fungal infection, and talaromycosis (formerly known as penicilliosis) was the most common fungal infection (24 patients) encountered. This was followed by oral mucosal candidiasis (14 patients), histoplasmosis (11 patients), tinea corporis (10 patients) and onychomycosis. Five patients had scabies infestation as their first presentation to the clinic. Of these 72 patients (38.1%) received ART within 12 months before they were referred to the Department of Dermatology and most of them has CD4 counts less than 200/mm3. In the subgroup of patients who received ART for a duration of 12 months or less, infective dermatoses were again the most common dermatoses encountered, occurring at 2.3x the number of non-infective dermatoses.

Table 1. Demographic characteristics of 424 patients infected with human immunodeficiency virus (HIV) referred to the Department of Dermatology Hospital Kuala Lumpur between 2016-2019

Characteristics		n=424(%)
Mean age in years (range)		31.74 ± 9.94 (15-74)
Age group	<20	11 (2.6)
	20-29	214 (50.4)
	30-39	115 (27.1)
	40-49	52 (12.3)
	50-59	28 (6.6)
	60-69	2 (0.5)
	70-79	2 (0.5)
Gender	Male	407 (96.0)
	Female	17 (4.0)
Nationality	Malaysian	417 (98.4)
	Non-Malaysian Indonesian Myanmar Pakistan American Not available	7 (1.6) 2 (0.5) 2 (0.5) 1 (0.2) 1 (0.2) 1 (0.2)
Race (n=417)	Malay	274 (65.7)
	Chinese	106 (25.4)
	Indian	30 (7.2)
	Others	7 (1.7)
Possible mode of HIV transmission (n=339)	Heterosexual	63 (18.5)
	Homosexual	222 (65.4)
	IVDU	16 (4.7)
	Blood transfusion	2 (0.59)
	Bisexual	33 (9.7)
	Homosexual + IVDU	2 (0.59)
	Heterosexual + IVDU	1 (0.29)
	Not available	85
HAART treatment (n=405)	Yes	189 (46.7)
	No	216 (53.3)
	Not available	19
CD4 count (cell/mm^3) (n=296)	<200	117 (39.5)
	200-500	98 (33.1)
	>500	81 (27.4)
	Not available	128

About a third of our patient (132 patients, 31.1%) was noted to have non-infective dermatoses. The most common non-infective dermatoses diagnosed among the patients infected with HIV was eczematous dermatoses (including papular eczema, seborrheic dermatitis, photodermatitis,

contact dermatitis, nodular prurigo, discoid eczema and stasis eczema; a total of 36 patients or 8.4%). Pruritic papular eruption and eosinophilic folliculitis which are commonly described among the HIV infected individuals occurred in 4.0% and 1.2% in our cohort respectively. Psoriasis was diagnosed in 1.6% of our cohort. These patients were not known to have psoriasis before the HIV was diagnosed. There were 15 patients (3.5%) diagnosed to have Kaposi sarcoma in our cohort.

Table 2. Comorbidities and concomitant illness(s) among 424 patients infected with HIV referred to the Department of Dermatology between 2016 and 2019

Comorbids/Concommitant illness(s)	n (%)
Extracutaneous tuberculosis	52 (36.4)
Hepatitis C	18 (12.6)
Extracutaneous fungal infection	16 (11.2)
Hepatitis B	11 (7.7)
Pneumocystis jiroveci pneumonia	7 (4.9)
Anaemia	6 (4.2)
Both extracutaneous tuberculosis and fungal infection occurring concurrently	4 (2.8)
Diabetes Mellitus	4 (2.8)
Bronchial Asthma	3 (2.1)
Toxoplasmosis	3 (2.1)
Dyslipidemia	3 (2.1)
Mood disorders	2 (1.4)
Neurosyphilis	2 (1.4)
Hypertension	2 (1.4)
Deep vein thrombosis	1 (0.7)
Ischaemic Heart Disease	1 (0.7)
Renal Tubular Acidosis	1 (0.7)
Cytomegalovirus retinitis	1 (0.7)
Upper gastro-intestinal bleed	1 (0.7)
Autoimmune encephalitis	1 (0.7)
Cardiomegaly	1 (0.7)
Adrenal insufficiency	1 (0.7)
Cerebral vascular accident	1 (0.7)
Post ictal psychosis	1 (0.7)
Total	**143 (100)**

Table 3. Number of cutaneous diagnosis in 424 individuals with HIV referred to the Department of Dermatology Hospital Kuala Lumpur between 2016 and 2019

Number of Cutaneous Diagnosis in One Patient	Number of Patients				Total n=424
	CD4 <200 cells/m^3	CD4 200-500 cells/m^3	CD4 >500 cells/m^3	CD4 Not Available	
	n=117	n=98	n=81	n=128	
1	61 (52.1)	66 (67.3)	58 (71.6)	87 (68.0)	272
2	40 (34.2)	22 (22.4)	19 (23.5)	25 (19.5)	106
3	14 (12.0)	8 (8.2)	2 (2.5)	9 (7.0)	33
4	2 (1.7)	2 (2.0)	2 (2.5)	4 (3.1)	10
5	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	3
Total Dermatoses	**191**	**142**	**110**	**195**	**638**

Table 4. Types of dermatoses detected among individuals with HIV between 2016 and 2019

Type of Dermatoses	Number				
	CD4 <200 cells/m³	CD4 200-500 cells/m³	CD4 >500 cells/m³	CD4 Not Available	Total
	n=117	n=98	n=81	n=128	n=424
Cutaenous Adverse Drug Reactions	**16**	**3**	**3**	**9**	**31**
Non life-threatening					
Maculopapular eruption	8	0	1	7	16
Erythema multiforme	1	1	1	0	3
Pruritus	0	0	0	1	1
Life threatening					
Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	4	1	1	0	6
Drug reaction with eosinophilia and systemic symptoms (DRESS)	3	1	0	1	5
Non Infective Dermatosis	**53**	**23**	**18**	**38**	**132**
Inflammatory					
Pruritic papular eruption	10	3	0	4	17
Papular eczema	3	1	4	2	10
Seborrhoeic dermatitis	3	4	0	3	10
Psoriasis	3	0	3	1	7
Acne vulgaris	2	1	2	1	6
Photodermatitis	1	3	0	1	5
Eosinophilic folliculitis	1	1	1	2	5
Contact dermatitis	2	1	0	2	5
Xerosis	2	0	1	1	4
Nodular prurigo	2	0	1	1	4
Proctitis	0	0	2	1	3
Chronic spontaneous urticaria	0	0	1	2	3
Papular urticaria	2	0	0	1	3
Anal fissure	0	1	0	1	2
Discoid eczema	0	1	0	0	1
Venous ulcer	1	0	0	0	1
Lichen planus	1	0	0	0	1
Icthyosis vulgaris	1	0	0	0	1
Alopecia	0	0	1	0	1
Neurogenic pruritis	0	0	0	1	1
Pityriasis lichenoides chronica	0	0	0	1	1
Post inflammatory hyperpigmentation	0	0	0	1	1
Stasis eczema	0	0	0	1	1
Viral exanthem	0	0	0	1	1
Milaria rubra	1	0	0	0	1
Eosinophilic dermatitis	1	0	0	0	1
Vasculitis	1	0	0	0	1
Sarcoidosis	1	0	0	0	1
Hidradenitis suppurativa	0	1	0	0	1
Vitiligo	1	0	0	0	1
Non inflammatory					
Benign growth					
Skin tag	0	2	2	2	6
Sebaceous cyst	1	2	0	1	4
Perianal cyst	1	1	0	0	2
Steatocytoma multiplex	0	0	0	2	2
Syringoma	0	0	0	1	1
Seborrhoiec keratosis	0	0	0	1	1
Lipoma	0	0	0	1	1
Malignant tumour					
Kaposi sarcoma	12	1	0	2	15
Infective Dermatoses/Infestation	**122**	**116**	**88**	**147**	**473**
Bacterial	28	28	25	50	131
Syphilis	16	22	18	38	94
Gonorrhea	4	3	2	6	15
Folliculitis	3	0	3	1	7
Abscess	1	1	1	0	3
Cellulitis	1	2	0	0	3

Furuncle	1	0	1	0	2
Chancroid	1	0	0	1	2
Carbuncle	0	0	0	1	1
Ecthyema	0	0	0	1	1
Rectal ulcer	0	0	0	1	1
Lymphogranuloma venereum	0	0	0	1	1
Chlamydia	1	0	0	0	1
Mycobacterial infection	0	1	1	0	2
Leprosy	0	0	1	0	1
Lupus vulgaris	0	1	0	0	1
Viral	59	74	59	71	263
Genital warts	27	47	48	43	165
Herpes genitalis	13	17	7	12	49
Molluscum contagiosum	7	2	1	9	19
Herpes zoster	4	3	0	1	8
Herpes labialis	3	1	1	2	7
Common warts	1	0	2	3	6
Viral exanthem	1	3	0	0	4
Leukoplakia	1	1	0	0	2
Herpes simplex	1	0	0	1	2
Plane wart	1	0	0	0	1
Fungal	33	11	3	25	72
Talaromycosis	13	1	0	10	24
Oral mucosal candidiasis	8	1	1	4	14
Histoplasmosis	7	0	0	4	11
Tinea corporis	3	4	1	2	10
Onychomycosis	1	2	0	2	5
Cryptococcus	1	0	0	1	2
Candida cheilitis	0	1	0	0	1
Chromoblastomycosis	0	1	0	0	1
Toe webs intertrigo	0	0	1	0	1
Candida balanitis	0	0	0	1	1
Sporotrichosis	0	0	0	1	1
Tinea cruris	0	1	0	0	1
Scabies infestation	2	2	0	1	5
Non Dermatological Diagnosis*	**0**	**0**	**1**	**1**	**2**
Total	191	142	110	195	638

Thirty-one patients were referred for cutaneous adverse drug reactions, of which majority was maculopapular eruption (51.6%) to the antibiotics received for their opportunistic infections (8 to bactrim, 3 to bactrim/anti-tuberculosis therapy, 1 to dapsone, 1 to efavirenz). Eleven patients (35.5%) suffered from severe cutaneous adverse drug reactions (SCARs) namely the Stevens Johnson Syndrome/Toxic epidermal necrolysis (metamphetamine (1), bactrim (1), Akurit-4 (1), carbamazepine (1)) and drug reaction eosinophilia with systemic symptoms (DRESS) due to fansidar (1), bactrim (2), anti-tuberculosis Akurit-4 (1), bactrim/pyrimethamine(1). Two patients developed erythema multiforme secondary to ART therapy and one to bactrim. There were two patients were found to have non dermatological disorders after assessment, which were reactive arthritis, and false positive rapid plasma reagin (RPR) test.

Based on the 1993 Centers for Disease Control and Prevention (CDC) case definition of AIDS,[6] we further analysed the type of dermatoses that were seen among patients with clinical category C (patients who have AIDS-defining conditions and/or CD4 count of less than 200cells//mm^3). As shown in Table 5, patients with AIDS were significantly more prevalent to suffer from cutaneous adverse drug reactions, non-infective dermatoses, viral and fungal infections. Cutaneous viral infections were the most frequent infections encountered in patients with AIDS and without AIDS. However, the rate was significantly higher among the patients without AIDS. The rate of cutaneous bacterial infections and scabies infestations were similar in patients with AIDS and without AIDS.

Table 5. Types of dermatoses in patients with and without AIDS

Types of Dermatoses		Patients with AIDS* n=144	Patients without AIDS n=167	*p* value
Cutaneous adverse drug reactions		21	5	*<0.05*
Non infective dermatoses		62	38	*<0.05*
Infective dermatoses	Bacterial infection	44	47	*0.64*
	Viral infection	72	126	*<0.05*
	Fungal infection	48	9	*<0.05*
	Scabies	2	2	*1.00*

**Clinical category C - patients who have AIDS-defining conditions and/or CD4 count of less than 200cells//mm^3*

Table 6. Literature review on the prevalence of skin disorders in HIV infected individuals

	Uthayakumar S et al.[39]	Coopman SA et al.[40]	Spira R et al.[18]	Spira R et al.[18]	Spira R et al.[18]
	Brighton	Boston	France	Dallas	Bangkok
Year	2017	1988-1991	1996	1989	2004
Total patients observed	151	684	450	100	120
Total patients with skin disorders	138 (91.4%)	540 (79%)	294 (65.2%)	92 (92%)	96 (80%)

Discussion

Cutaneous manifestations are very common in individuals infected with human immunodeficiency virus (HIV) and are associated with significant morbidity.[7] Our National Strategic Plan for Ending AIDS targets to end AIDS by 2030.[3] At the end of year 2018, it was estimated that 87,041 people were living with HIV in Malaysia and 41,430 (55%) of them are on antiviral therapy.[3] In this audit, only 46.7% of patients referred were on antiviral therapy, which is less than the national record. We are yet to achieve one of the main Global AIDS Monitoring indicators which is to have at least 90% of people who know their HIV-positive status are accessing ART by 2020.[8] More efforts are needed to screen and detect HIV infection early so that ART can be initiated early in order to improve the overall health of these group of patients and their quality of life.[9]

More than 75% of our patients were in the age group between 20 and 39 years. This is consistent with our national data[3] and another 2 studies, Halder et al in West Bengal, India[10] and Sanjay et al. in Maharashtra, India.[11] Our national data showed that 77% of individuals infected with HIV were 20-39 years old.[3] The trend of HIV epidemic in Malaysia has now shifted to sexual transmission since 2011. Men who have sex with men (MSM) was expected to become the main driver for the epidemic in the years to come beginning from 2018.[2] In our audit most patients contracted HIV via homosexual practice in males. This may also explain the reason of high prevalence in of genitourinary infections observed in our cohort.

The common denominator of the immunosuppressed state resulting from HIV infection is the destruction of T-helper cells that express CD4 receptors[12], causes profoundly impaired cellular immune response. The number of circulating CD4 T cells predicts the onset of overt immunodeficiency.[13] The suppression of HIV replication with ART improves the CD4 T-cell counts and was found to be able to reverse immunodeficiency.[14] The progression of disease is indicated by the detection of specifically defined opportunistic infections. CD4 count is a prognostic indicator and marker of stage of HIV-induced immunodeficiency and estimation of morbidity and mortality.[14] The classification system for HIV infection among adolescents and adults has been revised to include the CD4 + T-lymphocyte count into 3 categories i.e. CD4 counts <200, 200-499, >500. These categories reflect HIV-related immunosuppression, clinical status, risk of opportunistic infections and assist the clinicians in diagnostic decision-making.[6,15] A typical healthy, HIV negative individual has a CD4 count greater than 500cells/mm^3.[14] Individuals infected with HIV who have CD4 counts >500cells/mm^3 are expected to present with common non-infective skin conditions like normal healthy individuals. Patients with lower CD4 counts (<200cells/mm^3) may present with serious or fatal opportunistic infections with cutaneous manifestations.[14]

Immunodeficiency state is associated with a wide spectrum of clinical disorders that may range between asymptomatic to Acquired Immunodeficiency syndrome (AIDS).[12] Mucocutaneous eruptions associated with HIV infection are common and occur throughout the course of HIV infection.

Although mucocutaneous eruptions are not the direct result of HIV infection, most of these eruptions are resulted from immunosuppressive state or related to the HIV treatment.[12] These lesions may be the first manifestations of HIV infection. Pre-existing dermatoses may be aggravated or worsened when AIDS develops.[7,12] It was shown that greater than 90% of patients developed at least one skin or mucous membrane manifestation during the course of their infection in a study involving 100 patients done in Dallas (Table 6).[9,16] Another study in Bangkok in 1995 also showed that 95% of 248 observed patients had one or more skin disorders.[17] A cross sectional survey involving 450 patients in France done in 1996 observed 65.3% of them had at least one skin manifestation during the course of HIV infection.[18] Mucocutaneous eruptions in HIV can be classified according to its underlying aetiologies. Viral, fungal, and bacterial infections as well as inflammatory dermatoses have all been reported with an increased frequency in association with HIV infection.[7] It has been shown that herpes zoster infection is an early manifestation of HIV infection, whereas Kaposi sarcoma and cryptococcosis reflect more advanced immunosuppression. Hence certain skin conditions may guide the clinicians to stage the clinical progression of HIV infection.[7]

Traditionally lower CD4 counts are reported to be associated with infective dermatoses.[19-21] Unsurprisingly, infective dermatoses encountered among those with CD4 <500cells/m^3 in our cohort was 2.7x more that those with CD4 >500cells/m^3. Being the most common indication of referrals, viral infections in HIV infected patients contributed 41.2% of the total dermatology referrals. Genital warts contributed 62.7% of the total viral related dermatoses. This was higher than other studies done in South of Iran[22] and Maharashtra, India[11], whereby viral infections contributed about 17.9-27.3% of their total diagnosis. Genital warts caused by human papillomavirus (HPV) is the most common sexually transmitted infection in the United States of America. Common warts may occur in unusual locations, with unusual severity, and with high frequency in HIV-infected patients.[7]

The rising trend of primary and secondary syphilis worldwide has been primarily attributable to increased cases amongst men who have sex with men (MSM), highest among persons aged 25-29 years.[23] There is a higher rate of HIV coinfection among MSM with syphilis and the disease course is more aggressive.[24] Syphilis carries significant morbidities if left untreated as the infection can span decades and progresses through multiple stages of infection. In this audit, 94 patients presented with cutaneous manifestations of different stages of syphilis. Skin lesions in secondary syphilis can mimic many other diseases hence detailed workups are needed to exclude other bacterial or fungal infections in order to institute the appropriate treatment.

Malaysia is classified as a country with an intermediate TB burden, with less than 100 per 100,000 populations.[25] All patients who are diagnosed with tuberculosis will be screened for HIV. It was found that 1346 (6.3%) patients of a total of 21,296 new TB cases were infected with HIV (1234 pre TB diagnosis and 112 post TB diagnosis).[25] Systemic infections with *Mycobacterium tuberculosis* and non-tuberculous mycobacteria are common in HIV disease.[7] Despite tuberculosis being the most commonly reported opportunistic infection and the leading cause of death among people living with HIV, the prevalence remained below 6% since 2014. In our audit, 56 patients were infected with tuberculosis (pulmonary tuberculosis, tuberculosis meningitis and disseminated tuberculosis). We only encountered a case of cutaneous tuberculosis i.e. lupus vulgaris in our current cohort.

Interestingly, the number of non-infective dermatoses detected among those with CD4 counts <500cells/m^3 counts in our audit were 4 times more than those with CD4 counts >500cells/m^3. Most patients with non-inflammatory dermatoses were referred for pruritic papular eruptions (PPE), 14.9% followed by papular eczema and seborrhoiec dermatitis, 10%. However, Sivayathorn et al.[17] in 1993-1994 done in Bangkok involving 248 patients showed that there were 32.7% patients with PPE and 21.0% with seborrhoiec dermatitis. Another study in Shiraz, South Iran by Davarpanah et al.[22] also showed that 0.5% of the total 240 patients had eczema. About 19.6% of patients in that study had xerosis and pruritis. In our study only 4 patients (0.9%) patients had xerosis and 1 had neurogenic pruritis. Psoriasis affects 1% to 3% of patients with HIV infection in the United States of America, as compared with its prevalence of 1% in the general population.[26] In some studies patients infected with HIV had psoriasis as their first presentation to a clinician before the diagnosis of HIV, or at the late stage of HIV during the progression into AIDS.[27] A flare of psoriasis or worsening arthropathy can be seen in patients with pre-existing psoriasis following HIV infection.[28] Our audit showed that 7

(1.65%) patients had psoriasis diagnosed after they were confirmed to have HIV. This was comparable to an audit reported Davarpanah et al.[22], whereby 2.9% of the patients had psoriasis. Concomitant HIV infection with psoriasis complicates the management especially in patients who require systemic therapy owing the possibility of drug-to-drug interactions. Commonly used medications i.e. methotrexate or cyclosporin may predispose HIV patients to malignancies and opportunistic infections due to their immunocompromised state.

Human immunodeficiency virus (HIV)-infected patients have complex immunological alterations with higher risk of developing drug hypersensitivity to antiretroviral or multiple drugs that usually prescribed for prevention or treatment of opportunistic infections.[29] About 5% of the dermatoses among the HIV infected patients referred to us were cutaneous adverse drug reactions. About 82% of SCARs in our cohort developed in those with CD4 counts <500cells/m^3. Cutaneous ADRs increased as the immune system deteriorates with the apparent decreasing in CD4 T-cell count.[29] The pathophysiology of drug hypersensitivity in HIV is multifactorial and related to alterations in drug metabolism, dysregulation of the immune systems (immune hyperactivation, patient cytokine profile), oxidative stress, genetic predisposition, and also the viral factors.[28] Patients with HIV infections are at risk of developing severe adverse drug reactions (ADR) towards ART, anti-toxoplasmosis as well as co-trimoxazole (bactrim) used in PCP prophylaxis. Severe drug hypersensitivity reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis develop more often in HIV-infected patients compared to other populations.29 Davarpanah et al.[22] also observed that 10.8% of their patients had drug reactions. ADR was commonly seen with the initiation of ART (regardless of the CD4 counts) as well as with the use of anti-toxoplasmosis/bactrim (in patients with low CD4).

As life expectancy of HIV infected individuals increases, cancer has become a predominant cause of morbidity and mortality in this group of patients.[26] Patients with HIV infection are at higher risk of acquiring a few types of malignancies. Kaposi sarcoma, which is the most commonly reported malignancy in HIV infected patients. It occurs at a rate of more than 1000 folds greater than general population. Most Kaposi sarcoma traditionally occurs in individuals with low CD4 (<200cells/mm^3), however cases have been reported to occur at individuals with higher CD4 counts (>350cells/mm^3).[30] In our cohort, 12 (80%) patients with Kaposi sarcoma had CD4 counts less than 200. Apart from that, Non-Hodgkin Lymphoma (NHL) is also being classified as AIDS defining malignancy.[31] There were however no other malignancies observed in our cohort.

The introduction of ART has been shown to have a huge impact on the spectrum and severity of skin disease. Studies have shown an overall decrease in the prevalence of mucocutaneous manifestations with ART.[9] Advancement in ARTs have led to improved quality of life and life expectancies in HIV patients. It significantly changes the perception of HIV/AIDS from a fatal to a potentially manageable chronic disease.[4] Immune reconstitution inflammatory syndrome(IRIS) represents wide range of immunopathologic reaction resulting in restoration of immune function in HIV-infected patients after receiving ARTs.[32] Mucocutaneous presentations accounted for 68% of IRIS.[30] There are large varieties of presenting signs and symptoms for IRIS depending on the underlying infection acquired after a rapid decrease in HIV viral load and most IRIS results in mild to moderate symptoms.[33,34] However non dermatological manifestation related to IRIS may result in significant morbidity and mortality.[34] It may occur as early as 2 to 6 weeks of initiation of ART, but some may present within days to months.[35] It was found that the incidence of developing IRIS is particularly higher in patients starting ART at CD4 counts below 50cells/microL.[36] Cutaneous IRIS, may varies from infective, inflammatory, neoplastic to autoimmune disorders.[37] Patients may presents with acne, cutaneous ulcerations due to Mycobacterium avium, eruptions of warts, varicella zoster, herpes viruses, genital ulcers and folliculitis.[31,37,38] In our audit, 38.1% received ART within 12 months before they were referred to us. The dermatoses presented in these group of patients could be the manifestations IRIS. Infective dermatoses were noted to be the most common dermatoses in this subgroup of patients. Due to the retrospective nature of this audit, we could not ascertain that all the dermatoses described in these patients were truly manifestations of IRIS as we could not demonstrate presence of rebound of CD4 counts in them.

Our data is limited by the retrospective nature of the audit. Further prospective studies are in need for better describing the mucocutaneous manifestations of the HIV infected individuals based on the CD4

counts categories, as well as to monitor the evolution of skin diseases through the different stages of HIV. Nevertheless, our data illustrated the wide range of dermatoses in this group of patients which may be encountered by the clinicians. Clinicians should have a high index of suspicion when we manage such patients so that their skin conditions could be managed accordingly.

Conclusion

Our data showed that individuals with HIV infection may present with wide variety of skin disorders which included infective dermatoses, non-infective inflammatory dermatoses, cutaneous adverse drug reactions and tumours. About 35% of them had more than 1 dermatoses in our cohort. The most frequent infective dermatoses encountered were genital warts, syphilis, genital herpes, talaromycosis and molluscum contagiosum. The most frequent non-infective inflammatory dermatoses observed in our cohort was eczematous dermatoses. Kaposi sarcoma was the most frequent malignant tumour encountered in our cohort especially in those with low CD4 counts. About 7.3% of them developed cutaneous adverse drug reactions to the medications used to treat the HIV and co-morbidities.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

The Value of Adding 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang-ylang oil* to the European Baseline Series to Improve the Detection of Rubber and Fragrance Allergy Among Patients Suspected with Contact Dermatitis in Hospital Selayang

Fei Yin Ng[1,2], Min Moon Tang[2], Rohna Ridzwan[1], Asmah Johar[2]

[1]Department of Dermatology, Hospital Selayang, Selangor, Malaysia
[2]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Abstract

Introduction

Allergic contact dermatitis affects 15 to 20% of the population. The pattern of contact allergy varies across nations. Therefore, many countries utilize their unique individual baseline series for patch testing. In this study, we aimed to assess the outcome of rubber and fragrance allergy detection with the addition of 1,3-Diphenylguanidine. N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil.*

Methods

This a cross-sectional study on 292 patients who underwent patch testing with European Baseline Series, 3 additional rubber allergens namely 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil* between July 2015 to December 2016. Additional patch test series were also added based on relevant clinical history. The patch test reactions were read at 48 and 96 hours after application of the allergens.

Results

A total of 292 patients completed the study. There were 118 (40.4%) males and 174 (59.6%) females. The mean age was 43 years old (range 19 to 78 years). Two-third of patients had atopy. The sensitization rate increased to 70.5% from 67.1% with the four additional allergens included in the European Baseline Series. The rubber allergy detection rate significantly increased by 53.8% ($p<0.00001$) with the addition of 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, and N-Cyclohexylthiophthalimide to the European Baseline Series. The addition of 1,3-Diphenylguanidine alone to the baseline series improved the rubber allergy detection rate by 49.2%. The sensitization rate of 1,3-Diphenylguanidine was 10.6%, which ranked the third most sensitizing allergen in the cohort. The addition of N-Cyclohexyl-N-Phenyl-4-Phenylenediamine and N-Cyclohexylthiophthalimide only increased the detection rate of rubber allergy by 4.6%, where each had a sensitization rate of 1.4%. Fragrance allergy detection rate increased by 6.5% with the addition of *Ylang ylang oil* to the European Baseline Series. The sensitization rate of *Ylang ylang oil* was 3.4% in this cohort..

Conclusion

The overall detection rate of sensitization increased by 3.4% with the addition of 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil.* The addition of 1,3-Diphenylguanidine rubber in the baseline series improved the detection of rubber sensitization by 49.2% while the addition of *Ylang ylang oil* increased fragrance sensitization detection rate by 6.5%.

Key words: *Allergic contact dermatitis, 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide, Ylang ylang oil*

Corresponding Author
Dr Ng Fei Yin
Department of Dermatology,
Hospital Tengku Ampuan Rahimah,
41200 Klang, Selangor, Malaysia.
Email: willow_fy02@yahoo.com

Introduction

Allergic contact dermatitis affects 15 to 20% of the population in Europe. In United States, the point prevalence of allergic contact dermatitis is 15.2% in teenagers and 18.6% in adults.[1] The common causative allergens vary between nations due to the industrial policies and cultural practice. Thus many countries constructed their individual baseline series for patch test.

In a retrospective analysis of local patch test data[2], four emerging allergens were identified from the rubber additives series and fragrance series - 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil* with the sensitization rates of 11.1%, 3.9%, 3.6% and 14.6%.[2] The additional patch test series were tested on selected patients whom were clinically suspected with rubber or fragrance allergy.

In this study, we incorporated these 4 allergens into the European Baseline Series with the aim to assess the outcome of the overall contact sensitization rate as well as the detection rate of rubber and fragrance allergy.

Materials and Methods

A cross-sectional study was performed on selected patients aged 18 and above suspected with allergic contact dermatitis in Selayang Hospital between June 2015 and December 2017. We excluded patients with active dermatitis, excessive sun exposure, topical corticosteroid application on the test site within one week prior to the study, ingestion of oral prednisolone (exceeding 20mg daily) or other immunosuppressant agents, pregnant or lactating ladies, and those with previous history of patch test.

All candidates underwent patch test using European Baseline Series with the addition of 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil.* Additional patch test series were also added based on individual presentation as part of the daily routine practice.

The European Baseline Series from Chemotechnique Diagnostics in year 2015 consisted of 30 allergens:

potassium dichromate, p-phenylenediamine (PPD), thiuram mix, neomycin sulfate, cobalt (II) chloride hexahydrate, benzocaine, nickel (II) sulfate hexahydrate, clioquinol, colophonium, paraben mix, N-Isopropyl-N-Phenyl-4-Phenylenediamine (IPPD), lanolin alcohol, mercapto mix, epoxy resin, balsam of peru, 4-Tert-Butylphenol formaldehyde resin (PTBP), 2-merceptobenzothiazole (MBT), formaldehyde, fragrance mix I, sesquiterpene lactone mix, quaternium 15, propolis, methylisothiazolinone /methylchloroisothiazolinone, budesonide, tixocortol-21-pivalate, methyldibromo glutaronitrile, fragrance mix II, lyral, methylisothiazolinone and textile dye mix.

The patch test reactions were read at 48 and 96 hours after application of the allergens. Interpretation of patch test reactions were based on the reading criteria of International Contact Dermatitis Research Group (ICDRG) guidelines.

Data was analyzed using IBM SPSS® Statistics version 23.

Results

A total of 292 patients, comprising of 118 males (40.4%) and 174 females (59.6%) aged 18 years and above with the mean age of 43 years, were patch tested during the 18-month study period (Table 1). Among the subjects, 157 (53.8%) were Malay, 96 (32.9%) were Chinese, 37 (12.7%) were Indian and 2 (0.7%) of other races. Two-third of the patients had a background history of atopy.

Table 1. Patient Demographic and Characteristics

Characteristics	n=292 (%)
Age, median (IQR)	41 (28, 57)
Gender	
Male	118 (40.4)
Female	174 (59.6)
Ethnicity	
Malay	157 (53.8)
Chinese	96 (32.9)
Indian	37 (12.7)
Others	2 (0.7)
Atopy	
Presence	200 (68.5)
Absence	92 (31.5)

When tested with European Baseline Series, 67.1% of patients developed at least 1 positive reaction to the patch test allergens. The detected sensitization rate increased to 70.5% with the 4 additional allergens. The difference was not statistically significant (p=0.37). The top ten common allergens were nickel sulfate (22.9%), textile dye mix (13%), 1,3-Diphenylguanidine (10.6%), fragrance mix I (9.9%), methylisothiazolinone (7.9%), cobalt chloride (6.8%), balsam of Peru (6.8%), paraben mix (6.5%), formaldehyde (5.5%), and potassium dichromate (5.5%) (Table 2).

Table 2. Top 10 common allergens in the modified European Baseline Series in Hospital Selayang between July 2015 and December 2016

Allergen	Frequency of Tested Positive, n=292 (%)
Nickel Sulfate	67 (22.9)
Textile Dye Mix	38 (13.0)
1,3 Diphenylguanidine	31 (10.6)
Fragrance Mix I	29 (9.9)
Methylisothiazolinone	23 (7.9)
Cobalt Chloride	20 (6.8)
Balsam of Peru	20 (6.8)
Paraben Mix	19 (6.5)
Formaldehyde	16 (5.5)
Potassium Dichromate	16 (5.5)

Table 3. Sensitization rate of rubber allergens in the European Baseline Series

Rubber Allergen	Frequency of Tested Positive, n=292 (%)
Thiuram Mix	8 (2.7)
2-Mercaptobenzothiazole	4 (1.4)
Mercapto Mix	2 (0.7)
N-Isopropyl-N-Phenyl-4-Phenylenediamine	1 (0.3)

Table 4. Sensitization rate of fragrance allergens in the European Baseline Series

Allergen	Frequency of Tested Positive, n=292 (%)
Fragrance Mix I	29 (9.9)
Balsam of Peru	20 (6.8)
Fragrance Mix II	5 (1.7)
Lyral	2 (0.7)

Compared to the original European Baseline Series (EBS) with 3 rubber allergens, the modified baseline series detected a significantly higher number rubber allergy (p<0.0001). Among the EBS rubber allergens, thiuram mix (2.7%) had the highest sensitization rate, followed by 2-mercaptobenzothiazole (1.4%), mercapto mix (0.7%) and N-Isopropyl-N-Phenyl-4-Phenylenediamine (Table 3). The sensitivity of the combination of EBS with each individual additional rubber allergen was also analyzed. When compared to using EBS alone, the combination with 1,3-diphenylguanidine significantly raised the sensitivity of detecting rubber allergy by 49.2% (p<0.00001). Combination with either N-Cyclohexyl-N-Phenyl-4-Phenylenediamine or N-(Cyclohexylthio) phthalimide, did not contribute to significant improvement in the patch test results (p=0.545) (Table 5).

Table 5. The sensitization rate of European Baseline Series rubber allergens and its combination with additional rubber allergens

Test Allergens	Detection Rate, n (%)	*p* value
European Baseline Series Rubber Allergens Alone	15 (23.1)	-
European Baseline Series Rubber Allergens + 3 Additional Rubber Allergens	50 (76.9)	*<0.00001*
European Baseline Series Rubber Allergens + 1,3 Diphenylguanidine	47 (72.3)	*<0.00001*
European Baseline Series Rubber Allergens + N-Cyclohexyl-N-Phenyl-4-Phenylenediamine	18 (27.7)	*0.545*
European Baseline Series Rubber Allergens + N-(Cyclohexylthio) phthalimide	18 (27.7)	*0.545*

Fragrance mix I (9.9%) was the most common fragrance allergen in the EBS (Table 4). The 4 fragrance allergens in the EBS (balsam of Peru, fragrance mix I, fragrance mix II, lyral) detected 62.3% of the fragrance allergy cases. A further detection of 6.5% of cases were achieved with the addition of *Ylang ylang oil* though the difference was not significant (p=0.499).

There were 5 allergens in the EBS with low sensitization rates in our cohort. Lyral, mercapto mix and primin were each tested positive in 0.7% of the subjects. N-Isopropyl-N-Phenyl-4-Phenylenediamine and budesonide only showed 0.3% positive reactions.

Discussion

Historical Comparison

A historical comparison was made with a retrospective study from the same centre, Hospital Selayang. It studied the contact sensitization rate of 705 subjects between 2011 and 2013 (36 months) (Table 6). The overall sensitization rate of EBS in the study was almost similar to the current study (66.1% vs 67.1%). There was a reduction in the rate of positive reaction to N-Cyclohexyl-N-Phenyl-4-Phenylenediamine and *Ylang ylang oil.* This could be explained by patient selection to undergo patch test with extended series. They were strongly suspected to have allergic contact dermatitis to rubber or fragrance based on exposure history and were then tested with rubber or fragrance series. Hence, the subjects were not a random population. When the allergens were tested on all patients in our study, the sensitization rates were significantly reduced except for 1,3-diphenylguanidine and N-Cyclohexylthiophthalimide. The sensitizing rate of 1,3-Diphenylguanidine was hugging around 10%. The sensitizing rate of N-Cyclohexylthiophthalimide was 1.4% (decreased from 3.6%).

Bendewald et al. carried out an 8-year retrospective review on patch test using rubber allergens.[3] The positive rate of reaction to diphenylguanidine in this study was 7.5%. Bendewald et al also made a comparison with 3 other similar studies which showed a prevalence of diphenylguanidine allergy of 1% to 4.4%.[4,5,6] The rates of sensitisation to N-(Cyclohexylthio) Phthalimide (5.2%) and N-Cyclohexyl-N-Phenyl-4-Phenylenediamine (1.3%) were comparable to our data. The study also demonstrated that carba mix had a low sensitivity in detecting diphenylguanidine allergy. 1,3-Diphenylguanidine is a rubber accelerator which is also a component within carba mix. The prevalence of diphenylguanidine allergy is gradually rising. Most cases have been reported with exposure to synthetic gloves.[7]

Ylang ylang oil, well known for its fragrant scent, is a plant found in South East Asian countries such as in Malaysia, Indonesia, Vietnam and some islands of Indian Ocean. The essential oil extracted from the flower is widely used in aromatherapy, perfume and food industry. The plant is also used by traditional healers in many aspects, such as treatment of asthma, malaria, depression, itch, gout and headache.[8] *Ylang ylang oil* has been included within the North American baseline screening series since 2001.[9] Prior to that, a multicenter study on fragrance contact dermatitis involving centers from Japan, Northern Ireland, United States, Sweden, England and Switzerland showed that the addition of *Ylang ylang oil*, narcissus oil, and sandalwood oil to fragrance mix would detect 94.2% of the cases of fragrance contact dermatitis.[10] In this study, the sensitization rate to *Ylang ylang oil* was 17.4%, which was the third most common fragrance allergen. *Ylang ylang oil* is also present in the China baseline series. Studies which have included *Ylang ylang oil* in the routine testing of patients with contact dermatitis documented prevalence rates between 0.7% and 2.6%.[11,12] Our current study reported a sensitization rate of 3.4% with *Ylang ylang oil* was comparable to other parts of the world. The previous reported 14.6% in the same center reflected a patient selection bias instead of a true increase of *Ylang ylang oil* allergy. The addition of *Ylang ylang oil* in the EBS in our cohort improved the fragrance allergy detection rate from 62.3% to 68.8%.

Table 6. Comparison between 2 study findings in Hospital Selayang

		2011-2013	2015-2016	*p*
Duration of study period in months		36	18	-
Total number of subjects patch tested		705	292	-
Rate of positive reaction European Baseline Series		466 (66.1%)	196 (67.1%)	*0.755*
Rate of positive reaction European Baseline Series + Additional Series		546 (77.4%)	229 (78.4%)	*0.736*
Rate of positive reaction to specific rubber allergen [in the total number of patients tested with rubber series (2011-2013) or modified European Baseline Series (2015-2016)]	1,3 Diphenylguanidine	52 (11.1%) n=468	31 (10.6%) ↓ n=292	*0.824*
	N-Cyclohexyl-N-Phenyl-4-Phenylene-Diamine	18 (3.9%) n=462	4 (1.4%) ↓ n=292	*0.047*
	N-Cyclohexylthio phthalimide	17 (3.6%) n=472	4 (1.4%) ↓ n=292	*0.064*
Rate of positive reaction to *Ylang ylang oil* (in total number of patients tested with *Ylang ylang oil*)		21 (14.6%) n=144	10 (3.4%) ↓ n=292	*0.00002*

As seen in the results section (Table 5), incorporating all 4 additional allergens in the baseline series did improve the overall contact sensitization rate. The detection of rubber allergy was significantly improved with the presence of 1,3-Diphenylguanidine. Therefore, 1,3-Diphenylguanidine should be considered to be included in the baseline screening series in our population. We are yet to formulate our very own local baseline series which could detect at least 90% of fragrance and rubber contact dermatitis. A multicenter study involving a larger local population may provide a better reflection of the local pattern of contact sensitization. Based on the current data, there are other allergens which are locally important but yet to be identified to improve further the contact sensitization detection rate.

Comparison of Data With Other Countries

Studies published from the local patch test data in Singapore[13], Thailand[14], Hong Kong[15], and Korea[16], United Kingdom[12] and North America[17] were reviewed (Table 7). Females seemed to have a higher preponderance to develop contact dermatitis in all nations. The sensitization rates were as follow: Korea (85.8%), Thailand (73.8%), our study (70.5%), North America (63.8%), Singapore (47.1%) and the United Kingdom (43%).

Nickel sulfate remained the most common sensitizing allergen in all listed centres. Its presence in jewellery, cosmetics, household products, coins, and food explain the high prevalence of nickel sulfate allergy.[18] The European Union Nickel Directive regulation in 1994 had led to a temporary reduction in nickel allergy. However the improvement was not sustained in further analysis thereafter. Non-compliance to the legislation was a raised concern.[19]

Fragrance allergens were the next most common allergens across the countries, namely fragrance mix I and balsam of Peru. A Swedish study demonstrated that 88% out of 204 products (shampoos, hair conditioners, liquid soaps, wet tissues, washing-up liquids, and multipurpose cleansers) analysed contained sensitizing fragrance allergens.[20] Fragrance mix II and lyral were included in the EBS in 2008. The recommendation was based on the reported allergy rates of up to 5% to Fragrance mix II and between 1-3% to lyral in various centres in the Europe. The prevalence of lyral allergy in North America however was only 0.4%. The difference was attributed to the higher concentrations in the EU deodorants.[21] Fragrance mix II was among the top 10 common allergens in United Kingdom (3.2%), Singapore (3.9%) and North America (5.2%). In our study, the sensitization rate of Fragrance mix II and lyral were 1.7% and 0.7% respectively. Among the other countries, *Ylang ylang oil* was only present in the North American baseline series, and it was not among the top 20 common allergens list.

Apart from nickel sulfate and fragrance allergens, cobalt chloride, formaldehyde, neomycin sulfate, thiuram mix, para-phenylenediamne, paraben mix, methyl-chloroisothiazolinone and methylisothiazolinone were among the top 10 allergens in these studies. Besides textile dye mix (which was added to the EBS in 2015) and 1,3-Diphenylguanidine (which was not routinely tested in the other countries except for North America), the rest of the common allergens were comparable to the mentioned centres.

Rubber gloves usage among healthcare, industrial and domestic workers resulted in the increasing trend of rubber allergy. Latex allergy was a major concern due to the occurrence of immediate hypersensitivity reaction. Subsequently, synthetic rubber gloves gradually replaced natural rubber latex gloves. However, the rubber accelerators used in the vulcanization process such as thiuram and carbamates also induced allergic contact

dermatitis. Thiuram allergy seemed to have declined followed by a rise in sensitization to carbamates. 1,3-Diphenylguanidine, also a carbamate, is increasingly identified as a clinically significant sensitizing agent.[22,23,24] This phenomenon is probably related to the change in manufacturing ingredients. In a previous local study carried out between 1994 and 1996, Rohna et al demonstrated that thiuram was the most common sensitizing rubber allergen, while 1,3-Diphenylguanidine was less common.[25] In contrast, the results in our study showed that we have more patients sensitized to 1,3-Diphenylguanidine.

An allergen eligible for inclusion in the screening series should have a sensitization rate of 0.5% to 1%, when routinely tested on patients with suspected contact allergy.[26] In the current study, both budesonide and IPPD had only 0.3% positive reactions. IPPD is one of the components of black rubber mix, which functions as an antidegradant in the process of rubber manufacturing. Lam et al. and Waranya et al. reported a prevalence of 0.4% and 1.6% in Hong Kong and Thailand respectively.[26,27] Other centers utilized black rubber mix in the screening series instead of IPPD alone. In the previous study in Hospital Selayang performed between 2011 and 2013, the rate of positive reaction to IPPD was 3.8%. Our low detection rate could possibly be attributed to the change of ingredients in products.

Budesonide, a class B corticosteroid in the European Baseline Series is used as a marker to reflect corticosteroid allergy of the same class. Other class B corticosteroids include amcinonide, desonide, fluocinolone acetonide, halcinonide, triamcinolone (acetonide, diacetate), oral budesonide and oral triamcinolone. Budesonide also cross reacts with class D corticosteroids.[28] The studies performed in different continents have demonstrated a prevalence between 0.3% to 2% for budesonide (Ochi 2017, Dararattanaroj 2016, Yu DS 2016, Toholka 2015, Warshaw 2015).[13,14,16,17,29] Ochi et al. and Dararattanaroj et al each reported a sensitization rate of 0.3% and 0.5% in the single centre study carried out in Singapore and Thailand respectively.[13,14] We did not differ from our neighbouring countries. The low sensitization rate in our cohort could be due to the lower exposure rate to class B corticosteroids.

Conclusion

The overall detection rate of contact sensitization increased by 3.4% with the addition of 1,3-Diphenylguanidine, N-Cyclohexyl-N-Phenyl-4-Phenylenediamine, N-Cyclohexylthiophthalimide and *Ylang ylang oil*. The addition of 1,3-Diphenylguanidine rubber in the baseline series improved the detection of rubber sensitization by 49.2% while the addition of *Ylang ylang oil* increased fragrance sensitization detection rate by 6.5%. A multicentre study with a larger local population is very much needed to support the inclusion of these allergens in the local screening baseline patch test series. Apart from that, more studies are needed to identify other locally relevant allergens to improve the detection rate of contact allergy in our population.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Contact Cheilitis: A 5-Year Review in the Department of Dermatology, Hospital Kuala Lumpur

Sharifah Rosniza Syed Nong Chek[1], *AdvMDerm*, Min Moon Tang[1], *AdvMDerm*, Asmah Johar[1,2], *MMed*

[1]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[2]Klinik Pakar Kulit Dahlia, Bangi, Selangor, Malaysia

Abstract

Introduction

Contact cheilitis is a common cause of cheilitis. However, identifying the causative factor remains a challenge. This study aims to describe the characteristics of patients with cheilitis who underwent patch testing in Hospital Kuala Lumpur.

Methods

This is a 5-year retrospective study of patients who had cheilitis and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2013 and December 2017. Patch tests were performed with European Baseline Series and relevant extended series which include cosmetic, dental, metal series as well as patient's own products. Patch test readings were recorded according to the International Contact Dermatitis Research Group recommendation.

Results

There were 73 patients with cheilitis who underwent patch test. The median age of the patients was 26 (range 11 to 76) with 91.8% of patients being female. There were 52 (71.2%) patients who developed at least one positive reaction. The most frequent sensitizing allergens were nickel sulfate (30.1%), potassium dichromate (13.7%), thimerosal (12.3%), fragrances (9.6%) and cobalt chloride (8.2%). Ten (13.7%) patients developed positive patch test reactions to their own products such as toothpaste (n=5), lipstick (n=2), lip balm (n=1), facewash (n=1) and lotion (n=1). Current relevance was recorded in 14 patients (26.9%).

Conclusion

Contact sensitization was detected in about 70% of our patients with cheilitis. The most common sensitizing allergen was nickel sulfate. Toothpaste is more common than lip cosmetics as the likely cause of cheilitis.

Key words: *Cheilitis, allergic contact dermatitis, contact cheilitis, patch test*

Introduction

Cheilitis refers to superficial inflammation of the lips and can occur on its own or is associated with perioral dermatitis or other oral lesions such as stomatitis.[1] It excludes tumours, malformations, dystrophies, ulcerations or deep nodular lesions affecting this site.[2] Specifically, angular chelitis refers to inflammation involving only the angles of the mouth and can be either unilateral or bilateral.

There are many causes of cheilitis which include

Corresponding Author
Dr. Sharifah Rosniza Binti Syed Nong Chek
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586 Kuala Lumpur, Malaysia.
Email: srsyed@doctors.net.uk

contact cheilitis, atopic cheilitis, actinic cheilitis, drug-induced cheilitis, factitious cheilitis, infectious cheilitis and glandular cheilitis.[2] Contact cheilitis can be further divided into irritant contact cheilitis and allergic contact cheilitis. Irritants and allergens can come into contact with the lips via the use of personal care products such as toothpastes, lipsticks and lip balms, dental material such as braces or even via ingestion of food products. As with other cases of allergic contact dermatitis, patch testing plays an important role in diagnosing allergic contact cheilitis.

This study aims to describe the characteristics of contact cheilitis in Hospital Kuala Lumpur, Malaysia.

Materials & Methods

This is a 5-year retrospective study of patients with cheilitis and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2013 and December 2017.

Patch tests were performed with European Baseline Series and relevant extended series from Chemotechnique Diagnostics using IQ chambers™. Extended series used include cosmetic series, dental screening series, metal series, rubber series, plastic and glue series and hairdressing series. Patients were also tested with their own products, which include lipstick, lip balm, toothpaste, face wash and lotion. Cosmetics such as eye make-up, lipstick, facial powder, facial foundation, moisturizers, perfumes and deodorants were tested "as is". Toothpaste was also tested "as is". Cleaning products such as facial wash, shampoo and shower gel were diluted with water to 10% (w/w).

Patches were applied to the patients and removed after 48 hours. Initial reading was done at 48 hours and final reading was recorded at 96 hours after patch application. The parameters studied include positive patch test reactions and the source of allergens. Readings were recorded according to the International Contact Dermatitis Research Group recommendation.[3] In accordance to their recommendation, a positive patch test reaction is defined as a reaction that fulfils at least a 1+ reaction (i.e. +, ++ or +++). Other reactions that can be found during patch tests are irritant reaction (IR) and doubtful reaction (?/+), but these are not considered as a positive patch test reaction.

Results

A total of 73 patients with cheilitis underwent patch test. The demographic data is shown in Table 1. The median age of patients was 26 years old (range 11 to 76) and 91.8% of patients were female. There were 52 (71.2%) patients who developed at least one positive reaction. As shown in Table 2, the most frequent sensitizing allergens were nickel sulfate (30.1%), potassium dichromate (13.7%), thimerosal (12.3%), fragrances (9.6%) and cobalt chloride (8.2%). Ten (13.7%) patients developed positive patch test reactions to their own products such as toothpaste (n=5), lipstick (n=2), lip balm (n=1), facewash (n=1) and lotion (n=1).

Table 1. Characteristics of patients who underwent patch test

Characteristics		N=73 (%)
Median Age in Years (Range)		26 (11-76)
Male : Female Ratio		1:11.2
Ethnicity, n (%)	Chinese	38 (52.1)
	Malay	27 (37.0)
	Indian	7 (9.6)
	Others	1 (1.4)
Occupations, n (%)	Professional	25 (34.2)
	Clerks	7 (9.6)
	Manager	2 (2.7)
	Technician	2 (2.7)
	Services	2 (2.7)
	Agricultural	1 (1.4)
	Unemployed	34 (46.6)
Series used, n (%)	European Baseline	73 (100.0)
	Cosmetic	38 (52.1)
	Dental	17 (23.3)
	Metal	6 (8.2)
	Rubber	4 (5.5)
	Plastic and glue	2 (2.7)
	Hairdressing	1 (1.4)
	Own products	65 (89.0)

Seventeen (23%) patients had involvement of other sites on their body in addition to the cheilitis, most commonly on the face. Relevance of positive patch test reaction was assessed and 14 patients (26.9%) were found to have current relevance. Their current relevance were likely towards own toothpaste (35.7%), followed by their lips cosmetics (21.4%), facial wash (21.4%), facial cosmetic (7.1%), dentures (7.1%) and orthodontic braces (7.1%).

Irritant reaction was detected in 29 (39.7%) patients. Irritant reaction in these patients was caused by their own toothpastes in 24 (82.8%) patients. Other causes of irritant reactions are lipstick (10.3%), formaldehyde (6.9%), facial wash (6.9%), sorbitan sesquioleate (3.4%), cocamidopropyl betaine (3.4%), hand wash (3.4%) and facial mask (3.4%).

Toothpaste causes both irritant and allergic reactions in our study. Twenty-nine patients developed reaction to toothpaste; with 24 (82.8%) categorized as irritant reaction and 5 (17.2%) patients categorized as a positive patch test reaction.

Table 2. The sensitization pattern of current cohort

Positive Patch Test	n (%)
Nickel sulfate	22 (30.1)
Potassium dichromate	10 (13.7)
Thimerosal	9 (12.3)
Fragrances	7 (9.6)
Cobalt chloride	6 (8.2)
4-phenylenediamine base, formaldehyde and mercury	4 each (5.5)
Balsam of Peru, isothiazolinone and amalgam	3 each (4.1)
MDBGN, iron oxide and thiuram mix	2 each (2.7)
Wool alcohol, epoxy resin, SQL mix, BHT, BHA, chlorocresol, cocomidopropylbetaine, thiuram mix, iron chloride, stannous chloride, 2-bromo-2-nitro-propane-1,3-diol, benzocaine, palladium chloride, goldsodium thiosulphate, mercapto mix, dibutylthiourea, paraben mix, palladium chloride, copper oxide, copper sulphate, titanium, mercury, mercury ammonium chloride, neomycin, benzoyl peroxide, clioquinol, colophony	1 each (1.4)

MDBGN-Methyldibromoglutaronitrile; SQL-Sesquiterpine Lactone; BHT-Butylated Hydroxytoluene; BHA-BButylated Hydroxyanisole

Discussion

Contact sensitization was detected in about 70% of our patients with cheilitis. This finding is similar to a study conducted in Athens.[4] However, some studies only reported incidence with relevant sensitization and we found that our relevant sensitization of 26.9% is also comparable to other studies (Table 3).

The most common sensitizing allergen found in our study was nickel sulfate and this finding is similar to other studies.[4,5,6] Nickel is abundant in our environment and can be found in cosmetics, particularly in colour cosmetics. The fact that more females are wearing cosmetics and jewelleries and also undergo ear piercing may also explain why 91.8% of the patients that develop positive patch test reaction in our study are females. The presence of nickel in cosmetic products may originate from various sources such as use of raw materials and water contaminated with nickel to cosmetics production and use of metal coated apparatuses during cosmetics productions.[7] According to the Regulation No 1223/2009 of the European Parliament and the Council, the presence of cosmetics products of metals particularly dangerous for human health such as nickel is prohibited in the European countries. However, small quantities of nickel may be present as technically unavoidable contaminants if the preparations are safe for human health. The safe levels of these contaminants unfortunately, are not described.[7]

Lipsticks that contain traces of nickel may cause contact cheilitis in a sensitized individuals and certain lipstick that is encased in a metal sheath may also be contaminated with nickel, possibly via leaching of nickel from the metal casings. However, determining the current relevance of nickel in the context of cheilitis is challenging as the presence of nickel in cosmetics as a contaminant will not be noted in the ingredient list. Furthermore, another source of exposure to nickel to the lips may also be related to ingestion of food containing high level of nickel such as legumes, dark chocolates, shellfish, grains and canned food.[8] Patients may also be exposed to nickel via the use of stainless steel cookware as nickel has been found to leach from this cookware especially when used to cook acidic food.[9] Certainly, if cheilitis is accompanied by the presence of other signs of such as a more widespread eczema or systemic contact dermatitis, the relevance of nickel may become more established.

Another source of nickel exposure in the case of cheilitis is from dental restorative materials. Nickel is found in base-metal metal-ceramic alloy as nickel-chromium alloy.[10] In addition to cheilitis, allergic contact dermatitis to dental restorative materials may also include stomatitis, oral lichen planus, glossodynia, burning mouth/tongue, periodontitis and recurrent apthosis.[11] Although the release of nickel from these materials has been shown to be low[12], the corrosive effect of the oral environment is thought to increase the nickel release over time.[13] In our study, there was only one patient who developed cheilitis after commencing on orthodontic braces. This patient was found to have nickel allergy, however she declined to remove the braces. Cheilitis to orthodontic braces has been reported before and in such cases, substitution of nickel with vitallium can be suggested in those found to be allergic to the metal.[14]

We also found cobalt and chromium as common sensitizers in our cohort of patients. Patients who are sensitized to nickel are more prone to be sensitized to other metals and this may explain the high sensitization to cobalt chloride and potassium dichromate in our patients.[15] Cobalt and chromium can also be found in coloured cosmetics as pigments.[7] Dyes and pigments are essential in the production of coloured products such as lipsticks. Many pigments authorized to be used in cosmetics

contain or are made of metal oxides or minerals e.g. iron oxide, chromium oxide, aluminium silicate, and titanium oxide, which by their nature contain traces of heavy metals.[16] The law of the European Union (EU) allows the presence of various pigments in cosmetics.7 Colours such as green can contain chromium (III) oxide, chromium (III) hydroxide and cobalt aluminium oxide.[7] Another source of exposure to the lips from these metals may also be from dental alloys. Cobalt and chromium can be found in palladium-cobalt alloys, nickel-chromium alloys and cobalt-chromium alloys; which are used as dental restoration materials.[10] Although dental alloys are meant for long-term use and the metal leaching from these products are generally thought to be low, it is important to enquire about dental restoration work in patients who presented with cheilitis, especially if there are other concurrent oral symptoms such as stomatitis or oral lichenoid reactions.

Thimerosal was one of the most common allergens in this study. Thimerosal is a mercuric derivative of thiosalicylic acid and is used as a preservative in products including otic suspensions, ophthalmic solutions, nasal preparation, vaccinations and cosmetics.[17] Its use however has been limited in dermatologic medications and cosmetics because of concerns regarding mercuric absorption or sensitization. The relevance of thimerosal allergy is often unclear, so much so that it was named American Contact Dermatitis Society's "(non) allergen of the year" in 2002 due to its low clinical relevance.[18] Thimerosal has been removed from the North American Contact Dermatitis Group screening series and the last available data is from 2002.[19] However, it is still important to enquire about possible source of exposure to thimerosal from cosmetics when presented with patients with cheilitis.

Fragrance was one of the top allergens in this study and this is not surprising as many cosmetics and oral hygiene products contain fragrances as part of their ingredients.[20] Fragrances such as geraniol are also used as flavouring agents in sweet foods such as ice-cream and candy and has been reported to cause allergic contact cheilitis.[21] Fragrances are also used to mask certain odours and in this case, it might not be labelled as fragrance in the ingredient list.[22] Nowadays, there is a tendency to use "natural" products and this includes the use of essential oil. Essential oils are made by steam distillation of plant material and they are used in fragrances, foods, cosmetics and flavourings. Allergic contact dermatitis has been described for 80 essential oils.[23] Certain essential oil such as peppermint oil is often used in toothpaste and mouthwash and has been reported to cause allergic contact dermatitis.[24] This also highlights the fact that natural products are not entirely risk-free and allergic contact dermatitis can develop in patients who are sensitized to them.

Apart from fragrances found in foods, certain foods themselves have been reported to cause allergic contact cheilitis. This is especially relevant if the patient develops cheilitis after a reported change in dietary habit or consumption of a new food products including supplements and herbs. Foods that have been reported to cause allergic contact cheilitis include garlic,[25] rosemary,[26] propolis and beeswax.[27] Garlic contains diallyl sufide, which has been found to cause allergic contact dermatitis and even systemic contact dermatitis.[25] Propolis is a resinous substance manufactured by bees and it used for gluing and sealing cracks in the beehive. It is produced when plant material collected by the bees is mixed with *ß*-glycosidase from the bee's saliva and added to beeswax.[27] Apart from being consumed as food supplement, propolis and beeswax are also found in cosmetic products including lip balm and lipstick. Therefore, it is important to enquire about history of food that may have triggered cheilitis as avoidance of such food will render improvement or resolution of cheilitis.

We found current relevance in 26.9% of our patients, mainly towards own toothpaste. Toothpastes have complex formulations with often more than 20 ingredients and these ingredients can cause both allergic and irritant contact dermatitis.[28] Our study however, showed that the majority of the reactions towards toothpaste are classified as irritant reaction (82.8%). The main symptoms of allergic reactions to toothpastes are cheilitis, and to a lesser extent intraoral manifestations such as glossitis, gingivitis, and stomatitis. Potential allergens that can be found in a toothpaste include fragrances and flavorings such as cinnamon derivatives, peppermint oil, spearment oil and tea tree oil.

Other potential allergens include carvone, cocamidopropyl betaine, anethole, amine fluoride, triclosan, aluminium and chloroacetamide.[28] Toothpaste also contains abrasives and detergents such as sodium lauryl sulfate and these ingredients were known to cause irritant contact dermatitis. Sodium lauryl sulfate (SLS) is a surfactant and its

presence in toothpaste renders the formation of bubbles, which gives a favorable sensation to the user.

Although testing to toothpastes is undoubtedly useful, it has its own drawbacks. There is currently no consensus on patch testing to toothpaste. Irritant reaction is deemed to be common when patch testing using undiluted toothpaste due to the presence of abrasives and detergents. Diluting the toothpaste on the other hand will reduce its irritant potential but may cause false negative reaction. As a starting point, a semi-open test or closed patch test with the undiluted toothpaste can be performed. If a positive patch test reaction to an undiluted toothpaste developed, it should be followed with retesting and/or testing a dilution series (e.g undiluted, 40% pet or water and 20% pet or water) and/or control testing.[28] It is also important to obtain a full ingredient list of a toothpaste as the ingredients listed on the actual product are usually not complete. For example, a concurrent positive patch test reaction to allergens in the commercial series and to the patient's own toothpaste should not mean that these allergens are present in the toothpaste unless it is ascertained by obtaining the manufacturer's full ingredient list, or from analytical investigations.

Irritant reaction was detected in 29 (39.7%) patients, mainly towards toothpastes. Irritant reaction had been reported in patients investigated for cheilitis and the percentage of irritant contact dermatitis in these patients ranged from 5% to 37% (Table 3). Our study used undiluted toothpaste during patch test and we also diluted patients own rinse-off products to 10%, which is the highest dilution recommended by the European Society of Contact Dermatitis. This guideline recommended patients' own rinse-off products to be patch tested at 1-10% dilution, depending on the formulations.[3] However, no further explanation is given about the types of formulations. Both of these factors can contribute to the irritant reaction seen in our study. Perhaps a 1% dilution for rinse-off products and retesting the patients with positive patch test reaction to toothpaste with a serial dilution may reduce the chance of irritant reaction in our patients.

Testing to patients' own products is important as this study showed that 13.7% patients with positive patch test reaction would have been missed if testing to their own products is not performed. Apart from toothpaste, products that have been found to cause positive patch test reaction include facial wash, lip balm, lipstick and lotion. Testing can be done "as is" if the products are categorized as leave-on products; such as lipstick, lip balm, moisturizer and sunscreen. Products categorized as rinse-off products can be patch tested at 1-10% w/w dilution and these include products such as facial wash.[3] Apart from enquiring products that are applied directly to the lips, occupational and recreational activities must also be documented in patients with cheilitis. Although not found in our study, musical instruments such as trumpet and saxophone have also been implicated in causing cheilitis in patients.[29,30]

There are several limitations to this study. This is a single centre study and our findings may not be representative of the Malaysian population as a whole. We also did not repeat the patch test with 40% or 20% dilution for patients who had positive patch test reaction to undiluted toothpaste and this could pose a risk of a false positive patch test reaction.

Table 3. Contact cheilitis: a review of the literature

Author Country	Study Period	n	Mean Age (Years)	Positive PT Reaction (%)	Relevant Reaction (%)	Top Two Allergens	Irritant Reaction (%)
Current Study Malaysia	2013-2017	73	32	71.2	26.9	1) Nickel 2) Potassium Dichromate	39.7
Zoli et al. Italy[5]	2001-2005	83	40.3	54.2	18	1) Nickel 2) Thimerosal	37
Lim SW et al. Singapore[6]	1996-1999	202	30.9	NA	34	1) Nickel 2) Own Cosmetics	5
Katsarous et al. Greece[4]	1992-2006	106	F-35.1 M-38.5	71.7	NA	1) Nickel 2) Cobalt	NA
Milanesi et al. Italy[31]	2009-2013	38	37.9	52.6	36.8	1) Fragrance Mix 2) Eugenol	31.5
O'Gorman et al. USA[20]	2001-2011	91	51	NA	45	1) Fragrance Mix 2) Balsam of Peru	11

PT: patch test; F: female; M: Male; NA: not available

Conclusion

Contact sensitization was found in about 70% of our patients with cheilitis. Cheilitis is commonly found in women and the top 3 allergens in our study are nickel sulfate, potassium dichromate and thimerosal. Current relevance of positive patch test reaction was found in around 1/3 of the patients and these were mostly towards their own toothpaste and lips cosmetics. Testing to patients' own products is imperative to ensure that these relevant reactions are not missed.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Impact of Eczema Action Plan (EAP) on Disease Severity for Childhood Atopic Eczema

Mazliha Mashor[1], *MRCP*, Yoong Wei Lee[1], *Adv M Derm*, Siew Eng Choon[1,2], *FRCP*, Kwee Eng Tey[1], *MRCP*, Adawiyah Jamil[3], *Adv M Derm*

[1]Department of Dermatology, Hospital Sultanah Aminah Johor Bahru, Johor, Malaysia
[2]Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru, Johor, Malaysia
[3]Department of Dermatology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Abstract

Introduction

Poor adherence to topical treatment is common in atopic eczema (AE), which may result in treatment failure. Eczema Action Plan (EAP) is a self-management tool designed to improve adherence. This study aimed to assess the impact of EAP on disease severity in paediatric patients with AE.

Methods

A prospective, randomized controlled investigator-blinded study involving mild to moderate AE children aged below 18 was performed, comparing intervention group implementing EAP with control group on standard practice alone. Scoring Atopic Dermatitis (SCORAD) index, Investigator Global Assessment (IGA) scoring and adherence to treatment were assessed at baseline, week 4 and week 8.

Results

In total, 64 participants were randomised and 54 patients completed the study. The mean age of participants was 3.54 ± 3.95 years. Male to female ratio was 1:1.06. Compared to the control group, the intervention group had significantly greater improvement of the mean total SCORAD at week 4 (p<0.001) and week 8 (p=0.038), and IGA score at week 4 (p<0.001). Use of moisturisers was higher in intervention group at week 4 (p<0.001) and week 8 (p=0.014) in comparison to control group. Significantly smaller amount of high potency topical corticosteroid was used in the intervention group at week 4 (p=0.003).

Conclusion

Eczema Action Plan has significantly improved eczema severity. It acts as a simple self-management instrument which may aid in AE treatment. Future studies may be warranted to assess the long-term benefit of EAP.

Key words: *Atopic eczema, children, eczema action plan*

Corresponding Author
Dr Mazliha binti Mashor @ Mansor
Department of Dermatology,
Hospital Sultanah Aminah,
Jalan Persiaran Abu Bakar Sultan,
80100 Johor Bahru, Johor, Malaysia.
Email: ammz83@yahoo.com

Introduction

Atopic eczema (AE) is a chronic, pruritic, inflammatory cutaneous disorder that affects one quarter of children and 2% to 3% of adults. More than 50% of patients with AE are diagnosed during the first year of life and 90% within 5 years of age. Disease onset typically occurs around 3 and 6 months of age.[1] The most commonly used diagnostic tools in local setting is the U.K. Working

Party's Diagnostic Criteria which has been validated with sensitivity and specificity of 96% and 93.8%, respectively. There is no specific laboratory test required for the confirmation of AE diagnosis.[2,3] In 2017, the Malaysian's clinical practice guidelines (CPG) on Management of Atopic Eczema was published with written eczema action plan (EAP) integrated as one of the educational interventions for AE patients.[4]

Normal skin barrier function, which offers protection against environmental irritants and allergens, is impaired in patients with AE. In particular, alterations in the filaggrin gene have been identified to cause disruption to functional integrity of the skin barrier. Moisturisers can be occlusive, by providing a layer of lipid on the skin surface to limit the water loss. Some moisturisers act as humectant by increasing its moisture-retaining capacity in the stratum corneum. In addition, moisturisers can perform as emollient to lubricate and smoothen the skin.[5,6] Frequent application of moisturiser is vital at any stage of AE regardless of age group. The usage of moisturiser is associated with reduction in pruritus, erythema and lichenification, aiming to achieve the reduction in AE severity. Therefore, regular use of moisturiser should be an integral component of the AE management.[1,4,5]

The usage of topical corticosteroids (TCS) is supported as anti-inflammatory in addition to the use of moisturisers.[4] Various factors are taken into consideration when choosing a specific topical corticosteroid such as patient's age, location of the skin lesion, severity of skin inflammation, patient preference, and cost of medication.[1,7] The low-potency TCS can be considered in children to avoid the possible systemic side effects of corticosteroids due to the higher body surface area to weight ratio.[4] Nevertheless, the practice of short courses of high potency TCS can be contemplated during acute flares for better eczema control. Special sites such as face, flexural and genitalia should warrant the use of low potency TCS. Application of high potency TCS in those areas may result in greater steroid absorption particularly when they are being used for long term.[1,4,8] These few considerations, however, may inadvertently lead to confusion among patients and caregivers due to the different practices of TCS application depending on sites and severity.

Adherence to topical treatment is questionable in numerous AE cases.[9] Sixty-four (85.3%) patients demonstrated poor adherence to treatment in a local study published by Mazlin et al.[10] Reasons contributing to poor treatment adherence include intricacy of treatment regimen, lack of understanding about the disease, infrequent follow up, steroid phobia and use of complementary and alternative medicine.[7,9] Identifiable measures to enhance treatment adherence consist of providing education to patients and caregivers, utilisation of education adjuncts and frequent follow up.[9,11] Written action plan which has been established in paediatric asthma serves as a valuable measure to encourage treatment adherence. Both asthma and AE are similar in several aspects considering the chronicity of the conditions. They require the step-wise approach in the management guided by the disease severity.[8,12] EAP is designed to provide patients and caregivers specific instructions on the correct application of topical medications.[8] The content of EAP should comprise individualised action steps during basic maintenance and flares, when to seek medical attention, recognising flares and superimposed infection. Ideally, it is preferred that all the information in EAP is contained in less than two A4 pages.[13] The instruction on the treatment regimen should be kept simple and clearly written.[7]

Our study aims to determine the impact of EAP on disease severity in paediatric patients with AE. At present, the utilisation of EAP in dermatology clinic in Malaysia has not been studied.

Materials and Methods

Study Design

This was a single-centre, prospective, randomized, two-arm, investigator-blinded trial conducted from March 2019 until June 2019. The study intervention group used EAP versus standard practice alone in the control arm. Patients were recruited from the Dermatology Clinic of Hospital Sultanah Aminah Johor Bahru, a tertiary care centre for southern region of Peninsular Malaysia. Approval from the Medical Research & Ethics Committee (NMRR-18-2728-43492) was obtained before the commencement of the study. Written consents were obtained from all parents or guardians, whilst assent were obtained from children aged above 7 years old.

Participant Recruitment

Patients aged below 18 years old, diagnosed with AE based on the U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis were recruited. Those with mild to moderate AE according to SCORAD score without modifications in their treatment for the

past 3 months were selected. Parents or caregivers who are illiterate and unable to read the EAP and those who were on systemic treatments (including systemic corticosteroid, immunosuppressant and light therapy) in last 6 months were excluded.

Randomization and Blinding

Randomization was carried out anonymously by an independent research staff using computer generated Randomization Allocation Software version 2.0. The randomisation code was concealed in sealed envelopes arranged in random order. Enrolled subjects were randomly assigned to EAP arm (intervention group) or usual education session (control group) in 1:1 ratio. The study researcher who performed the assessment was masked, whereas the attending clinicians and patients/ caregivers were unmasked as this was a single-blinded study. This blinding of the researcher was to ensure that the objective assessment of eczema severity was unbiased. Researcher would not have access to the randomization system and would not be able to identify which group the participants had been assigned to. During baseline clinic visit, an attending clinician would educate the intervention group on how to use the EAP. The clinician involved is a dermatologist working in the dermatology clinic who was not involved in patient assessment in the study. To maintain the masking process, the clinicians and parents were instructed not to disclose the information about the group allocation to the study researcher.

Due to the nature of the intervention, it was not possible to blind the participants. Every participant from both groups would receive an envelope. Only those from intervention group would receive the EAP which was concealed within an envelope. Caregivers were also asked to ensure that the content of each envelope is hidden from view. Follow-up of any non-responders would be made via telephone. The withdrawn subjects would not be replaced.

Development of EAP

The written eczema action plan (EAP) in Malaysia for AE was developed and included in the Clinical Practice Guidelines (CPG) on Management of Atopic Eczema. The EAP is a colour-coded document which comprises a set of written instructions on eczema care regimen in three different circumstances depending on disease severity. The content of EAP would describe instructions about when to apply moisturisers and topical corticosteroids, and when to call the clinic during severe flare. EAP is available in English and Malay as shown in Figure 1 & 2.

Standard Management with EAP

The participants were randomized into two groups either intervention or control group. The allocation to each group is 1:1 ratio. During baseline clinic visit, participants in intervention group were given EAP plus the standard eczema practice. The participants and caregivers were counselled by a clinician (other than primary investigator) on the use of EAP to facilitate them to use it while at home. The subjects in the intervention group would be asked not to reveal the content inside the envelope to the primary investigator. No new topical or systemic treatment was allowed during the study period. Therefore, the participants would maintain their routine treatment regime of moisturisers, topical corticosteroids and oral antihistamines.

A clinician would educate on how to use the EAP during baseline clinic visit for the intervention group. Meanwhile the control group would receive verbal information on management of AE only without EAP. They were provided with the usual treatment including basic education regarding the use of moisturizers and topical corticosteroid medications in accordance to the current standard practice. Hence, they were not deprived from the standard care. Upon completion of the trial, participants in the control group were offered the opportunity to use EAP if they were interested.

Outcome Measures

The primary outcome of this study was to determine whether the EAP, when used in addition to standard eczema care, leads to greater reduction of disease severity compared to standard care alone. Data were collected at baseline, week 4 and week 8.

Data on the assessment of patients' sociodemographic information comprised of age, gender, ethnicity, caregivers' marital status, education level and employment status were recorded on the day of the enrolment.

The primary outcome was measured by the investigator using Scoring Atopic Dermatitis (SCORAD) index at baseline, 4-week and 8-week follow-up. It combines an objective assessment of the extent of disease using the rule of nines, six clinical features of disease intensity, including erythema, oedema/papulation, oozing/crust, excoriation, lichenification and dryness. The maximum score for SCORAD is 83. The subjective SCORAD score is

an add-on score to the objective SCORAD, which assesses symptoms of pruritus and sleep loss on a scale of 0 to 10. The subjective score adds up to an additional 20 points to the objective SCORAD score. Disease severity can be categorized as mild (<25), moderate (25–50) or severe (>50). The SCORAD index has undergone testing for validity and reliability.13,14

In addition, Investigator Global Assessment (IGA) is another parameter assessed by investigator at baseline, 4 and 8 weeks. It is rated as clear, almost clear, mild, moderate, severe, or very severe. This is a second validated tool to measure eczema severity.15

During each visit, the subjects were asked to bring all the remaining topical medications and each medication was weighed separately using the same digital scale. Adherence to treatment was assessed by comparing amount of topical treatment used. The usage of topical moisturisers, low and high potency TCS was recorded in a diary. This caregiver-completed diary will capture the number of days each topical treatment used in a month. Changes in adherence to topical treatment was the secondary objective of this study.

Statistical Analysis

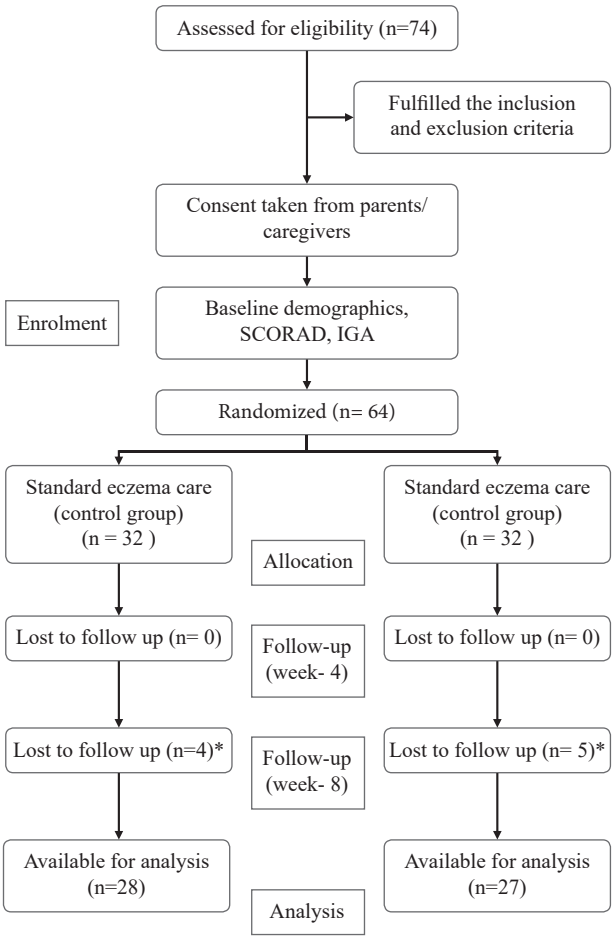
The data collected was analysed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows. The socio-demographic characteristics of the intervention and control groups were described using frequency, percentage, mean and standard deviation. The comparison at baseline between both groups was made by using the appropriate inferential tests such as the Chi-square, independent t-test and Fischer's Exact test. The two-way repeated measures ANOVA was used to measure the changes in the mean score of SCORAD and IGA between intervention and control groups at various time points. P- value <0.05 is considered as statistically significant.

Results

Baseline Data

In total, 74 patients were assessed for eligibility to take part in the study. Of these, 64 participants were randomised into 32 participants for each group. Fifty-five patients completed the study (28 intervention group and 27 control group). Nine participants dropped out at week 8 as they were no longer interested to continue the study. (Figure 3).

Figure 3. Flow chart of the study participants in intervention and control groups



**4 participants allocated to intervention group and 5 participants in control group dropped out at week 8 (not interested to continue).*

The mean age of the study participants upon diagnosis and on recruitment were 2.27 ± 3.37 and 3.54 ± 3.95 years old, respectively. Male to female ratio was 1:1.06. The majority of participants were Malays (87.5%), whereas 12.5 % were Chinese. More than one-quarter of the participants had other atopic predispositions including allergic rhinitis or bronchial asthma. Three-quarter of the participants had family history of atopy. More than 90% of the caregivers were patients' own parents, and 3 (4.7%) were grandparents. Thirty-eight (approximately 60%) of the caregivers had completed tertiary level education and 29 (45.3%) were employed full-time. Detailed sociodemographic and baseline characteristics of the study population are shown in Table 1.

Changes in Measures of Eczema Severity

At the baseline visit, the difference of mean total SCORAD and IGA between both groups was not statistically significant (p=0.224 p=0.156,

respectively). Of note, there was a significantly greater improvement of mean total SCORAD (p<0.001), subjective and objective SCORAD and IGA score (p<0.001) in the intervention group at week 4 compared to the control group. At week 8, there was also significantly greater improvement in mean total SCORAD (p=0.038) and objective SCORAD in the intervention group, but the differences were not significant in subjective SCORAD (p=0.793) and IGA score (p=0.283). (Refer Table 2)

Changes in Adherence to Topical Treatment

No difference was observed in the amount of the initial moisturisers for both control and intervention groups during baseline visit. The intervention group showed significantly higher amount of moisturisers used compared to those in the control group at week 4 and week 8 (p=<0.001, p=0.014 respectively). No significant difference in the mean weight of low potency topical corticosteroid among study groups at week 4 and week 8 (p=0.979, p=0.424 respectively). However there is a significant reduction in the amount of high potency topical corticosteroid observed for intervention group during week 4 (p<0.001), but no significant difference at week 8 (p=0.787) (Table 2). When comparing the frequency of topical agents used in both groups as recorded in the caregiver diary, the difference was not statistically significant (p=0.093) (Table 3).

Discussion

Eczema Action Plan, which is modelled on the asthma action plan, is part of the self-management to empower patients and caregivers aiming for reduction in AE severity and prevention of flare.[4,8] Our study has illustrated that the intervention group demonstrated significantly greater improvement in eczema severity particularly at week 4 indicated by lower total SCORAD and IGA score. This finding is consistent with previous studies which revealed improvement in the AE management with EAP utilisation.[17] One of the benefits of EAP is enhancing patients' and caregivers' understanding of their individualized treatment plan.[4,18,19,20] A written plan acts as a quick reference to patients and their families. This encourages them to be more confident and motivated in following the treatment regime.[12,21] Even though EAP lengthens the initial clinic visit by 3 to 5 minutes, it is expected to improve future visit duration, and improve long-term clinical outcomes.[17,19,21]

Whilst the total SCORAD demonstrating significant improvement (p=0.038) at week 8 compared to baseline, the expected reduction in the mean IGA score for the intervention group was not significant at week 8 (p=0.283). This finding at week 8 was inconsistent and has to be explored further. In the randomised trial on Eczema care plan by Rea et al, it has been suggested that a greater impact of the EAP can be expected if eczema is observed for a longer duration . This observation may reflect the natural variation in eczema severity with relapsing and remitting phases.[18] There is a probability that children might experience flare intermittently during their clinic visits which might improve in the subsequent weeks irrespective of any intervention. Another possible explanation is the lack of use of EAP by patients or caregivers beyond 8 weeks. Rea et al found that only half of the caregivers has been using the action plan more than once or twice since initial visit.[18] Thus, a more regular use of written plan is desirable to make it more effective in reducing the eczema severity expectantly in longer period.

A study by Mason et al has shown there is a substantial underutilisation of moisturisers in children with AE as caregivers expressed frustration at the irregularity of information provided on eczema management.[23] Common misconception among patients is that an ideal moisturiser can be used in limited frequency. According to a survey in Hong Kong, most of the patients believe that ideal moisturisers are non-fragrant and non-herbal creams which require only two to three applications per day.[24] They are often incorrectly advised on the amount and frequency of moisturisers required to maintain good skin barrier function.[5] In comparison to oral medication, there are difficulties in applying topical treatment which are contributed by various factors including lack of time to apply medications, extent of skin involvement, differing opinion towards the vehicle of the medications and chronicity of the illness. From our study, the intervention arm has shown significantly greater amount of moisturiser compared to those in control arm during week 4 and week 8 (Table 2). Education on moisturiser is crucial for AE management as improving the amount of moisturiser used was associated with less pruritus and reduction in sleep disturbance.[23] In a study by Moore et al, the mean weekly use of moisturiser increased from 54.5 g at baseline to 426 g at the final visit, with a significant reduction in eczema severity after attending an education session with the nurse indicating that education may result in enhanced use of moisturiser.[25]

Table 1. Sociodemographic characteristics of the participants

Characteristics		Total (n=64)	Control (n=32)	Intervention (n=32)	*p*-value
Age on recruitment, in year (mean ± SD)		3.54 (3.95)	3.74 (4.34)	3.33 (3.57)	*0.676*[a]
Age on diagnosis, in year (mean ± SD)		2.27 (3.37)	2.68 (3.89)	1.86 (2.75)	*0.336*[a]
Gender, n (%)	Male	31 (48.4)	15 (46.9)	16 (50.0)	*0.802*[b]
	Female	33 (51.6)	17 (53.1)	16 (50.0)	
Ethnicity, n (%)	Malay	56 (87.5)	27 (84.4)	29 (90.6)	*0.708*[c]
	Chinese	8 (12.5)	5 (15.6)	3 (9.4)	
Personal history of atopy other than AE, n (%)	No	47 (73.4)	23 (71.9)	24 (75.0)	*0.777*[b]
	Yes	17 (26.6)	9 (28.1)	8 (25.0)	
Main caregiver, n (%)	Mother/Father	61 (95.3)	31 (96.9)	30 (93.8)	*1.00*[c]
	Grandparent	3 (4.7)	1 (3.1)	2 (6.2)	
Caregiver education level, n (%)	Secondary school	26 (40.6)	13 (40.6)	13 (40.6)	*1.00*[b]
	College/ university	38 (59.4)	19 (59.4)	19 (59.4)	
Caregiver employment status, n (%)	Non-working	35 (54.7)	21 (65.6)	14 (43.8)	*0.079*[b]
	Working	29 (45.3)	11 (34.4)	18 (56.2)	
Family history of atopy, n (%)	No	16 (25.0)	8 (25.0)	8 (25.0)	*1.00*[b]
	Yes	48 (75.0)	24 (75.0)	24 (75.0)	
Mean (SD) baseline score for eczema severity	Objective SCORAD	32.08 (8.18)	30.52 (8.32)	33.65 (7.84)	*0.126*[a]
	Subjective SCORAD	10.53 (4.19)	10.44 (4.36)	10.63 (4.07)	*0.859*[a]
	IGA score	2.77 (0.43)	2.69 (0.47)	2.84 (0.37)	*0.145*[a]
Mean (SD) baseline quantity of medication (g)	Topical moisturiser	574.23 (6.46)	574.60 (6.64)	573.85 (6.35)	*0.647*[a]
	Topical CS (low potency)	58.17 (2.50)	58.49 (2.46)	57.84 (2.55)	*0.303*[a]
	Topical CS (high potency)	19.80 (4.74)	19.18 (0.46)	20.41 (6.68)	*0.305*[a]

[a]Independent t-test; [b]Pearson Chi Square; [c]Fischer's Exact test; SD standard deviation

Table 2. Comparison between control and intervention group on Total SCORAD, Objective SCORAD, Subjective SCORAD, IGA score and amount of topical agents used

Parameters		Control Mean (SD)	Intervention Mean (SD)	Mean difference (95%CI)	*p*-value
Total SCORAD	Week 0	39.68 (11.28)	43.95 (11.38)	3.32 (-2.08, 8.73)	*0.224*
	Week 4	33.55 (13.95)	27.04 (12.02)	-9.29 (-15.60, -2.98)	*0.005*
	Δ week 0-4	5.64 (11.30)	18.26 (10.59)	12.62 (7.14, 18.09)	*<0.001*
	Week 8	21.08 (15.77)	17.56 (11.92)	-3.52 (-11.07, 4.02)	*0.353*
	Δ week 0-8	18.60 (13.76)	26.39 (13.36)	7.80 (0.46, 15.13)	*0.038*
Objective SCORAD	Week 0	30.52 (8.32)	33.65 (7.84)	3.13 (-0.91, 7.17)	*0.126*
	Week 4	26.34 (10.77)	18.98 (9.01)	-7.36 (-12.32, -2.39)	*0.004*
	Δ week 0-4	4.18 (9.49)	14.67 (9.14)	10.49 (5.83, 15.15)	*<0.001*
	Week 8	13.41 (13.19)	10.02 (8.60)	-3.39 (-8.96, 2.17)	*0.227*
	Δ week 0-8	17.10 (12.78)	23.63 (10.87)	6.53 (0.60, 12.46)	*0.031*
Subjective SCORAD	Week 0	9.63 (4.16)	10.82 (4.16)	0.188 (-1.92, 2.30)	*0.859*
	Week 4	8.22 (4.28)	7.36 (3.77)	-1.94 (-4.01, 0.13)	*0.066*
	Δ week 0-4	1.47 (2.90)	3.59 (2.83	2.13 (0.69, 3.56)	*0.004*
	Week 8	5.19 (3.71)	6.11 (4.65)	0.92 (-1.36, 3.20)	*0.421*
	Δ week 0-8	4.44 (3.56)	4.71 (4.00)	0.27 (-1.78, 2.31)	*0.793*
IGA score	Week 0	2.67 (0.48)	2.82 (0.39)	0.16 (-0.06, 0.37)	*0.156*
	Week 4	2.30 (0.61)	1.96 (0.64)	-0.38 (-0.67, 0.08)	*0.015*
	Δ week 0-4	0.34 (0.65)	0.88 (0.49)	0.53 (0.24, 0.82)	*<0.001*
	Week 8	1.59 (0.93)	1.50 (0.88)	-0.09 (-0.58, 0.40)	*0.706*
	Δ week 0-8	1.07 (0.87)	1.32 (0.82)	0.25 (-0.21, 0.71)	*0.283*
Amount of moisturiser used (g)	Week 0	574.25 (6.18)	574.18 (6.54)	-0.75 (-4.00, 2.50)	*0.647*
	Week 4	176.11 (88.97)	270.78 (123.47)	99.73 (46.80, 152.66)	*<0.001*
	Week 8	252.97 (125.41)	343.17 (138.20)	90.20 (18.74, 161.66)	*0.014*
Amount of low potency topical corticosteroid used (g)	Week 0	58.31 (2.62)	58.13 (2.29)	-0.65 (-1.90, 0.60)	*0.303*
	Week 4	23.63 (15.63)	25.09 (15.18)	-0.10 (-7.69, 7.49)	*0.979*
	Week 8	23.50 (14.71)	20.41 (13.82)	-3.10 (-10.81, 4.62)	*0.424*
Amount of high potency topical corticosteroid used (g)	Week 0	19.14 (0.43)	20.50 (7.16)	1.23 (-1.14, 3.59)	*0.305*
	Week 4	9.27 (6.20)	5.44 (4.63)	-4.48 (-7.08, -1.88)	*<0.001*
	Week 8	8.49 (6.33)	7.85 (10.57)	-0.64 (-5.38, 4.09)	*0.787*

**ANOVA, significant at p<0.05; SD standard deviation; CI confidence interval*

Table 3. Comparison of frequency of the topical agents used per month as recorded in caregiver diary

Diary (Number of days / month)		Control Mean (SD)	Intervention Mean (SD)	Mean difference (95%CI)	*p*-value[a]
Moisturiser	Week 4	21.89 (4.73)	25.75 (4.30)	1.77 (-0.31,3.84)	*0.093*
	Week 8	25.37 (5.65)	27.46 (4.20)		
Low potency topical corticosteroid	Week 4	24.85 (3.26)	23.54 (2.98)	-2.19 (-6.03,1.66)	*0.259*
	Week 8	17.56 (8.68)	18.43 (7.04)		
High potency topical corticosteroid	Week 4	14.93 (4.79)	12.46 (5.41)	-1.41 (-4.28,1.45)	*0.327*
	Week 8	10.33 (7.99)	9.29 (5.66)		

[a]*Independent T test; SD standard deviation; CI confidence interval*

Difficulties in providing effective treatment for AE may be contributed by misunderstanding about the treatment regime or steroid phobia among parents of atopic children.[7] A study by Shin et al has demonstrated that a considerable proportion of patients believed that the use of corticosteroids is unsafe and ineffective, compared to Chinese herbal therapies.[26] Numerous studies have attributed steroid phobia as a major cause of low compliance leading to treatment failure which can exacerbate AE. Fear of corticosteroids appears to be closely related to preference for alternative and complementary medicines.[26] In our study, there is no significant difference reported in the mean weight of low potency topical corticosteroid used among study group. We found that the intervention group had used significantly lower amount of high potency topical corticosteroid at week 4, possibly due to greater use of moisturiser which might lead to the steroid-sparing effect and improve the effectiveness of the TCS.[4]

Targeted education regarding TCS is critical at the time of prescription to overcome the effect of steroid phobia. Poor adherence with therapy is usually closely linked to inadequate understanding about the nature of the disease and role of topical treatments prescribed.[7] Providing proper counselling to patients and caregivers about the frequency and amount of TCS to be applied, using the TCS with appropriate potency, and the duration of treatment, may encourage higher acceptance of TCS and reduce fear of steroid use.[7,11] Potential side-effects from TCS are relatively uncommon and usually caused by an incorrect use of the TCS or inappropriate use of high potency formulations.[11] Whenever TCS is correctly applied, it is usually well tolerated.

Our study has a few limitations. Firstly, this study was conducted at a single site; hence it is uncertain whether our findings could be generalized to other settings such as primary care. Highly selected patients in tertiary hospital are more likely to volunteer in participating in the study. Larger randomised multi-centre studies in primary care centres are necessary to explore the role of EAP in managing AE in primary care setting. Secondly, the majority of the participants were Malays, whereas small proportion were Chinese. This may be explained by sampling bias as our majority of clinic patients were Malays. Selecting more participants with diverse ethnicities may reduce the threat of selection bias. Thirdly, another limitation was we did not follow these patients beyond 8 weeks due to the time constraint placed on the study. Therefore, the long-term improvement is still unclear. Future work should examine longer-term studies and multiple exposure of EAP to evaluate the longstanding benefit of this intervention. Lastly, we did not include EAP presented in languages other than English and Malay due to the restriction in our resources. Further development of EAP available in various languages should be considered to benefit more patients and caregivers in the multi-racial community.

Conclusion

The use of EAP in AE management has significantly improved eczema severity. Adherence to topical treatment is enhanced by increasing moisturiser usage and appropriate utilisation of TCS. This study highlighted the EAP as a simple and useful self-management tool which may aid in the AE treatment.[20] Future studies may be warranted to assess the long-term benefit of EAP.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

A Case-control Study: Comparison of Zinc Level in Androgenetic Alopecia Patients with Control Group

Kwan JW, *MRCP*,Tang JJ, *AdvMDerm*

Department of Dermatology, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

Abstract

Introduction

Zinc is known to be an essential trace element that acts as an enzyme cofactor and has important functional roles within the hair follicles. Several studies reported that zinc deficiency is associated with Androgenetic Alopecia (AGA). However, there is a lack of information on the prevalence of zinc deficiency among Malaysians with AGA. This study is aimed to evaluate the serum level of zinc in male patients with AGA compared to healthy controls. The relationship of zinc deficiency with the severity and duration of AGA was also determined.

Methods

This is a case-control study involving male AGA patients in the Department of Dermatology, Hospital Raja Permaisuri Bainun. Serum zinc level is analyzed using atomic absorption spectroscopy technique. The study group was then compared with age- and sex- matched control group. AGA severity was evaluated using the Norwood-Hamilton classification system.

Results

A total of 70 subjects were recruited, consisting of 35 subjects in each arm. The median serum zinc was 74.46 ug/dl (IQR 17.17) and 80.37 ug/dl (IQR 17.70) in AGA group and control group respectively. Although the median of serum zinc was lower in AGA group, there was no statistically significant difference between both groups (U=596, p=0.846). This study showed no statistically significant difference of zinc level between patients with different disease severity (H=0.927, p=0.629). There was no correlation between AGA disease duration with zinc level (rs=-0.022, p=0.901).

Conclusion

There was no significant difference in serum zinc level between AGA group and controls, however, the median serum zinc was lower in the AGA group. There was no correlation between serum zinc level with AGA disease severity and duration. There is a paucity of evidence for zinc supplementation, further study is required to determine the role of zinc in AGA.

Key words*: serum zinc, zinc deficiency, AGA, male pattern hair loss, androgenetic alopecia*

Corresponding Author

Dr Kwan Jing Wern

Department of Dermatology,
Hospital Raja Permaisuri Bainun,
Jalan Raja Ashman Shah,
30450 Ipoh, Perak, Malaysia.

Email: kwanjingwern@gmail.com

Introduction

Androgenetic alopecia (AGA) is a common form of non-scarring hair loss among men. In the Asian population, a prevalence of 46.9-60.0% has been reported in males older than 70 years.[1,2] In Singapore, Tang et al. reported 63% prevalence of AGA among men in Bishan east in a community study.[3] A variety of genetic and environmental factors play a role in causing AGA.[1,4] It results from the conversion

of scalp terminal hair into miniaturized vellus hair in genetically predisposed individuals.[4] The underlying causes of AGA is related to androgens, particularly dihydrotestosterone (DHT).[4]

Zinc is an essential trace element in the body, skin (5%) is the third most zinc abundant tissue after skeletal muscle (60%) and bones (30%).[5] Zinc is essential in various biological functions, including DNA synthesis, gene expression, hormone control, enzymatic reactions, and cell proliferations.[6] In animal experimental models, zinc is an ambivalent and potent modulator of murine hair growth. It accelerates the regrowth of pigmented hair shafts and promotes hair follicles recovery.[7] It influences the function of hair follicle metabolism by inhibiting follicle regression and accelerates follicle recovery.[5] Zinc also possesses antioxidant properties and has been found useful in preventing photodamage and reducing the incidence of malignancies. It has also been demonstrated to possess antiandrogenic properties as it causes modulation of 5 alpha-reductase type 1 and 2 activity, thus promoting hair growth.[8] Zinc is also required in thyroid hormones synthesis, deficiency can lead to hair loss.[9]

The prevalence of zinc deficiency worldwide is estimated at more than 20%.[10] A study of 14770 individuals aged 3-74 years estimated the prevalence of zinc deficiency in the USA at 1-3%.[10] Based on the composite nutrient composition database, International Zinc Nutrition Consultative Group (IZINCG), the estimated country-specific prevalence of inadequate zinc intake for Malaysia was 15-25%.[11]

Several studies reported that zinc deficiency has association with alopecia.[12] A case-controlled study done by Seong Kil et al showed that serum zinc is significantly lower in subjects with alopecia than the control group, with the mean of 87.74 ± 21.2 ug/dl and 97.94 ± 21.05 ug/dl in respective group ($p=0.002$).[13] Another study done by Ozturk et al found that the levels of zinc in hair were significantly lower in the patients with AGA compared to the control group among Turkish ($p<0.05$).[14]

Nutrition affects hair condition, for instance, many studies have shown that the administration of zinc sulfate and other multivitamins could improve hair growth.[15] Unfortunately, the inconsistencies among the findings in previous studies preclude definitive recommendations at present. The zinc level among patients in Malaysia with androgenic alopecia is not known and hence the findings from our study may justify incorporating zinc supplement as adjunct therapy on top of the standard therapy.

Due to the lack of information regarding serum zinc level among AGA and its association with the severity of the disease in Malaysia. Thus, our primary objective of this study was to evaluate the serum zinc levels among men in Malaysia with androgenetic alopecia (AGA) and to compare with controls without AGA. Secondary objective was to assess the relationship of zinc deficiency with disease duration and disease severity.

Materials and Methods

Study Design and Subject Recruitment

This was a case-control study conducted at Dermatology Clinic of Hospital Raja Permaisuri Bainun, Perak, Malaysia from September 2019 to December 2019. Male subjects aged 18 years old and above diagnosed with androgenetic alopecia (AGA) were included using convenient sampling. The diagnosis of androgenetic alopecia was based on the progression of hair loss, family history of hair thinning, visual confirmation of a receding frontal hairline, and the presence of thin and short hairs in the frontal area and vertex. The assessment of the AGA severity was performed by investigators using the Norwood-Hamilton classification.[16] Subjects were then categorized into mild (I and II), moderate (IIA, III, IIIA and IV), and severe (IVA, V, VA, VI and VII) to facilitate analysis.[17] Subjects taking supplements which may alter zinc level, malabsorption disorders (e.g.Inflammatory bowel disease, short gut syndrome, bariatric surgery) and or previously diagnosed with any disease associated with zinc deficiency (e.g. acrodermatitis enteropathica) were excluded. Other causes of hair loss were assessed and ruled out (e.g. telogen effluvium, anagen effluvium and alopecia areata etc). Subjects in the control arm were selected randomly among patients and hospital staffs without alopecia. Control group subject were assessed clinically with detailed history and thorough examination. Any subjects with early signs of AGA e.g.frontal recession were excluded. The controls were age and sex matched. Patient's data collection form was utilized to gather demographic data, significant family history, duration of the disease, presence of autoimmune diseases, if any, smoking, drinking habits and dietary restrictions.

Serum Zinc Sampling and Analysis

5 milliliters (mls) of random venous blood were obtained using lithium heparin tube from all subjects. The estimation of serum zinc was done by atomic absorption spectroscopy technique (AAS), the flame conditions were fixed as recommended by instrument manufacturer, with wavelength of 213.9nm using Argon as fuel, lamp current setting at 440mA at variable lamp position. The values obtained were used as continuous variables with the normal reference range of 70-150 ug/dl.[18,19] Serum zinc were also categorized into normal ≥70 ug/dl and deficient <70 ug/dl. Serum zinc levels of the AGA cohort were compared with the controls and correlated with parameters as shown in the results.

Sample Size Calculations

The sample size of this study was calculated based on the case-control study carried out by Seong Kil et al on Analysis of Serum Zinc and Copper Concentration in Hair Loss.[13] Calculation was performed using PS Power and sample size calculations software Version 3.0, January 2009. The sample size calculated was 70 subjects (35 subjects with androgenetic alopecia and 35 subjects in the control group).

Data Analysis

Descriptive statistics was presented as counts and percentages for categorical variables. All data was tested for normality using the Shapiro-Wilk test. Non- parametric data was expressed as median with interquartile range (IQR), parametric data was expressed in mean with standard deviation (SD). A *p* value <0.05 is considered as statistically significant. Mann-Whitney test was used to compare the difference in zinc level between AGA and healthy controls. The relationship of zinc deficiency with disease severity was analyzed by using Kruskal Wallis H test. The correlation of disease duration (continuous data) and the level of zinc deficiency (categorical data) was analyzed by using Spearman's rank order correlation test.

Ethical Approval

This study was registered with the National Medical Research Registry (NMRR-19-401-46873). Ethical approval for the study was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

Results

Table 1 shows the demographic and clinical characteristics of subjects with AGA and controls. A total of 70 subjects were recruited in the study: 35 subjects in the AGA group and 35 subjects in the control group. The mean age of the patients with AGA and controls was comparable with 45.71 ± 12.78 ug/dl, and 45.69 ± 12.71 ug/dl respectively. There is no significant difference between the two arms in terms of, body mass index, ethnicity, education levels, smoking and drinking habits and diet. There is a higher incidence of autoimmune diseases in AGA arm, two of the AGA subjects had hypothyroidism. *(refer table 1)*

The median serum zinc was lower in AGA group (74.46 ug/dl; IQR 17.17) compared to the control group (80.37 ug/dl; IQR 17.70). Although the median of serum zinc level is lower in AGA group than control group, there is no statistically significant difference of zinc level between both groups (U=596, p=0.846). 42.9% (n=15) of the subjects in AGA group have zinc level less than 70 ug/dl while 31.4% (n=11) subjects in control group have low serum zinc level, however the difference is not statistically significant (*p*=1.0). *(Table 2)*

The mean disease duration among AGA patients is 14.71 ± 9.63 years. In term of disease severity, 48.6% have severe disease, 40% have moderate disease and the remaining 11.4% have mild disease. The relationship between serum zinc level and AGA severity was examined using Kruskal Wallis H test, as the distribution of serum zinc level is not normal. Statistical analysis showed that there is no statistically significant difference of zinc level between patients with different disease severity (H=0.927, *p*=0.629). *(refer figure 1)* In terms of the relationship between disease duration and serum zinc level, Spearman's rank order correlation test was utilised, it showed no statistically significant relationship between AGA disease duration and zinc level (rs=-0.022, *p*=0.901). *(refer figure 2)*

Further sub-analyses show that serum zinc was not affected by BMI, smoking and drinking habits. Older age is not associated with lower serum zinc levels. Association of zinc deficiency and vegetarian diet was unable to assess in this study due to small numbers of vegetarian in the disease group and none were in the control group. *(refer table 3)*

Discussion

The argument that zinc deficiency is a risk factor for hair loss is questionable. Numerous studies have been carried out in the past to evaluate zinc

and AGA. So far, there is no study done in Malaysia to evaluate the role of zinc level and alopecia. The exact mechanism of zinc deficiency and alopecia is not fully understood. A potential explanation was dysregulation of zinc-related metalloenzymes, as zinc is known to accelerate hair growth and inhibiting follicle regression.[5]

In the present study, we found lower median serum zinc among AGA subjects in comparison to the controls, with the median zinc of 74.46 ug/dl (IQR17.17) and 80.37 ug/dl (IQR17.70) respectively. Although the difference was not statistically significant, our finding showed findings consistent with the case-control study done by Kil et al, recruiting 312 subjects with non-scarring alopecia, showing that serum zinc is significantly lower than the control group, with the mean of 87.74 ± 21.2 ug/dl and 97.94 ± 21.05 ug/dl in respective group.[13] A study in Thailand by Aiempanakit et al revealed significantly lower mean plasma zinc levels among both female and male AGA patients than the control group, with the mean of 56.63 ug/dl (11.44 SD) and 63.47 ug/dl (11.10SD) in the respectively group (p=0.002).[20] Sub-analysis in the same study also showed lower zinc among male AGA patients compared to the controls although it was not statistically significant (p=0.09).[20] A recent case control study in Egypt involving 60 AGA subjects noted serum zinc was significantly lower compared to controls, with the mean of 60.26 ± 10.81 ug/dl) and 80.8 ± 6.47 ug/dl respectively (p=0.01).[21] A case control study by Dhaher et al in Iran showed that the mean of serum zinc concentration level in the women with AGA was significantly lower than that observed in the control group (65.6 ± 14.2 µg/dl, 128.4 ± 41.4 µg/dl, respectively) (p<0.05).[22]

In our study, 42.9% (n=15) subjects in AGA group had zinc level deficiency (<70 ug/dl) while 31.4% (n=11) subjects in control group had zinc deficiency. However, the ratio of patients with low serum zinc concentration was not statistically significant (p=1.0). Kil et al revealed that serum zinc was significantly lower in non-scarring alopecia group than in the control group with the mean serum zinc of 84.33 ± 22.88 µg/dl and 97.94 ± 21.05 µg/dl respectively (p<0.03).[13] However, patients with serum zinc concentration lower than 70 µg/dl was only significantly in the AA group.[13] Our study also showed lower median serum zinc concentration among AGA group but the median serum zinc still falls within the normal range (≥70 ug/dl).

Although we expected that zinc levels correlate with the severity of alopecia, but in the present study, we were unable to demonstrate significant correlation of serum zinc level and the disease severity (p=0.629, H=0.927) and disease duration (p=0.901, rs=-0.022). Dhaher et al, a case control study estimating zinc among women with AGA in Iraq also showed no significant correlation between both serum zinc level and disease severity.[22] Another study by El-Esawy et al also showed a non-significant relation between AGA severity and serum zinc level (p=0.485).[21]

Our present study did not attempt to measure zinc concentration in the hair. Hematological analysis using blood sample has been commonly used to determine status of trace elements in the body.[23] The serum level shows current or short-term body status and it tends to fluctuate.[23] Plasma zinc represents only 0.1% of total zinc stores, but its concentration is tightly regulated within a range of approximately 10-15mmol/l. This concentration is often maintained despite fluctuations in zinc intake, unless the changes in zinc intake are severe or prolonged or both.[10] Hair zinc level possibly represents a depot for trace elements and accumulate in hair and possibly more sensitive and more precise.[10] For instance, there were studies measuring hair zinc level carried out in the past. Ozturk et al found that hair zinc level was significantly lower in AGA group (p<0.05) even though they were not able to demonstrate a significant difference in serum zinc levels among Turkish with AGA compared to controls.[14]

Numerus studies showed that administration of zinc sulfate and other multivitamins could improve hair growth. A study by Siavash et al in Iran showed that concomitant use of oral zinc sulfate and pantothenic acid as pulse therapy is effective to increase hair count and hair thickness in women with alopecia.[24] In a randomized-controlled clinical study by Berger in AGA, a considerable hair growth was observed with topical zinc pyrithione 1% solution in androgenic alopecia.[25] In Korea, Hoon et al evaluated therapeutic effects of oral zinc gluconate 50mg/day supplementation for 12 weeks in alopecia areata patients with low serum zinc level. It was shown that 9 (66.7%) out of 15 subjects had positive therapeutic effects after therapy.[26] After the 12-week therapy, the serum zinc levels increased significantly from 56.9 ug/dl to 84.5 ug/dl (p=0.002).[26]

Table 1. Demographic and clinical characteristics of subjects with AGA and control (n=70)

Demographic		AGA (Case), n=35	Control, n=35	*p* value
		n (%)	n (%)	
Age (in years)	20-34	7 (20.0)	7 (20.0)	*0.986*[a]
	35-49	16 (47.7)	16 (47.7)	
	50-64	10 (28.6)	9 (25.7)	
	65 and above	2 (5.71)	7 (20.0)	
Ethnicity	Malay	15 (42.9)	14 (40.0)	*0.879*[b]
	Chinese	14 (40.0)	16 (45.7)	
	Indian	6 (17.1)	5 (14.3)	
Body Mass Index (kg/m^2)	Normal	9 (25.7)	9 (25.7)	*0.35*[a] *0.148*[b]
	Overweight	11 (31.4)	18 (51.4)	
	Obese	15 (42.9)	8 (22.9)	
Education Level	Primary	1 (2.9)	4 (11.4)	*0.204*[c]
	Secondary	18 (51.4)	12 (34.3)	
	Tertiary	16 (45.7)	19 (54.3)	
Vegetarian Diet	Yes	2 (5.7)	0 (0)	*0.493*[c]
	No	33 (94.3)	35 (100.0)	
Smoking	Yes	13 (37.1)	7 (20.0))	*0.202*[b]
	No	15 (42.9)	22 (62.9)	
	Ex-smoker	7 (20.0)	6 (17.1)	
Alcohol	Yes	5 (14.3)	6 (17.1)	*0.743*[b]
	No	30 (85.7)	29 (82.9)	
Autoimmune Disease	Yes	2 (5.7)	0 (0)	*0.054*[c]
	No	33 (94.3)	35 (100.0)	

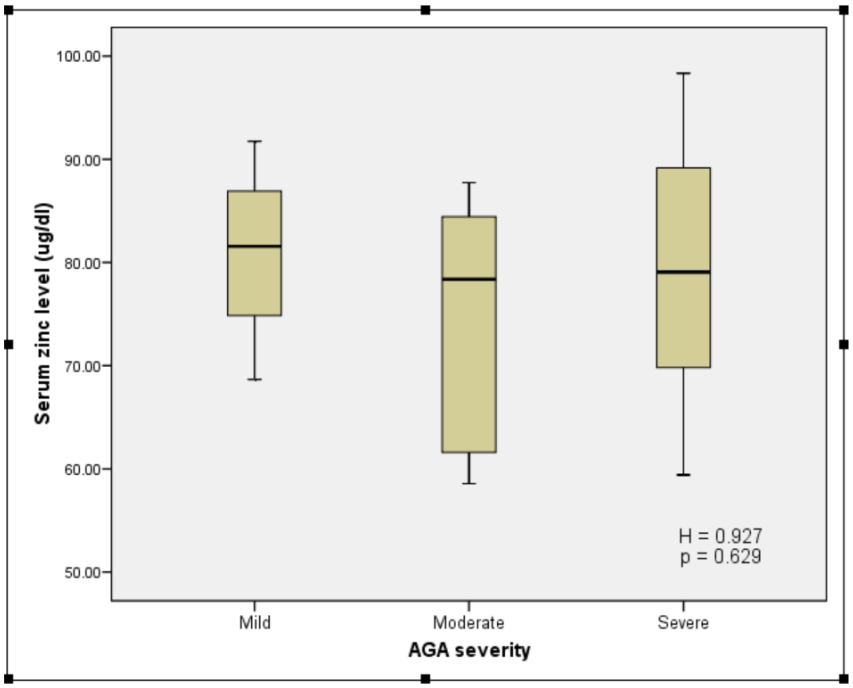
[a]*Mann-Whitney U test;* [b]*Chi-Square test;* [c]*Fisher's exact test*

Table 2. Comparison of serum zinc levels between AGA cohort and controls.

Serum Zinc	Case (n=35)	Control (n=35)	*p* value
Zinc level in ug/dl Median (IQR)	74.46 (17.17)	80.37 (17.70)	*U=596*[a] *p=0.846*
Normal (≥70 ug/dl) Deficient (<70 ug/dl)	20 (57.1) 15 (42.9)	24 (68.6) 11 (31.4)	*p=1.000*[b]

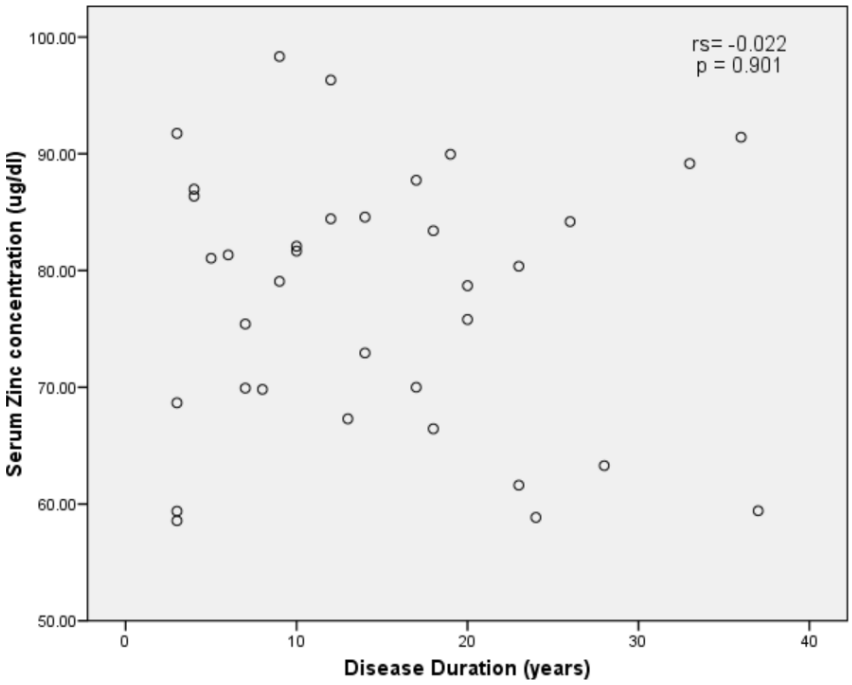
[a]*Kruskal Wallis H test;* [b]*Fisher's exact test*

Figure 1. Correlation between Serum Zinc and disease severity



**Kruskal Wallis H test*

Figure 2. Correlation between Serum zinc level and disease duration



**Spearman's rank order correlation test*

Table 3. Association between socio-demographic factors and levels of serum zinc among AGA group and control group

Factors		Level of Serum Zinc					
		AGA (Case) n =35			Control n =35		
		n	Median (IQR) ug/dl	P value	n	Median (IQR) ug/dl	*p* value
Age (in years)	20-34	7	69.93 (17.76)	0.135[a]	7	91.14 (29.44)	*0.149[a]*
	35-49	16	81.19 (13.26)		16	71.30 (9.86)	
	50-64	10	73.00 (20.28)		9	74.46 (16.17)	
	65 and above	2	90.29 (2.25)		3	82.13 (14.30)	
Ethnicity	Malay	15	72.94 (18.05)	0.100[a]	14	74.36 (17.19)	*0.466[a]*
	Chinese	14	83.80 (10.68)		16	73.45 (18.04)	
	Indian	6	72.71 (19.85)		5	79.78 (47.63)	
	Others	0	0 (0)				
Body Mass Index (kg/m^2)	Normal	9	72.94 (21.39)	0.908[a]	9	73.48 (23.94)	*0.980[a]*
	Overweight	11	78.70 (14.61)		18	74.87 (15.97)	
	Obese	15	81.05 (21.29)		8	76.39 (20.23)	
Vegetarian Diet	Yes	2	74.69 (14.78)	0.670[b]	0	0 (0)	*NA*
	No	33	80.37 (17.42)		35	74.46 (17.17)	
Smoking	Yes	13	75.81 (17.58)	0.866[a]	7	82.13 (25.23)	*0.712[a]*
	No	15	81.67 (20.44)		22	75.34 (22.14)	
	Ex-smoker	7	79.07 (15.52)		6	73.18 (5.78)	
Alcohol	Yes	5	87.74 (10.10)	0.06[b]	6	69.71 (20.83)	*0.126[b]*
	No	30	78.88 (17.17)		29	75.28 (19.85)	

[a]Kruskal Wallis H test; [b]Mann-Whitney U test

The major limitation of this study is a limited sample size. It is a single-center and hospital-based study and may not be truly representative of the whole of Malaysia population. Larger trials are necessary to validate the observation of lower zinc level among patients with AGA and as well as to clarify the advantage of zinc supplementation as adjunct treatment.

Conclusion

In summary, our study showed that zinc level was lower in the AGA group compared to the control group. However, there was no statistical difference between the two groups. There was no correlation between serum zinc level with severity of alopecia and disease duration. At present, evidence to support the use of zinc as supplement in AGA is still lacking. Further studies are required in the

future to justify the need for serum and hair zinc levels monitoring and zinc supplementation in the treatment of alopecia.

Conflict of Interest Declaration

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Association between Vitiligo and Neutrophil-To-Lymphocyte Ratio in Dr Sardjito General Hospital, Yogyakarta, Indonesia

Niken Trisnowati, *PhD*, Angela Mistralina Lukito, *MD*, Yohanes Widodo Wirohadidjojo, *PhD*

Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Dr. Sardjito General Hospital, Yogyakarta, Indonesia

Abstract

Introduction

Vitiligo is an acquired depigmenting disorder, characterized by circumscribed hypomelanosis of the skin and hair. Vitiligo is presumed to be associated with systemic inflammation implied in the presence of metabolic syndrome in vitiligo. This study aimed to investigate the association between vitiligo and neutrophil-to-lymphocyte ratio (NLR) as a biomarker of systemic inflammation and correlations between vitiligo disease severity and NLR.

Methods

This case-control study involved 24 patients with vitiligo and 24 healthy individuals as control group. Inclusion criteria of the vitiligo group were: age 18-40 years-old, having vitiligo for at least 6 months, whereas exclusion criteria were: receiving corticosteroids or other immunosuppressant drugs, having diabetes mellitus or other systemic diseases. In both groups NLR was calculated, whereas in the vitiligo group Vitiligo Area Scoring Index (VASI) and disease duration were examined.

Results

NLR values were higher in the vitiligo group than those in the control group, however the difference was not statistically significant ($p>0.05$). Correlation between VASI and NLR showed a weak correlation, as well as correlation between duration of disease and NLR, but they were not statistically significant ($p>0.05$).

Discussion

The findings of this study possibly suggest an association between vitiligo and NLR, although it was not statistically significant. The relatively small sample size may have contributed to the insignificant statistical results.

Conclusion

Vitiligo was possibly associated with systemic inflammation and NLR could be utilized as a biomarker of systemic inflammation in vitiligo.

Key words: *Vitiligo, non-segmental vitiligo, neutrophil-to-lymphocyte ratio, systemic inflammation*

Corresponding Author

Dr Niken Trisnowati

Department of Dermatology and Venereology,
Faculty of Medicine, Public Health and Nursing,
Universitas Gadjah Mada,
Dr Sardjito General Hospital,
55281 Yogyakarta, Indonesia.

Email: nikentris@ugm.ac.id

Introduction

Vitiligo is an acquired depigmenting disorder characterized by circumscribed hypomelanosis of the skin and hair, resulting in psychological problems and decreased quality of life particularly in racial or ethnic groups with darker skin.[1–3]

Prevalence of vitiligo varies among countries, with 0.05% (claimed-based prevalence) in the United States of America[4] and 8.8% in India,[5] whereas worldwide prevalence is estimated to be 0.5-1%.[6] The prevalence of vitiligo in Indonesia countrywide is not known, but that in Dr Sardjito General Hospital, Yogyakarta, Indonesia from 2015-2018, it was around 1%.

Based on the Vitiligo Global Issues Consensus Conference (VGICC), vitiligo is classified into vitiligo (formerly non-segmental vitiligo/ NSV), segmental vitiligo (SV) and unclassified/ undetermined vitiligo. Vitiligo/NSV is an umbrella term for all forms of generalized vitiligo, where lesions are often symmetrical, increasing in size progressively or during flares. In SV, depigmented lesions are focal or restricted to a segment of the skin, whereas in unclassified/undetermined vitiligo skin lesions are focal but do not fit a segmental distribution.[6] Vitiligo/NSV is more common than SV and has a potential lifelong evolution.[7]

Pathogenesis of vitiligo/NSV is not completely understood, however autoimmunity is considered the key mechanism in this subclass of vitiligo.[7,8] Besides autoimmunity, several hypotheses are proposed to explain the pathogenesis of vitiligo/ NSV, including the adhesion defect theory and the biochemical theory.[8] Vitiligo/NSV is thought to be associated with systemic abnormalities implied in the presence of metabolic syndrome in vitiligo.

Neutrophil-to-lymphocyte ratio (NLR) is a recently found systemic inflammatory parameter, which is calculated by dividing the number of neutrophils by the number of lymphocytes.[9] It is a simple biomarker derived from a patient's complete blood count. Some studies have found that abnormal NLR is associated with autoimmune diseases, for example psoriasis and systemic lupus erythematosus.[10]

Research exploring associations between vitiligo and NLR is still limited. This study aimed to investigate the association between vitiligo and NLR (as a biomarker of systemic inflammation) and correlation between vitiligo disease severity, represented by Vitiligo Area Scoring Index (VASI) and disease duration, and NLR.

Materials and Methods

This case-control study was conducted at the outpatient Dermatology clinic of Dr Sardjito General Hospital, Yogyakarta, Indonesia. Twenty-four consecutive patients with vitiligo were recruited as the case group with inclusion criteria were: patients with age 18-40 years-old, having vitiligo for at least 6 months. Exclusion criteria of the case group were: patients receiving corticosteroids or other immunosuppressant drugs, having diabetes mellitus or other systemic diseases. Twenty-four healthy individuals with age 18-40 years-old were recruited as the control groups. The participants in both groups were matched according to age and gender. This study was conducted in July-August 2019.

Demographic characteristics were recorded from all participants, including gender and age. A total of 5 ml of peripheral blood samples was collected from all participants to examine the complete blood count (including the number of neutrophils and lymphocytes). NLR is calculated by dividing the number of neutrophils by the number of lymphocytes. In the case group, duration of disease and VASI were examined. VASI is a validated assessment tool used to measure the degree of depigmentation of vitiligo. VASI was measured as follows: in each body region, VASI was calculated by the product of the area of vitiligo in hand units (1% per unit) and the extent of depigmentation within each hand unit-measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90% or 100%). Subsequently, VASI of the whole body was calculated using the following formula (possible range 0-100):[11] VASI = ∑ all body site hand units x residual depigmentation

NLR values of the vitiligo and the control groups were compared using student's t test. Correlation between duration of disease and NLR was analyzed using Pearson correlation coefficient, as well as correlation between VASI and NLR. P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistics version 26 software (IBM Corp., Armonk, NY).

Ethical clearance of this study was obtained from the Institutional Review Board of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Results

Twenty-four patients with vitiligo and 24 healthy participants were enrolled in this study. Distribution of demographic, clinical and laboratory results of vitiligo and normal participants were presented in Table 1.

Table 1. Distribution of demographic, clinical and laboratory results of the vitiligo and normal participants

	Vitiligo	Controls	*p*-value
Gender, n (%)			
Female	13 (54.2)	13 (54.2)	
Male	11 (45.8)	11 (45.8)	
Age, mean (SD)	40.8 (14.1)	40.2 (14.2)	
NLR, mean (SD)	2.4 (1.5)	2.2 (0.7)	*0.65*
VASI score, median (IR)	2.6 (2.9)	-	
Duration (months), mean (SD)	43.3 (23.7)	-	

SD standard of deviation; IR interquartile range; NLR neutrophil-to-lymphocyte ratio; VASI Vitiligo Area Scoring Index

In the vitiligo group, there were slightly more female participants than male participants (13 and 11 participants, respectively). Median of VASI was 2.6 ± 2.9, whereas mean of disease duration was 43.3 ± 23.7 months. Results showed the NLR values were higher in the vitiligo group than those in the control group, however this finding was not statistically significant (p>0.05). Correlation between VASI and NLR showed a weak correlation, as well as correlation between duration of disease and NLR, but they were not statistically significant (p>0.05), as presented in Table 2.

Table 2. Correlation between VASI score and disease duration and NLR

	r	*p*-value
VASI score-NLR	-0.02	*0.93*
disease duration-NLR	0.26	*0.22*

r coefficient correlation; NLR neutrophil-to-lymphocyte ratio; VASI Vitiligo Area Scoring Index

Discussion

The findings of this study possibly suggest that there is an association between vitiligo and NLR, which could be seen from the higher NLR values in the vitiligo group compared to that of the control group, even though the difference is not statistically significant. The results tend to show a correlation between vitiligo disease severity, represented by VASI score or disease duration, and NLR, although they are also not statistically significant.

Recently, there were several studies utilizing NLR as biomarker of systemic inflammation in vitiligo. Solak et al. in 2017 showed that NLR values and serum C-reactive protein levels were significantly higher in vitiligo/NSV patients who had generalized vitiligo compared with those with localized vitiligo and controls.[9] Similar results were also observed by Karagun in 2019 who compared NLR values in patients with vitiligo/NSV and controls.[12] However, another study comparing NLR values in vitiligo/NSV and control groups found no significant difference between them.[13]

NLR is an easy to calculate biomarker of systemic inflammation. NLR has been shown to be a potential predictor of systemic inflammation in internal diseases.[14,15] NLR is also associated with disease activity in some immune disorders, including psoriasis,[16] systemic lupus erythematosus[17] and Behcet's disease.[18] There is strong evidence that vitiligo is an autoimmune disease, involving both humoral and cellular immunities. Furthermore, it has been found that several proinflammatory cytokines, including interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-17 are implicated in vitiligo.[19-21] IL-8 in particular, is involved in attracting cytokines to neutrophils.[19] Hence, the chronic pro-inflammatory environment in vitiligo might result in increased numbers of neutrophils and subsequently cause increased inflammation and tissue injury.

There is increasing evidence that vitiligo may be associated with metabolic syndrome which is a systemic disturbance. It has been known that proinflammatory cytokines (TNF-α, IL-1, IL-6) and other inflammatory factors in vitiligo contribute to insulin resistance and other metabolic complications.[22] One study found that insulin resistance and lipid profile disturbance were present in patients with vitiligo.[23] Furthermore, it was shown that decreased number of melanocytes in adipose tissue in vitiligo caused decreased anti-inflammatory reactions and decreased reduction or binding with radical oxygen species.[24] These factors contribute to produce systemic inflammation which has the potential to cause metabolic syndrome characterized by increased insulin resistance, decreased high density lipids (HDL) and increased low density lipids (LDL)/HDL ratio. The findings of our study might support the hypothesis that vitiligo may be associated with systemic inflammation.

We have to mention limitations in our study, mainly relatively small sample size, which might explain the insignificant statistical results observed. In future research, we might consider dividing the vitiligo/NSV participants into those with more generalized and localized types to examine whether different distribution of vitiligo lesion may affect the NLR. It is recommended to measure clinical and biochemical manifestations of the metabolic syndrome, such as blood pressure, waist circumference, insulin resistance, serum lipids, etc., in order to determine

the existence of metabolic syndrome in the patients with vitiligo.

Conclusion

Nevertheless, our study findings may add to other studies exploring NLR as a biomarker of systemic inflammation in vitiligo. The presence of systemic inflammation and metabolic syndrome in vitiligo requires more investigation. As the growing evidence become clear, therapies reducing inflammation are important in patients with vitiligo particularly to prevent metabolic syndrome.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

Nil.

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ORIGINAL ARTICLE

Cutaneous Manifestations in Patients with End Stage Renal Disease Undergoing Hemodialysis

Harish MR, *MD (DVL),* Sriramanan Anandbabu, *MD*, Shashikumar BM, *MD (DVL)*, Deepadarshan K, *MD (DVL)*

Department of Dermatology, Mandya Institute of Medical Sciences, Mandya, Karnataka, India

Abstract

Introduction

End stage renal disease (ESRD) is a decline in the function of the kidneys that usually develops over many years. At least one dermatologic condition is considered to be present in most end stage renal disease patients.

Methods

This is a prospective observational study of 83 patients in dialysis seen in Mandya Institute of Medical Sciences, Mandya. Detailed medical history and demographic data was obtained. A thorough dermatological examination was performed to note the various cutaneous manifestations seen in our patients.

Results

Out of 83 patients enrolled, 81 had at least one cutaneous manifestation (97.6%), 40 had at least one mucosal manifestation (48.2%), 72 had at least one nail change (86.7%) and 27 had at least one hair change (32.5%). The most common cutaneous manifestation was xerosis with 75 patients (90.4%) showing this finding. Xerostomia was the most common mucosal manifestation, seen in 25 patients (64.1%). Nail pallor and absent lunula were the most common nail findings, seen in 60 (83.3%) and 35 (48.6%) patients respectively. Dry, lustreless hair was the most common hair change seen in 18 patients (66.7%).

Conclusion

Xerosis, pruritus, pigmentary changes, nail pallor, absent lunula, xerostomia and dry lustreless hairs were the most common mucocutaneous manifestations in our patients. In order to reduce the morbidity from end stage renal disease specific dermatoses in dialysis patients, long term and regular follow up is required.

Key words*: : End stage renal disease, xerosis, pruritus*

Introduction

Chronic kidney disease is defined as kidney damage or glomerular filtration rate of <60 ml/min/1.73m² for 3 months or more regardless of etiology.[1] This is a global issue with nearly 850,000 deaths every year and 15 million disability adjusted lives.[2] This chronic kidney disease progresses to end stage renal disease over a period of time. Moreover, end stage renal disease patients have a high prevalence of cutaneous manifestations (about 50-100%) during the course of their illness.[3,4] It has been reported that

Corresponding Author

Dr. Shashikumar BM
OPD Room 13, RDL First Floor,
Department of Dermatology,
MIMS, Nehrunagar, Mandya,
571401 India.
Email: shashikumarbm@gmail.com

the prevalence of end stage renal disease is around 17.3% in India.[5]

End stage renal disease has complex consequences because it affects the normal functioning of multiple organ systems. Skin changes are a late clinical manifestation of end stage renal disease. There are two groups of cutaneous manifestations of end stage renal disease divided into specific and nonspecific.[6] Non-specific disorders include pigmentary disorders, pruritus, xerosis, acquired ichthyosis, and half-and-half nail. Specific disorders include acquired perforating dermatosis, calciphylaxis, bullous dermatoses, and fibrosing dermopathy of uremia.[7]

Materials and Methods

This prospective study was conducted in the outpatient Department of Dermatology at Mandya Institute of Medical Sciences, a tertiary care hospital in Mandya after obtaining permission from Institutional Ethics Committee for a period of 6 months from 15th March 2020 to 15th August 2020. During this period, 83 patients who were known cases of end stage renal disease diagnosed at nephrology department/medical department were thoroughly screened by dermatologists for the evidence of any cutaneous manifestations. After taking informed consent, a thorough history was taken and general examination was done. The following were the inclusion and exclusion criteria. The inclusion criteria were patients above the age of 18 years undergoing hemodialysis and patients who were willing to participate and consent for the study. The exclusion criteria included pregnant & lactating women.

The patient's basic demographic data such as age, sex, and a detailed medical history with regard to duration of ESRD, duration of dialysis, duration of skin ailment, onset of changes with relation to diagnosis of ESRD and starting dialysis and improvement noticed following dialysis was recorded. The skin, hair, nails and mucosa were examined in detail for

a. Specific lesions of chronic kidney disease.
b. Presence of cutaneous infections.
c. Associated skin lesions.

The diagnosis and clinical staging of ESRD was as per the National Kidney Foundation severity assessment criteria, and the severity of pruritus and xerosis was graded as mild, moderate, and severe.[1,8,9] Specific investigations like skin biopsy, culture and sensitivity for bacterial infections, Gram's stain, potassium hydroxide mount and fungal culture were done where indicated, after informed consent. Routine investigations for monitoring renal functions were also recorded. Serological testing for HIV, Hepatitis B and C were done in all patients.

Data was entered in MS excel spreadsheet. Descriptive analysis like proportion, mean, standard deviation, etc. were used. Tests to detect significant difference or association like chi square test, etc were used. Data was analysed using SPSS software version 20.

Results

The basic clinic-demographic profile is shown in Table 1. Among 83 patients, there were 48 males and 35 females (M:F = 1.4:1) aged between 21 and 83 (mean +/- SD = 52.3 + 14.6) years. The majority of the patients were in the 41-60 age group. The duration of ESRD ranged from 8 months to 216 months (18 years) with mean duration 62.1 +/- 47.7. Majority of patients had ESRD duration of more than 5 years (43.4%). All patients had undergone hemodialysis for a variable period of time. The duration of hemodialysis ranged from 5 months to 180 months (15 years) (mean +/- SD = 40.6 + 30.4).

The serum creatinine levels ranged from 4.7 to 20.9 (mg/dl) (mean +/- SD = 10.3 + 3.1). The blood urea levels ranged from 39 to 287 (mg/dl) with the Mean and Standard deviation 116.2 + 38.9. Hemoglobin levels ranged from 4.7 to 13 (mg/dl) with the Mean and Standard deviation of 8.3 + 1.63.

Table 1. Basic clinico-demographic characteristics

Age Group (Years)	Female	Male
20-40	13 (65%)	7 (35%)
41-60	13 (36.1%)	23 (63.9%)
61 & above	9 (33.3%)	18 (66.7%)
Total	35 (42.2%)	48 (57.8%)
Duration of ESRD in Months	**Number**	
1-12	10 (12%)	
13-24	11 (13.3%)	
25-36	12 (14.5%)	
37-48	6 (7.2%)	
49-60	8 (9.6%)	
>60	36 (43.4%)	
Total	83 (100%)	
Duration of Dialysis	**Number**	
<6 months	2 (2.4%)	
6 months - <2 years	35 (42.2%)	
2 years - <5 years	26 (31.3%)	
>5 years	20 (24.1%)	
Total	83 (100%)	

A wide variety of etiologies were found in our patients (Table 2). Hypertension and Diabetes were the most common causes of ESRD with 77 (92.8%) and 38 (45.8%) patients affected respectively. None of the patients were positive for Human immunodeficiency virus, Hepatitis B virus and Hepatitis C virus. All patients were receiving atleast one medication including antihypertensives, antidiabetics, diuretics, iron, or vitamins etc.

Table 2. Distribution according to etiology of ESRD

Etiology	Female	Male	Total
Hypertension	34 (44.2%)	43 (55.8%)	77 (92.8%)
Diabetes Mellitus	10 (26.3%)	28 (73.7%)	38 (45.8%)
Polycystic Kidney Disease	3 (75%)	1 (25%)	4 (4.8%)
Ectopic Kidney	0 (0)	2 (100%)	2 (2.4%)
Obststructive Nephropathy	0 (0)	2 (100%)	2 (2.4%)
IgA Nephropathy	1 (100%)	0 (0)	1 (1.2%)
Analgesic Nephropathy	0 (0)	1 (100%)	1 (1.2%)
Kidney Infection	0 (0)	1 (100%)	1 (1.2%)
Glomerulonephritis	1 (100%)	0 (0)	1 (1.2%)
Systemic Lupus Erythematosus	1 (100%)	0 (0)	1 (1.2%)
Single Kidney	0(0)	1 (100%)	1 (1.2%)

One or more mucocutaneous manifestations occurred in 81 of 83 patients (97.6%), although only 48 (57.8%) patients complained of skin problem (Table 3). Xerosis was the most common cutaneous manifestation seen in 75 out of 83 patients (90.4%) (Figure 1a). Among these, 50.7% had mild xerosis, 44% had moderate xerosis and 5.3% were afflicted with severe xerosis. Pruritus was the second most common manifestation that was seen in 43.4% of patients. Among those patients who had pruritus, 77.8%, 13.9% and 8.3% had mild moderate and severe pruritus respectively. Pruritus was unaffected by cold and heat, exacerbated by dry skin and ameliorated by dialysis and sleep.

Table 3. Mucocutaneous manifestations of ESRD patients

Cutaneous Manifestation	Number of Patients
Xerosis	75 (90.4%)
Pruritus	36 (43.4%)
Sun-Exposed Skin Hyperpigmentation	25 (30.1%)
Diffuse Hyperpigmentation	15 (18.1%)
Icthyosis	14 (16.9%)
Yellowish Tinge	5 (6%)
Pallor	4 (4.8 %)
Purpura	3 (3.6%)
Early Wrinkling	1 (1.2%)
Mucosal Manifestation	
Xerostomia	25 (64.1%)
Fissured Tongue	4 (10.3%)
Pigmented Tongue	4 (10.3%)
Macroglossia	2 (5.1%)
Coated Tongue	2 (5.1%)
Aphthous Stomatitis	2 (5.1%)
Nail Manifestation	
Nail Pallor	60 (83.3%)
Absent Lunula	35 (48.6%)
Nail Discoloration	21 (29.2%)
Longitudinal Ridging	20 (27.8%)
Longitudinal Melanonychia	17 (23.6%)
Beau's Lines	17 (23.6%)
Half and Half Nails	14 (19.4%)
Koilonychia	14 (19.4%)
Terry's Nails	9 (12.5%)
Pitting	1 (1.3%)
Hair Change	
Dry, Lusterless Hair	18 (66.7%)
Diffuse Alopecia	9 (33.3%)
Loss of Hair	7 (25.9%)
Sparse Scalp Hair	1 (3.7%)
Sparse Body Hair	1 (3.7%)

Other skin changes seen were sun-exposed skin hyperpigmentation (SH) in 30.1%, diffuse hyperpigmentation (DH) in 18.1%, icthyosis in 16.9% (Figure 1b), yellowish tinge to skin in 6%, pallor in 4.8%, and purpura in 3.6% patients. One patient had early wrinkling. Mucosal abnormalities occurred in 46.9% patients and in the order of frequency were xerostomia in 64.1%, fissured tongue and pigmented tongue in 10% patients each, coated tongue, macroglossia with teeth markings (Figure 1c) and aphthous stomatitis in 5% patients each.

Nail changes in 86.7% patients comprised nail pallor in 83.3%, absent lunula in 48.6%, nail discoloration in 29.2%, Lindsay's nails (half and half) in 19.4% (Figure 4), Terry's nails in 12.5%, Beau's lines in 23.6%, koilonychia in 19.4% patients. Other nail changes included longitudinal ridging in 27.8 %, longitudinal melanonychia in 23.6%, and pitting in one patient respectively. Hair abnormalities in 32.5% patients included dry, lusterless hair in 66.7%, diffuse alopecia in 33.3%, loss of hair in 26%, and sparse scalp hair and sparse body hair in 3.7% patient each.

Discussion

The mean age of CRF patients in the present study is 52.3 which is close to the studies of Sultan MM et al10 (49.5) whereas other studies report lower mean age, such as Singh G et al.[11] (40.5). The differences in these statistics could be due to varied demographic profile of patients enrolled in the respective studies. In the present study, majority of patients (43.4%) belonged to the age group of 41-60 years, followed by 32.5% in above 61 years age

group. Even in the studies of Udaykumar et al.[12], the majority of patients belonged to the age groups of 41-50 and 40-60 respectively. In present study, male preponderance (1.4:1) is seen which is consistent with the studies of Singh G et al.[12] (1.7:1). The most common etiologies of ESRD in our study was hypertension (92.8%) and diabetes (45.8%). The percentage of patients with diabetes in our study is consistent with study of Thomas EA et al (42.4%).[13]

Nunley et al.[3] have found that at least one cutaneous manifestation was present in 50-100% of patients. Cutaneous manifestations in ESRD patients were observed in 97% patients in this study, which correlates with the findings of studies of Pico et al.,[4] who reported skin findings in 100% of his patients. Xerosis, pruritus and hyperpigmentation were the three most common cutaneous manifestations in our patient population, consistent with reports from other studies Robinson et al.[14] Xerosis of variable severity has been well documented in 23-90% patients irrespective of dialysis status.[15] The primary factors likely to have played a role in causing xerosis in our patients might be reduced sebum/sweat excretion, altered skin barrier, reduced emollient usage, and dehydration of the skin.[15] Xerosis was the most common cutaneous manifestation (72%) reported by Khanna et al.[15] We report that 90.4% of our patients had xerosis which was also the most frequent cutaneous manifestation seen. This finding is higher than that seen by Amatya et al.[16] (28%). A possible reason for this discrepancy in the percentage of patients with xerosis might be the prolonged duration of ESRD in most of our patient population. Application of moisturizers can help with the xerosis.

Various studies show the prevalence of pruritus in the hemodialysis patients to be between 19% to 90%.[12] A number of different mechanisms have been proposed to explain the origin of pruritus. One important reason is that Xerosis itself predisposes to pruritus. Other risk factors include male sex, old age, high pre-dialysis level of blood urea nitrogen, and high levels of β2-microglobulin, calcium, and phosphate.[17] The number of patients having pruritus in our study (43.4%) was lower than that of studies by Singh G et al11 where the number of patients having pruritus were 46.7% and 53% respectively. This may be because most of our patients initiate dialysis soon after the diagnosis of ESRD.

In our study, a majority of patients, i.e, 28 (80%), and 24 (68.6%) reported amelioration of pruritus with sleep and dialysis respectively. While heat and cold had no effect on pruritus, dry skin exacerbated itching in 32 (91.4%) patients. The pigmentation in the present study is seen in 30.1% which is similar to studies of Udaykumar et al.[12] (43%). In some other studies, the frequency of skin discoloration was reported between 20% and 80%.4 Pico and coworkers studied 102 patients on hemodialysis, in whom skin discoloration was the most common finding.[4] Melanocyte Stimulating Hormone (MSH) accumulates due to failure of kidney function and this may be the reason for pigmentation. The most severely affected areas were the extremities and photo-exposed areas. We did not find any correlation between the incidence of pigmentation abnormality and duration of hemodialysis. However, Pico and colleagues noticed a decrease in pigmentation with increasing duration of dialysis.[4] They postulated this to be due to reduced exposure to sunlight and the chronicity of the disease.

It is important to acknowledge that assessment of skin color is dependent on the subjective factors such as accuracy of the examiner's visual ability and objective factors like the type and intensity of the environment light. In order to prevent a wrong diagnosis, color meter reflectance can be used for the examination.[18] Sun avoidance is important for reducing the incidence of pigmentation. In the present study pallor of the skin is evident in only 4.8% patients which is less when compared to studies of Sultan MM et al.[10] (45%). In studies of Falodun O et al.[19] pallor was seen in 2.5% which is nearer to our present study. In present study purpura is seen in 3.6% of patients which is lower than that in studies of Thomas E A et al. (10%).[13]

Xerostomia in 62.5% patients was the most common mucosal abnormality. Some studies indicate that fissured tongue affects 4-8% ESRD patients and up to 20% of the general population, but was seen in only 10% of our patients.[20] The various triggers for this could be nutritional deficiencies, poor oral hygiene, smoking, consumption of alcohol or hot/spicy foods.[21] Macroglossia with teeth markings was seen in 5% patients and this is usually seen in 9-43% cases and is considered characteristic of uremia.[11] Proper mouth hygiene will help prevent such mucosal changes.

Nail pallor in 83.3% patients was the most common finding consistent with its reported prevalence of 67% in ESRD patients and 96% in patients on hemodialysis.[22] Absent lunula was observed in

48.6% patients and reportedly occurs in 17-63% patients irrespective of dialysis status.[21] Lindsay's nails also known as half and half nails are characterized by a proximal white part and a distal reddish pink part that does not fade on pressure. These two zones show a sharp demarcation between them. Half-and-half nail in our study was observed in 19.4% of the patients, while others reported it in 7% to 39% of the patients.[12]

In the majority of our patients, hairs were normal (67.5%). 66.7% of our patients had dry, lusterless hairs, 33.3% had diffuse alopecia. Only one patient each had sparse scalp and sparse body hair. Dry lustreless hair may be attributed to decreased secretion of sebum. The numbers of patients having hair changes were more in present study compared to that of Falodun et al (2.5%).[19] The reason for this may be due to associated anemia in the present group. Udaykumar P et al.[12] found sparse body hair (30%), sparse scalp hair (11%) and brittle and lusterless hair (16%) in his study. In study of Sultan MM et al.[10] reported brittle and lusterless hair in (47%), sparse scalp hair (46%) and sparse body hair (27%). Hajheydari Z et al6 noticed scalp alopecia in 9.9%, drying and hair fragility in 2% and hair discolouration in 2% of patients.

There were 8.4% cases of skin infection in our study. Pico and colleagues reported infections in 70% of the patients.[4] Sultan et al. reported an incidence of 33% for fungal infections[10] and Udaykumar et al. reported bacterial infections in 13% of cases.[12] Additionally, in this study, no case of metastatic calcification, bullous dermatosis, or acquired perforating dermatosis was observed. In other studies, 2% to 21% of the patients were found to have acquired perforating dermatosis.[12] The complete lack of ESRD specific findings can partially explained by the specific etiologies of ESRD seen in our patients. Most of our patients had hypertension as the etiology of ESRD. It is probable that due to this, we did not record any such findings.

Short duration and the cross-sectional nature of the study are some of the limitations of this study.

Figure 1. (a) Xerosis; (b) Icthyosis; (c) Macroglossia with teeth markings; (d) Half and half nails

Conclusion

The number of patients presenting with mucocutaneous manifestations in our study far outnumbered those that actively complained of a skin problem. This indicates that cutaneous manifestations can be subtle and not noticeable by the patient. By actively looking for skin changes in this patient population, we can avoid the progression of such changes with better management. Hypertension was the commonest etiology noted. Patients with a severe grade of xerosis were significantly lower compared to mild and moderate grades. This might be attributable to effect of early hemodialysis which could have prevented the progression of xerosis severity. Xerosis, pruritus, pigmentary changes, nail pallor, absent lunula, nail discoloration, xerostomia and dry, lusterless hairs were the most common mucocutaneous manifestations in the majority of studied patients. Lifelong follow-up is needed to reduce the morbidity from dermatoses considered ESRD/hemodialysis specific that may appear over time. We observe that future studies are needed for a better determination of the various mucocutaneous manifestations seen in ESRD patients.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

Nil.

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ORIGINAL ARTICLE

Psoriasis and Metabolic Syndrome in Rural India: Case Control Study

Priyanka Date, *MD*, Sonia Jain, *MD*

Department of Dermatology, Venereology and Leprosy, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, Maharashtra, India

Abstract

Introduction

Psoriasis is a chronic, common, inflammatory disorder of the skin and joints. Globally Metabolic Syndrome (MS) is found to be significantly associated with psoriasis but there is a paucity of data from rural in Indian literature. The aim of this study is to study the association of metabolic syndrome (MS) with psoriasis and the relationship between its severity, duration of the disease and presence of MS in patients of psoriasis of rural setting.

Methods

A prospective, hospital-based case-control study was carried out consisting of 65 psoriasis cases and 65 healthy controls within duration from November 2016 to August 2018 started after ethical clearance from institute with detailed written consent from both cases and controls. MS was diagnosed by the presence of ≥3 criteria of the South Asian Modified National Cholesterol Education Program Adult Treatment Panel III Criteria (SAM NCEP ATP III). Statistical analysis was done by descriptive and inferential statistics using chi-square test and software SPSS 22.0 version, EPI Info version 7 and Graph Pad Prism 6.0 version.

Results

Metabolic syndrome was significantly more common in psoriatic patients than controls (35.38% vs 18.46%, P=0.004). Cases also had significantly higher prevalence of hypertriglyceridemia (32.31% vs 17.91%), hypertension (43.08% vs 26.57%) and impaired fasting plasma glucose levels (33.85% vs 14.93%). MS was significantly correlated to the disease severity irrespective of the disease duration.

Conclusion

Metabolic syndrome is more frequent in patients with psoriasis. This study highlights the need of screening of all psoriatic patients for early diagnosis and treatment of associated MS.

Key words: *Psoriasis, metabolic syndrome, hypertriglyceridemia, hypertension*

Introduction

Psoriasis is a chronic inflammatory disorder of the skin and joints that affects 2% of the population and poses a lifelong burden for those affected.1 Association of psoriasis and other disorders associated with psoriasis are interlinked by a common pathway of presence of raised levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[2]

Metabolic Syndrome (MS) is defined as a

Corresponding Author
Priyanka Date
Department of Dermatology, Venereology & Leprosy,
Mahatma Gandhi Institute of Medical Sciences,
Sewagram, Maharashtra,
442102 India.
Email: priyankadate16@gmail.com

constellation of abdominal obesity, increased insulin resistance, elevated fasting glucose level, decreased high-density lipoprotein cholesterol, hypertriglyceridemia, and hypertension.[3] It is shown that patients with psoriasis have an increased risk of developing cardiovascular disease (CVD) and metabolic syndrome in comparison to non-psoriatic patients.[3] The main hypothesis for an association between psoriasis and CVD and its risk factors is increased systemic inflammation and is a complex of several reasons such as unhealthy lifestyles due increased likelihood of smoking, little physical activity and obesity.[4] CVD risk factors like diabetes, hypertension and hyperlipidaemia have been associated with psoriasis and remedies of psoriasis like cyclosporine and methotrexate.[5] Thus many factors may confound the association between the two disorders.

However only few studies have highlighted on this association, prominent being Zindancı et al6 and few Indian studies like the one conducted in South India by Madanagobalane in 2012,[7] using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. There is enigma regarding the association of psoriasis and metabolic syndrome and if so, by what magnitude. None of the Indian studies have data from rural population. Recent studies have estimated a prevalence of 15% to 24% for MS in the general population.[8,9]

Because the implications of the metabolic syndrome over healthcare are substantial and psoriasis being a common disorder, we have undertaken this study to assess the prevalence of the metabolic syndrome and its associated components among individuals with psoriasis in a rural hospital in Central India. By doing this we as dermatologists can help in early diagnosis and also contribute in pharmacologic as well as non-pharmacologic management for our patients.

Materials and Methods

Patients Selection

It was a prospective, case control study, performed in a rural tertiary care hospital of India from November 2016 to August 2018. Study was approved by Institutional ethical committee.

We included biopsy proven psoriasis patients of more than 18 years of age, with disease duration of at least 6 months and who had not received any systemic treatment for at least 1 month as cases. Patients less than 18 years of age, disease duration of <6 months and patients with systemic treatment within past 1 month were kept as exclusion criteria for cases. To avoid bias in the study we selected age and sex matched controls from same study population. We have taken healthy relatives accompanying patients in outdoor patient department (OPD) as controls.

Study Procedures

Informed written consent from adult research participants, 65 psoriatic patients and 65 age and sex matched controls were taken. We collected data by pre–prepared questionnaire which include demographic details, age of onset, duration and progression of psoriasis, percentage body surface area (BSA) of involvement, psoriasis area severity index (PASI) were noted. Composite score of PASI has been calculated as mild = 0-7, moderate = 8-12 and severe = ≥12.[7]

In the personal history cases were asked about habits of smoking and alcohol and it's relation with psoriasis (whether the habit started before, after or at the same time of the disease onset), the number of cigarettes smoked daily as well as duration and amount of alcohol consumption of the patients who had alcohol consumption habit. Same data is noted in control group also.

Blood pressure (BP) was measured as per standard protocol. Venous blood samples collected after 8 hours of fasting were evaluated for fasting blood glucose, HDL and triglyceride levels. Metabolic syndrome was diagnosed by South Asian Modified National Cholesterol Education Program Adult Treatment Panel III criteria (SAM NCEP ATP III),[9,12] If three or more of the following were present, the patient was diagnosed as having MS:

1. Abdominal obesity as waist circumference (≥102 cm for males and ≥88 cm for females)
2. Blood pressure >130/85 mmHg
3. Fasting blood glucose ≥100 mg/dl
4. Hypertriglyceridemia >150 mg/dl or
5. Low HDL cholesterol (<40 mg/dl for males and <50 mg/dl for females).

Statistical Analysis

Sample size of 108 (54 cases and 54 controls), were calculated using Software Open EPI-with 95% Confidence Interval, power 80% and alpha-5%.[10] We included 130 patients (65 cases and 65 controls) as results will be more conclusive as sample size increases.[11] Collected data was analysed by using

descriptive and inferential statistics using chi square test and software SPSS 22.0 version, EPI Info version 7 and Graph Pad Prism 6.0 version and p<0.05 was considered as level of significance.

Results

Demographic and disease characteristic of the study population is summarized in Table 1. In present study, we found male preponderance. Maximum patients were in the age group of 38-47 years (23 patients). Out of 65 cases 12 were smokers, all of them were males and started smoking before the onset of disease. Of the smokers, 8 (66.6%) males smoked 1-10 cigarettes daily; and 4 (33.3%) males smoked 11-40 cigarettes daily. Among controls 10 were smokers and all of them smoked 1-10 cigarettes daily.

There was no significant association of smoking with metabolic syndrome among cases as well as controls. The ratio of alcohol use was 23 (35.38%) vs 12 (18.46%) among cases and controls.

There was a significant association of psoriasis with metabolic syndrome p=0.029, ϰ2-value = 4.73, Odds ratio = 2.41, 95% CI = 1.07-5.42, Relative risk = 1.48, 95% CI = 1.07-2.06. Correlation of metabolic syndrome with duration of psoriasis in cases was not statistically significant. *(p value 0.72)*

The mean percentage BSA of cases having psoriasis and Metabolic syndrome was 22.9%. PASI of <8 were taken as mild psoriasis and ≥8 was set to define both moderate to severe psoriasis. 20 out of 23 patients with metabolic syndrome had PASI of more than 8, thereby making the difference statistically significant with a P-value of 0.0001. (Refer Table 4) Out of 23 cases, 12 (52.17%) were taking 6 drinks per week and 11 (47.82%) were taking 4 drinks per week, all the cases were male, and they had been drinking alcohol before the onset of disease. In contrast, out of 12 (18.46%) controls all of them were drinking <4 drinks per week, since 10-15 years and all were males. As MS is not significantly seen in alcoholic drinker cases as compared to controls, in our study we can say that alcohol intake is not a confounding factor for MS. (Refer Table 5)

Body mass index (BMI) of cases and controls shows no significant difference (*p*=0.86), maximum cases as well as controls has BMI <23 and mean BMI of 22.62 ± 4.19 among cases (Table 6). Our study shows no significant association of metabolic syndrome with waist circumference.

Table 1. Sociodemographic characteristics of the participants

Characteristics	Cases	Controls	*p*-value
Sex M*/F†	48/17	46/19	*0.69*
Age, Mean ± SD‡	43.89 ± 14.48	42.24 ± 13.13	*0.79*
Smokers	12 (18.46%)	10 (15.38%)	*0.70*
Alcohol Consumption	23 (35.38%)	12 (18.46%)	*0.004*
Metabolic Syndrome	23 (35.38%)	12 (18.46%)	*0.004*
Waist Circumference >102 cm(M)* or >88 cm(F)†	26 (40%)	26 (38.81%)	*0.88*
Triglyceridemia >1.7 mmol/l (150 mg/dl)	21 (32.31%)	12 (17.91%)	*0.006*
HDL <1 mmol/l (40mg/dl)(M)* or <1.3 mmol/l (50 mg/dl)(F)†	25 (38.46%)	10 (14.93%)	*0.0002*
Blood Pressure >135/85 mmHg	28 (43.08%)	18 (26.67%)	*0.017*
Fasting Plasma Glucose >6.1 mmol/l (>100 mg/dl)	22 (33.85%)	10 (14.93%)	*0.0018*

**M:Male,†F: Female ,‡SD-Standard deviation*

Table 2. Metabolic syndrome in cases and control groups compared by odds ratio

Metabolic Syndrome	Cases	Controls	ϰ2-value	Odds Ratio
Metabolic Syndrome	23 (35.4%)	12 (18.5%)	4.73 *p*=0.029	OR†=2.41 95% CI§=1.07-5.42 RR‡=1.48 95% CI§=1.07-2.06
Non Metabolic Syndrome	42 (64.6%)	53 (81.5%)		
Total	65 (100%)	65 (100%)		

†OR: Odds ratio, ‡ RR: Relative risk, §CI: Confidence interval

Table 3. Correlation of metabolic syndrome with duration of psoriasis in cases

	Duration of Disease			Total
	<1 year	1-5 years	>5 years	
Metabolic Syndrome	7 (30.43%)	7 (30.43%)	9 (39.13%)	23 (35.38%)
Non Metabolic Syndrome	11 (26.19%)	17 (40.48%)	14 (33.33%)	42 (64.62%)
Total	18 (27.69%)	24 (36.92%)	23 (35.38%)	65 (100%)
ϰ2-value	0.64, *p*=0.72			

Table 4. Correlation of metabolic syndrome and its components with PASI score

Metabolic Syndrome and Its Components	PASI* <8 Mild	PASI* ≥8 Moderate to Severe	*p*-value
Metabolic Syndrome	3 (4.62%)	20 (30.77%)	*0.0001*
Waist Circumference >102 cm(M)† or >88 cm(F)‡	7 (10.77%)	20 (30.77%)	*0.0005*
Triglyceridemia >150 mg/dl	5 (7.69%)	16 (24.62%)	*0.0012*
HDL <40 mg/dl(M)† or <50 mg/dl(F)‡	5 (7.69%)	20 (30.77%)	*0.0001*
Blood Pressure >135/85 mmHg	6 (9.23%)	22 (33.85%)	*0.0001*
Fasting Plasma Glucose >100 mg/dl	6 (9.23%)	16 (24.62%)	*0.0026*

**PASI: Psoriasis area severity index, †M: male, ‡F: female*

Table 5. Metabolic syndrome in alcohol drinkers in two groups

Metabolic Syndrome	Cases	Controls	ϰ2-value	Odd's Ratio
Metabolic Syndrome	9 (39.1%)	3 (25%)	0.69 *p*=0.40	OR*=1.92 95% CI‡=0.40-9.10 RR†=1.23 95% CI‡=0.77-1.95
Non Metabolic Syndrome	14 (60.9%)	9 (75%)		
Total	23 (35.38%)	12 (18.46%)		

**OR: Odds ratio, †RR: relative risk, ‡CI: confidence interval*

Table 6. Distribution of patients in cases and control group according to Body mass index (BMI-kg/m2)

Body Mass Index (kg/m2)	Cases	Controls	ϰ = value
<23	37 (56.92%)	37 (56.92%)	0.29 *p*=0.86
23-24.9	11 (16.92%)	13 (20%)	
≥25	17 (26.15%)	15 (23.08%)	
Total	65 (100%)	65 (100%)	
Mean±	22.62 ± 4.19	22.46 ± 3.82	

Discussion

Metabolic syndrome as a whole is a strong predictor of cardiovascular risk, rather than its individual components which includes central obesity, atherogenicdyslipidemia, hypertension and glucose intolerance.[13]

Mean age of patients in our study was (43.89 ± 14.48 years) in concordance with Khungar et al.[14] and Gelfand et al.[15] We found male preponderance with male to female ratio of 2.8:1 similar to Nisa et al.[16] and Gangaiah N et al.[17] We found that not only MS but its individual components are also significantly correlated with psoriasis. 35.38% of psoriasis patients had MS whereas only half of control patients i.e. 18.46% suffered from MS which is statistically significant (*p*=0.004). Madanagobalane S et al.[7] and Nisa et al.[16] also reported statistically significant results (*p* value <0.05).

We found statistically significant correlation of triglyceride levels (32.31% vs 17.91%; *p*=0.006) similar with Madanagobalane et al,[7] hypertension in psoriatics as 43.08% (*p*=0.017) consistent with Nisa et al.[16] and diabetes (33.85% vs 14.93%; *p*=0.0018) consistent with Gangaiah et al[17] and Nisa et al.[16] However, Madanagobalane et al.[7] found highly significant prevalence of 81% between psoriasis and diabetes. All the parameters of the MS were significantly correlated in our cases except waist circumference. The mean BMI of both cases and controls were 22.62 ± 4.19 and 22.46 ± 3.82 respectively.

The objectives of our study are fulfilled, showing that the prevalence of MS is more in psoriasis patients than general population, as well as to establish a correlation of duration and severity of

psoriasis with MS. Psoriasis acts as an independent risk factor for MS irrespective of its duration but with increasing severity definitely the chances of MS increases. Hence, psoriasis is a definitive risk factor for development of MS.

Our study was conducted in a rural set up and data from rural source is meagre in literature. We included all biopsy proven cases and took age and sex matched controls from same set up to reduce chances of bias are the strengths of our study. We have not taken occupational history into consideration, is a limitation of our study, as sedentary lifestyle can also be one of the risk factors for MS. Our study interprets that psoriasis has a strong association with MS. Although psoriasis increases morbidity but MS increases both morbidity as well as mortality. We should be highly vigilant regarding MS in psoriasis cases. Advanced investigations like carotid intima-media thickness, TNF alpha, IL-6 levels and echocardiography should also be done if facilities are available.

Conclusion

Through our study we want to convey that in future screening for MS should be a compulsory tool for all psoriasis patients as they have set up an alarming situation due to strong and definite correlation with MS.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowlegdement

Nil.

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CASE REPORT

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis Overlap as a Presentation of Acute Cutaneous Lupus Erythematosus

Wen Foong Tan[1], *MRCP*, Sook Yee Michelle Voo[1], *AdvMDerm*, Sandhya Rajaintharan[2], *MPath*

[1]Department of Dermatology, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia
[2]Department of Pathology, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia

Summary
Stevens Johnson/toxic epidermal necrolysis-like (SJS/TEN-like) acute cutaneous lupus erythematosus (ACLE) is a life-threatening condition with similar presentation to SJS/TEN. Herein, we report a case of a lady who presented to us with SJS/TEN like ACLE.

Key words: *Stevens Johnson syndrome/toxic epidermal necrolysis overlap, acute cutaneous lupus erythematosus, interface dermatitis*

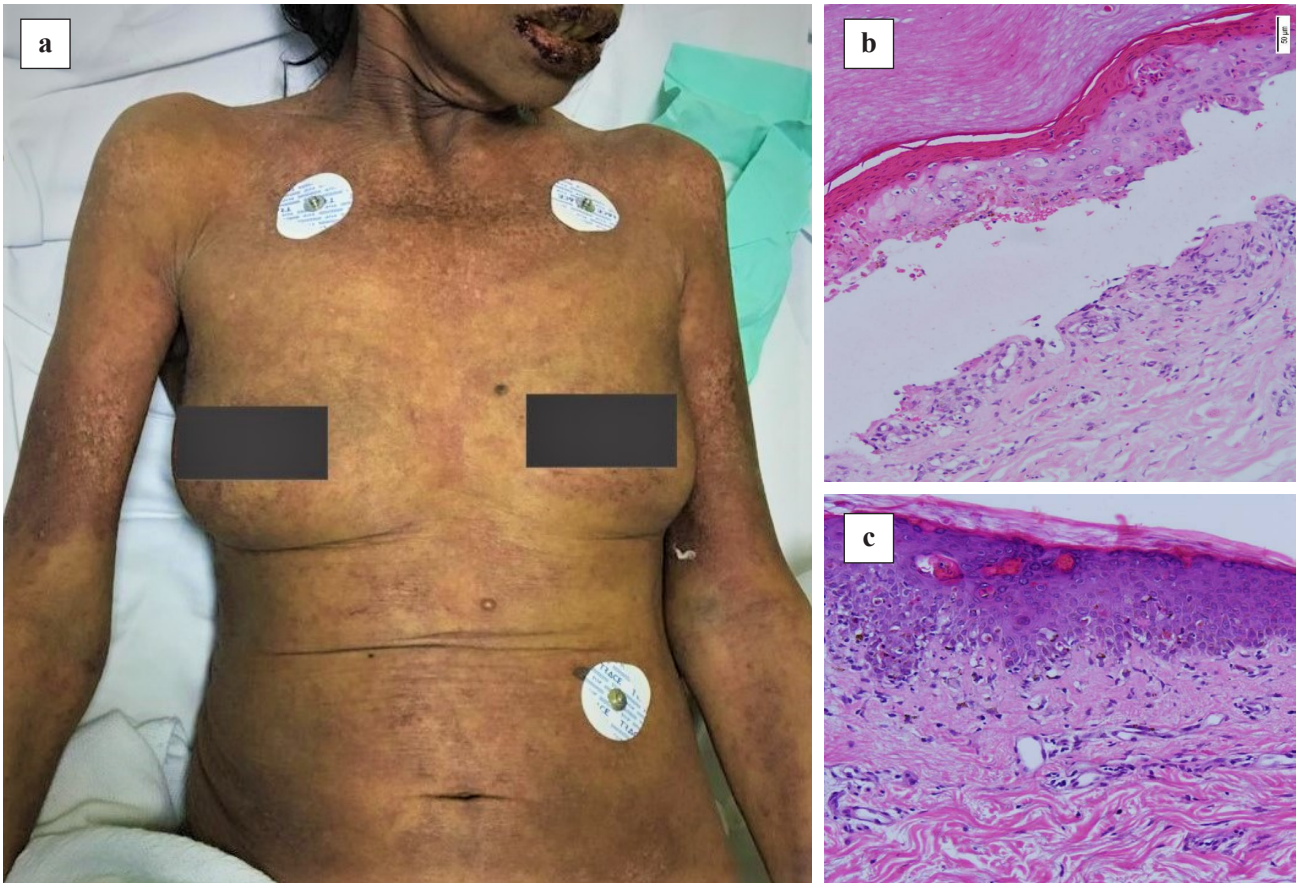
Introduction
SJS/TEN-like ACLE is a rare entity that has been described in recent years. The main distinguishing features include no recent precipitating infection or drug ingestion, subacute onset, involvement of photo-distributed area, strongly positive antinuclear antibodies (ANA) and suggestive histological and immunological findings.

Case Report
We present a case of a 55-year-old lady with 2 days history of severe conjunctivitis, oral mucositis and painful erythematous patch and bullae over her palms and soles associated with fever. Prior to this, she had generalised itchy rash at the trunk and limbs for the past 2 months. There were no preceding respiratory, musculoskeletal, gastrointestinal or genitourinary symptoms. There was no significant history of recent drug ingestion except for vitamins. There was no previous history of similar episode.

Examination revealed a frail lady with diffuse mild non-scarring alopecia, purulent conjunctivitis, extensive haemorrhagic cheilitis with mucositis and generalised purpuric patch over her trunk and limbs (Figure 1a). She also had purpuric macules over her upper and lower limbs with tender bullae over her palms and soles. Nikolsky's sign was negative. There was no genitalia involvement. There was no lymphadenopathy and examination of the respiratory, cardiovascular and abdominal systems were unremarkable.

Corresponding Author
Dr Tan Wen Foong
Department of Dermatology,
Hospital Queen Elizabeth,
2029, Karung Berkunci,
88586 Kota Kinabalu, Sabah, Malaysia.
Email: wftan85@gmail.com

Figure 1. (a) Purpuric patches over trunk and limbs with haemorrhagic crusting on lips; (b) Full thickness epidermal necrosis with subepidermal split (Hematoxylin & Eosin x100); (c) Dyskeratotic cells in all layers of epidermis, basal vacuolar degeneration with mild perivascular lymphohistiocytic infiltrate (Hematoxylin & Eosin x100)



Laboratory investigations revealed bicytopenia (haemoglobin 9.5 g/dl, platelet 102x103 /µL) with lymphopenia (0.55x103 /µL), and raised C-reactive protein 55.3 mg/L. Liver function tests were deranged (AST275 U/L, ALT209 U/L, ALP454 U/L, GGT275 U/L) with hyperbilirubinemia, hypoalbuminemia (albumin 16 g/L) and coagulopathy (INR1.94). Her ANA was positive with a titre of >1:1280 and her complements were low (C3-0.4 g/L, C4-0.09 g/L). However, dsDNA, anti-smith, anti-Ro and anti-La antibodies were negative. Hepatitis B, C, HIV and mycoplasma serology were also negative.

A skin biopsy taken from the left sole and abdomen for histopathological examination showed full thickness epidermal necrosis (Figure 1b) and dyskeratotic cells in all layers of epidermis, with vacuolar interface dermatitis and perivascular lymphohistiocytic infiltrate (Figure 1c) respectively. Direct immunofluorescence (DIF) study showed granular deposition of IgG, IgM and C3 at the basement membrane zone.

She was diagnosed with SJS/TEN-like ACLE in view of a blistering rash which progressed to full epidermal detachment, characteristic histological and DIF findings, no history of recent drug ingestion with cytopenias, hypocomplementemia and positive ANA.

She was started on intravenous hydrocortisone 100mg 8 hourly and antibiotics for presumed infection. She was co-managed with rheumatology, gastroenterology, ophthalmology and dental team. Oral hydroxychloroquine 200mg was added. Cutaneous involvement progressed over the next 5 days with epidermal detachment involving 27% body surface area (BSA) which subsequently re-epithelialized.

Discussion

SJS/TEN-like lupus is an uncommon manifestation of ACLE. This condition is triggered by exposure to ultraviolet (UV) light in an individual with SLE predisposition which leads to keratinocyte apoptosis.[1] This condition must be differentiated from SJS/TEN induced by drugs or infection, which also occurs more commonly in patients with SLE.[2] Other differentials to consider include bullous LE, TEN-like acute graft versus host disease (GVHD)

Table 1. Differential diagnoses to consider[8-12]

Characteristics	SJS/TEN	SJS-TEN-like ACLE	Bullous LE	TEN-like acute GvHD	TEN-like Pseudoporphyria
Onset	Acute - hours to days	Subacute - days to weeks	Acute	Subacute - days to weeks	Subacute
Comorbid/ Etiology	Drugs (80%), rarely infection	Triggered by UV, may have underlying lupus	Unknown	Recent history of bone marrow transplant	History of ingestion of nonsteroidal anti-iflammatory drugs or photosensitising drug with UV exposure, in a patient undergoing hemodialysis
Skin manifestations	Painful, purpuric macules and patches with blistering	Purpuric macules and patches with blistering, photo distributed areas	Tense bullae at photo distributed area	Morbilliform eruption with predilection for acral areas and upper trunk, folliculocentric pattern, pruritus	Extensive area of flaccid bulla, with epidermal sloughing
Mucosal Involvement	Present	May be present	May be present	Present	Present
Systemic involvement	Present	May be present	May be present	May be present (gastrointestinal/ hepatobiliary involvement)	May be present
Autoimmune serology	Negative	ANA, dsDNA, anti-Ro, rheumatoid factor may be positive	ANA, anti-Ro, anti-La, rheumatoid factor may be positive	Negative	Negative
Histological findings	Full thickness epidermal necrosis with subepidermal separation, sparse to absent lymphocytic infiltrate	Full thickness epidermal necrosis with subepidermal separation, moderate to dense superficial dermal lymphocytic infiltrate at perivascular and periadnexal areas, interface dermatitis and mucin deposition	Subepidermal blister with neutrophils, vacuolar interface dermatitis with mucin deposition	Keratinocyte apoptosis, basal layer hydropic degeneration, band-like lymphohistiocytic infiltrate in upper dermis	Subepidermal bullae with minimal perivascular lymphocytic infiltrate, festooning of the dermal papilla
Direct Immunofluorescence	Negative	Granular IgG, IgM, and/or C3 may be present at dermoepidermal junction (DEJ)	Linear or granular IgG, IgM, IgA and C3 at DEJ	Negative	May have granular deposits of C3 and IgG at DEJ
Treatment	Stop the offending drug, IVIg, Systemic corticosteroids, cyclosporin	Systemic corticosteroids, immunosuppressants	Dapsone, systemic corticosteroids	Systemic corticosteroids, immunosuppressants	Stop the offending drug, sun protection

and TEN-like pseudoporphyria.

The distinctive feature in both SJS/TEN and SLE is keratinocyte apoptosis. In SJS/TEN, the pathogenesis is postulated to be due to cytotoxic T cell damage mediated by granzyme, granulysin, perforin and Fas-fas ligands interactions.[3] In cutaneous lupus, UV exposure leads to keratinocyte apoptosis, increased chemokine production and subsequent activation of autoreactive T cells.[4,5] Fas expression is also upregulated in ACLE.[5,6]

Most of the patients with SJS/TEN-like ACLE are middle-aged females with the onset of rash preceding epidermal detachment for days up to 2 weeks. Up to half of the patients have no prior diagnosis of SLE.[2] The rash may initially be photo-distributed, then become generalised.[7] Earlier studies have reported that mucous membranes were usually spared,[2,8] however a recent case series by Tankunakorn et al. reported that half of the patients had severe mucositis. In their cohort, palms and soles involvement were also noted.[4] Lee HY et al. also reported presence of oral mucositis in his patients with no genital or perineal involvement.[5] Similarly, our patient had blistering rash over her palms and soles with haemorrhagic mucositis and conjunctivitis.

Serological markers for SLE such as ANA, anti-Ro, anti-La, anti-dsDNA, anti-ribonuclear protein (anti-RNP) and anti-smith antibodies were commonly present in patients with SJS/TEN-like ACLE. In addition, high disease activity is denoted by hypocomplementemia, elevated ESR and organ involvement in these patients.[2] Histological findings

are summarised in Table 1.

Management of SJS/TEN-like ACLE involves hospitalisation with administration of high dose corticosteroids or pulse therapy. Corticosteroids were used in most cases to control the disease activity of ACLE.[5,9] In extensive cases, intravenous immunoglobulin (IVIG) has been successfully used. IVIG blocks the interaction of Fas-Fas ligand, halting the process of keratinocyte apoptosis.[9] For refractory cases, plasmapheresis which has been used to remove circulating autoantibodies and immune reactants, has led to treatment success.[2,9]

Conclusion

This rare condition must be considered in patients who has no clear precipitating drug history with multisystem involvement as prompt recognition and early treatment with systemic corticosteroids is associated with good prognosis.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CASE REPORT

Acne Fulminans Sine Fulminans

Nidhi Yadav, *MD*, Sumit Kar, *MD*, Pooja Bonde, *DDVL*, Pooja Manwar, *MBBS*, Komal Ramteke, *MBBS*, Safa Patrick, *MBBS*

Department of Dermatology, Venereology and Leprosy, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, Maharashtra, India

Summary

Acne fulminans is a rare and most serious form of acne. It is characterized by the sudden onset of nodular and ulcerative acne lesions with systemic symptoms. It can be triggered by initiation of isotretinoin however these patients do not have systemic involvement. Some authors have recognised this entity as "pseudo-acne fulminans" or "acne fulminans sine fulminans," We report a case with these features of pseudo-acne fulminans.

Key words: *Acne fulminans, acne vulgaris, pustules, nodules, scarring, acne fulminans sine fulminans, pseudo-acne fulminans*

Introduction

Acne fulminans is uncommon and severe complication of acne vulgaris. Its onset is rapid associated with painful erosions and haemorrhagic crusts. In most severe cases it manifests as fever, arthralgia and osteolytic lesions. Pseudo-acne fulminans is one entity which does not show these features. Isotretinoin is most common cause of acne fulminans. For combating this unusual but serious complication low dose steroids should be started along with isotretinoin.[1,5]

Case Report

A 17-year-old female patient presented in Skin OPD with a clinical picture of macro-comedones which later progressed to pustule-nodular lesions on face and chest. History of application of topical steroid was present. We started patient on topical clindamycin 1% and adapalene 0.1% for 3 weeks; due to no response to treatment with topical medications, she was prescribed azithromycin 500 mg pulse therapy along with topical medications for next 3 weeks but patient did not improve. We shifted her to oral isotretinoin 20mg (0.3mg/kg/day) for another 15 days. After 15 days of isotretinoin, the girl returned with severe ulcerative crusting acne and nodular acne over face and chest (Figure 1a & 1b). There was no history of fever, arthralgia or other systemic symptom and the laboratory parameters remained within normal limits.

Gram stain and pus culture report showed growth of MRSA after 48 hours of incubation. Isotretinoin

Corresponding Author

Prof Dr Sumit Kar

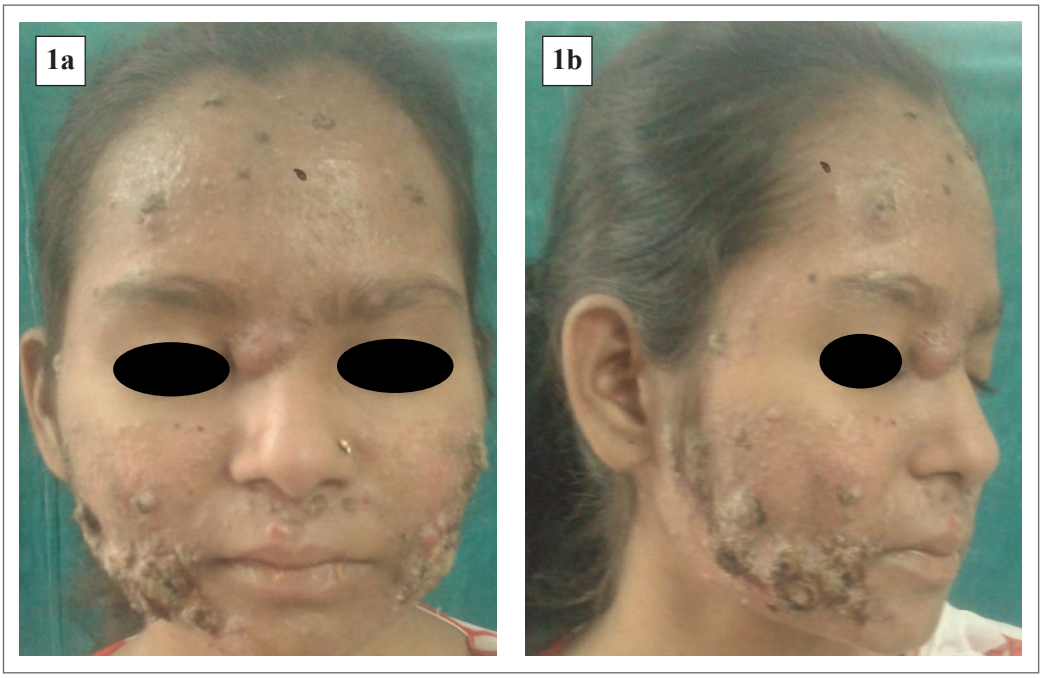
Department of Dermatology, Venereology & Leprosy, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Maharashtra, 442102 India.

Email: karmgims@gmail.com

was stopped. Later she was started on tab prednisone 1mg/kg/day and injectable ceftriaxone for 7 days but no improvement was seen after 7 days of injectable antibiotic. After 7 days intralesional triamcinolone acetonide (2.5mg/ml) was given daily for next 7 days with oral prednisolone following which dramatic improvement was recorded with decreased crusting and size of nodulocystic acne. He was maintained on topical adapalene and clindamycin later. But within a week, it was followed by eruption of new pustular and ulcerative crusting acne. As patient was not satisfied with the above treatment she visited another dermatologist and was prescribed with oral doxycycline 100 mg twice daily for 2 weeks but no improvement was seen. Again patient visited us and was prescribed Tab linezolid 600 mg twice daily for 3 days with prednisolone (1mg/kg/day). Oral linezolid was stopped after 3 days and she was maintained on low dose oral prednisolone for next 3 months.

We followed up the patient after every 7 days and tapered off the steroid dose by 5 mg in each visit. Oral prednisolone was tapered by 5 mg after every 7 days. After 3 days of this therapy (Oral linezolid with oral prednisolone) there was significant improvement. Later patient was followed up till completion of treatment with oral steroid (3 months). Since the patient had complete resolution of lesions with antibiotic and steroid we did not consider reintroducing oral isotretinoin to the patient.

Figure 1a & 1b. Multiple nodular lesions and ulcerative lesions with adherent crusting over face



Discussion

Acne fulminans (AF) is a rare and severe form of acne vulgaris. AF was initially labeled acne maligna or acute febrile ulcerative acne conglobota. The term acne fulminans was first coined by Plewig and Kligman in 1975.[1] Young males are affected most commonly.[2] It is characterised by abrupt onset of nodular and ulcerative crusting acne. It is associated with systemic symptoms like fever, myalgia, arthralgia and osteolytic lesions.

Most common site is trunk mainly back, however face and chest can be involved, Initial lesions are usually sterile may get infected secondarily during progression.[2] Acne fulminans presents as abrupt onset of nodular and ulcerative crusting acne in a patient having mild to moderate acne vulgaris.

Burns and Colville[3] has proposed five criteria for the diagnosis of acne fulminans:

1. Sudden onset of lesions;
2. Severe ulcerated acne which determine cicatricial lesions;
3. Systemic symptoms like fever and polyarthralgia;
4. Absence of response to antibiotics;
5. Favourable response to corticosteroid therapy

Pseudo-acne fulminans, also known as acne

fulminans sine fulminans occurs in patients started on isotretinoin. These patients usually do not have systemic symtoms. The etiology of acne fulminans is not yet clearly elucidated. Risk factor include, hereditary, bacterial infections, drugs and immunological mechanisms have been proposed as its triggering factors.[4]

Various drugs have also been proposed as a triggering factor for the development of this entity. It includes isotretinoin, tetracycline and testosterone[1,4]. Of note, acne fulminans is a rare complication of oral isotretinoin therapy. Isotretinoin causes increased fragility of epithelium of pilosebaceous ducts leads exposure of Propionobacterium acne to systemic environments. This leads to exaggerated type III and IV hypersensitivity reactions in some patients.[5]

A common characteristic to virtually all patients was the presence of macro-comedones and use of oral isotretinoin before the onset of the clinical picture. Use of topical steroids may further lead to thinning of their follicular wall.[6] To avoid development of this troublesome condition in patients with macro-comedones, early introduction of prednisone with a dose of 0.5 or 1.0 mg/kg/day for 4-6 weeks slowly decreasing later on.[4,6]

As far as isotretinoin induced acne fulminans is concerned, isotretinoin should be discontinued and should be started only when the inflammation decreases. Isotretinoin should be restarted at a very low dose of 0.25-0.5 mg/kg/day; dose of isotretinoin can then be increased and corticosteroid gradually tapered off. Oral antibiotics are usually ineffective. But In our case, pus culture sensitivity reports showed MRSA and we saw improvement without restarting low dose isotretinoin, we decided to maintain patient on low dose steroids only.

Conclusion

Pseudo-acne fulminans presents with abrupt onset of flare of inflammatory acne with ulceration and crusting of nodules or plaques without systemic symptoms triggered by initiation of isotretinoin. Awareness of this entity among dermatologists is important so that appropriate measures can be taken in the patients at risk of developing this entity when starting isotretinoin.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CASE REPORT

Concurrent Occurrence of Papulonecrotic Tuberculid and Erythema Nodosum: A Case Report

Safa Patrick, *MBBS*, Sumit Kar, *MD*, Nidhi Yadav, *MD*, Nitin Gangane, *MD*, Abhay Deshmukh, *MD*, Priyanka Date, *MD*, Ajinkya Sawant, *MBBS*

Department of Dermatology, Venereology & Leprosy, Mahatma Gandhi Institute of Medical Sciences. Sewagram, Maharashtra, India

Summary

Despite having a large national and international burden of tuberculosis, still only one single case report has been published on papulonecrotic tuberculid with erythema nodosum. Herein we are reporting a case of 40-year-old female who presented with both papulonecrotic tuberculid and erythema nodosum type of lesions.

Key words: *Papulonecrotic tuberculid, erythema nodosum, tuberculosis, panniculitis, lichen scrofulosorum*

Introduction

Many types of hypersensitivity reactions to Mycobacterium tuberculosis antigens have been described but few entities such as papulonecrotic tuberculid and lichen scrofulosorum are classified as true tuberculids. Papulonecrotic tuberculid (PNT) generally presents as an asymptomatic and chronic disorder. The lesions of PNT tend to occur in crops. An underlying focus of tuberculosis is usually present.[1] Most commonly the lesions of papulonecrotic tuberculoid are distributed symmetrically over the extensor aspect of extremities, face and ear.[2] A characteristic feature of this condition is that the lesion heals with varioliform scarring. Erythema nodosum (EN) is clinically the most frequent form of panniculitis and is triggered by a wide variety of stimuli. We are reporting this case report as only one case report has been published on concurrent papulonecrotic tuberculid and erythema nodosum until now.

Case Report

A 40-year-old female patient presented with recurrent crops of tender; erythematous nodules present symmetrically over extensor aspect of both lower limbs over past six years. After three months, she developed multiple crusted papulo-pustular lesions over the extensor aspect of both upper limbs (Figure 1a). She also gave a history of fever and arthralgia. There was no history of any substance abuse.

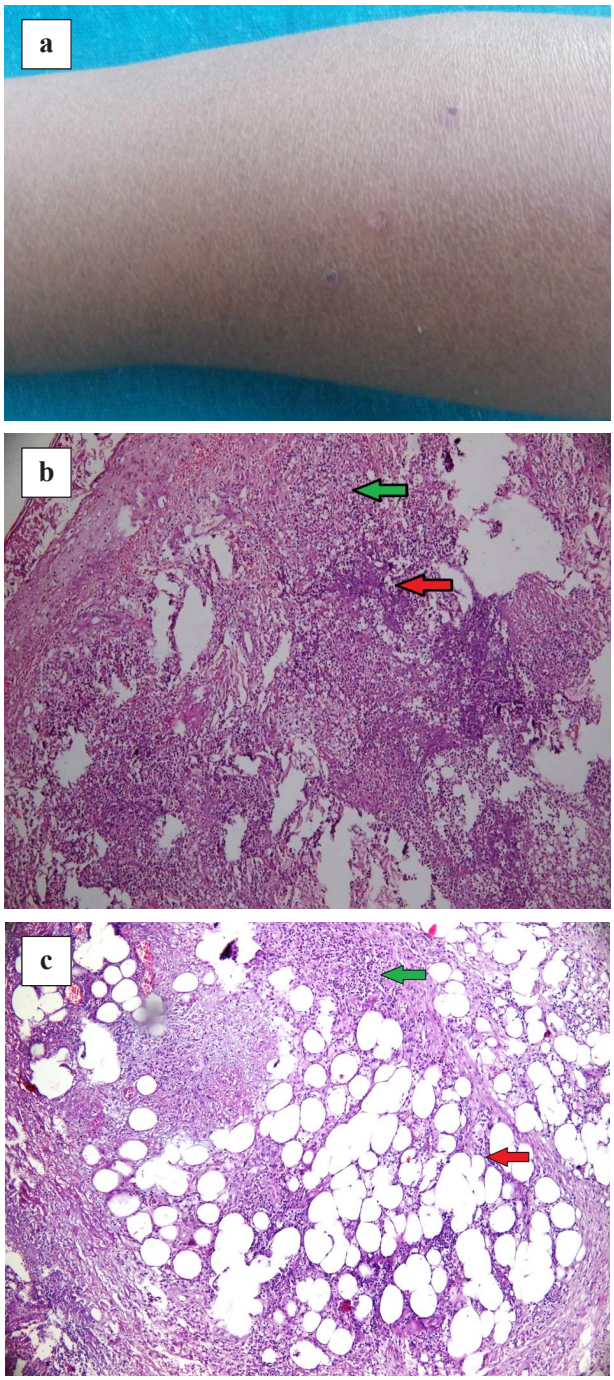
Corresponding Author

Prof Dr Sumit Kar

Department of Dermatology, Venereology & Leprosy, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Maharashtra, 442102 India.

Email: Karmgims@gmail.com

Figure 1. (a) Photograph showing papular lesions with crusting over forearm; (b) Section showing an area of necrosis in dermis (red arrow) surrounded by granulomatous infiltrate and giant cells (green arrow) (H&E, 400x); Section showing septal panniculitis (red arrow) with superficial and deep perivascular inflammatory lymphocytic infiltrate (green arrow) (H&E, 400x)



Review of systems revealed no No history of cough or dyspnea. There was also no history of past tuberculosis. There was hilar lymphadenopathy with consolidation in upper lobe of right lung detected on Chest X-ray. Erythrocyte sedimentation rate was elevated at 110 mm/hr. Sputum examination for acid fast bacilli was negative. Slit skin smears for acid fast bacilli were negative.

A skin biopsy was done from both types of lesions and it confirmed the lesions histopathologically to be consistent with erythema nodosum and papulonecrotic tuberculid (Figure 1b & c). Histological findings of papulonecrotic tuberculid included an area of necrosis in dermis surrounded by granulomatous infiltrate and giant cells. Histological findings of erythema nodosum included a septal panniculitis with a superficial and deep perivascular inflammatory lymphocytic infiltrate. A biopsy sample was also sent for AFB culture, which returned as negative.

She was empirically started on category 1 antitubercular treatment (ATT) based on her Chest X-ray findings and raised ESR levels. A rapid response to anti-Tuberculosis treatment as expected with tuberculids was seen after initiating the treatment.

Discussion

The concept of tuberculids was introduced by Darier in the year 1896. Tuberculids traditionally include Papulonecrotic tuberculid (PNT), lichen scrofulosorum and erythema induratum of Bazin.[3] It is mostly seen in females. Its pathophysiology is still not clear. A hypersensitivity reaction to tuberculosis antigens from a distant focus of infection is thought to be held responsible for the papulonecrotic tuberculid.[4,5]

Main diagnostic criteria for PNT include absence of mycobacterial organisms in skin culture and smear, a positive tuberculin test and rapid resolution of lesions with the start of Antitubercular treatment. Erythema nodosum typically presents as painful, erythematous nodules on the anterior aspect of the legs. Sometimes the lesions may be ecchymotic too. This condition is mostly idiopathic but can occur secondary to internal diseases, medication or many other conditions. EN is also thought to be a hypersensitivity reaction to antigens associated with a wide variety infection such as tuberculosis, streptococcal infections, Yersinia enterocolitica, Y. pseudotuberculosis, cat scratch disease, tularemia and acute upper respiratory tract infections.[6]

PNT seems to be the least common form of cutaneous tuberculosis reported even in area endemic for cutaneous tuberculosis. Co-existence of PNT and lichen scrofulosorum has been reported previously in 4 case reports[7,8,9,10] but only one case report has been published on concurrent papulonecrotic tuberculoid and erythema nodosum to date.

Conclusion

Based on the present case, PNT and EN lesions can coexist with distinct uncommon clinical findings. Therefore, a high index of suspicion is needed for early diagnosis.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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