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REVIEW

Review of Current Leprosy Programme and Achievement in Malaysia

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Summary:
Leprosy is still a relevant public health concern in Malaysia. Efforts made to eliminate leprosy go beyond the elimination phase. Aspects that need to be taken into consideration include disability prevention, rehabilitation and ensuring maintenance of skills for diagnosing and treating the small number of new cases that will continue to occur. This review article discussed about the experiences of the past, achievement at present and the future challenges during the implementation of National Leprosy Control Program in Malaysia.

Key words: *Leprosy, Hansen's disease, National Leprosy Control Program, Malaysia*

Introduction

Leprosy control programme in Malaysia was started in 1969 when the National Leprosy Control Centre (NLCC) was built in Sungai Buloh, Selangor. With the implementation of multidrug therapy (MDT) in 1985, the prevalence of leprosy was reduced from 5.7 per 10,000 population in 1983 to 1.7 per 10,000 in 1992.[1] Malaysia has managed to eliminate leprosy in 1994 when the prevalence was less than 1 case per 10,000 population. In 1994, the incidence was 1.7 per 100,000 population.[2] This achievement was maintained throughout the years and in 2016, the prevalence was 0.1 case per 10,000 population and incidence was 0.6 per 100,000 population.[3]

In East Malaysia such as Sabah, where the earth terrain can pose logistic problems contributed to as high as 30% of the yearly total case load in Malaysia. The overall leprosy control in Malaysia was good with a prevalence of 0.7 case per 10,000 population from 1999. However, the prevalence of leprosy in districts like Kudat, Lahad Datu, Kota Kinabalu and Semporna were more than one case per 10,000 population.[4] In 2016, Tawau, Lahad Datu and Kota Kinabalu were still having a lot of new cases of leprosy.[3]

In some publications, leprosy is now quoted as one of the neglected tropical disease in Southeast Asian Nations (ASEAN).[5,6] However in Malaysia, it is not a neglected disease as many programmes are still active either in the Ministry of Health lead by TB/Kusta sector, individual state public health, health centers and public hospitals with resident or visiting dermatologists. Active case detection is still on-going through screening of contacts, rapid survey programmes in pockets of endemic areas especially among the indigenous community and screening of foreign workers.[7]

Increasing number of foreign workers in Malaysia is one of the significant contributing factors to the persistent cases of leprosy. In year 2015, as high as 40.5% of the notified leprosy cases were foreigners.[2] This factor contributes to the transmission of disease among local population although there are also active transmission among the Malaysians. Another important indicator for active transmission in the community is the new cases that were detected among children. There were 22 and 11 children diagnosed with leprosy in 2014 and 2015 respectively in Malaysia. Of the 11 children with leprosy in 2015, 8 had grade 2 deformity.[2] With grade 2 deformity, the patient may have either poor eye sight (<6/60 or unable to count fingers at 6 meter), lagophthalmos, iridocyclitis, opaque cornea or obvious limbs deformity.[7]

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National Leprosy Control Program in Malaysia

The national strategic plan for leprosy programme in Malaysia for 2016-2020 has been published in 2017 and uploaded for reference.[2] The main objectives include achieving elimination status in certain district areas, to achieve less than 2 per 100,000 population of grade 2 deformity and no children with grade 2 deformity. Hopefully by 2020, we can achieve all the objectives outlined in the national strategic plan which is in line with the World Health Organisation (WHO) global leprosy strategy 2016 to 2020.

Diagnosis of Leprosy

Mouse footpad (MFP) culture is considered relevant in Malaysia as many dermatology clinics in various states are still sending MFP culture to determine the resistance pattern of *Mycobacterium leprae*. The MFP cultures of 651 patients with borderline lepromatous and lepromatous leprosy which were sent to the Leprosy Unit, National Public Health Laboratory, Sungai Buloh between 1997 to 2013 were retrospectively studied.[8] Earlier, Jamil A et al reported a 22.1% intermediate and high level dapsone resistance between 1997 and 2008.[9] Low level resistance was observed in 31% of cases. Dalawi I et al in our latest study reported dapsone resistance rate of 55% (32.3% with low degree of resistance), clofazimine resistance rate of 23.5% and rifampicin resistance rate of 2.9%.[8] Rifampicin, clofazimine and dapsone are being used in the MDT regime for the treatment of leprosy for many years and therefore continuous monitoring of drug resistance is important to ensure that these antibiotics can still be used in MDT regime.

The molecular methods for detection of mutations in *Mycobacterium leprae* associated with dapsone, rifampicin and fluoroquinolone resistance are not yet widely provided in Malaysia. However, it is available in the National Public Health Laboratory in Sungai Buloh to support the diagnosis of leprosy via the detection of *Mycobacterium leprae* using PCR-based gene amplification assays on skin biopsy specimens.[10] Missense mutations in the DNA region of *folP1*, *rpoB* and *gyrA* were found to correspond to resistance to dapsone, rifampicin and quinolones respectively using the gold standard mouse footpad cultivation.[11,12] However, there is none to test on resistance to clofazimine and minocycline. Minocycline is being used for second line treatment. Due to this matter, MFP is still revelant and the knowledge and skill still need to be maintained.

MDT Treatment

Multidrug therapy regime in Malaysia was started since 1985 with the use of Sungai Buloh Augmented MDT (SBA-MDT) which was modified by the Malaysian National Leprosy Control Centre. It consisted of an initial intensive phase of 3 weeks or until the morphological index was 0 in multibacillary leprosy. It was then followed with a longer duration of treatment subsequently. For paucibacillary (PB), the treatment was 1 year and for multibacillary (MB), the treatment was 3 years or until the bacteriological index was 0. Based on the results of the paper published by Yap et al in 2012 which compared the treatment outcome and side effects of SBA-MDT and WHO-MDT, the MDT regime was modified to shorter period.[13] Now the treatment for PB consist of 600mg rifampicin monthly and 100mg dapsone daily for a six months duration. For MB, the regime consists of 600mg rifampicin and 300mg clofazamine monthly with 100mg dapsone and 50mg clofazamine daily for twelve months for BI < 4 and 18 months for BI >4.[7]

Yap FBB et al reviewed patients' records treated from 1985 to 2009 and found a relapse rate of 1.7% with SBA-MDT and 1.4% with WHO-MDT (p = 0.79). For multibacillary leprosy, the relapse rate was 0.9% with SBA-MDT and 0 with WHO-MDT (p = 0.32). For paucibacillary leprosy, it was 3.1% and 5.0% respectively (p = 0.52). The relapse interval ranges from 3 months to 59 months[13]. Longer period of surveillance is important for future reference in determining the success of treatment regime especially when the duration of MDT is getting shorter and the BI of patients are still positive after completed MDT. It is also important as there may be a rise of resistant rate in the future when the first line antibiotics have not changed since MDT was first introduced.

Besides the Ministry of Health and some public universities who play a big role in controlling this disease, none profit organisation such as Malaysian Leprosy Relief Association (MaLRA) which was formed in 1959 is still assisting the older generation of leprae patients with various deformity in their old age. They provide financial aids for various amenities such as wheelchair, walking sticks, artificial limbs and many more including rehabilitation services which covers the medical, social and vocational assistance.[8]

Conclusion

Malaysia National Leprosy Control Program is running in line with WHO recommendation and target. MDT services have been integrated within the general health services. However, an effective referral system needs to be maintained at an appropriate level to deal with problems which may need specialized care. Continuous education and training are crucial to ensure the continuity of quality care.

Conflict of Interest Declaration

The author has no conflict of interest to declare.

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ORIGINAL ARTICLE

Retrospective Analysis of Patch Test Results Between 2011 and 2013 in Hospital Selayang, Malaysia

Fei Yin Ng[1], *AdvMDerm,* Wan Ahmad Kamal Wan Syameen Afira[2], *AdvMDerm*, Logesh A/P Sinnaiyah[2], *MD*, Hazfaneza Bt Ab Halim[2], *MPH*, Rohna Ridzwan[2], *MRCP*

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Abstract

Introduction:
Patch test is the gold standard diagnostic test for contact allergy. Periodic analysis of the trend of contact allergy provides a valuable guide to clinicians. We aim to study the pattern of contact allergy in adults at Hospital Selayang.

Methods:
This is a retrospective review of patch test data in adults suspected with allergic contact dermatitis between January 2011 and December 2013 at Hospital Selayang.

Results:
There were 705 subjects with 247 males (35%) and 458 females (65%). At least 1 positive reaction was detected in 546 (77.4%) subjects patch tested with European Baseline Series (EBS) and additional series. The top 5 common allergens in the EBS were nickel sulfate (28.7%), cobalt chloride (13.6%), paraben mix (11.6%), balsam of peru (10.6%), and potassium dichromate (10.5%). Among those patch tested with rubber additives series, the top 3 allergens were N,N-Diphenylguanidine (DPG), N-Cyclohexyl-N-phenyl-4-phenylenediamine (CPPD), and N-Cyclohexylthiophthalimide. Of the top 5 common allergens in the group tested with fragrance series, all except *Ylang ylang* oil were components of fragrance mix I. Among the subjects tested with fragrance series, the top 5 common allergens were individual components of fragrance mix I and *Ylang ylang* oil.

Conclusion:
A multicentre study would reflect better the pattern of allergen exposure of the nation. Further evaluation of the prevalence of contact allergy to DPG, CPPD, N-Cyclohexylthiophthalimide and *Ylang ylang* oil would guide the need to incorporate these allergens in routine testing along with EBS.

Key words: *Allergic contact dermatitis, Patch test, European baseline series, Additional series*

Introduction

Allergic contact dermatitis (ACD) is a delayed, cell-mediated hypersensitivity reaction to a substance in a previously sensitized person. Patch test is the gold standard investigative method to aid in establishing the diagnosis. Patch test is routinely preformed using a standard series supplemented with the additional series when required. Various regional standard series have been constructed in different regions of the world. Periodic review of allergen trends is

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necessary to understand the local epidemiology and detect changes in the community allergen exposure from the past.

This study aimed to review the allergen trends in the European baseline series and the additional series in Hospital Selayang between the year of 2011 and 2013.

Materials and Methods

This is a retrospective review of the patch test results performed on patients attending the Dermatology Clinic from January 2011 till December 2013. The information were retrieved from the medical records. All subjects were patch tested with European baseline series. Additional series were applied to subjects based on clinical judgement from the history taking. The allergens were products of Chemotechnique Diagnostics. The allergens were applied on the subjects using Finn chambers. Reading of patch test reactions was performed on day 3 and day 5. Patch test results were interpreted according to the recommendation of the International Contact Dermatitis Research Group (ICDRG). The data were analyzed using SPSS version 21.

Results

A total of 705 patients suspected with allergic contact dermatitis were patch tested. The subjects' age ranged from 3 to 87 years. The patient demography is shown in table 1. Hand eczema was the most common presentation of suspected contact allergy.

Table 1. Patients Demographic and Characteristics

Characteristics	Frequency, n (%)
Age, mean	35.9
Gender	
Male	247 (35.0)
Female	458 (65.0)
Ethnicity	
Malay	363 (51.5)
Chinese	241 (34.2)
Indian	95 (13.5)
Others	6 (0.8)
Site of dermatitis	
Hands	154 (21.8)
Feet	117 (16.5)
Hand and feet	93 (13.2)
Face	65 (9.2)
Trunk	38 (5.4)
Various combinations	238 (33.8)

The sensitization rate of patch testing with both the European Baseline Series and additional series was 77.4%. Among the subjects tested with European Baseline Series alone, 466 (66.1%) had positive reaction to at least 1 allergen. There were 61 subjects (8.7%) who reacted positively to the additional series exclusively. The frequently utilized additional series were rubber additives series (462), shoe series (191), plastic and glue series (169), fragrance series (144), cosmetic series (136) and textile and dye series (111).

Table 2. Top 10 common allergens in the modified European Baseline Series

Allergen	Frequency of tested Positive, n (%)
Nickel sulfate	202 (28.7)
Cobalt chloride	96 (13.6)
Paraben mix	82 (11.6)
Balsam of peru	75 (10.6)
Potassium dichromate	74 (10.5)
Formaldehyde	49 (7.0)
Cl+Me-isothiazolinone	46 (6.5)
Neomycin sulfate	45 (6.4)
Colophony	45 (6.4)
Para phenylenediamine	37 (5.2)

We analyzed further the top 5 common allergens of both rubber additives and fragrance series. Among those with positive reaction to the rubber additives, 60% were female subjects. Similarly, two-thirds of the subjects who reacted to the fragrance series were females. The main sites affected in rubber sensitization were hands (27.0%), feet (20.0%) and hands and feet combination (18.4%). Fragrance sensitization had a similar distribution: hands (22.2%), hands and feet combination (20.4%), feet (13.0%).

Table 3. Top 5 common allergen of Rubber Additives Series

Allergen	Frequency of tested Positive, n (%) N=462
N,N-Diphenylguanidine, DPG	51 (11.0)
N-Cyclohexyl-N-phenyl-4-phenylenediamine, CPPD	17 (3.7)
N-Cyclohexylthiophthalimide	17 (3.7)
Tetramethylthiuram monosulfide, TMTM	16 (3.5)
N-Isopropyl-N-phenyl-4-phenylenediamine, IPPD	14 (3.0)

Table 4. Top 5 common allergen of Fragrance Series

Allergen	Frequency of tested Positive, n (%) N=144
Cinnamic alcohol	28 (19.4)
Ylang ylang oil	21 (14.6)
Cinnamic aldehyde	17 (11.8)
Eugenol	16 (11.1)
Isoeugenol	14 (9.7)

Discussion

Apart from confirming the suspected allergens elicited from detail history and physical examination, patch test also had an important role in unveiling the hidden causal allergens.[1,2] Fleming et al. had demonstrated that clinical history alone could only provide accurate allergen identification in half the cases.[3] Positive reaction to an allergen is an evidence of previous sensitization and may not necessarily indicate the source of current dermatitis. Understanding the possible pitfalls of patch test along with cautious interpretation is of practical importance.[4,5]

The available patch test standard series consist of a mixture of common allergens based on the statistics. Research groups periodically review and update the standard series, which expand with time. Variations in the standard series among nations are related to the regional differences in exposure.

In contrary to the historical belief that standard series can detect 70-80% of the allergic contact dermatitis cases,[6] a large European multicentre trial involving 4824 patients revealed a wide range of sensitivity between 37 and 73% using standard patch test series.[7]

There is always a tendency to underdiagnose contact allergy when testing with standard series alone. The essential role of supplementary allergens or series have been evaluated. Previous data had demonstrated that 7-40% of contact allergies would have been missed without the supplementary allergens. [8,9]

Alongside with our study, How et al[10] performed a 5-year retrospective review of contact allergy in another tertiary centre within the nation. The rate of positive reaction to at least 1 allergen were similar (76.6% vs 77.4%). Using additional series improved the detection of contact allergy in both centres. We had a higher proportion of cases with at least 1 positive reaction to the additional series allergens but negative reaction to EBS (11.6% vs 4.5%). Nickel sulfate was the top most common allergen in both centres. Among the top 10 allergens, both centres shared 8 common allergens. Paraben mix and formaldehyde which were present in our list of top 10 common allergens were taken over by fragrance mix I and II in our counterpart.[10] Being a multiracial nation, this differences in patterns of contact allergy can be explained by the diversity of the cultural practices and the distribution of ethnic groups in various regions.

We compared our results with other the studies from Singapore, China and the United States of America (Table 5). The standard series were not identical. Nickel sulfate which is widely used in cosmetic jewelry, clothing, electronics, coins and household objects remains as the highest ranking allergen across the countries. Contact allergy to metals, preservatives and fragrance was most prevalent in our centre. In contrast to the other 3 centres, the fragrance mixes did not yield high sensitization rates. In both the other Asian centres, rubber allergy seemed more common.[11-13]

The European baseline series has a wide coverage of rubber and fragrance allergens. Thiuram mix, N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD), mercapto mix and 2-mercaptobenzothiazole are the rubber additives allergens in European baseline series. Balsam of peru, lyral, fragrance mix I and II which consist of 14 haptens are the main fragrance components in European baseline series.

In this study, we analysed the top 5 common rubber and fragrance allergens in the additional series. In the rubber additives series, the top 3 allergens N,N-Diphenylguanidine (DPG), N-Cyclohexyl-N-phenyl-4-phenylenediamine (CPPD), and N-Cyclohexylthiophthalimide were not present within the rubber mixes in European baseline series. The other 2 allergens, tetramethylthiuram monosulfide (TMTM), a component of thiuram mix, and N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) had since long been incorporated in the European baseline series.

Rubber additives play an essential role in the manufacturing process of many household products, stationary, sports equipments, personal and healthcare products. They are widely used in the automotive industry as well. Rubber additives serve their functions as accelerators, antioxidants, antidegradants, bonding agents, retarders, stabilisers or plasticizers. DPG is a rubber accelerator, CPPD an antidegradant, and N-Cyclohexylthiophthalimide a retarder.[14]

The European Surveillance System on Contact Allergies (ESSCA) network gathered data from from 12 European countries between 2009 and 2012 reviewing the pattern of rubber allergy. Prevalence of thiuram mix showed a trend of decline (1.87%). On the other hand, carba mix allergy was on a

rise (2.29%). Diphenylguanidine is a component of carba mix. The shift was due to the gradual replacement of thiuram mix in manufactured gloves by dithiocarbamates. The main use of N-Cyclohexylthiophthalimide is in producing thick rubber goods like tyres. ESSCA detected a prevalence of contact allergy to N-Cyclohexylthiophthalimide of 0.49%.[15] Our study data was in agreement with the trend of rubber allergy observed by the ESSCA network.

N-Cyclohexyl-N-phenyl-4-phenylenediamine is a member of the black rubber mix which is present in the standard series in few countries. Bendelwald et al, in their 8-year retrospective review of patch testing 773 patients with rubber allergens described the following sensitization rates to the allergens: thiuram mix (7.6%), DPG (7.5%), N-Cyclohexylthiophthalimide (5.2%), N-Cyclohexyl-N-phenyl-4-phenylenediamine (1.3%).[16]

With the exception of Ylang ylang oil, the other 4 most common fragrance allergens - cinnamic alcohol, cinnamic aldehyde, eugenol and isoeugenol are components of fragrance mix I. Ylang ylang oil which is extracted from the flowers of the *Cananga odorata* tree, is popular with its presence in aromatherapy, cosmetics and body products. It also has been used in food preparation, and in ethnomedicine where it serves as an anxiolytic, mosquito repellent and treatment for malaria.[17] Wetter et al. and Uter et al. studied the patch test results in patients with suspected cosmetic or fragrance contact dermatitis. The sensitization rates to Ylang ylang oil ranged from 0.9% to 3.1%.[18,19]

The subjects tested with the supplementary series were a selected group with high suspicion of allergy to the respective allergens. Therefore, the results would have shown a higher detection rate.

However, it should concern us that using supplementary series is not a routine practice in all patch test centres. With reference to our data, 11% of the rubber allergy and 14.6% of the fragrance allergy cases would have been missed without testing diphenylguanidine and Ylang ylang oil. Bearing in mind that this study only involved a single centre in the country, it may not reflect the exact epidemiology of the nation.

Voon et al[20] in their single-centre study on preservative allergy involving 243 patients over a 12-month period in 2011, illustrated paraben mix as the allergen with the highest sensitization rate. The retrospective analysis studied patients tested with both the European Baseline Series and additional series. Our study data which extended from 2011 to 2013, still showed paraben mix as the highest ranking preservative allergen in the European Baseline Series. Paraben mix allergy is still prevalent in Thailand and China. In the European countries, the legislation controlling the concentration of paraben mix in cosmetics have led to a reduction in the prevalence of contact allergy.[20]

Table 5. Comparison of the top 10 common allergens among different centres

	Malaysia Current Study N=705	**Malaysia How et al[10] N=689**	**Singapore Ochi et al[12] N=2598**	**China Cheng et al[11] N=1354**	**America Warshaw et al[13] N=4238**
Study period	2011-2013	2011-2015	2009-2013	2001-2006	2011-2012
Top 10 common allergens	Nickel sulfate (28.7%)	Nickel sulfate (35.5%)	Nickel Sulfate (23.9%)	Potassium dichromate (50.1%)	Nickel Sulfate (18.5%)
	Cobalt chloride (13.6%)	Potassium dichromate (16.5%)	Fragrance Mix I (6.7%)	Nickel Sulfate (42.9%)	Fragrance Mix I (12.1%)
	Paraben mix (11.6%)	Methylchloroisothiazolinone +Methylisothiazolinone (12.9%)	PPD (6.2%)	Carba mix (24.9%)	Neomycin sulfate (9.1%)
	Balsam of peru (10.6%)	Fragrance Mix I (12.6%)	Colophony (4.6%)	Fragrance Mix I (22.2%)	Balsam of Peru (7.9%)
	Potassium dichromate (10.5%)	Cobalt chloride (10.2%)	Potassium dichromate (4.6%)	Thimerosal (21.0%)	Bacitracin (7.8%)
	Formaldehyde (7.0%)	Fragrance mix II (8.7%)	Balsam of Peru (4.2%)	Paraben mix (20.0%)	Cobalt chloride (7.3%)
	Cl+Me-isothiazolinone (6.5%)	Balsam of peru (7.3%)	Fragrance mix II (3.9%)	Formaldehyde (15.8%)	Formaldehyde (6.6%)
	Neomycin sulfate (6.4%)	PPD (6.7%)	Neomycin sulfate (2.5%)	PPD (13.5%)	Quatermium-15 (6.4%)
	Colophony (6.4%)	Neomycin sulfate (6.1%)	Lyral (1.9%)	Benzocaine (12.7%)	PPD (6.3%)
	PPD (5.2%)	Colophony (5.7%)	Thiuram mix (1.9%)	Ethylenediamine dihydrochloride (12.2%)	Fragrance Mix II (5.2%)

PPD = p-phenylenediamine

Conclusion

Our study has illustrated the pattern of allergen sensitization in subjects with suspected allergic contact dermatitis in Selayang Hospital. We have highlighted the potential significance of diphenylguanidine, N-Cyclohexylthiophthalimide N-phenyl-4-phenylenediamine and Ylang ylang oil in establishing the diagnosis of rubber and fragrance allergy. To demonstrate a more representative the pattern of contact allergy of the nation, a multicentre study involving the rest of the patch test centres in Malaysia is required. This 4 allergens could be considered to be incorporated to modify our baseline series in the future.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Comparison of the Efficacy of Intralesional Triamcinolone Acetonide and Silicone Gel Sheeting for the Treatment of Keloids

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Abstract

Intoduction:

There are multiple treatment modalities for keloids but no single modality has been proven to be the gold standard. This study aims to compare the efficacy of intralesional triamcinolone acetonide (TAC) with silicone gel sheeting (SGS) in treating keloids and their effect on patients' quality of life(QoL).

Methods:

This was a two-arm randomized-controlled trial involving 56 subjects in which intralesional TAC 20 mg/mL after dilution with 2% lignocaine was administered on keloids monthly for patients in group 1 while patients in group 2 applied SGS on keloids daily. Patients were treated for 12 weeks and followed-up for 16 weeks. Patient and Observer Scar Assessment Scale (POSAS) and Dermatology Life Quality Index (DLQI) were assessed to monitor treatment efficacy and patients' QoL respectively.

Results:

There was 44.2% of improvement in the mean of total score of POSAS in group 1 as compared to 11.6% in group 2 ($p<0.001$). Both groups showed significant improvement in vascularity, pigmentation, thickness and pliability but the improvement was more significant in group 1. Subjects in group 1 demonstrated a 67.3% of DLQI score improvement as compared to 13.1% in group 2 ($p<0.001$). Side effects reported were pain during procedure in group 1 and pruritus in group 2.

Conclusion:

Intralesional TAC was superior than SGS in treating keloids as well as improving patients' QoL and hence recommended as the first-line treatment. SGS can be considered as an alternative treatment for patients who are intolerable to pain or as an adjunctive treatment.

Key words: *Intralesional triamcinolone, Silicone gel, Keloid*

Introduction

Keloids give rise to pain and pruritus in 80% of patients,[1] cause functional impairment and psychological burden, both of which affect patients' quality of life (QoL). Literature has shown that keloids give acceptability problems in up to 91% of patients and influence social functioning in 82% of patients especially those on visible body sites.[1] A study in 130 patients with scars reported a lower quality of life in patients with keloids.[2] Another study comparing QoL in patients with keloids and

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hypertrophic scars with patients with psoriasis reported that the QoL of patients with keloids and hypertrophic scars are impaired as much as that of those with psoriasis. Total DLQI scores of patients with keloids and hypertrophic scars and psoriasis were comparable and significantly higher than that of healthy control.[3]

There are substantial differences between Asian and Caucasian skin which contribute to a higher risk of scar formation in Asian population. A retrospective review of 180 patients who underwent cleft lip repair reported a threefold increased rate of hypertrophic scarring in Asian patients as compared to Caucasians.[4] Asians have a thicker dermis than equivalently pigmented Caucasians.[5] There is a tendency toward a more vigorous fibroblastic response during wound healing in Asian patients which results in hypertrophic scarring and prolonged erythema during scar maturation.[5,6] Besides, Asian skin has increased melanin,[6,7] and a greater number of sebaceous glands, leading to increased sebum production. Hence, there is a greater propensity toward hyperpigmentation and scar formation after skin injury. Furthermore, Asian skin is characterized by a higher rate of fibroblast proliferation resulting in a more vigorous collagen formation and fibroplasia during wound healing.[5] Therefore, the scars in Asian patients may require a longer time for maturation and healing which further complicates their management.[5]

Although multiple treatment modalities exist for keloids, due to lack of level-one evidence, no single treatment has been defined as gold standard. These include non-invasive treatments such as silicone sheets or gels, tape, compression therapy and physiotherapy, as well as invasive treatments such as intralesional corticosteroid injections, 5-fluorouracil injections, cryotherapy, radiotherapy and laser therapy. They can be used as monotherapy or in combination. An article published in the Journal of American Academy of Dermatology in January 2012 commented that both intralesional corticosteroids and silicone gel sheeting as level-three evidence treatment modalities for scars.[8] For Asian population, steroid monotherapy is effective for symptom management for keloids and recommended as first-line treatment.[9] Combination of excision plus steroid injections or other adjuvant therapies such as silicone dressing, cryotherapy, laser, intralesional 5-fluorouracil, pressure therapy is effective and safe.[9]

It is crucial to explore the efficacy of various treatment modalities for keloids in view of the great implication of keloids on patients physically as well as psychologically. Trials evaluating silicone gel sheeting as a treatment for keloid scarring are commented as poor quality and highly susceptible to bias by the Cochrane Database systematic review.[10] Despite discouraging Cochrane review, it is still widely used due to its good safety profile. It is non-invasive, easy to be used but compliance can be a major issue. Side effects include skin itchiness, irritation or rashes. The efficacy of silicone gel sheeting in treating keloids in local population has not been studied before.

Therefore, we aim to compare the efficacy of intralesional triamcinolone acetonide with silicone gel sheeting in the treatment of keloids by employing a validated scar assessment scale (POSAS) which take into account both the patient and provider perspective. In addition to evaluating the physical characteristics of a scar (eg, vascularization, pigmentation, thickness, relief, and pliability) the POSAS also asks patients to rate any pain and pruritus associated with their scar on a 1-10 ordinal scale. We also aim to assess patients' quality of life by using a validated assessment tool (DLQI).

To minimize the risk of bias in our trial, our study focused only on keloid patients as the results may vary depending on the types of scars. Clinical differentiation between hypertrophic and keloid scars is crucial before the initiation of treatment due to increased recurrence rates of keloid.

We hope that the results of this study will clarify the efficacy of intralesional steroid and silicone gel sheeting in keloid management and facilitate further research.

Materials and Methods

This was a two-armed 16-week randomized controlled trial conducted in Dermatology clinic Hospital Tengku Ampuan Rahimah (HTAR), Selangor, Malaysia from 1st August 2014 to 31st December 2014. The target population was patients with clinical diagnosis of keloid attending the clinic during the study period. Inclusion criteria were patients above 12 years of age with keloids measuring between 1cm x1cm to 6cm x 6cm. For patients with more than one keloid, only one keloid was chosen for the purpose of this study. Exclusion criteria were patients with hypertrophic scars or keloids aged less than 1 year, patients

who had received another topical or systemic scar treatment in the last one month prior to recruitment, patients who were pregnant or breastfeeding and patients with known hypersensitivity to any of the constituents of triamcinolone acetonide, lignocaine or silicone gel sheeting.

This study was funded by the Department of Dermatology, HTAR. Recruited patients were randomized into group 1(intralesional triamcinolone acetonide) or group 2 (silicone gel sheeting), interviewed followed by physical examination. Randomization was done through sealed envelope system. Once a patient has consented to enter the study, an envelope was opened and the patient was then offered the allocated treatment regimen. The POSAS blinded to the treatment was assessed.

Patients in group 1 received intralesional triamcinolone acetonide 20 mg/ml 4 weekly for 12 weeks. Triamcinolone acetonide at concentration of 20 mg/ml was prepared by mixing 1ml of triamcinolone at concentration of 40 mg/ml with 1ml of 2% lignocaine. Keloid was injected by using 1ml syringe and 26-gauge needle. Needle was inserted parallel to the skin surface into the mid-dermis of keloid, then triamcinolone injected slowly while withdrawing the needle until the injection site was elevated slightly and blanched (usually 0.1 to 0.2mls was injected per cm^2). Maximum dosage per patient per treatment session was 40mg.

Cicacare silicone gel sheet which was a commercially available product was used for patients in group 2. The Cicacare silicone gel sheet was measured according to the size of keloid then cut and trimmed slightly larger than the size of the keloid. Patients were educated and demonstrated on proper technique of silicone gel sheeting application on keloid. They were required to self-apply the silicone gel sheet on the keloid for 4 hours per day on the first 2 days, 8 hours per day the next 2 days, and increased usage time by 2 hours per day until the optimal 12 hours per day was achieved. The silicone gel sheet was changed after 14 days and continued for 12 weeks.

The duration of treatment for all patients was 12 weeks. Follow-up assessments were performed at week 4, 8 and 12 and 16 by using POSAS and DLQI score. POSAS score was recorded at week 0, 4, 8 and 12 and 16. Assessment was done by one observer (investigator). The use of POSAS in keloid assessment was tested on ten patients for two months at monthly interval prior to the study to ensure the consistency in the assessment of different variables in the scale and to avoid intra-observer variability.

The POSAS consists of a Patient Scale and an Observer Scale. The Patient Scale gives the POSAS an important extra dimension because the patient's opinion is mandatory for a complete scar evaluation. The first publication on the POSAS (Version 1.0) was in 2004 by Draaijers et al. With one extra item for the Observer Scale and minor textual modifications POSASv2.0 was tested on linear scars and published in 2005 by Van de Kar et al.

Besides, DLQI score was recorded at week 0, 12 and 16. For patients in group 1, pain score during intralesional TAC injection was assessed by using the 0 to 10 Numeric Pain Rating Scale. Digital photographs were taken with the same camera settings and under the same lighting conditions before treatment, and at week 0, 12 and 16.

To evaluate for safety and tolerability, the patients were interviewed at every visit after initiation of treatment and any side effects reported will be documented and managed accordingly. Compliance of patients in group 2 was monitored by additional clinic visit weekly in the first month of enrolment.

Statistical analysis was performed with IBM SPSS Statistics for Windows software (Version 20.0. Armonk, NY: IBM Corp). Descriptive statistics were presented as frequencies and percentage for categorical data, the numerical data which was normally distributed was presented as mean and standard deviation. If not normally distributed, the data was presented as median and interquartile range. Comparing outcome for numerical data between two groups was analyzed by using the independent t-test and Mann-Whitney test if the assumptions of independent t-test were not met. The changes in mean scores over three or more time points within or between groups were analyzed using repeated measures ANOVA. Two-tailed tests were used for all analyses, and the probability value of less than 0.05 (p-value < 0.05) was considered as statistically significance.

Results

Fifty six subjects participated in this study which comprised of 28 subjects in group 1 and 28 subjects in group 2. However, only 51 participants (26 in group 1; 25 in group 2) completed the entire study as 2 subjects from group 1 and 3 subjects from group 2 defaulted follow-up during the study period due to

logistic reason (2 at week-4; 1 at week-8; 1 at week-20). Demographic and baseline characteristics of the subjects are shown in Table 1.

The male to female ratio for subjects in our study was 1.15 to 1. The mean age was 27.9 ranging from 12 to 79 years old. Malays made up the largest ethnic group; followed by Chinese and Indian. Majority of subjects has Fitzpatrick skin type III (44.6%) and IV (48.2%). Almost half of the subjects had Fitzpatrick type IV which corresponds to the skin type in Asians. Median area of keloid was 4.25 cm^2. Almost 80% of subjects had keloid for more than 2 years. Majority of subjects had a single keloid. Almost two-third of the keloids were located at upper extremities and thorax, followed by head and neck, back, lower extremities and abdomen. Most of the keloids were due to previous injury. 23.3% of subjects were unsure of the cause for their keloids. Table 2 presents the baseline POSAS and DLQI score of subjects. There was no statistically significant difference between the two groups in terms of baseline demographic characteristics, POSAS and DLQI score.

Table 1. Demographic and baseline characteristics between patients with keloids randomized to either intralesional Triamcinolone acetonide orsilicone gel sheeting treatment

Characteristics	Overall (n=56)	Triamcinolone Acetonide (n=28)	Silicone Gel Sheeting (n=28)	*p*-value
Mean age (SD)	27.9 (13.56)	28.6 (10.33)	27.2 (16.34)	0.690[c]
Gender, n (%)				
Male	28 (50.0)	14 (50.0)	16 (57.1)	0.592[a]
Female	28 (50.0)	14 (50.0)	12 (42.9)	
Ethinicity, n (%)				
Malay	40 (71.4)	18 (64.3)	22 (78.6)	0.411[b]
Chinese	9 (16.1)	5 (17.9)	4 (14.3)	
Indian	7 (12.5)	5 (17.9)	2 (7.1)	
Fitzpatrick Skin Type, n (%)				
II	2 (3.6)	1 (3.6)	1 (3.6)	1.000[b]
III	25 (44.6)	12 (42.9)	13 (46.4)	
IV	27 (48.2)	14 (50.0)	13 (46.4)	
V	1 (1.8)	0 (0.0)	1 (3.6)	
VI	1 (1.8)	1 (3.6)	0 (0.0)	
Median area of keloid cm^2 (Range)	4.25 (1 – 75)	4.5 (1 - 75)	4.3 (1 - 32)	0.577[d]
Age of keloids, n (%)				
≤ 2 years	12 (21.4)	5 (17.9)	7 (25.0)	0.515[a]
> 2 years	44 (78.6)	23 (82.1)	21 (75.0)	
Number of keloids, n (%)				
1	32 (57.1)	19 (67.9)	13 (46.4)	0.247[b]
2	9 (16.1)	4 (14.3)	5 (17.9)	
>2	15 (26.8)	5 (17.9)	10 (35.7)	
Location of keloids, n (%)				
Head / Neck	8 (14.3)	4 (14.3)	4 (14.3)	0.694[b]
Upper extremities	22 (39.3)	11 (39.3)	11 (39.3)	
Thorax	14 (25.0)	5 (17.9)	9 (32.1)	
Abdomen	3 (5.4)	2 (7.1)	1 (3.6)	
Back	5 (8.9)	4 (14.3)	1 (3.6)	
Lower extremities	4 (7.1)	2 (7.1)	2 (7.1)	
Etiology of keloid, n (%)				
Surgery	6 (10.7)	3 (10.7)	3 (10.7)	0.951[b]
Injury	21 (37.5)	11 (39.3)	10 (35.7)	
Vaccination	6 (10.7)	4 (14.3)	2 (7.1)	
Acne	10 (17.9)	5 (17.9)	5 (17.9)	
Unknown	13 (23.3)	5 (14.3)	8 (21.4)	

[a]Chi-Squared Test, [b]Fisher Exact Test, [c]Independent t-test, [d]Mann Whitney Test, SD standard deviation

Table 2. Baseline POSAS and DLQI score between patients with keloids randomized to either intralesional Triamcinolone Acetonide or Silicone Gel Sheeting treatment

Score	Triamcinolone Acetonide Mean (SD)	Silicone Gel Sheeting Mean (SD)	*p*-value[a]
Total POSAS (Subject Scale + Observer Scale)	72.4 (13.90)	63.6 (19.63)	0.059
Total Observer Scale	34.7 (8.11)	29.9 (11.05)	0.070
Total Subject Scale	37.7 (10.33)	33.7 (12.01)	0.187
DLQI	10.1 (5.72)	7.9 (5.61)	0.156

[a]Independent t-test

To measure the improvement with treatment at the end of the study, the significance of the difference between the POSAS and DLQI score at week-16 and baseline were analyzed. The analysis compared the scores between baseline and week-16. Table 3 summarizes the changes in the score from baseline to week-16 for each of the parameters measured in the POSAS as well as the DLQI score. At week 16, subjects treated with intralesional triamcinolone acetonide reported a significant improvement in all the parameters in POSAS Patient Scale ($p<0.001$) which signified an improvement in the symptom of pain and pruritus as well as quality of keloids (color, stiffness, thickness and irregularities). Observer reported a significant improvement in all the parameters in POSAS Observer Scale, i.e. vascularity, pigmentation, thickness, relief, pliability and surface area of keloids in group 1.

Subjects treated with silicone gel sheeting reported a significant improvement in all the parameters in the POSAS Patient Scale except scale 2 (Has the scar been itching the past few weeks?) ($p=0.537$). This means they have a significant reduction in pain and improvement in terms of color, stiffness, thickness, and irregularities of keloids. Observer found a significant improvement in terms of vascularity, pigmentation, thickness and pliability of keloids but not in terms of relief ($p=0.055$) and surface area ($p=0.137$) in this group. The improvement in total score of the POSAS in both groups was significant.

Besides, subjects in group 1 demonstrated a significant improvement in QoL after the treatment. However, subjects in group 2 did not manifest a significant improvement in QoL ($p=0.081$).

Table 3. POSAS and DLQI score changes from baseline to week-16 between patients with keloids randomized to either intralesional Triamcinolone Acetonide or Silicone Gel Sheeting treatment

Score	Triamcinolone acetonide (n=26) *p*-value[a]	Silicone Gel Sheeting (n=25) *p*-value[a]
POSAS Patient Scale 1: Has the scar been painful the past few weeks?	0.001	0.023
Patient Scale 2: Has the scar been itching the past few weeks?	< 0.001	0.537
Patient Scale 3: Is the scar color different from the color of your normal skin at present?	< 0.001	0.007
Patient Scale 4: Is the stiffness of the scar different from your normal skin at present?	< 0.001	0.031
Patient Scale 5: Is the thickness of the scar different from your normal skin at present?	< 0.001	< 0.001
Patient Scale 6: Is the scar more irregular than your normal skin at present?	< 0.001	0.003
Patient Scale Overall	< 0.001	< 0.001
Total Patient Scale	< 0.001	0.003
Observer Scale 1: Vascularity	< 0.001	0.011
Observer Scale 2: Pigmentation	< 0.001	0.021
Observer Scale 3: Thickness	< 0.001	0.005
Observer Scale 4: Relief	< 0.001	0.055
Observer Scale 5: Pliability	< 0.001	0.005
Observer Scale 6: Surface area	< 0.001	0.137
Observer Scale Overall	< 0.001	0.020
Total Observer Scale	< 0.001	0.004
Total POSAS score (Patient score + Observer score)	< 0.001	0.001
DLQI	< 0.001	0.081

[a]Repeated measure ANOVA (Time Effect) for each Group

Figure 1 demonstrated the means of the total score of POSAS during each follow-up visit. At the end of the study, there was 44.2% of improvement in the mean of total score of the POSAS in group 1 as compared to 11.6% in group 2. The mean total POSAS score in group 1 decreased tremendously from 72 at baseline to 49.5 after treatment at week 12 and 40.2 at week-16. The reduction in the score in group 2 was less than group 1.

In this result, the POSAS patterns were significantly different between 2 groups (p<0.001). The patterns were statistically significant at week-4 to week-8 (p=0.008), week-8 to week-12 (p=0.001) and week-12 to week-16 (p<0.001) (Post-hoc analysis done by using Bonferroni procedure and p-values were adjusted for multiple comparison). The data indicated that the appearance of keloids became closer to the normal adjacent skin in subjects who were treated with intralesional triamcinolone acetonide as compared to silicone gel sheeting.

Figure 2 presents the comparison of means of DLQI score between the 2 groups. Subjects in group 1 demonstrated a 67.3% of improvement in DLQI score as compared to 13.1% in group 2. The patterns were statistically significant at baseline to week-12 period (p=0.004) and week-12 to week-16 (p=0.044). (Post-hoc analysis done by using Bonferroni procedure and p-values were adjusted for multiple comparisons).

With regards to side effects of treatment, subjects in group 1 experienced pain during intralesional triamcinolone acetonide administration with an average mean pain score of 5 while subjects received silicone gel sheeting did not experience any pain. Subjects treated with silicone gel sheeting reported pruritus on skin with treatment (mean pruritus score increased from 4.4 at baseline to 4.8 at week-16) while this was not observed in subjects treated with intralesional triamcinolone.

Figure 1. Comparison of means of total POSAS score between 2 groups

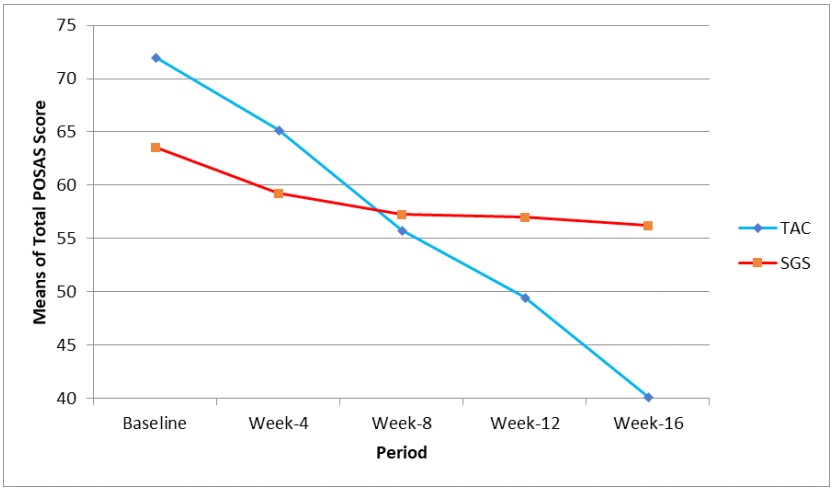
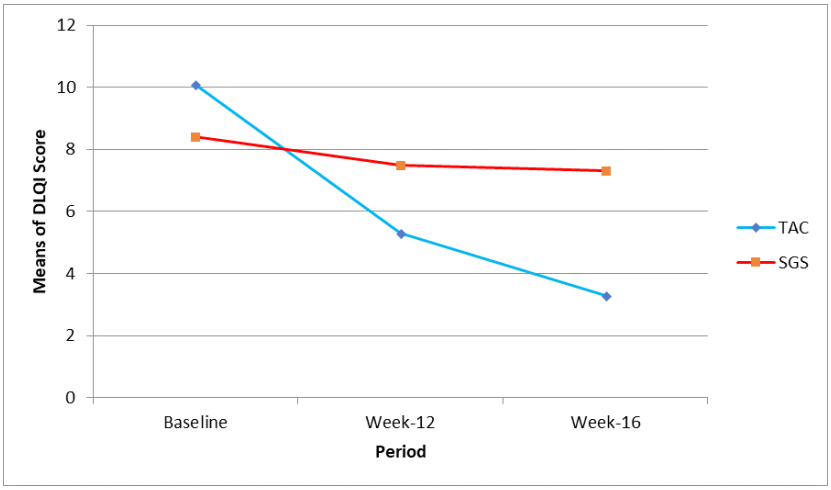


Figure 2. Comparison of means of DLQI score between 2 groups



Discussion

There was a slight male preponderance in our study. Previous study in Taiwan showed that women were more prone to develop keloids with a female to male ratio of 1.33 to 1 with the incidence rate of 0.15% for the general Taiwan population which mainly consists of ethnic Chinese.[11] The mean age of our subjects was 27.9 years old which is compatible with other studies done.[12-14] Lu WS 2015 et al found that keloids occurred typically between the ages of 10 and 30 years, and the mean age of initial onset was 21.14 ± 13.45 years in females and 22.55 ± 11.36 years in males. The difference in the mean age of onset was not significant between males and females (p>0.05). Adegbidi H showed that the mean age was 29 for patients with acne keloides nuchae.[13]

Malay made up the largest of the ethnic group followed by Chinese and India. This is surprising as it did not reflect the ethnic distribution of the clinic attendees to HTAR which comprised of 60% Indian, 20% of Malays and 20% of Chinese. The influence of ethnicity on keloid formation is significant. Keloids are an important clinical problem in certain ethnic populations, as there is a higher prevalence of keloids in individuals with colored skin.[15-17] Keloids are reported to be particularly high in individuals of African, Asian and Hispanic descent. A strong genetic predisposition for keloids have been suggested due to familial preponderance, increased prevalence in certain ethnicities and the reported presence of keloids in identical twins.[18] ommon genetic factor predisposing to the development of keloid was shared by the Chinese Han and Japanese populations with the loci 1q41 and 15q21.3 being detected in both populations.[19]

Majority of our subjects had keloids for more than 2 years while. Subjects with keloids aged less than 1 year were excluded in our study. This is crucial to ensure that only patients with keloids and not hypertrophic scars were recruited. While hypertrophic scars usually develop within 3 months of injury, keloid scars often form within or beyond the first year of injury and tends to persist over time, continuing to grow over the years.[20] 40% of our patients had more than one keloid. A retrospective study involving 868 patients demonstrated that younger age of onset and the presence of family history were significantly associated with the occurrence of keloids at multiple sites.[21]

Keloids occur predominantly on the upper chest, shoulders, upper back, and head and neck, especially on the ear. The locations of keloids in our subjects in order of frequency included upper extremities, thorax, head and neck, back, abdomen and lower extremities. The common etiology for keloid in our subjects in order of frequency included trauma, acne, surgery and vaccination. Keloid can form spontaneously[22] as in 13% of our subjects who were unsure of the etiology of their keloid formation.

To the best of our knowledge and from the MEDLINE search, there were 3 previous studies which compared intalesional triamcinolone acetonide with silicone gel sheeting in treating scars (Table 4). The results on comparison of efficacy of intralesional triamcinolone acetonide and silicone gel sheeting in our study may not be directly comparable to other studies as different methodology was used. Besides, there were also variations in term of type of scars, duration of study which may affect the study outcome.

We found that intralesional triamcinolone acetonide was superior to silicone gel sheeting in treating keloids. Our results were in keeping with E Tan et al which was also done in Asian population in Singapore. E Tan et al reported intralesional triamcinolone was superior to silicone gel sheeting in keloid size reduction of at least 50% at week 12 (94% versus 12%); causing improvement in patients' pain (59% versus 6%) and erythema of keloids (18% versus 0%). The authors therefore did not support the use of silicone gel sheeting as an effective treatment for keloids and concluded that intralesional triamcinolone acetonide should remain the mainstay of treatment.

E Tan et al is thus far the most similar study to our present study as the study was conducted on subjects with keloid scars while JE et al and Kelemen et al were done on subjects with hypertrophic scars. 2 studies on hypertrophic scars as shown in Table 4 have demonstrated a promising outcome.[24,25] Sproat JE et al compared these two treatment modalities on 14 subjects with post-sternotomy scars by assigning one half of scars to each treatment modality. The study demonstrated that silicone gel sheets provided earlier symptomatic relief and a more aesthetic scar and are the preferred treatment of patients.[24] Keleman et al randomized 24 subjects with hypertrophic scars into either intralesional triamcinolone or silicone gel sheeting group. The results showed that both methods were equally efficient although intralesional steroid resulted a more rapid effect and lasted longer than silicone

Table 4. Studies done in comparing intalesional Triamcinolone Acetonide with Silicone Gel Sheeting in treating different types of scars

	Present study, 2015, Malaysia	**Tan et al, 1999, Singapore**	**Sproat et al, 1999, Canada**	**Keleman et al, 2007, Hungary**
Types of scar	Keloid	Keloid	HS	HS
Study duration	16 weeks	12 weeks	12 weeks	Unclear
Participants, n	56 (age: 12-79)	20 (age: 19-40)	14 (age: 33-81)	24 (age: 17-67)
Study design and Interventions	**RCT** Gp 1: TAC 20mg/ml Gp 2: SGS 12 H/day	**RCT with control** 1 - control 1 - SGS 12 H/day 1 - TAC 40mg/ml	**Matched design** Half - TAC 20mg/mL Half : SGS 12H/day	**RCT** Gp 1: TAC 40mg/mL Gp 2: SGS 12 H/day
Outcome assessment tools	1. POSAS 2. DLQI	1. Scar length, width, height, change in colour & texture 2. Pain & pruritus relief	1. Scar length, width, height, change in colour, texture 2. Pain & pruritus relief	1. Vancouver scar scale 2. Subjective patient experience (5-point Likert scale)
Results	**1. Total POSAS score improvement:** 44.2% (TAC) vs 11.6% (SGS) **2. DLQI score improvement:** 67.3% (TAC) vs 13.1% (SGS)	**1. Size reduction ≥ 50%:** 94% (TAC) vs 12% (SGS)	**1. Time to improvement:** 3.9 ± 0.62 days (SGS) vs 6.8±1.86 days (TAC) **2. Patient's preference:** 11 (SGS) vs 2 (TAC)	Both methods were efficient but TAC was more effective, worked faster and reduced subjective symptoms a lot quicker than SGS
Conclusion	Intralesional TAC is superior than SGS in treating keloids.	Intralesional TAC significantly more effective than SGS and should remain one of the primary methods for the treatment of keloids.	SGS provided earlier symptomatic relief and a more aesthetic scar and were the preferred treatment of patients	SGS recommended as the first-line treatment for primary linear HS while TAC as second-line.

RCT randomized controlled trial, HS Hypertrophic scars, TAC triamcinolone acetonide, SGS silicone gel sheeting, vs versus

gel sheeting.[25] From the results of these studies, it is evident that silicone gel sheeting appears to be effective in treating primary hypertrophic scars but not recurrent linear hypertrophic scars or keloids. The ultimate benefit of silicone gel sheeting on keloids remains to be evaluated.

Our subjects treated with intralesional triamcinolone acetonide showed a significant improvement in all the parameters in POSAS Patient Scale as well as POSAS Observer Scale. Our results were comparable with multiple previous studies which showed positive results. In a long-term study done on 94 Asian patients with 109 keloids who were treated with intralesional TAC 1 to 10 mg/mL every four weeks, 83% of patients receiving more than 10 injections reported reduction of itching and pain. Excellent or good improvement of prominence and redness was observed in 39% of patients who received 20 to 30 injections over three to five years.[29] Intralesional triamcinolone monotherapy has been useful in reducing the volume of keloids in most of the patients.[30-33] Previous studies has showed a significant reduction in scar volumes after monthly intralesional steroid injections.[29,34] The disadvantages of intralesional steroid injection include pain during the injections, skin atrophy or dyspigmentation, and recurrence rates of 9% to 50%.[35] Multiple previous studies have demonstrated the effectiveness of intralesional steroids (as monotherapy or combination) in treating keloids and hypertrophic scars.[29, 36-41]

Our subjects treated with silicone gel sheeting reported a significant improvement in the color, stiffness, thickness and irregularities of keloids. From the perspective of observer, we noted a significant improvement in terms of scar vascularity, pigmentation, thickness and pliability. This is supported by previous study which showed that silicone gel sheeting has proven to initially improve texture, then pigmentation, then height of keloids.[28] Nevertheless, there were no significant improvement in relief (irregularities) and surface area.

Our subjects in group 2 reported a significant improvement in the symptom of pain but not in pruritus. On the contrary, they reported a worsening of pruritus after treatment. This is in consistent with a previous study which reported that persistent pruritus (reported by 80% of patients) was the main problem associated with the use of silicone gel sheet for hypertrophic scars in the hot climate of Saudi Arabia.[42] Possible explanation for this finding is that prolonged application of silicone gel sheet for long hours might result in skin irritation which gives rise to pruritus. This is especially so if the hygiene of the topical silicone gel sheet was not well-maintained with regular washing and cleaning. Sweating induced by hot climate is another contributing factor.

Previous studies that demonstrated a promising result of silicone gel sheeting were mainly done on hypertrophic scars rather than keloids.[43-47]

The improvement in quality of life measured via DLQI was significant in subjects treated with intralesional triamcinolone but not with silicone gel sheeting. When compared between the two treatment modalities, intralesional triamcinolonewas superior than silicone gel sheeting in improving patients' DLQI score from baseline at week 0 to week 12 and from week 12 to week 16. Previous study had shown that the DLQI was useful in assessing the quality of life in patients suffering from all types of scars and in monitoring the progress of scar treatments.[48]

From the results of our study, we would like to recommend intralesional triamcinolone acetonide as the first-line treatment in keloids in view of its superiority to silicone gel sheeting. According to the Update on Scar Management: Guidelines for Treating Asian Patients, steroid monotherapy was recommended as the primary method for the treatment of keloids.[9] However, the guideline also recommended that silicone gel therapy can be used as first-line treatment for the management of both hypertrophic and keloid scars in selected patients. Silicone gel sheeting may still be a useful alternative in a selected group (especially children) who may not tolerate the pain and inconvenience of other treatment procedures. Besides, silicone gel sheeting could be recommended as an adjunctive treatment together with intralesional triamcinolone acetonide in view of its positive results as shown in our study.

Our study has several strengths. Treatment of hypertrophic and keloid scars is dependent on scar grading, location and age of scar. Therefore, it is crucial to classify and define the type of scar. Besides, clinical differentiation between hypertrophic and keloid scars is central before the initiation of treatment due to increased recurrence rates of keloid. Realizing this fact, our study recruited subjects with keloids only and subjects with hypertrophic scars were excluded. In our study, keloids were differentiated from hypertrophic scars

clinically and based on duration of the lesions.

To produce reliable results, a scar needs to be assessed using validated scar assessment tools, and consideration must be given both to objective aspects of the scar such as pigmentation and height and to subjective aspects that reflect the individual's response to the scar such as pain and itching. However, an ideal SAT is not available currently, and there still is no general agreement on the most appropriate tool for scar evaluation. We used a validated scar assessment tool POSAS. Draaijers et al compared the reliability and validity of the POSAS to the most frequently used scale, the Visual Analogue Scale (VSS), and found less variability and greater reliability for single observers.[49]

There were few limitations in our study. The duration of our study period (only 16 weeks) and patients' compliance may be the confounding factors that could influence our results. Previous study showed there was significant improvement in scars treated with silicone cushions over a period of few weeks to 12 months.[26] Therefore, it will be ideal if our study can be conducted for a longer duration to assess the clinical response of keloids to silicone gel sheeting.

Silicone gel sheeting should be applied for at least 12 hours a day for up to 3 months in order to exert its effects in treating hypertrophic scars and keloids.[27,28] Although every effort had been carried out painstakingly to ensure patients' compliance, subjects' compliance to treatment remained a limitation in our study.

Besides, there was a risk of bias of assessment as there was only a single investigator in the study. A second investigator for measurements is useful to avoid bias. Treatment naïve patients would be more ideal to be recruited in the study. Dental syringe and needle is more preferred than conventional needle as causing less pain.

Further studies should be done for a longer duration on wider range of keloid scars such as typical post sternotomy scar versus burn scars or keloids in various areas. Ideally, patients recruited in future studies should be treatment naïve. The use of new technologies such as digital imaging in future studies would be of great help in scar assessment.

Conclusion

Intralesional triamcinolone acetonide was more effective than silicone gel sheeting in improving the vascularity, pigmentation, thickness, relief, pliability and surface area of keloids as well as patients' quality of life. From the perspective of patients, intralesional triamcinolone was superior to silicone gel sheeting in reducing the symptom of pruritus as well as improving the stiffness, thickness and irregularities of keloids. The effectiveness of intralesional triamcinolone acetonide was well demonstrated by this study and should remain one of the primary methods for the treatment of keloids.

Although inferior to intralesional triamcinolone, silicone gel sheeting has shown a significant improvement in terms of vascularity, pigmentation, thickness and pliability of keloids and the symptom of pain. Therefore, silicone gel sheeting may be considered as an alternative treatment in selected group who are unable to tolerate the pain during intralesional steroid injection or even as an adjunctive treatment in between intralesional triamcinolone injections. Further studies are needed to clarify the efficacy of silicone gel sheeting in the management of keloids.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Food and Aeroallergens Sensitisation Pattern amongst Atopic Dermatitis Children in Hospital Kuala Lumpur

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Abstract

Introduction:
Various foods and aeroallergens are commonly attributed as the cause and exacerbating factors of atopic dermatitis (AD) in children. This study aim to describe the common food and aeroallergens Immunoglobulin E (IgE) sensitisation pattern and the association between atopic dermatitis (AD) children of varying eczema severities and age groups.

Methods:
Patients who fulfil the criteria of AD were recruited and their eczema severities were assessed using Eczema Area and Severity Index (EASI) score. Skin prick test (SPT) was performed and serum total IgE and specific IgE taken for 6 common foods (cow's milk, soya, egg white, peanut, wheat and chicken) and 4 aeroallergens [cat dander (*Felix domesticus*) and house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae and Blomia tropicalis*)]. IgE sensitisation was diagnosed positive when the SPT yield a wheal of ≥3mm compared with the negative control and/or serum specific IgE level of >0.35ku/L. Data was analysed using SPSS®v20.

Results:
Overall IgE sensitisation to at least one food and/or aeroallergen was 95%. The most prevalent food allergen in Group A [≤1 year old] (n=10) was egg white in which both tests showed statistical significant results when compared with Group B [>1 year old] (n=50). Other common food allergens included cow's milk and peanut. *D. pteronyssinus* was the commonest aeroallergen. Aeroallergens were significantly more prevalent in Group B when comparing both groups.

Conclusion:
Food and aeroallergen sensitisations were very common among AD children. Food allergens were more common in infants and aeroallergens in older children. Bigger sample size may provide more representative results.

Key words: *Atopic dermatitis, Skin prick test (SPT), Specific IgE test*

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Introduction

Various foods and aeroallergens are commonly attributed as the cause and exacerbating factors of atopic dermatitis (AD) in children.[1,2] Food avoidance is commonly seen in AD infants, occasionally to the extent of resulting in malnutrition.[3] To our knowledge, there is no similar study in Malaysia till date. Immunoglobulin E (IgE) food/ aeroallergen sensitisation is diagnosed by skin prick test (SPT)

and/or serum specific IgE test. The main objective of this study is to describe the common food and aeroallergens IgE sensitisation pattern. We also aim to investigate the association of IgE sensitisation among the varying severities and age groups of AD children at our centre.

Materials and Methods

All paediatric patients, aged 12 years and below, who fulfilled the UK Working Party diagnostic criteria of atopic dermatitis[4], seen at paediatric dermatology clinic Hospital Kuala Lumpur were recruited over a study period of 8 months (November 2014 to June 2015). Children diagnosed with immunodeficiency disorders were excluded from this study. Written consent was obtained from parents. Atopic dermatitis severity was assessed using Eczema Area and Severity Index (EASI) score[5]. Skin prick test (SPT) was performed in paediatric clinic or paediatric dermatology laboratory. Blood was taken for total IgE and serum specific IgE; analysed in the hospital laboratory using Phadia® Immunocap machine. The tested food allergens were cow's milk, soya, egg white, peanut, wheat and chicken. The aeroallergens studied were cat dander (*Felix domesticus, F. domesticus*) and house dust mites (*Dermatophagoides pteronyssinus, D. pteronyssinus; Dermatophagoides farinae. D. farinae; and Blomia tropicalis, B. tropicalis*).

IgE mediated allergen sensitisation was diagnosed positive when the skin prick test resulted in an indurated wheal of 3 mm or more compared with negative control and serum specific IgE level of greater than 0.35 ku/L. Subjects were divided into 2 groups based on age (Group A: ≤ 1 year old; Group B: > 1year old). According to eczema severities, patients were divided into 2 groups (mild: EASI score < 6 and moderate to severe: EASI score ≥ 6). Sensitisation patterns were studied between these groups. SPSS®v20 was utilised to analyse the data using non-parametric tests namely chi-square test (CST) or fisher exact test (FST), based on the suitability of the data.

Results

A total of 60 patients were recruited. They were divided into Group A (≤1-year-old) and Group B (>1 year old), consisted of 10 patients and 50 patients respectively. All patients in Group A were 6 months old and above. Out of the 50 patients in Group B, 19 patients were >1-3 years old, 15 patients were >3-6 years old, 8 patients were >6-9 years old and 8 patients were >9-12 years old. Group A had 30% girls and 70% boy whereas Group B had 49% girls and 51% boys. There were 70% Malays, 30% Chinese and no Indians in Group A; 86% Malays, 8% Chinese and 6% Indians in Group B. Demographically, no difference was observed between the two groups (Table 1).

Table 1. Demographic data of the two groups of patients

Age groups	**Group A (Age ≤ 1 year old) (%) n=10**	**Group B (Age > 1 year old) (%) n=50**	***p* value**
	10 (16.7)	50 (83.3)	0.439
Race	**Group A (Age ≤ 1 year old) (%) n=10**	**Group B (Age > 1 year old) (%) n=50**	***p* value**
Malay	7 (70)	43(86)	0.116
Chinese	3 (30)	4 (8)	
Indian	0 (0)	3 (6)	
Gender	**Group A (Age ≤ 1 year old) (%) n=10**	**Group B (Age > 1 year old) (%) n=50**	***p* value**
Female	3 (30)	19 (49)	0.727
Male	7 (70)	31 (51)	

Overall 95% of them had at least one IgE positive result by skin prick test or serum specific Ig E, food or aeroallergen. Only 3 participants were negative for all. The overall commonest IgE sensitisation for food allergen based on serum IgE results were cow's milk (n=34; 57%) followed by egg white (n=29; 48%) and peanut (n=23; 38%). Based on SPT results, the commonest food allergen were egg white (n=25; 42%) and peanut (n=25; 42%) followed by cow's milk (n=6; 10%). The overall commonest IgE sensitisation for aeroallergen based on serum specific IgE results were *D. pteronyssinus* (n=50;

83%), *D. farinae* (n=49; 82%) and *F. domesticus* (n=38; 63%). Similar results were obtained for SPT, which were *D. pteronyssinus* (n=34; 57%), *D. farinae* (n=28; 47%) and *B. tropicalis* (n=22; 37%).

When comparing Group A and Group B, egg white was the only food allergen that showed significant statistical results with serum specific IgE (p=0.039) (Table 2) and SPT (p=0.011) (Table 3). The serum specific IgE for cow's milk and peanut were the second and third commonest sensitisation respectively among the infants in Group A. In the older children in Group B, serum specific IgE for cow's milk and soya were more commonly seen. However when these food allergens were compared between the 2 age groups, the results were not statistically significant.

House dust mite sensitisation was more common among older AD children in Group B as compared to infant in Group A (Table 2 and Table 3). The results for serum specific IgE were statistically significant (p<0.05) for all 3 types of dust mites including *D. pteronyssinus*, *D. farinae* and *B. tropicalis*. For SPT, only *D. farinae* and *B. tropicalis* were statistically significant.

Table 2: Comparison between age groups and serum specific IgE using fisher exact test (FET) (p value ≤ 0.05)

Allergen	Number with positive serum specific IgE (%)		*p* value
	Group A: ≤ 1 year old n=10 (%)	Group B: > 1 year old n=50 (%)	
Cow's milk	7 (70)	27 (54)	0.491 (FET)
Soya	4 (40)	18 (36)	1.000 (FET)
Egg white	8 (80)	21 (42)	***0.039 (FET)***
Peanut	6 (60)	17 (34)	0.161 (FET)
Chicken	1 (10)	17 (34)	0.256 (FET)
Wheat	3 (30)	17 (34)	1.000 (FET)
F. domesticus	2 (20)	13 (26)	1.000 (FET)
D. pteronyssinus	5 (50)	45 (90)	***0.008 (FET)***
D. farinae	4 (40)	45 (90)	***0.001 (FET)***
B. tropicalis	1 (10)	37 (74)	***0.000 (FET)***

Table 3: Comparison between age groups and skin prick test using fisher exact test (FET) (p value ≤ 0.05)

Allergen	Number with positive skin prick test (%)		*p* value
	Group A: ≤ 1 year old n=10 (%)	Group B: > 1 year old n=50 (%)	
Cow's milk	3 (30)	3 (6)	0.052 (FET)
Soya	0 (0)	0 (0)	-
Egg white	6 (60)	9 (18)	***0.011 (FET)***
Peanut	1 (10)	3 (6)	0.528 (FET)
Chicken	1 (10)	2 (4)	0.427 (FET)
Wheat	0 (0)	3 (6)	1.000 (FET)
F. domesticus	0 (0)	9 (18)	0.333 (FET)
D. pteronyssinus	3 (30)	31 (62)	0.085 (FET)
D. farinae	0 (0)	28 (56)	***0.010 (FET)***
B. tropicalis	0 (0)	22 (44)	***0.010 (FET)***

On another aspect, the more severe AD appeared to be associated with higher total IgE. However, this result was not statistically significant. In terms of comparison between disease severities and serum specific IgE, IgE sensitisation for soya, wheat and cat dander were significantly higher among patients with moderate to severe AD as compared to the group with mild AD (Table 4). However for the SPT group, there were no association between the IgE sensitisation and eczema severities groups.

Table 4: Comparison of eczema severity (EASI score) with serum specific IgE using chi-square test (CST) or fisher exact test (FET)

No.	Allergen	EASI score		p value
		Mild (EASI score < 6) n=19 (%)	Moderate-severe (EASI score ≥ 6) n=41 (%)	
1.	Cow's milk	9 (47)	25 (60.9)	0.322 (CST)
2.	Soya	2 (10.5)	20 (48.8)	***0.004 (CST)***
3.	Egg white	7 (36.8)	22 (53.7)	0.225 (CST)
4.	Peanut	4 (21.1)	19 (46.3)	0.061 (CST)
5.	Chicken	3 (15.8)	15 (36.6)	0.102 (CST)
6.	Wheat	2 (10.5)	18 (43.9)	***0.011 (CST)***
7.	*F. domesticus*	1 (5.3)	14 (34.1)	***0.023 (FET)***
8.	*D. pteronyssinus*	16 (84.2)	34 (82.9)	1.000 (FET)
9.	*D. farinae*	15 (78.9)	33 (80.5)	1.000 (FET)
10.	*B. tropicalis*	11 (57.9)	27 (65.9)	0.552 (FET)

Discussion

Atopic dermatitis (AD) is a common inflammatory skin disease characterised by chronically relapsing and pruritic eczematous flares. In 1915, Schloss first reported AD patients who improved by avoiding offending food allergens[6]. Since then, many studies focused on the relationship between AD and food hypersensitivity. Of late, many well designed studies have demonstrated strong association between AD children with Ig E food allergy.[6]

In our study, egg white sensitisation was significantly higher among the infants (Group A) for both SPT and serum specific IgE. Cow's milk and peanut showed similar pattern but the results were not statistically significant when comparing the 2 age groups. This is in keeping with some previous reported studies.[1,2] Many studies, including this study, showed that egg allergy was the most common allergy in AD children.[1,2,7,9] Kim HO et al and Ho MHK et al reported egg white to be the commonest food allergen of 17.9%[9] and 51.9%[1] in their respective studies.

Aeroallergen sensitisation has been shown to be more prevalent among the older AD children and this study supported this association as reported in previous studies.[7,8] Naspitz CK et al reported similar findings of high overall prevalence of *D. pteronyssinus* (66.7%), *D. farinae* (64.5%) and *B. tropicalis* (55.2%) and significantly higher in older children.[10]

Total IgE has been repeatedly reported to be higher in more severe AD patients.[6] Thus it is not surprising that our study showed similar association. However, the result in this study was of no statistical significance. Interestingly, the serum specific IgE for wheat, soya and cat dander showed positive association with eczema severities (Table 4). This association was not seen in SPT. These results were unexpected and we were unable to explain this positive inter-relationship but we reckoned that this may be just a random coincidence.

We have high food sensitization among our AD children. However, sensitisation does not equate to allergy and the diagnosis of food allergy is never a straightforward process. Double-blind, placebo-controlled oral food challenge test is the gold standard for the diagnosis of food hypersensitivity.[9] Prudent and sensible use of allergen testing in concurrence with clinical history association may assist in the diagnosis.

The limitation of this study was the small sample size and the number of subjects in Group A was much smaller than Group B. Hence, there may be bias when comparing the IgE sensitisation of these 2 age groups. Further study involving a larger cohort encompassing both the urban and rural eczema children may be able to generate better notable results and outcome.

Conclusion

IgE food and aeroallergen sensitisation was very common in this small number of AD children. Sensitization to food was more common among the younger children (Group A) while sensitisation to aeroallergen seen more commonly in the older children (Group B). Nevertheless, this study focuses on sensitization pattern and the positive results may not equate to allergy. Thus careful clinical assessment and association is essential to tie-in the positive results to the individual patients. A bigger

sample to represent the paediatric population, coupled with more detailed history of participants may yield more accurate pattern and results.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Patch Testing in Children and Adolescents: 7 Years' Experience in Hospital Kuala Lumpur

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Abstract

Introduction:
Allergic contact dermatitis (ACD) was thought to be infrequent in children. However, there is increasing number of case reports and cross-sectional studies that indicate ACD is not as rare as previously thought. This study aims to explore the pattern of allergic contact dermatitis in children and adolescent patients.

Methods:
This is a retrospective study of children and adolescent patients between 5 and 19-years-old who underwent patch test in the Department of Dermatology, Hospital Kuala Lumpur, Malaysia from January 2010 to December 2016. Patch tests were performed with European Baseline Series and other additional commercial series. Readings were recorded according to the International Contact Dermatitis Research Group recommendation.

Results:
There were 116 children and adolescent patients who underwent patch test. The median age of patients was 14 years (range: 5-19) with a male to female ratio of 1: 2.7. Seventy patients had dermatitis involving the upper limbs (60.3%), followed by 61(52.6%) patients with dermatitis involving the lower limbs, 36(31.0%) patients with face and ears involvement and 31(26.7%) patients with truncal involvement. Of the 116 patients, 74(63.8%) had at least one positive patch test reaction. The 5 most common allergens were nickel sulfate (39.2%), fragrance mix (17.6%), potassium dichromate (14.9%), cobalt chloride (12.2%), methylcholoroisothiozolinone and methylisothiozolinone (Kathon CG) (8.1%) and thimerosal (8.1%).

Conclusion:
Around 64% of our children and adolescents had a positive patch test reaction. Patch testing should be recommended for children and adolescents suspected to have allergic contact dermatitis.

Key words: *Patch test, Paediatric, Adolescent, Allergic contact dermatitis, Nickel sulfate*

Introduction

Allergic contact dermatitis (ACD) was thought to be infrequent in children. However, recent reports have proven otherwise. There is now an increasing awareness about this condition amongst both the paediatricians and dermatologists, which has resulted in the increased use of patch tests and consequently the number diagnosed. Recent review articles which included studies involving 65 to 2460

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subjects revealed that positive patch test reactions have been detected in 26.6% to 95.6% of children and sensitization was found even at infantile stage.[1,2] Most of the studies involved children with atopic dermatitis.[1] This wide range of sensitization was due to several factors including the populations studied, their age, sex, inclusion criteria, choice of patch test series, and patch test methodology.[1,2]

Allergic contact dermatitis is a type IV delayed hypersensitivity reaction and thus it involves an immunological mechanism that requires an initial sensitization phase followed by elicitation phase that causes the skin lesions. The legs and feet, hands and face are the sites most frequently affected in paediatric ACD, which is mainly caused by metals, footwear, topical medications and cosmetics.[3] There are numerous allergens that may contribute to ACD, however the most common allergens in children were nickel, thimerosal, cobalt, fragrance, lanolin and neomycin.[2] In adolescents, they were nickel, thimerosal, cobalt, fragrance, potassium dichromate, and *Myroxylon pereirae*.[2]

Exposure to allergens that have the potential to cause ACD varies according to the geographical distribution. This is partly due to the local regulations which may restrict the usage of certain chemicals. In addition, in the cases of ACD caused by allergens found in natural products, it may also represent the types of natural remedies available in that region. Apart from that, patients' cultural beliefs do play important roles. Most of the data involving ACD in children are derived from studies conducted in Europe and North America. In the South East Asian continent, a study conducted in Singapore between 1986 and 2003 showed that 45.4% of subjects less than 20 years old was sensitized with nickel being the most common sensitizing allergens.[4] ACD was first reported in Malaysian children in 1994.[5] In this 2-year audit on all 346 subjects with positive reaction in patch test, nickel was the most sensitizing allergen. Interestingly, 6 children (below 14 years old) were found to be sensitized to rubber chemicals.[5] Furthermore ACD to cosmetics was also reported in children of Malaysian population.[6] A more recent 15-month audit done in Hospital Selayang Malaysia in 2013 revealed that 60.7% of 84 school children studied developed at least one positive reaction in the patch test. The sensitizing allergens include nickel, preservatives, rubber chemicals, fragrances and topical medicaments.[7]

Recognizing the need of a more tailored approach to ACD in our local population, this study aims to explore the pattern of allergic contact dermatitis in children and adolescents in Hospital Kuala Lumpur, Malaysia.

Materials and Methods

This is a retrospective review of all children and adolescent patients between the age of 5 to 19-year-olds who underwent patch test in Hospital Kuala Lumpur between January 2010 to December 2016. Based on the definition by World Health Organization, patients were categorized as children if they are less than 10 years old and adolescents if they are between 10 to 19 years old. Patch test was performed using IQ chambers and allergens purchased from Chemotechnique Diagnostics. Patients were patch tested with European Baseline Series, other appropriate series and patients' own products as directed and recorded in the patients' clinical notes. For example, patients with feet dermatitis were tested with European Baseline Series and shoe series, and patients with cheilitis were tested with European Baseline Series, dental series, cosmetic series and their own lip products. Patients' own products were diluted according to the nature of the products and were based on the recommendations from the book by Frosch et al.[8] Cosmetics such as eye make-up, lipstick, facial powder, facial foundation, moisturizers, perfumes and deodorants were tested as is. Cleaning products such as soap bar, shampoo, shower gel and toothpaste were diluted with water to 1% (w). Readings were recorded according to the recommendations by the International Contact Dermatitis Research Group.[9,10]

Results

There were 116 children and adolescent patients who underwent patch test (Table 1). Nineteen (16.4%) patients were categorized as children (<10 years) and 97 (83.6%) patients were adolescents (10-19 years). Most of the patients (88%) were of school-going ages (7 to 17) and there was no occupation recorded in any of our patients. Seventy-four patients (63.8%) had at least one positive patch test reaction. There were 11 (57.9%) positive patch test in children and 63 (66.0%) in adolescent patients and this difference was not statistically significant ($p=0.56$).

There were 85 females and 31 male patients (Table 2). Positive patch test reactions were recorded in 51 females (60.0%) as compared to 23 male patients (74.2%) and the difference was not statistically significant ($p=0.16$). When comparison was made

between female children and female adolescents, 5 (41.7%) female children had positive patch test reactions as compared to 46 (63.0%) female adolescents and this difference was however not statistically significant (*p=0.16*). When comparison was made between male children and male adolescents, 6 (85.7%) male children had positive patch test reactions as compared to 17 (70.8%) male adolescents and this difference was not statistically significant (*p=0.43*)

Table 1. Characteristics of 116 children and adolescents who underwent patch test

Characteristics		**n=116**
Median age in years (range)		14 (5-19)
Male : female ratio		1 : 2.7
Ethnicity, n (%)	Malay	75 (64.7)
	Chinese	25 (21.6)
	Indian	15 (12.9)
	Others	1 (0.9)
Site of lesions, n (%)	Upper limbs	70 (60.3)
	Lower limbs	61 (52.6)
	Face and ears	36 (31.0)
	Trunk	31 (26.7)
	Generalized	3 (2.6)
Clinical diagnosis, n (%)	Contact dermatitis	87 (75.0)
	Eczema	6 (5.2)
	Atopic eczema	5 (4.3)
	Hand and foot eczema	5 (4.3)
	Foot eczema	4 (3.4)
	Hand eczema	3 (2.6)
	Discoid eczema	3 (2.6)
	Pompholyx	1 (0.9)
	Facial eczema	1 (0.9)
	Lip eczema	1 (0.9)
Patch test series used, n (%)	European Standard	115 (99.1)
	Shoe	31 (26.7)
	Rubber	29 (25.0)
	Cosmetic	20 (17.2)
	Plastic and glue	10 (8.6)
	Textile and dye	9 (7.8)
	Metal	7 (6.0)
	Medicaments	3 (2.6)
	Dental	3 (2.6)
	Photoallergen	1 (0.9)

All of the patients were patch tested with European Baseline Series, except for 1 patient who was patch tested only to shoe and plastic and glue series. Other extended series which were used in this study include shoe series, rubber series, cosmetic series, plastic and glue series, textile and dye series, metal series, medicaments series, dental series and photoallergen series. Seventeen patients (14.7%) were also tested with their own products which include various brands of make-up and personal care products. From the total number of patients tested, 17 (14.7%) developed positive patch test reactions only to the extended series and not to the European Standard series.

The most common sensitizing allergens in this study were nickel sulfate, fragrance mix, potassium dichromate, cobalt chloride, MCI/MI (Kathon CG) and thimerosal (Table 3). In children, the most common allergen was nickel sulfate, followed by paraphenylenediamine, disperse orange 3 and sesquiterpine lactone (SQL). In adolescents, the most common allergen was also nickel sulfate, followed by fragrance mix, potassium dichromate, cobalt chloride and thimerosal. Nickel sensitization was found in 22 (25.9%) female patients and 7 (22.6%) male patients. There was no statistically significant difference between nickel sensitization in female or male patients in our study (*p=0.13*). In patients with positive patch test to nickel sulfate, 5 (17.2%) patients were also positive to cobalt chloride and 6 (20.7%) of these patients were also

positive to potassium dichromate.

The most common site of involvement was the upper limbs. Seventy patients had dermatitis involving the upper limbs (60.3%), followed by 61 (52.6%) patients with dermatitis involving the lower limbs, 36 (31.0%) patients with face and ears involvement and 31 (26.7%) patients with truncal involvement. In patients with upper limb involvement, 54 (78.3%) patients had hand eczema. Positive patch test was recorded in 53.7% of patients with hand eczema. In all of the sites of lesions, nickel sulfate was found to be to most common sensitizing allergen.

Table 2. Patch test results according to age and gender (n=116)

		Children		Adolescent	
		Total patch tested (n)	Number sensitized n (%)	Total patch tested (n)	Number sensitized n (%)
Overall		19	11 (57.9)	97	63 (64.9)
Gender	**Female**	12	5 (41.6)	73	46 (63.0)
	Male	7	6 (85.7)	24	17 (70.8)
Ten most sensitizing allergens, n (%)		Nickel sulfate, 6 (54.5)		Nickel sulfate, 23 (63.9)	
		4-phenylenediamine base, 2 (18.2)		Fragrance mix, 12 (19.1)	
		Disperse orange 3, 2 (18.2)		Potassium dichromate, 11 (17.5)	
		Sesquiterpine lactone, 2 (18.2)		Cobalt chloride, 8 (12.7)	
		Cobalt chloride, colophony, mercapto mix, palladium, fragrance mix, N-isopropyl N-phenyl paraphenylenediamine, neomycin, epoxy resin, MCI/MI, formaldehyde, benzoyl peroxide, acid yellow 36, 4-aminobenzene, 1 each (9.1)		Thimerosal, 6 (9.5)	
				MCI/MI, 5 (7.9)	
				Colophony, neomycin, formaldehyde, 4 each (6.3)	
				Chloromycetin, 3 (4.8)	

MCI/MI-methylcholoroisothiozolinone/methylisothiozolinone

Table 3. The contact sensitization pattern in the current cohort (n=116)

Positive patch test	n (%)
Nickel sulfate	29 (39.2)
Fragrance mix	13 (17.6)
Potassium dichromate	11 (14.9)
Cobalt chloride	9 (12.2)
MCI/MI (Kathon CG) and thimerosal	6 each (8.1)
Colophony, neomycin, formaldehyde	5 each (6.8)
4-phenylenediamine base and SQL mix	4 each (5.4)
Disperse orange 3, acid yellow 36, 4-aminobenzene, epoxy resin, mercaptobenzothiazole	3 each (4.1)
Mercapto mix, dibutylthiourea, paraben mix, palladium chloride, cocomidopropylbetaine, tixocortol-21-pivalate, N-isopropyl N-phenyl paraphenylenediamine, thiuram mix	2 each (2.7)
Balsam of Peru, primin, disperse yellow 9, benzoyl peroxide, MDBGN, mercury ammonium chloride, disperse red 1, wool alcohol, 4-ter-butylphenol formaldehyde resin, benzocaine, amalgam, mercury, copper oxide, copper sulphate, lead chloride, chlorocresol, dimethylaminopropylamine, gold sodium thiosulphate, hexamethylene tetramene, disperse blue mix 106/124, dithiodimorpholine, amalgam alloying metal	1 each (1.4)

MCI/MI: methylcholoroisothiozolinone / methylisothiozolinone; MDBGN: methyldibromoglutaronitrile; SQL: sesquiterpine lactone

Discussion

Around 64% of our patients had positive patch test reactions and this confirms the notion that allergic contact dermatitis is not rare amongst our children and adolescent. As shown in Table 4, the reported contact sensitization rates in these groups of patients ranges between 27.0 - 95.6% in different countries.[1] The sensitization rates were remarkably higher in studies with smaller number of subjects.

The most common allergen is nickel sulfate, and this finding is similar to other studies[11-36] (Table 4). Female patients could be exposed to nickel from jewelleries and ear piercing.[37] Girls and female adolescents are also exposed to makeup, although direct associations between nickel containing eye makeup and cosmetic dermatitis have not been found. Make-up applicators (ferrules) such as eyelash curlers, hairdressing scissors, hair curlers, and eye shadow and makeup applicators can also become the sources for nickel in this population.[38] Other common items that contain nickel include zippers, belts, tools and dental appliances. Toys were often overlooked as a source for nickel exposure and a study have found that nickel was released in 34.4% toys bought from Denmark and the United States.[39] Another common nickel-containing appliances that are increasingly used in children and adolescents are

Table 4. Patch test results in children and adolescents reported by various countries

Region	Country	Author & year	n	Age (year)	Sensitization rate (%)	Relevance rate (%)	Top 3 sensitizing allergens
United State & Canada	USA	Zug et al, 2008[11]	391	0-18	65.7	51.2	Nickel, cobalt, thimerosal
	Canada	Hogeling et al, 2008[12]	100	4-18	70.0	55.8	Nickel, cobalt, fragrance mix
	USA	Jacob et al, 2008[13]	65	1-18	83.0	77.0	Nickel, thimerosal, Myroxylon pereirae
	USA	Hammonds et al, 2009[14]	136	3-18	61.0	53.0	Nickel, cobalt, gold
	USA	Jacob et al, 2010[15]	69	6m-18	95.6	76.7	Nickel, cocamidopropylbetaine, Myroxylon pereirae
South America	Brazil	Duarte et al, 2003[16]	102	10-19	56.0	100	Nickel, tosylamide-formaldehyde resin
European	France	Roul et al, 1999[17]	337	1-15	67.1	NA	Nickel, fragrance, wool alcohol
	Austria	WÖhrl et al. 2003[18]	79	1-10	62.0	NA	Nickel, ethyl mercury, thimerosal
	Germany	Heine et al, 2004[19]	285	6-12	52.6	NA	Thimerosal, benzylperoxide, phenylmercuricacetate
			2175	13-18	49.7	NA	Nickel, thimerosal, benzylperoxide
	UK	Lewis et al 2004[20]	191	<16	41.0	51.7	Nickel, fragrance mix, thiuram
	UK	Clayton et al, 2005[21]	500	0-16	27.0	61.0	Nickel, fragrance mix, cobalt
	Spain	Vozmediano et al 2005[22]	96	<15	54.2	57.7	Fragrance mix, thimerosal, nickel
	Italy	Seidenari et al, 2005[23]	1094	<12	52.1	70.0	Neomycin, nickel, lanolinalcohols/ thimerosal
	UK	Beattie et al 2006[24]	114	3-15	53.5	100	Nickel, cobalt, rubberchemical
	Turkey	Onder et al, 2008[25]	360	2-16	32.8	93.2	Nickel, cobalt, PPD
	Netherlands	De Waard-van der Spek, 2009[26]	79	1-18	50.6	84.7	Nickel, ownshoes, potassium dichromate
	Poland	Czarnobilska et al, 2009[27]	96	7	43.8	NA	Nickel, thimerosal, cobalt
			133	16	52.6		
	Greece	Milingou et al, 2010[28]	232	<16	47.8	NA	Nickel, cobalt, potassium dichromate
			255		60.0		Nickel, thimerosal, cobalt
	Spain	Toledo et al, 2011[29]	111	0-15	46.8	77.6	Nickel, MCI/MI, fragrance mix I
	Poland	Czarnobilska et al, 2011[30]	103	7-8	67.0	NA	Nickel, propolis, thimerosal
			93	16-17	58.1	NA	Thimerosal, nickel, Cobalt
	Italy	Fortina et al, 2011[31]	321	3months – 3 years	62.3	49.3	Nickel, potassium dichromate, cocamidopropylbetaine
	Edinburgh UK	Darling et al, 2012[32]	41	<18	41	NA	Mercaptobenzothiazole, mercapto mix, potassium dichromate
	Poland	Silny et al, 2013[33]	104	1-20	45.2	NA	Nickel, cobalt, potassium dichromate
	Dundee UK	Vongyer et al, 2015[34]	137	3-15	36.5	NA	Nickel, potassium dichromate, woolalcohol
	11 European countries	Belloni-Fortina et al, 2015[35]	6708	1-16	36.9	NA	Nickel, cobalt, potassium dichromate
Asia Pacific	Singapore	Goon et al, 2006[4]	2340	<21	45.4	NA	Nickel, thimerosal, colophonium
	India	Sarma et al, 2010[36]	70	1-15	80.0	60.7	Nickel, cobalt, potassium dichromate
	Malaysia	Current study, 2017	116	5-19	63.8	NA	Nickel, fragrance mix, potassium dichromate

UK: United Kingdom; US: United State of America

the tablets laptops and smartphones that have metal casings.[40] Nickel allergy can manifest in different ways and apart from causing eczema at the contact area, nickel allergy can be associated with systemic contact dermatitis. The baboon syndrome is a typical presentation of systemic contact dermatitis which shows a classical distribution of maculopapular erythematous lesions, pruritic and confluent, located in the gluteal and flexural regions.[37] In Europe, there are mandatory restrictions for nickel content in consumer products. This may explain the striking findings in some European countries where nickel sulfate was no longer the most common sensitizing allergen. In Denmark, it has been demonstrated that regulation of the nickel content has reduced the risk of developing allergic contact dermatitis and the associated costs arising from excess nickel exposure.[41] It would be interesting to observe if stringent regulation regarding the permissible nickel content in consumer products in Malaysia would produce similar result.

Other metals such as cobalt chloride and potassium dichromate were also common allergens in this study. Patients who are sensitized to nickel are more prone to be sensitized to other metals such as cobalt and chromium and this may explain the high sensitization to cobalt chloride and potassium dichromate in our patients.[37] Cobalt is used in the production of metal alloys and pigments such as cobalt blue and cobalt green. Most of the sources of cobalt are found in costume jewelleries but detergents and cosmetics may also contain this allergen.[42] Chromium is used in the tanning process of leather and in children, the most common source of chromium is leather and it is associated with shoe contact dermatitis.[42]

Fragrances and preservatives were also found to be common allergens in this study and these could be due to exposure to toiletries and cosmetic products aimed at children and adolescent population. There is an increasing interest in the choice of "natural" skin care products which are perceived to be less allergenic for their children but these products may also contain fragrances and preservatives which may elicit ACD.[43]

Fragrances are a large and heterogenous group of chemical and continuous exposure to these allergens on a daily basis is not uncommon. While obvious sources are perfumes, toiletries and cosmetics, they are also widely used in household cleaning products, topical medications and even in foods and spices.[44] Children's cosmetics contain fewer and less concentrated allergenic fragrance ingredients than those of adults.[45] Fragrances that are derived from botanical products and in particular, usage of essential oils have been associated with ACD.[46,47] Fragrances are also used in foods consumed by children and adolescent population and these include chewing gum, soft drinks and ice creams. These fragrances could be synthetic or natural in origin. The natural sources include clove, vanilla and cinnamon. Ingestion of these allergens in susceptible subjects may give rise to systemic contact dermatitis.[44]

Two preservatives namely methylcholoro-isothiozolinone / methylisothiozolinone (MCI/MI) and thimerosal were in the list of 5 most common allergens in this study. MCI/MI is a combination preservative found in personal care such as cosmetics, wet wipes and household products including cleaning products and paints. In an attempt to reduce the incidence of ACD to this preservative, MI alone has been increasingly used in these products.[48] Methylisothiozolinone was initially thought to be safer as MCI was a significantly more potent allergen than MI.[49] However, it is now known that allergic contact dermatitis can also occur to MI; with the first few cases of allergic contact dermatitis to MI in cosmetics reported in 2010.[50]

Thimerosal on the other hand is used as a preservative in vaccines and can also be found in ophthalmic solutions and cosmetics. However, many tertiary centres including the North American Contact Dermatitis Group (NACDG) have removed this allergen from their screening panel due to the high positive patch test reactions without clinical relevance.[51] Currently, the inactivated influenza vaccine recommended for children below the age of seven is the only vaccine that contains thimerosal.[52] However, it is still important to enquire about the usage of cosmetics and ophthalmic solutions as patients may still be exposed to thimerosal in these products and patch testing with patients' own products should be considered to determine the relevance of the positive finding.

Our results are also similar to a study conducted in an adult population in our centre, whereby nickel sulfate, potassium dichromate, MCI/MI, fragrance mix and cobalt chloride were also reported to be the top five sensitizing allergens.[53] The similar finding means that positivity to allergens during childhood and adolescence may persist into adulthood and this

information may be used as a guide when choosing their future occupations. Interestingly, their study found that nickel sensitization is significantly more common in female; which was not shown in our cohort of patients. This may reflect the increased exposure to nickel in females as they grow older, possibly from costume jewelleries.

There were concerns from dermatologist and parents alike on whether patch test is practical for patients especially in the younger children. Limited area on patient's back is definitely going to affect the number of allergens that can be tested. There were also concerns whether the concentration used for adults might give rise to more irritant contact dermatitis in this population. To address this issue, EACCI (European Academy of Allergy and Clinical Immunology) has published a position paper on patch testing in children with allergic contact dermatitis in 2015.[54] This paper noted that most of authors used the same concentration of allergens as in adult population, although the risk of irritant reactions may be higher in infants when tested with metal salts. This paper also advocated 9 allergens to be tested in standard series for children (nickel sulfate, thiuram mix, colophonium, mercaptobenzothiazole, fragrance mix I, fragrance mix II, mercapto mix, MCI/MI and SQL mix); together with additional allergens based on clinical history and allergen exposure. Testing with additional expanded series is important. This is shown in our study where 14.7% of positive patch test reactions would have been missed if the patients were only tested to European Standard series.

There were several limitations to this study. This was a single centre study and our findings may not be similar to the rest of Malaysian children and adolescent population. The records on the relevance of the positive patch test reactions were lacking and therefore the positive allergens found in the patch test may not necessarily be the cause of patients' clinical condition.

Conclusion

In conclusion, contact sensitization is not rare in our children and adolescence as 64% of our patients in this study developed at least one positive reaction to patch test. Our top 3 sensitizing allergens were nickel, fragrance mix and potassium dichromate. Patch test should be considered in children and adolescents presenting with history and clinical findings suggestive of contact dermatitis. Findings from this study could contribute to the development of paediatric baseline series suited for Malaysian population.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Cutaneous Adverse Drug Reactions in Sabah: A 3-year study between 2014 - 2016

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Abstract

Introduction:
Cutaneous adverse drug reactions are one of the most common adverse drug reactions. Publications on clinical correlation between cutaneous presentations and causative agents are limited among the local population. This study aims to determine the clinical presentations of cutaneous adverse drug reactions and the causative drugs in the local population.

Methods:
A retrospective, cross sectional study was conducted from the pharmacy cutaneous adverse drug reaction database from January 2014 to December 2016 in Tawau, Keningau & Queen Elizabeth (Kota Kinabalu) Hospitals.

Results:
A total of 859 cases of cutaneous adverse drug reactions were identified. Out of these, 53.3% (n=458) were females and 46.7% (n=401) were males. The mean age was 36 years old. Majority of patients were 20-29 years old (16.6%) followed by 50-59 years old (15.1%). Most of the cases were reported among the Chinese community (16.4%), followed by the Malay (15.9%), Dusun (14.7%) and Bajau (14.0%) populations. The most common cutaneous manifestations were urticaria and or angioedema (49%, n= 421) and maculopapular rash (39.6%, n=340). Severe cutaneous adverse reactions (SCAR) constituted 2.8% in total. The major causative agent was antibiotic which accounted for 55.1% (n=473), followed by nonsteroidal anti-inflammatory drugs (NSAIDs), 28.1% (n=241) and analgesics, 10.8% (n=93).

Conclusion:
The types of cutaneous manifestations and causative drugs in Sabah are similar to those reported in other states of the country and abroad. This study provides evidence of local cutaneous adverse drug reaction characteristics in different ethnic group.

Key words: *Cutaneous adverse drug reactions (CADRs), Maculopapular rash, Urticaria*

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Introduction

Cutaneous adverse drug reactions (CADRs) are commonly reported in different forms in our clinical practice, with a prevalence of 0.2% to 3.3%.[1,2] The clinical presentations of CADRs vary from mild urticaria and maculopapular eruption to potentially

life-threatening severe cutaneous adverse reactions (SCAR), which include drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A recent study from US using the inpatients sample data base showed high health care cost and mean adjusted mortality rate of 4.8%, 14.8%, 19.4% for SJS, TEN and SJS/TEN respectively.[3]

Sabah is the 3rd most populous state in Malaysia, and the ethnic distributions are vastly different from the rest of Malaysia. As clinical manifestations and the causative drugs vary among different populations, and the data available in our local setting is limited, this study aims to providing a better understanding of the cutaneous adverse drug reactions in Sabah.

Materials and Methods

This is a retrospective cross sectional study done in Tawau, Keningau and Queen Elizabeth Hospitals from January 2014 to December 2016. Tawau and Keningau Hospitals are district hospitals in the respective towns, whereas Queen Elizabeth Hospital is a tertiary hospital in Kota Kinabalu. Pharmacists were the main reporters. Data was collected and retrieved from database of adverse drug reaction registry from January 2014 to December 2016. Data were analysed using Microsoft Office Excel.

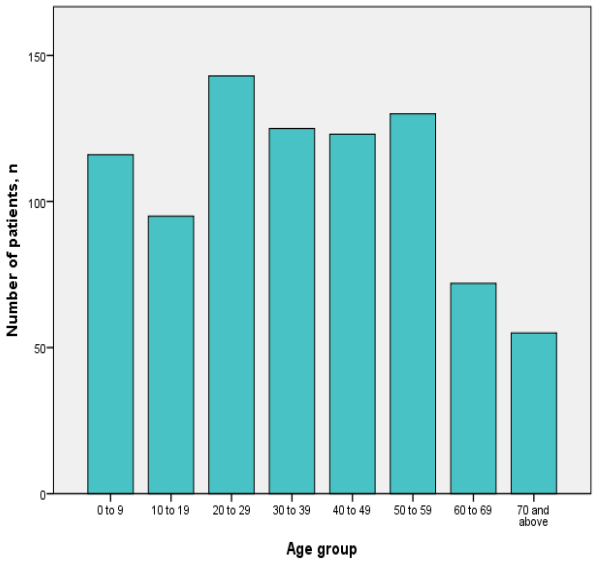
Results

A total of 925 cases of adverse drug reactions were reported during the study period from 1st January 2014 to 31st December 2016, of which 859 cases (92.9%) were cutaneous and 66 cases (7.1%) were non-cutaneous. Among the cutaneous adverse drug reactions reported, Queen Elizabeth Hospital contributed to 389 cases (45.3%), followed by 296 cases (34.5%) from Tawau Hospital and 174 cases (20.3%) from Keningau Hospital.

The mean age was 36.0 ± 21.2 years, ranging from 15 to 57 years old. The highest number of cases was seen in the age group of 20-29 years (16.6%) followed by the age group of 50-59 years (15.1%) as shown in Figure 1. Among the total of 859 cutaneous cases, 458 were females and 401 were males. The female-to-male ratio was 1.1:1.

Cutaneous adverse drug reactions were most commonly observed among the Chinese community (16.4%), followed by the Malay (15.9%), Dusun (14.7%) and Bajau (14.0%) populations as shown in Table 1. This is unsurprising given that Chinese made up 29.8% of the population combined in Kota Kinabalu, Tawau and Keningau. Other ethnic groups are Dusun (29.9%), Bajau (22.5%), Malay (10.7%) and Murut (7.1%).[4]

Figure 1. The distribution of CADRs according to age group



Urticaria and or angioedema (*n*=421, 49%) and maculopapular rash (*n*=340, 39.6%) made up the majority of manifestations of cutaneous drug reactions. Severe cutaneous adverse reactions (SCAR) constituted 2.2% in all. Amongst the life-threatening skin conditions, Stevens-Johnson syndrome (*n*=10, 1.2%) was the commonest, followed by DRESS (*n*=6, 0.7%), AGEP (n=5, 0.6%), SJS-TEN overlap (*n*=2, 0.2%) and TEN (*n*=1, 0.1%) as shown in Table 2. Antibiotics (55.1%) were implicated in more than half of the cutaneous drug reactions. This was followed by NSAIDs (28.1%), analgesics (10.8%) and anti-histamines (3.7%) as shown in Table 3. In this study, penicillin group accounted for 68.7% of antibiotics causing CADRs. The most common NSAIDs and analgesics associated with CADRs were diclofenac and paracetamol respectively. Other common drugs presenting with CADRs were ranitidine, phenytoin and allopurinol.

Allopurinol was implicated in 5 of the 24 cases (20.8%) of SCAR reported, making it the leading cause of SCAR in this population. Drugs reported to cause SCAR are listed in Table 4.

Table 1. Prevalence of CADRs according to ethnicity

Ethnicity	Number, n	Percentage, %
Malay	137	15.9
Chinese	141	16.4
Indian	9	1.0
Bajau	120	14.0
Dusun	126	14.7
Kadazan	65	7.6
Bugis	65	7.6
Murut	50	5.8
Tidung	14	1.6
Jawa	12	1.4
Others	120	14.0
Total	859	100

Table 2. Prevalence of different CADRs

Types of reaction	Number, n	Percentage, %
Urticaria/ Angioedema	421	49.0
Maculopapular rash	340	39.6
Drug-induced pruritus	47	5.5
SJS	10	1.2
DRESS	6	0.7
AGEP	5	0.6
Vesiculobullous reaction	4	0.5
Exfoliative dermatitis	4	0.5
Erythema multiforme	3	0.3
SJS-TEN Overlap	2	0.2
TEN	1	0.1
Others	16	1.9
Total	859	100.0

SJS = Stevens-Johnson syndrome; DRESS = Drug reaction with eosinophilia and systemic symptoms; AGEP = Acute generalised exanthematous pustulosis; TEN = Toxic epidermal necrolysis; SJS-TEN overlap = Stevens-Johnson syndrome – toxic epidermal necrolysis overlap

Table 3. Types of drugs causing cutaneous adverse drug reactions

Drug groups	Number, n	Percentage, %
a) Antibiotics	473	55.1
1. Penicillin	325	37.8
2. Cephalosporin	71	8.3
3. Sulfonamide	39	4.5
4. Macrolide	37	4.3
5. Tetracycline	13	1.5
b) NSAIDs	241	28.1
1. Diclofenac	89	10.4
2. Ibuprofen	85	9.9
3. Mefenamic acid	48	5.6
c) Analgesics	93	10.8
1. Paracetamol	60	7.0
2. Opioid	33	3.8
d) Anti-Histamines	32	3.7
1. Ranitidine	15	1.7
2. Chlorphenamine	10	1.2
e) Anti-Hypertensives	18	2.1
1. Calcium channel blocker	8	0.9
2. Angiotensin-converting enzyme inhibitor	5	0.6
3. Beta blocker	3	0.3
4. Thiazide diuretic	2	0.2
f) Anti-Convulsants	21	2.4
1. Phenytoin	15	1.7
2. Carbamazepine	2	0.2
3. Benzodiazepine	2	0.2
4. Gabapentin	2	0.2
g) Anti-Gout	10	1.2
1. Allopurinol	9	1.1
2. Colchicine	1	0.1
h) Others	89	10.4
1. Vitamin & mineral supplement	8	0.9
2. Topical	7	0.8
3. Anaesthetic drug	6	0.7
4. CT Contrast	6	0.7
5. Steroid	5	0.6
6. Statin	4	0.5
7. Proton pump inhibitor	4	0.5
8. Anti-hyperthyroid	3	0.3
9. Anti-platelet	3	0.3
10. Mucolytic	3	0.3
11. Vaccine	2	0.2
12. Disease modifying antirheumatic drug	2	0.2
13. Miscellaneous	36	4.2

Table 4. Drugs causing severe cutaneous adverse reactions (SCAR)

Type	Drug implicated	Number, n
AGEP	Penicillin	3
	Carbamazepine	1
	Clopidogrel	1
DRESS	**Allopurinol**	**3**
	Trimethoprim/sulfamethoxazole	1
	Anti-tuberculous	1
	Phenytoin	1
SJS	Amoxycillin	2
	Penicillin	1
	Ceftriaxone	1
	Cefuroxime	1
	Pyrazinamide	1
	Mefenamic acid	1
	Phenytoin	1
	Allopurinol	**1**
	Ergotamine	1
TEN	**Allopurinol**	**1**
SJS-TEN	Phenytoin	1
	Erythromycin	1

AGEP = Acute generalised exanthematous pustulosis ; DRESS = Drug reaction with eosinophilia and systemic symptoms ; SJS = Stevens-Johnson syndrome; TEN = Toxic epidermal necrolysis; SJS-TEN overlap = Stevens-Johnson syndrome – toxic epidermal necrolysis overlap

Discussions

The majority of cases reported in this study were among the 20-29 years age group. This finding is different from a previous study in Malaysia by Talib et al, who reported an older mean age of 47.0.[1] It is similar to a study in a tertiary centre in India.[5] This could be due to under-reporting of adverse drug reactions among the elderly population in our setting as cases were mainly reported by pharmacists. Mild skin manifestations may be neglected and hence unreported. Under-reporting is a common problem in our country due to uncertainty of type of reactions and lack of awareness of adverse drug reactions (ADR) reporting system. As high as 81% of physicians who suspected ADR did not report it.[6] Furthermore, our data are collected from hospitals which may not fully represent the population, as a significant proportion of adverse reactions from public health clinics may not be reported.

The male to female ratio was equal in this study, which was similar to other studies.[1,5] The mean age group of 36 years is similar to a local study.[7] The most common cutaneous manifestation was urticaria and or angioedema followed by maculopapular rash. This was in discordant with other studies done in Johor and Kuala Lumpur tertiary hospitals, with the most common cutaneous manifestations being maculopapular rash.[1,7,8] However, a study in Turkey showed a similar result with a predominance of urticaria and or angioedema.[9] Urticaria is a common disorder worldwide with the lifetime incidence of 8.8%.[10] Not only due to drugs, urticaria could be caused by underlying infections. About half of the patients with acute urticaria were having infections, especially those with upper respiratory tract infections, either bacteria or viral and gastrointestinal tract infection, such as *Helicobacter pylori* infection.[11,12]

CADRs normally occur within hours to days of drug consumption. A detailed drug history, time of drug ingestion and the onset of adverse reactions should be explored in order to diagnose CADRs. It would be helpful for pharmacists to improve on the knowledge of common morphology of skin reactions in order to identify CADRs accurately. The development of CADRs are determined by several factors, include drug dose and frequency, patient's age and gender, underlying disease and allergy, as well as socially related habits such as smoking and alcohol.[13]

Numerous local and oversea data were compared as shown in Table 5. Antibiotics were the most common culprit drug associated with CADRs across the world, either mild or life threatening, followed by NSAIDs, analgesics and anticonvulsants.

In this study, antibiotics were the major causative drugs of CADRs (55.1%) which is consistent with Malaysian and overseas studies.[1,7,8,15] Penicillin, cephalosporin, sufonamide and macrolide were the common antibiotics reported. Comparable to another study in Malaysia, allopurinol was the main contributor to SCAR.[8] There is a strong association between allopurinol-induced SCARs and HLA-B*58:01 allele.[16] The prevalence of this allele carriers in the ethnically diversed population in Malaysia is estimated to be 12.4%. As there is no provision to screen for this allele prior to the initiation of allopurinol, due caution must be practised in all patients receiving this drug.[17]

Limitations of study

Although the research has its aims, there were some unavoidable limitations. Firstly, the information was retrieved from adverse drug reaction registry which will be submitted to Malaysian Adverse Drug Reactions Advisory Committee (MADRAC). Therefore, to generate better and more accurate results, the study should have involved more patient interaction during data collection. Secondly, pharmacists were the main reporters of adverse drug reactions based on patient's description and self diagnosis. Moreover, with the lack of dermatology expertise in district hospitals, the description of skin reactions vary and hence less accurate. Thirdly, there is lack of information on types of patients, either inpatients or clinic attendees. Finally, we did not follow up on patients with severe cutaneous adverse reactions (SCARs) and therefore the outcome and mortality rate data is not available.

Conclusion

In conclusion, this study described the adverse drug reactions (ADRs) at three main hospitals in Sabah, with majority reported as cutaneous manifestations. The most commonly implicated drugs were antibiotics and NSAIDs which were similar to other local and oversea studies. All ethnic groups in Sabah were predisposed. However, this may not fully represent the local population due to under-reporting. Reporting rate need to be improved by increasing the awareness on the importance of being informed on drugs which commonly cause ADRs among the local community.

Table 5. Comparison table of CADRs among different populations [1,5,7,14]

Country/ State / Types of drugs	Malaysia			India	China
	Sabah	Kuala Lumpur	Johor		
Antibiotics	55.1%	36.6%	40.3%	48.3%	29.2%
NSAIDs	28.1%	-	9.9%	21.9%	-
Analgesics	10.8%	13.4%	-	-	17.1%
Anti-Histamines	3.7%	-	-	-	-
Anti-Convulsants	2.4%	-	22.4%	13.2%	26%
Anti-Hypertensives	2.1%	10.4%	-	-	-
Traditional & complementary medicine	-	17.9%	-	-	2.2%
Anti-Gout	1.2%	-	13.8%	-	11%
Anti-Rheumatics	-	-	2.7%	-	-
Antacids	-	-	-	-	5.8%
Combination	-	-	-	4.39%	-
Anaesthetics	-	-	-	-	3%
Others	-	7.4%	-	8.79%	-

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Leprosy in Pregnancy: A Case Series in 4 Dermatology Clinics in Malaysia

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Abstract

Introduction

Management of leprosy in pregnancy is challenging. Here we aim to describe the clinical characteristics and the management of leprosy in pregnancy.

Methods

This is a retrospective study on pregnant women with leprosy managed in the Department of Dermatology in Hospital Kuala Lumpur, Hospital Pulau Pinang, Hospital Sultanah Bahiyah and Hospital Queen Elizabeth between 1994 and 2015.

Results

There were ten patients with 12 pregnancies with a median age of 27.5 years (range: 16-33). Five were foreigners. There were four cases of lepromatous leprosy, two cases of borderline lepromatous, two cases borderline tuberculoid leprosy and one case each for tuberculoid and mid borderline leprosy. Seven pregnancies (58%) were documented to have reactions. Four reversal reactions (33%), three erythema nodusom leprosum (25%) and two Lucio's phenomenon (17%) were documented. Both patients with Lucio's phenomenon had undiagnosed leprosy and presented with preterm labour, anemia, oligohydramnios and intrauterine growth restriction. Mortality was recorded in one patient due to dapsone induced hypersensitivity syndrome complicated with septicaemia. All patients were prescribed multidrug therapy but in three pregnancies, the patients chose to defer the treatment. There was a spontaneous miscarriage at second trimester and a case of early neonatal death. The neonatal complications recorded for the 10 live deliveries were low birth weight, jaundice and clofazimine-induced hyperpigmentation.

Conclusion

The majority of our patients with leprosy had complications throughout the pregnancies. Early detection and prompt treatment can prevent unfavorable fetal outcome & threatened maternal health.

Key words: *Leprosy, Pregnancy, Eyrthema nodusom leprosum, Lucio's phenomenon, Reversal reactions*

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Introduction

Leprosy or Hansen's disease is a chronic infectious disease caused by *Mycobacterium leprae* which primarily affects the skin and nerves. Women are described as cases of "triple jeopardy" in leprosy as they are discriminated because of their

gender, the disabilities that can result from leprosy and the societal stigmatization.[1] In 2016 WHO weekly epidemiology report (WER) stated that the proportions of females affected by leprosy were ranging between 22.5% and 54.4% of all new cases globally.[2] In Malaysia, 35.7% of the new cases detected in 2016 were female patients.[2] The percentage of females affected by leprosy was regularly monitored and analyzed by WHO in order to understand the access to leprosy services for women and the possible effects of discrimination against women with leprosy.[2] There is lack of scientific evidence that men are more prone to leprosy compared to women. Risk of leprosy transmission is higher within households through contact.[3,4] Hence, females affected by leprosy are an important potential source of infection to other family members including children if not detected and treated early. An audit among 271 children with leprosy (aged less than 15 years) in Ethiopia showed that 53% of the children had a relative with leprosy. The likelihood for the mother of these children having active leprosy was greater especially if the children developed leprosy at a much younger age.[5]

Pregnancy in women with leprosy may lead to serious repercussions. Leprosy affects every phase of pregnancy including the puerperium and lactating period.[5] It may manifest for the first time during pregnancy. In addition, relapses of leprosy during pregnancy have been reported predominantly in the third trimester. Pregnant women with leprosy are vulnerable to serious complications from the disease. Pregnancy induces a state of immunological changes which may lead to worsening of leprosy in the mother and precipitation of leprae reactions.[6-8] Without prompt treatment, the damage to the skin, nerves, limbs, and eyes can have serious consequences. In addition, the placenta and its functions are affected in pregnant women with leprosy[9] resulting in premature babies with low birth weight. *Mycobacterium leprae* has been isolated from the breast milk of mothers with untreated lepromatous leprosy.[10] About 5% of children whose mothers had active lepromatous leprosy developed leprosy before the age of two.[11] In another review, 16% of adolescents whose mothers had leprosy developed indeterminate leprosy at puberty. Therefore, it is important to manage leprosy aggressively in women more so when they are pregnant. Here we describe a case series of patients with leprosy in pregnancy in Malaysia.

Materials & Methods

This is a retrospective study of all cases of leprosy with pregnancy treated at the Dermatology Clinics of Hospital Kuala Lumpur, Hospital Pulau Pinang, Hospital Sultanah Bahiyah and Hospital Queen Elizabeth between 1994 and 2015.

Results

There was a total of ten patients with 12 pregnancies encountered. There were two patients with two pregnancies while on treatment. The median age of the patient at the time of pregnancy was 27.5 years old (range 16-34). There were five Malaysians, four Indonesians and one Burmese. Among all the Malaysians, there were four Malays and one from an indigenous tribe. The majority of the cases (70%) were from Hospital Kuala Lumpur.

In term of Ridley-jopling classification, there were four cases of Lepromatous leprosy (LL), two cases of Borderline lepromatous (BL) and Bsorderline Tuberculoid (BT), one case of Mid borderline (BB) and Tuberculoid leprosy (TT) respectively. The mean bacteriologic index was 2.4 ranging from 0-4.7.

Four patients were diagnosed as having leprosy at second trimester of gestation and three at third trimester of gestation. Another four pregnancies occurred after the leprosy was diagnosed. Of note, four patients had the symptoms of leprosy at least one year before the pregnancy and yet were not captured or diagnosed.

All patients were prescribed multidrug therapy but in three pregnancies, patients deferred the treatment. Six patients received the Sungai Buloh Augmented regime and three patients took the WHO regime. One patient chose to defer her treatment in her second pregnancy as she had spontaneous miscarriage at second trimester while taking multidrug therapy (Table 1, Patient 4).

Seven pregnancies (58%) were documented to have leprae reactions; four reversal reactions (33%), three erythema nodusom leprosum (25%) and two Lucio's phenomenon (17%). Interestingly, two cases of Lucio's phenomenon had concurrent erythema nodusum leprosum which is rarely reported in the literature. We detected 3 (30%) of the patients had WHO Grade 2 deformity which is defined as visible deformity or damage present due to leprosy.

The two lepromatous leprosy patients who presented with Lucio's phenomenon shared many similarities in their clinical characteristics. Both patients had have signs and symptoms of leprosy that went undiagnosed about three years before their pregnancy. They were only diagnosed at 3rd trimester of pregnancy when they presented with severe Lucio's phenomenon, concurrent erythema nodusum leprosum and WHO grade 2 deformity. They were both started on systemic steroid and multidrug therapy. Their pregnancies were also complicated with preterm labour, anemia, oligohydramnios and intrauterine growth restriction. They underwent emergency caesarean sections due the severe oligohydramnios (Table1, Patient 9 and 10). They were both started on systemic steroid and multidrug therapy after diagnosis. On contact screening, patient 9 had a 9-year-old child who was subsequently diagnosed with tuberculoid leprosy. Their newborns have not been diagnosed with leprosy to date.

There was a mortality in our cohort. This was a 21-year-old Indonesian, gravida 2 (table 1, patient 6) who was diagnosed with borderline lepromatous leprosy in her second trimester of pregnancy. WHO multidrug regime was initiated without delay. However, she presented with exfoliative dermatitis, fever, profound jaundice at 27 weeks of gestation (6 weeks after initiation of MDT). Laboratory investigations revealed severe hemolytic anemia (Hemoglobin: 6.6g/dL; reticulocytes count:12.8 %), raised white cell count ($13x10^9$/L); normal platelet count ($317x10^9$/L); normal eosinophil count (0 $x10^9$/L); raised creatinine (124mol/L); elevated alanine transferase (116u/L) and alkaline phosphatase (306u/L); markedly raised direct bilirubin (326mol/L); raised indirect bilirubin (101mol/L); and a prolonged coagulation profile (INR=4.28). Peripheral blood film revealed increased polychromasia with spherocytosis suggestive of hemolysis. Hepatitis B, Hepatitis C and Human Immunodeficiency Virus (HIV) serology were negative. Her subsequent blood culture grew *Acinetobacter sp*. Ultrasound of the hepatobiliary system revealed no obstructive features in the biliary tract. She was suspected to have dapsone induced hypersensitivity syndrome complicated by septicaemia. She was started on intravenous hydrocortisone and antibiotics which included ceftriaxone, later meropenem and piperacillin-sulbactam. She had premature delivery on the third day of admission. The birth weight of the newborn was 850g. Unfortunately, the baby passed away after one day due to severe prematurity. The mother eventually succumbed at day nine of admission despite of aggressive treatment and vigorous resuscitation.

In total there was one miscarriage and three preterm deliveries in the 12 pregnancies. Neonatal jaundice was noted in one newborn. Another newborn had clofazimine-induced hyperpigmentation which resolved on follow up. No congenital malformations were detected among the newborns. However, information for most of the infants was lacking and incomplete. Some of the adverse events of leprosy treatments during pregnancy reported were fever, nausea, vomiting, lethargy, new peripheral neuropathy and worsening of reversal reactions.

Discussion

The relationship between leprosy and pregnancy is tortuous. There are only a handful of case series[12-16] describing the effect of pregnancy on leprosy as shown in Table 2. Most of them had adverse consequences not only during the pregnancies, but during post-partum and lactation as well. Multidrug therapy consisting of rifampicin, clofazimine and dapsone, is considered safe in pregnancy. However, it does come with side effects that need stringent monitoring. Furthermore, the neonates and infants of mother with leprosy are susceptible to morbidity too. Children born to mothers with leprosy are at higher risk of acquiring leprosy when they grow older.

Pregnancy is known to cause a relative decrease in cellular immunity especially in third trimester, which enables the organism *M. leprae* to proliferate.[6] Thus, symptoms of leprosy are more severe during pregnancy. Case studies have shown neuritis especially silent neuritis affects almost half of the pregnant women with leprosy.[6-8] Studies have shown lepra reactions can be triggered by pregnancy due to variations in cell mediated and humoral immunity. Both types of reactions can continue long into lactation.[6-8] In our cohort, 58% of patients developed reactions. Type 1 reaction (reversal reaction) typically occurred post partum[6], but all our four patients who had reversal reactions developed the symptoms in their early pregnancy. Classically erythema nodosum leprosum peaks during late pregnancy[6], but one of our patients (Table 1, Patient 8) had ENL from the pre-pregnancy stage that continued into her early pregnancy before she defaulted.

Table 1. Characteristics of ten pregnant patients with leprosy

No	Age (years)	Nationality	Classification of Leprosy	Baseline Slit skin smear		Gravida	Diagnosis of Leprosy in relation with terms of the pregnancy	Duration of leprosy Symptoms before pregnancy	Leprosy treatments during pregnancy	Reactions during pregnancy	Maternal Outcome	Fetal Outcome	Neonatal Complications
				BI	MI								
1.	33	Indonesian	TT	0	0	G4 P2+1	2nd trimester	1 year	WHO PB regime 6 months	No	Alive	Term Baby	N/A
2.	32	Malaysian	BT	0	0	G8 P7	2nd trimester	2 years	Sg Buluh Augmented regime	Reversal	Alive	Term Baby	N/A
	34					G9 P8	Pregnant during treatment	-	Sg Buluh Augmented regime	Reversal	Alive	Term Baby	N/A
3.	27	Malaysian	BT	0.9	0	G1 P0	2nd trimester	NA	WHO MB regime 12 months	Reversal	Alive	Term Baby	Clofazamine –induced hyperpigmentation , Neonatal Jaundice
4	26	Indonesian	BB	2.3	0.9	G1 P0	2nd trimester	NA	Sg Buluh Augmented regime	Reversal	Alive	Abortion	-
	27					G2 P0+1	Pregnant during treatment	-	Deferred treatment	No	Alive	Term, LBW baby (1.8kg)	No
5.	16	Malaysian	BL	3.2	5.0	G2 P1	Pregnant during treatment	-	Deferred treatment	No	Alive	Term Baby	N/A
6	21	Indonesian	BL	3.5	2.5	G2 P1	1st trimester	6 months	WHO MB regime 12 months	No	Deceased	Preterm , LBW baby (0.85 kg)	Deceased after 1 day
7.	28	Burmese	LL	2.6	0	G2 P0+1	Pregnant during treatment	-	Deferred treatment	No	Alive	Term Baby	N/A
8.	31	Indonesian	LL	4.7	4.6	G4 P3	3rd trimester	NA	Sg Buluh Augmented regime	ENL	Alive	Term Baby	N/A
9.	31	Malaysian	LL	2.3	4.8	G5 P3+1	3rd trimester	3 years	Sg Buluh Augmented regime	Lucio's phenomenon and ENL	Alive	Preterm, LBW baby (1.9kg)	No
10.	23	Malaysian	LL	4.5	0.7	G2 P1	3rd trimester	3 years	Sg Buluh Augmented regime	Lucio's phenomenon and ENL	Alive	Preterm , LBW baby (2.2kg)	No

TT – tuberculoid leprosy; BT – borderline tuberculoid leprosy; BB – mid borderline leprosy; BL – borderline lepromatous leprosy; LL – lepromatous leprosy; LBW- Low birth weight; ENL – Erythema Nodusum Leprosum; N/A – Data not available; WHO PB regime – World Health Organisation Paucibacillary regime; WHO MB regime - World Health Organisation Multibacillary regime

Table 2. Literature review on case series of leprosy in pregnant women from different countries

Author, year	Country	No of pregnant women studied	No of pregnancies	% of women with lepromatous leprosy	Important findings
King et al[12], 1958	United State	26	52	100	• 78% of pregnancies with untreated leprosy had disease aggravation versus only 21.7% of pregnancies had disease progression when they were treated with sulfone drugs.
Hardas et al[13], 1972	India	59	Each ranged from 3-17	NA	• 61% (36 of 59 women) developed first symptoms of leprosy during puerperium, 15.2% during lactational amenorrhoea, 10.1% during pregnancy.
Duncan et al[14,15], 1981 & 1982	Ethiopia	114	119	28.1	• Increased leprosy activity in 49.4% of women during pregnancy • About 48% of women with "cured" tuberculoid leprosy relapsed with new lesions or nerve damage. • 50% of RR occurred during first 6 months of lactation • 68% of ENL occurred during third trimester of pregnancy or the first 6 months of lactation
Nogueira et al[16], 2015	Brazil	49	49	NA	• Symptoms of leprosy occurred in the last trimester of pregnancy in 36.3% • 22.3% of cases with low birth weight newborn (<2kg) • 18.6% with leprae reactions • 5.5% had relapse of leprosy
Loh et al, 2018	Malaysia	10	12	40	• 58.3% of the women had leprosy diagnosed during pregnancies • 20% of the patients developed ENL and LP • One maternal mortality due to dapsone induced drug hypersensitivity syndrome complicated with sepsis

RR- reversal reaction, ENL- erythema nodosum leprosum, LP- Lucio's phenomenon

Lucio's phenomenon (LP) is an occlusive condition of small vessels in dermis caused by invasion of endothelial cells by *Mycobacterium leprae.*[17] It is characterized by irregularly shaped purpuric or necrotic macules or plaques with sharply marginated serrated borders.[18] The mortality rate of LP is high.[19] Pregnancy is a well-known predisposing factor of LP due to a thrombophilic and immunosuppressive state.[19,20] Both our patients with LP were successfully treated with Sungai Buluh Augmented Multidrug therapy and systemic corticosteroids. Benard G et al[21] had reported a rare case of a pregnant lady with concurrent ENL and Lucio's phenomenon in 2009, which also occurred in two of our patients (Table 1, Patient 9 and 10). Lucio's phenomenon and ENL arise from different pathogenetic mechanisms.[21] ENL is the result of an immune complex mediated reaction whereas LP is due to invasion of endothelial cells by bacilli. However, necrotic ENL can sometimes mimic LP in clinical presentation. There are several distinctive histopathological and clinical features in both entities.[17,21,22] This distinction is important because a decrease in bacillary load through multidrug therapy is the main target in LP, whereas in ENL, concomitant reduction of the reaction by means of high-dose steroids is recommended.

Of note, four patients had the symptoms of leprosy at least one year before pregnancy including the two patients with LP. Delay in diagnosis for leprosy is a common problem worldwide.[23] Common reasons identified included patients' ignorance to the symptoms and misdiagnosis by doctors due to low awareness of the disease.[24-27] Although Malaysia has achieved the WHO target of elimination of leprosy as a public health problem to less than a case per 10,000 population in 1994, new cases of leprosy continued to be detected every year. Hence, the continuous training of primary care doctors to improve their diagnostic skills is needed. Vigilant contact tracing, early detection and treatment may prevent all the sequelae.

Babies of mothers with leprosy especially in the lepromatous leprosy pole are associated with lower birth weight, smaller placentae, developmental delay, more infections and higher infant mortality.[11,28] Three low birth weight babies (27%) were born in our cohort. Congenital leprosy was well described by Duncan et al in 1983.[11] The postulated routes of transmission include skin-to-skin contact, through breast milk, inhalation of droplets or transplacentally.[11] None of the babies born in our cohort had congenital leprosy at their mothers' last visit. Another study reported 16% of adolescent with leprous mothers developed leprosy at puberty.[28] Thus continuous follow up and screening of the children whose mothers have leprosy is vital.

The benefits of treating leprosy during pregnancy far outweigh the risks of the medications. Since 1998, WHO has recommended that the standard regime which consists of rifampicin, dapsone and clofazamine is safe and not teratogenic.[29] Therefore, this standard regime should be continued unchanged during pregnancy. Dapsone may however cause hemolytic anemia in the mother or baby. In addition, it may cause dapsone hypersensitivity syndrome which is a severe adverse drug reaction. This syndrome may lead to mortality as shown in patient 6 in our cohort. As a result, very stringent monitoring of the blood count and the liver function test with the interval of weekly at the beginning is mandatory. Immediate cessation of dapsone is imperative should hemolytic anemia and dapsone hypersensitivity syndrome develop. Clofazamine causes reversible skin discoloration in the fetus.[16,30] Drugs such as quinolones and minocycline should be avoided in pregnancy. For babies born to untreated multi-bacillary mothers, a different handling protocol is recommended. Newborns should be isolated until morphological index of the mother reaches zero. Furthermore, the direct latching mode of breastfeeding is not encouraged.[29,30]

Before the era of MDT, it was found that the mortality rate for lepromatous patients was four times more as compared with the general population.[31] Leprosy is often not considered a direct cause of death. However, leprosy patients are exposed to increase mortality risks due to its indirect effects. A study in Brazil reported the burden of leprosy deaths was higher for lepromatous leprosy, among males, elderly, the black race and in leprosy-endemic regions.[32] Rocha et al in 2016 reported significant mortality rates in Lucio's phenomenon and mostly associated with pregnancy and secondary infection.[19] The mortality case in our cohort had borderline lepromatous leprosy. She had unfortunately developed severe dapsone hypersensitivity reaction complicated with hemolytic anemia and septicaemia. The idiosyncratic drug hypersensitivity reaction resulted in an adverse outcome to the fetus and the mother.

There is always considerable anxiety among the pregnant women and clinicians with regards to the effect of MDT to the fetus, as demonstrated in

one of our patients (Table 1, Patient 4) who had an abortion while taking MDT, and she adamantly refused treatment during her next pregnancy. In addition, a lack of understanding about the disease and its complications will certainly affect the compliance. Therefore, proper counselling is crucial to convince mothers with leprosy to complete their treatment. Home visits must be made immediately when patient defaults follow up. Another method is direct observed therapy similar to the treatment for tuberculosis. A responsible person like community volunteer or a family member should be involved to supervise the treatment of the patient at home. This is called Accompanied MDT.[34]

Conclusion

Our review showed that majority of mothers with leprosy had severe reactions, neonatal complications. Regrettably one third of them had already developed permanent WHO Grade 2 deformity at presentation. Nearly 40**%** had symptoms of leprosy undiagnosed at least 1 year before pregnancy. Therefore, early detection and early treatment is the key to prevent unfavorable fetal outcome and threatened maternal health.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CASE REPORT

Rhabdomyosarcoma Arising in A Giant Congenital Melanocytic Nevus

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Summary

A variety of malignancies have been documented to arise within congenital melanocytic nevi (CMNs). Although the most frequent malignancy arising within a CMN is melanoma, the association between rhabdomyosarcoma and CMN has rarely been documented. We report a 4-month-old girl presented with ulcerated nodule overlying a giant CMN at the posterior back that exhibited rapid growth. Biopsy of the nodule revealed embryonal rhabdomyosarcoma in association with CMN. She received chemotherapy with vincristine and actinomycin D. This the first case of rhabdomyosarcoma associated with giant CMN reported in our local setting. Clinicians must consider rhabdomyosarcoma as one of the differential diagnosis in patients presenting with ulcerated nodules on giant CMN.

Key words: *Rhabdomyosarcoma, Giant congenital melanocytic nevus, Malignant transformation*

Introduction

Congenital melanocytic naevus (CMN) is a benign proliferation of melanocytic naevus cells that is present at birth or develops shortly after birth. Giant congenital melanocytic naevus (GCMN) is defined as predicted diameter greater than 20cm by adulthood, commonly occurs in newborns in approximately 1in 20 000 live births.

A variety of malignancies have been reported to arise within congenital melanocytic nevi, most commonly malignant melanoma, but rarely rhabdomyosarcoma, liposarcoma, and malignant peripheral nerve sheath tumor as well. Neurocutaneous melanocytosis is a rare condition characterized by the proliferation of melanocytes in the central nervous system (brain and spinal cord) in presence of a CMN and its estimation of 5-10% of people with GCMN.

There have been seven documented cases of rhabdomyosarcoma developing within congenital melanocytic nevi, one of which was associated with neurocutaneous melanosis.[1-3] We report a newborn with rhabdomyosarcoma arising within a giant congenital melanocytic nevus and associated with neurocutaneous melanosis.

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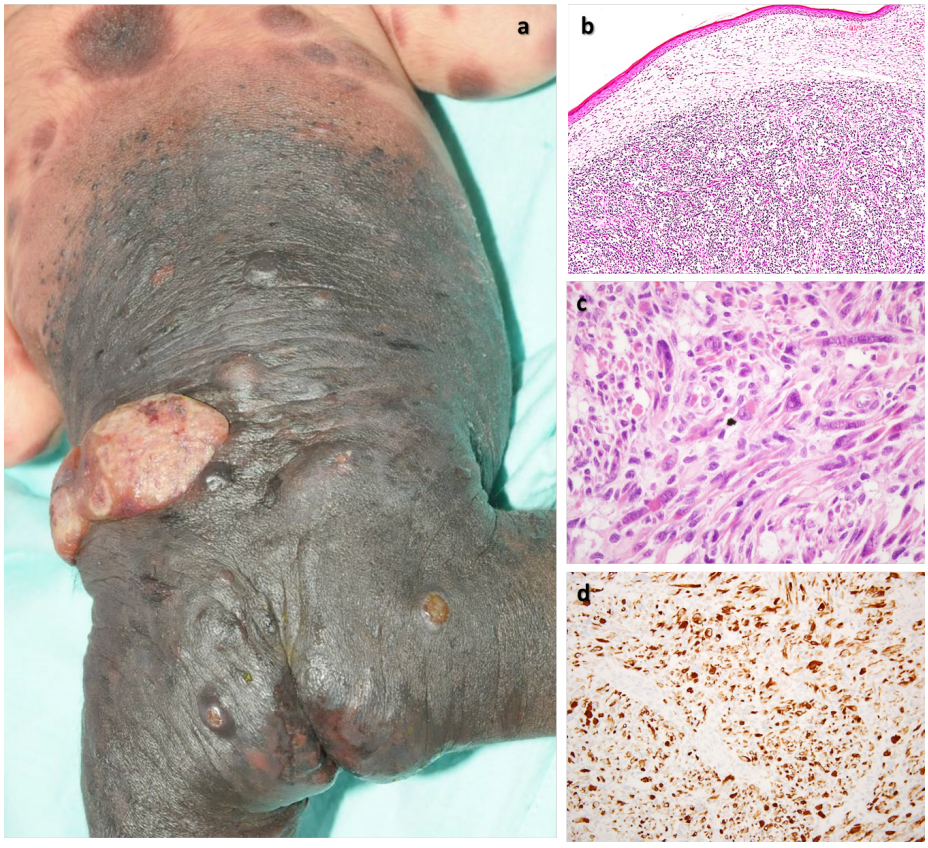
Case Report

A full term female infant was born with giant CMN, covering the whole of lower back extending anteriorly to the abdomen, buttock and both lower thighs, described as bathing trunk naevus. There were numerous hyperpigmented satellite nevi of variable size over the face, upper chest, upper back and bilateral extremities. Also noted an ulcerated nodule measuring 5cm X 6cm over the left lower back at birth, which rapidly increased in size into a fungating mass as shown in figure 1a.

She was thriving well and other systemic examinations were normal with normal neurodevelopment milestone. The ulcerated mass was excised and histopathological examination showed a lesion with two distinct components. Beneath an ulcerated epidermis, there was an expansile hypercellular proliferation of pleomorphic cells within a fibromyxoid stroma in the dermis and sub- cutaneous tissue (Figure 1b). Most of the neoplastic cells were spindled with hyperchromatic nuclei. In some areas of the tumor, they were oval to round with abundant eosinophilic cytoplasm and eccentric nuclei (Figure 1c). Some had cross-striations characteristic of rhabdomyoblasts. Numerous abnormal mitotic figures were identified. These cells were strongly immunoreactive for desmin and myogenin (Figure 1d). They were negative for S-100 protein and HMB-45.

MRI of brain showed increase melanin patches over the left cerebellum consistent with neurocutaneous melanosis. Computed tomography scans of the chest, abdomen, and pelvis showed no evidence of metastatic disease. Bone marrow aspiration was negative for tumour cell. She received chemotherapy consisting vincristine and Actinomycin D in 3 blocks. She tolerated chemotherapy and remained well at 6 months follow-up.

Figure 1. (a) Note the large, ulcerated and fleshy fungating tumour over left lumbar region of the back measured 6cm x 5cm with minimal contact bleeding. Also note the giant congenital melanocytic naevus with satellite lesions over the upper back; **(b)** Histopathological examination (H&E) x 100 shows superficial dermis is composed of irregular nests of larger melanocytic cells closer to the dermoepidermoal junction containing coarse melanin pigments; **(c)** H&E x 600 magnification shows a large part of the lesion is infiltrated and replaced by malignant spindle shaped cells seen arranged either loosely or compact cellular pattern with mitotic figures; **(d)** Immunohistochemical studies x 600 magnification shows tumour cells are strongly immunoreactive to Desmin and Myogenin but negative to S100, HMB45, Caldesmon and Cytokeratin



Discussion

Congenital melanocytic nevi are cutaneous maldevelopmental lesions of the ectoderm, specifically the neural crest. There is evidence the CMNs arise as a result of an oncogenic mutation, most commonly involving NRAS, occurring in a melanoblast or neural crest precursor cell before its migration along the dorsolateral pathway to the skin.[1-2] These lesions are commonly characterized according to the greatest predicted diameter they may attain in adulthood as small (<1.5 cm), medium (1.5–20 cm), large (>20 cm), and giant (occupying a significant proportion of the cutaneous surface).[1-2]

Congenital giant melanocytic nevi may occur in association with leptomeningeal melanocytosis, a related neural crest maldevelopmental abnormality.[3] This lethal condition is characterized by a benign or malignant melanocytic proliferation in the central nervous system in association with a giant congenital melanocytic nevus.

Malignant melanoma is the most frequent neoplasm complicating giant congenital melanocytic nevi, with a reported incidence of 2% to 13%.[4-6] Other malignancies have been reported include malignant melanoma with rhabdomyoblastic differentiation, sarcoma with liposarcomatous and rhabdomyoblastic differentiation, rhabdomyosarcoma, and malignant peripheral nerve sheath tumor.[8-9] There have been only seven previously documented cases of rhabdomyosarcoma originating from congenital melanocytic nevi[3,5,7-11] as summarized in table 1.

Table 1. Summary of the clinical, histology and outcome of seven cases previously reported with rhabdomyosarcoma originating from congenital melanocytic nevi

Authors	Age at presentation	Site	Rhabdomyo-sarcoma sub-type	Treatment & Outcome
Christman et al	4 months old	Bathing suit distribution	Embryonal	Chemotherapy & alive at 6 years follow-up
Houng et al	4 years old	Left gluteal & sacral	Embryonal	Refused chemotherapy, died 13 months after diagnosis
Zuriga et al	Newborn	Post neck & upper back	Embryonal	Had leptomeningeal melanosis Chemotherapy, died at Day 30 of life
Schmidt et al	7 months old	Trunk & thigh	Embryonal	Chemotherapy, alive at 1-year follow-up
Hendrikson et al	7 months old	Left cheek & scalp	Mixed with liposarcoma	Chemotherapy, alive at 3-years follow-up
Chikhalkar et al	21 years old	Gluteal and sacral	Alveolar	Chemotherapy died 1 month after diagnosis
Ilyas et al	4 months old	Bathing suit distribution	Embryonal	Chemotherapy, alive at 1-year follow-up

Histologically, giant CMN demonstrate mixtures of tissues derived from the neural crest that show melanocytic and occasionally neural supportive differentiation[5]. It is likely that the common pluripotent stem or neural crest cells from which these elements are derived cause these combined features.

Reports of proliferating mesenchymal elements within CMN are rare, which might suggest that the culprit oncogenic mutations occur in more primitive precursor or stem cells before their differentiation into a melanoblast.

Conclusion

Rhabdomyosarcoma is a rare tumour associated with congenital melanocytic naevus, nevertheless, clinicians should consider rhabdomyosarcoma in the differential diagnosis of lesions arising within the nevus.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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CASE REPORT

Diagnostic Biopsy Site in Cutaneous Angiosarcoma: Reflections from 3 Cases

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Summary
Angiosarcoma is a rare, malignant vascular endothelium neoplasm with poor prognosis. Cutaneous angiosarcoma makes up a majority of its presentation. Diagnosis is often delayed due to the nature of its clinical presentation. We report 3 cases of cutaneous angiosarcoma to focus on the importance of biopsy site selection in securing the histopathological diagnosis.

Key words: *Angiosarcoma, Soft tissue sarcoma, Radiotherapy, Skin biopsy*

Introduction
Angiosarcoma is a rare and aggressive malignancy of the blood or lymphatic endothelium. It accounts for about 3.9%-5% of all soft tissue sarcomas,[1,2] 15% of the soft tissue sarcomas located in the head and neck[3] and 1.6% of all cutaneous soft tissue sarcomas.[4] Angiosarcoma occurs at anywhere but it has a predilection for the head and neck.[3,4,5] The skin is a common site of angiosarcoma presentation.[2,6] There are 3 types of cutaneous angiosarcomas: primary sporadic, post-radiation, and chronic lymphedema-associated angiosarcoma.

Cutaneous angiosarcoma classically present as purpuric, ecchymotic or erythematous swelling, patches or plaques that may look benign initially. Early diagnosis of cutaneous angiosarcoma based on clinical features alone is challenging as it can mimic other conditions like ecchymoses, rosacea, vasculitis and cellulitis. Tissue biopsy is important in establishing the diagnosis and the biopsy site affects the histopathological yield. Inconclusive histopathology will further delay the diagnosis and treatment of patients. In this report, we demonstrate the importance of the correct biopsy site and recommend the best site for biopsy. Three cases of cutaneous angiosarcoma diagnosed in our center from 2007 to 2017 are presented.

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Case 1

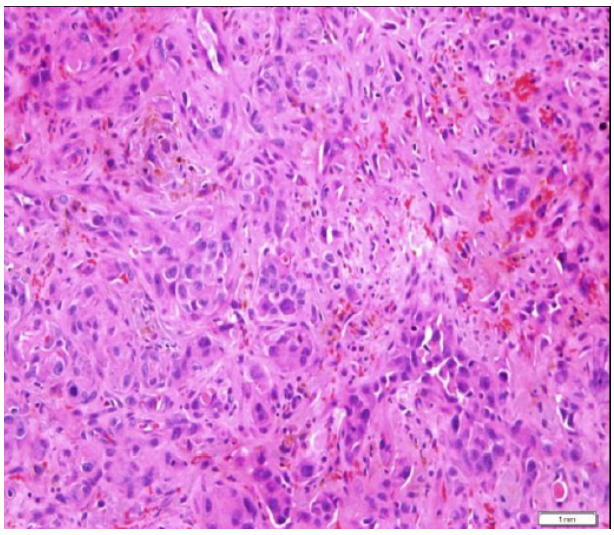
A 78-year-old Chinese man with transglottic laryngeal squamous cells carcinoma presented with a 3 weeks history of blood stained secretions from his tracheostomy stoma. Total laryngectomy was performed for the T3N0M0 laryngeal carcinoma about 2 years ago, the surgery was followed by radiotherapy. He has been well since completion of his cancer treatment. He noticed a rash on his chest 2 months prior to his bleeding tracheostomy stoma. The rash was asymptomatic but spread rapidly. He was a chronic smoker and had type 2 diabetes mellitus, hypertension, and dyslipidemia.

On examination, blood stained secretions and small blood clots were observed at the stoma. There were purpuric plaques, papules and nodules surrounding the stoma, extending to his upper anterior chest. The lesions were non-tender, the larger nodules and plaques were fluctuant while the papules were firm. Telangiectatic patches were seen especially at the edges of the abnormal skin area on the chest (Figure 1A & 1B). Computed tomography (CT) scan of neck, thorax, and abdomen showed a left posterior cervical mass with matted cervical lymphadenopathy measuring 6.0x 4.8x 7.0 cm.

Figure 1A & 1B. Multiple purpuric plaques, nodules and papules with telangiectatic patches on the anterior chest. A: site of the first biopsy. B: site of the repeat biopsy

Punch biopsy was performed on a well formed purpuric patch, unfortunately it did not reveal any specific abnormality. A second biopsy was then performed at a purpuric, fluctuant nodule. It showed intradermal proliferation of atypical plump epithelioid endothelial cells with hyperchromatic nuclei and moderate amount of granular eosinophilic cytoplasm. The atypical cells formed indiscernible vascular spaces containing few red blood cells. Mitoses were easily seen. Chronic inflammatory cells with scattered melanophages were seen interspersed throughout the specimen. The deeper dermis displayed areas of hemorrhage and solar elastosis (Figure 2). The atypical cells were diffusely positive to CD31, focally positive to CD34 and negative to CKAE1/AE3 and S100. The findings were consistent with angiosarcoma. Treatment with radiotherapy stopped the bleeding from the tracheostomy stoma. The patient did not return for follow up after completion of radiotherapy.

Figure 2. Irregular dilated vascular channels lined by plump endothelial cells with hyperchromatic and pleomorphic nuclei (H&E x 40)



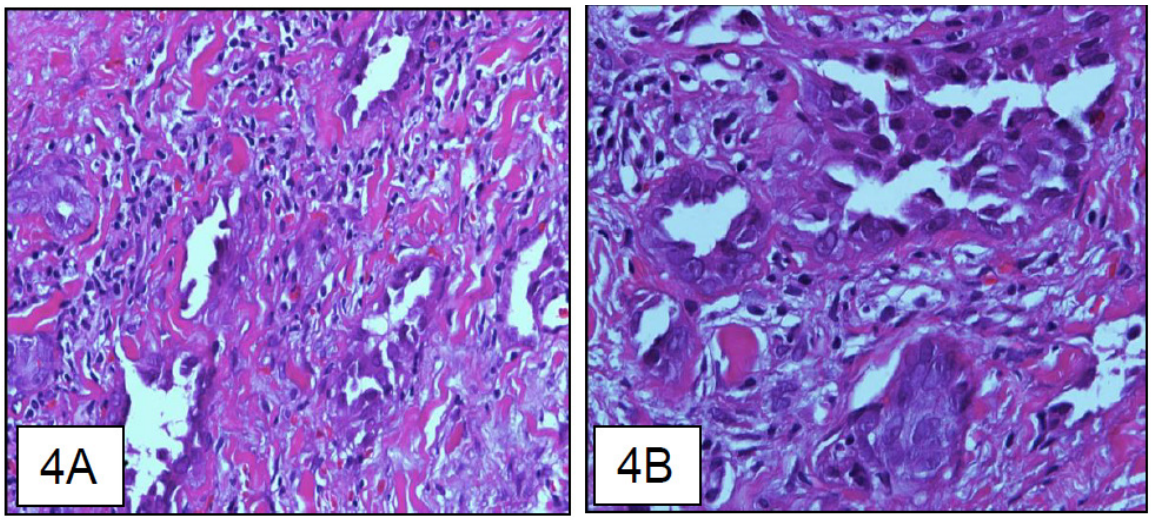
Case 2

An 82-year-old Malay man presented with swelling and redness of his left face of 3 months duration. It was thought to occur following an insect bite on his left pinna, the swelling later spread to forehead, orbital and cheek. He was treated with cloxacillin for chronic left perichondritis and preseptal cellulitis, however the lesion persisted. His co-morbidities included hypertension, gouty arthritis, lumbar spondylolisthesis and chronic kidney disease. On examination, there was a large, non-tender, indurated, erythematous plaque involving the left retro-auricular region extending to the pinna, left temple, cheek and periorbital area with marked eyelid oedema (Figure 3).

CT scan showed thickened and enhanced subcutaneous tissue at left forehead, preseptal region, left anterior cheek and pinna including the pre and post auricular regions. The left globe was normal. The masseter muscles, infra-temporal and masticator spaces were normal without fat stranding or enhancement within. There were no significantly enlarged lymph nodes. Punch biopsy was performed on a thick, indurated area at the pre-auricular area (Figure 3). Histopathological examination showed irregular anastomosing vascular channels, which dissect trough the fibro-collagenous stroma. Papillary tufting was seen within the vascular spaces which were lined by atypical endothelial cells displaying irregular and hyperchromatic nuclei. The surrounding stroma is sclerotic and heavily infiltrated by lymphocytes and histiocytes (Figure 4A & 4B). Immunohistochemistry showed the atypical endothelial cells were reactive towards CD31. A diagnosis of cutaneous angiosarcoma was made. Surgery was not feasible as the tumour was extensive. Radiotherapy was recommended but the patient refused. He succumbed to the condition six months later.

Figure 3. Swollen, erythematous, indurated left face and pinna with periorbital oedema. Biopsy site is marked with a black circle

Figure 4A (H&E x40) &4B (H&E x60). Anastomosing, dilated vascular channels. Papillary tufting was seen within the vascular spaces which were lined by atypical endothelial cells displaying irregular and hyperchromatic nuclei



Case 3

A 55-year-old Chinese man presented a plaque on the forehead of 3 months duration. The initial lesion was described as a reddish papule. He was a chronic smoker with type II diabetes mellitus, hypertension and dyslipidemia. On examination, there was a large purpuric plaque over the forehead with an ulcerated, necrotic area. The plaque was fluctuant around the ulcer and indurated laterally. A purplish hue was observed around the plaque extending to the periorbital and upper cheek areas. There was bilateral periorbital oedema (Figure 5).

Skin biopsy was performed at an indurated area near the edge of the plaque. It showed non-specific acute on chronic inflammation. A second biopsy was performed at a fluctuant area at the edge of the ulcer, extending into the ulcer (Figure 5). The histopathology was consistent with angiosarcoma, positive to CD31 immunohistochemically. There were infiltration of the papillary dermis, dermis and subcutis by malignant endothelial cells. The malignant cells lined the vascular spaces and displays oval, plump nuclei and inconspicuous nucleoli. Mitosis and areas of necrosis are seen (Figure 6). CT scan showed soft tissue swelling of forehead and scalp with no distant metastasis. Complete surgical excision was not possible, therefore the patient was treated with tomotherapy. However, he succumbed after about 10 months.

Figure 5. A large purpuric plaque over the forehead with an ulcerated, necrotic area. The plaque was fluctuant around the ulcer and indurated at the peripheries. Area marked B was the site of the first biopsy, area marked A was the site of the second biopsy

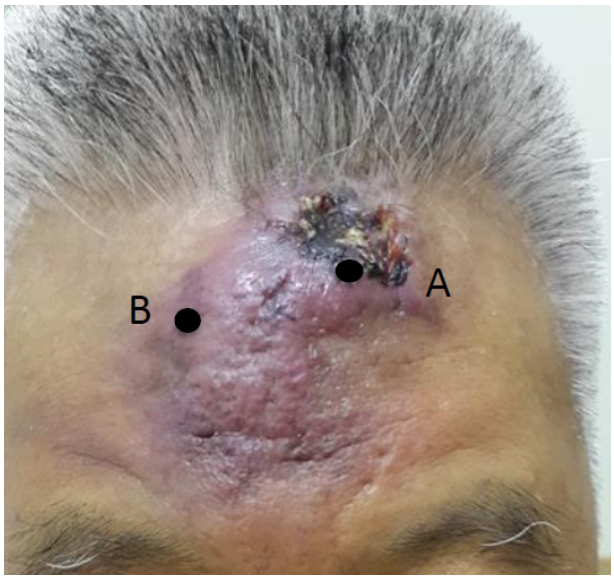
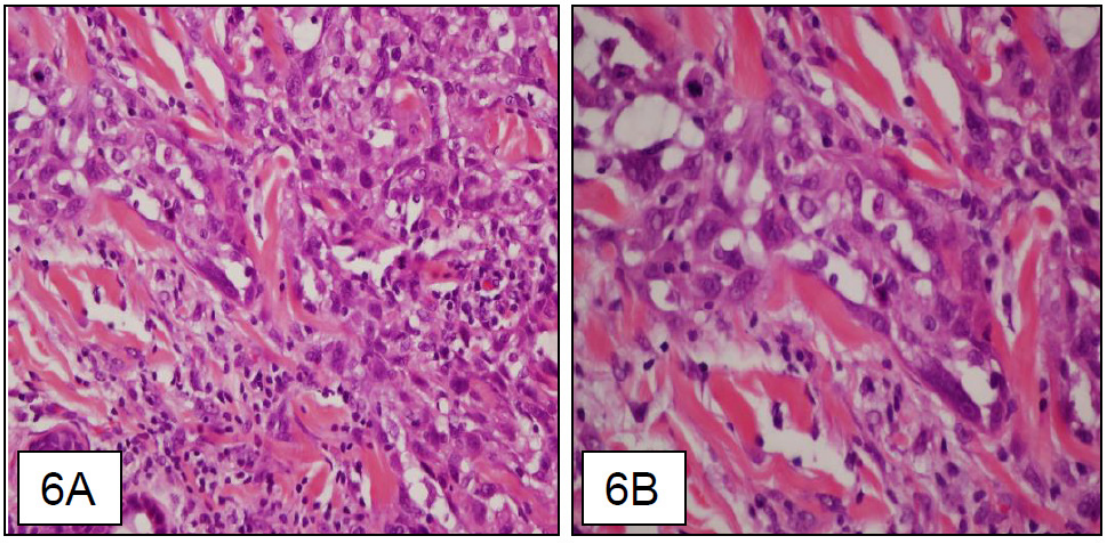


Figure 6A (H&E x 40) & 6B (H&E x 60). Infiltration of the skin by malignant endothelial cells. The cells displays oval, plump nuclei and inconspicuous nucleoli



Discussion

Cutaneous angiosarcoma is more common in elderly males.[2,4,7] All of our patients were male, however, one of our patient with primary sporadic type was of slightly younger age. Of the 3 types of cutaneous angiosarcoma, the primary sporadic type typically affects sun-damaged skin of the head and neck region in elderly males. Post-radiation angiosarcoma may occur as early as 1 year after the exposure. The latency period for breast cancer patients is shorter compared to patients that received radiation therapy for other types of cancer.[8] The risk is highest between 5 to 10 years for post breast cancer radiation therapy.[9,10] The latency

period for post-radiation sarcoma in patients with nasopharyngeal carcinoma is around 9-10 years.[11,12] Our patient developed angiosarcoma much earlier. A latency period of less than 3 years is rare.[11,12]

The clinical features of cutaneous angiosarcoma may delay the diagnosis as it frequently mimics other diseases. Due to its rarity, it may not be clinically recognized or suspected, especially for the primary sporadic type. Histopathology is the key for diagnosis. Obtaining a good biopsy specimen for histopathological examination will prevent further delay in the diagnosis and treatment. The diagnoses in two of our patients were delayed as their first biopsies from well- formed purpuric patches at the periphery of the lesion showed non-specific findings. From our experience with these 3 cases, we would like to recommend the biopsy to be performed at the center of the lesion where it is thickest, most indurated or most fluctuant. This would be the area where the lesion initially appeared.

Angiosarcoma usually spread aggressively through the lymphatic or hematogenous route. The lung is the most common site of distant metastasis followed by bone, liver and lymph nodes.[5,13] About 20% to 30% of patients had metastases at presentation.[5,6,13] Combination of surgery and radiotherapy is the mainstay treatment for cutaneous angiosarcoma. It results in better overall survival compared to surgery or radiation alone.[6,14,15,16] Regional lymph nodes were not affected and distant metastases were not found in our patients at presentation. Case 3 succumbed within 6 months of diagnosis despite radiotherapy. The prognosis for angiosarcoma is poor. The 5-year disease specific survival rate is between 40% to 60%.[6,13,17,18,19,20] The benefit of chemotherapy is still unclear.[16,19] Promising results have been demonstrated with taxanes.[21] None of our patients received chemotherapy.

Conclusion

Cutaneous angiosarcoma should be considered in purpuric lesions affecting the head and neck of elderly males and in those with prior radiation therapy. The thickest, most indurated or most fluctuant area where the lesion first appeared yields the best diagnostic biopsy outcome.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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CASE REPORT

Verrucous Hemangioma of the Thumb in Children: A Rare Presentation

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Summary
Verrucous Hemangioma (VH) is a rare capillary vascular anomaly, frequently clinically mistaken to Angiokeratoma. It's frequently reported to manifest in lower extremity and is commonly unilateral. Other locations of its presentation are scarcely reported. We demonstrated a Verrucous Hemangioma of unusual location at the thumb of child and its surgical management which remain as a primary modality of the treatment.

Key words: *Verrucous Hemangioma, Vascular Malformation, Vascular Tumor*

Introduction

Verrucous hemangioma (VH) is an uncommon capillary anomaly, frequently mistaken for its mimic; Angiokeratoma. About 95% of the cases arise from lower extremity and are commonly unilateral. It might involve unusual anatomic locations such as the abdomen, arm, and glans penis.[1] Worldwide only a few had it reported at upper extremity with a mere cases occurred on digits. Verrucous haemangioma if left incompletely excised has a great chance of recurrence. In this report, we demonstrated VH of unusual location on the right thumb in a child and its surgical management with a cutaneous skin graft that was successfully used as skin coverage without relapse.

Case Report

A two years and six months old boy presented to the out-patient clinic with a swelling on his right thumb noted since birth. The lesion gradually increased in size, was painless and occasionally bled upon contact. Physical examination revealed a well-defined 2 cm x 2 cm hard dome shaped mass with multiple dark bluish blebs on the skin overlying the ulnar aspect of right interphalangeal thumb (Figure 1a). The mass was firm, immobile, non-tender, non-pulsatile, no ulceration nor bleeding noted. Based on clinical findings a provisional diagnosis of a low flow vascular malformation was made.

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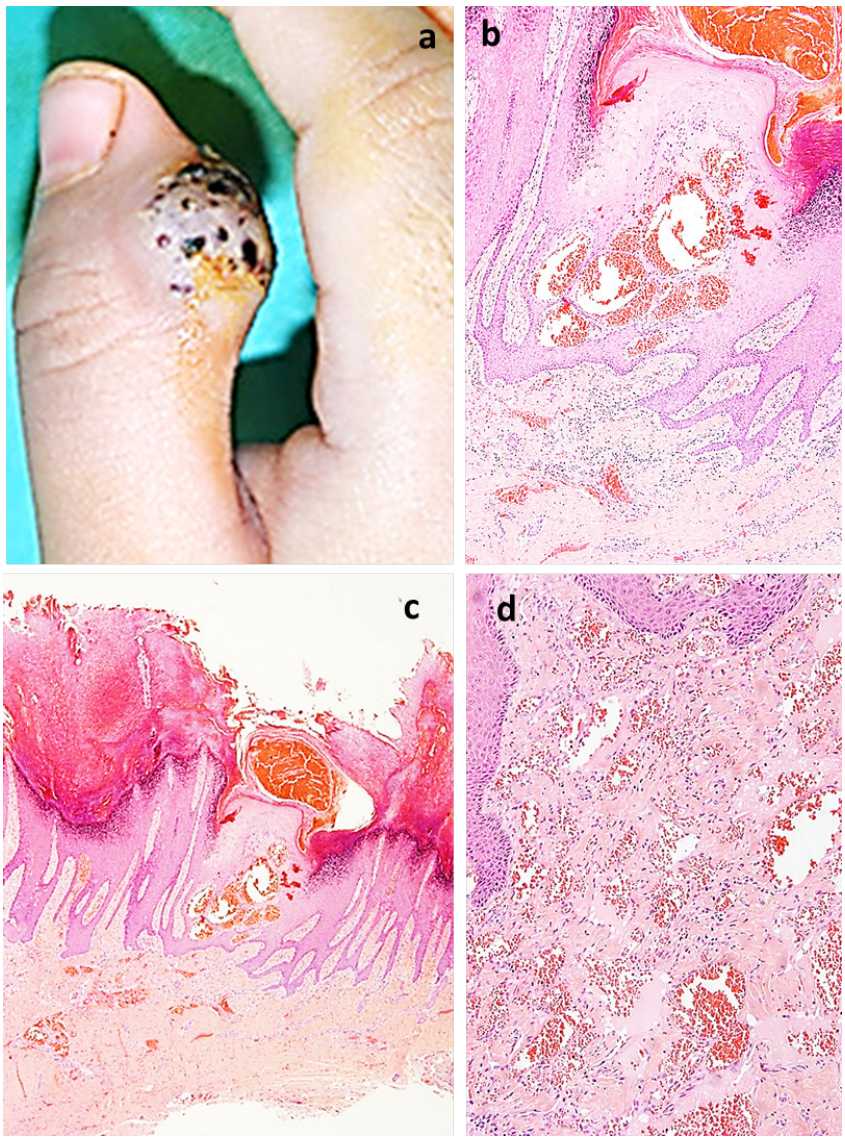
Figure 1. (a) Vascular anomaly of the right thumb; **(b)** The epidermis showed hyperkeratosis and acanthosis with intact granular layer as well as elongation of the rete ridges (H&E: 40x); **(c)** There was proliferation of capillaries within epidermis and dermis (H&E: 100x); **(d)** These capillaries were lined by flattened endothelial cells without nuclear atypia and no mitosis was seen (H&E: 400x)



The child underwent an excision with a cutaneous graft as coverage for the defect. The graft take was 100%. Histopathological examination revealed proliferation of anastomosing capillaries with focal cavernous dilatation. The epidermis layer showed hyperkeratosis and acanthosis (Figure 1b). There was intact basal granular layer with elongation of the rete ridges. Vascular proliferation was also seen at mid-dermis (Figure 1c) and these capillaries were lined by flattened endothelial cells without nuclear atypia and no mitosis noted (Figure 1d). Hence the final diagnosis of Verrucous Haemangioma was made. Six months post-operative follow up showed the skin graft healed well with no functional limitation. There was also no residual or new vascular anomaly to note.

Discussion

The clinic-pathologic characteristics of VH were first reported by Imperial and Helwig in 1967 in a study of 21 cases and distinguished it from its imitator, Angiokeratoma. Verrucous Hemangioma signifies a rare congenital vascular anomaly that presents at birth or in early childhood. It is usually unilateral and localized to the lower limbs. Verrucous Hemangioma in upper limb is very unusual and although few had described it on digits in adult but no literature had ever reported it at thumb in children as in our case. It does not involute spontaneously and can persist after inadequate excision. With time it darkens, thickens to become hyperkeratotic, and occasionally bleed with ulceration, without regression.[2]

Contrarily to other forms of vascular anomalies, in VH categorisation as a vascular neoplasm or vascular malformation cannot be established. Its classification is still uncertain because it demonstrates clinical features alike to those seen in vascular malformations, but expresses an immune-profile similar to vascular neoplasms (WT1 and Glut-1 positivity).[3] Regardless of its misrepresentative name, VH is considered by most a malformation rather than a true hemangioma.[4] and it was lately been categorized as provisionally unclassified vascular anomalies in the 2014 International Society for the Study of Vascular Anomalies (ISSVA) classification. However, North et al. textbook on vascular anomalies pathology as well as per McCuaig CC proposal (2017), proposes that Verrucous Venulocapillary Malformation is a more appropriate designation for this lesion.[2]

By histopathology examination, it should be distinguished from other vascular anomalies by the presence of epidermal verrucous hyperplasia along with dilated capillaries and venules extending deep into the dermis with a low mitotic rate.[1] It also marks proliferative response of the epidermis highlighting hyperkeratosis, irregular epidermal acanthosis and papillomatosis. There is presently no specific immune-histochemical marker for VH and therefore the diagnosis should be considered after vigilant clinic-pathological correlation.[4]

Early diagnosis and intervention is vital in selected patients for timely surgical excision and better cosmetic outcome as they do not involute spontaneously. As in our case, early diagnosis and surgical excision is essential to prevent further growth and recurrence. However the excision of the lesion to a free margin had left the defect too large to be closed primarily hence a full thickness skin graft was utilized to cover the defect. The lesion was surgically excised and showed no relapse at 6 months, indicating that surgery remain as a primary modality of treatment for a localized VH.

Conclusion

Verrucous Hemangioma or Verrucous Venulocapillary Malformation is a rare condition, must be distinguished early for surgical intervention and for better cosmetic outcome. We present this case for its sheer rarity of its presentation, its notoriety for recurrence and the use of cutaneous graft as a successful coverage after an excision.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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

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CASE REPORT

A Case of Basal Cell Carcinoma on the Left Cheek in a 62-Year-Old Woman, Operated by Wide Excision with V-Y Subcutaneous Tissue Pedicle Island Advancement Flap Under Bilevel Surgical Tumescent Anesthesia

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Summary
Basal cell carcinoma (BCC) is a nonmelanocytic skin cancer that arises from basal cells, slow-growing tumors that almost never metastasize. Untreated BCCs have the potential to continue to grow and destroy surrounding skin and nearby structures leading to physical deformity. The key to treatment is to ensure that there is no more cancer left in the skin. Reconstruction with V-Y skin flaps can be performed in several areas of the face. We reported a 62-year-old female patient with pigmented nodular BCC tumor on left cheek who was successfully treated with wide excision with V-Y skin flap under bilevel surgical tumescent anesthesia.

Key words: *Basal cell carcinoma, Wide excision, V-Y flap*

Introduction
The incidence of skin tumors is increasing in parallel with numbers of elderly patients. Furthermore, because skin tumors are asymptomatic, outpatient department visits are commonly delayed. Basal cell carcinoma (BCC) is defined by the World Health Organization Committee on the histological typing of skin tumours as "a locally invasive, slowly spreading tumour which rarely metastasise, arising in the epidermis or hair follicles and in which, in particular, the peripheral cells usually simulate the basal cells of the epidermis". Basal cell carcinoma (BCC) is the most common skin cancer with significant local tissue invasion and morbidity.[1,2]

Current treatment modalities for skin cancers and premalignant lesions include surgical excision, electrocautery, curettage, cryotherapy, and irradiation, but surgical excision has been reported to be the best treatment modality for cancer treatment and preventing recurrence. On the other hand, surgeons select the methods of reconstruction for the soft tissue defects after surgical excision based on considerations of the tumor type and location, patient age, and cosmetic and functional factors. There are four methods of reconstruction: primary closure, skin grafting, and local and free flaps.[1,3]

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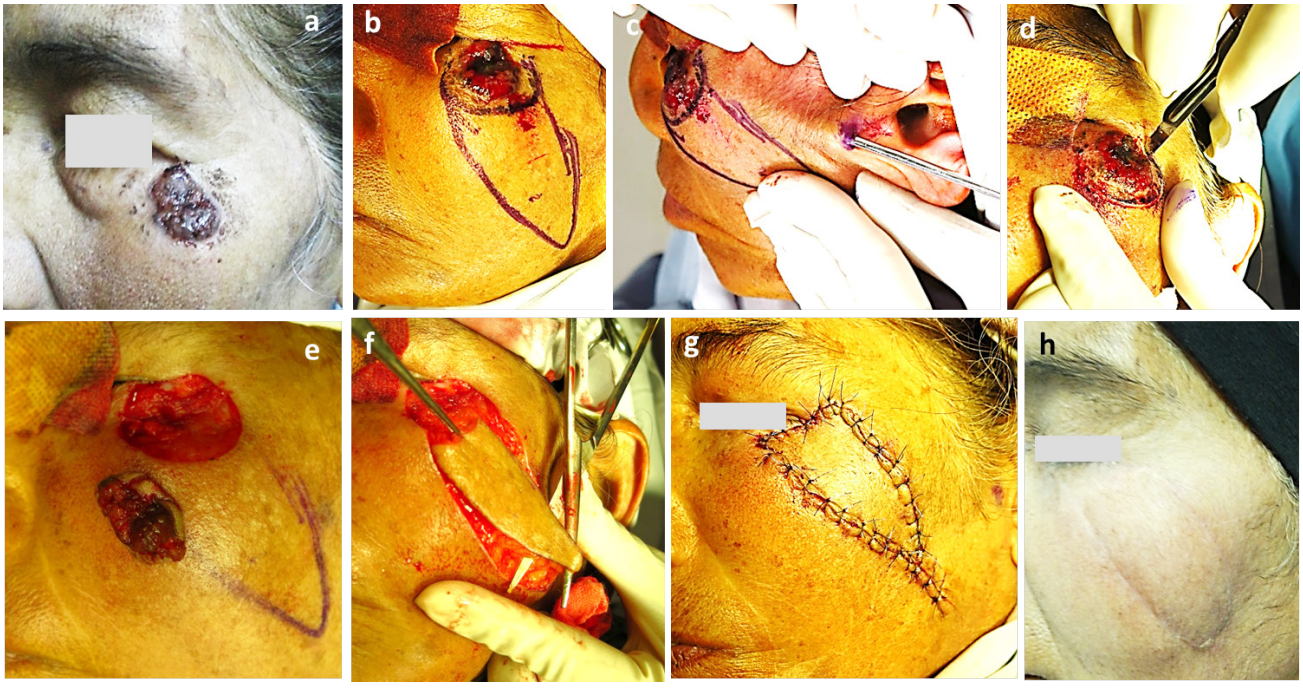
No single flap is optimal for every defect. Each defect must be individually analyzed for depth, distortion of surrounding subunits, and normal tissue available for reconstruction.[3-5] Flaps include advancement, pivotal, transpositional, rhombic, and bilobed flaps. Advancement flaps are subclassified as simple, single pedicle, bipedicle, and V-Y flaps. The subcutaneous pedicled V-Y flap is an advancement flap first described by Barron and Emmett. This flap usually has random vascularization. Technically, it consists of a triangular island designed adjacent to the defect, with its base along one of the borders of the defect. The width of the flap should be similar to the width of the defect and its length should be twice the height of the defect.[6,7] Dissection of the deep part of the flap is avoided as this will be its vascular pedicle. If necessary, the incisions that make up the triangle can be curved in those areas in which the tension lines suggest such a design, as this will better camouflage the scar. The design of a V-Y flap is very simple. The concept is to use skin from an area of relative excess to fill an area of deficiency. A "V"-shaped flap is incised adjacent to and advanced into the defect. The donor site is then closed in a straight line, which gives rise to the "Y"- shaped closure.[8,9]

Case Report

We present a case 62-year-old female, farmer by occupation came with complaints pigmented skin tumor on left cheek since ten months,.There was gradual increasing in size of the pigmented tumor. There was no history of bleeding or discharge. Patient refuses to use sunscreen and denies use of long-sleeved shirts, hat or other forms of protection against UV rays. She did not know about occurrence of skin cancer in her family. Vitals and general examination were normal on presentation. Based on dermatological examination there was pigmented tumor 2x2x0,3 cm in size with irregular border (Figure 1a). Histopathological examination revealed the diagnosis of nodular BCC. Patient was operated by V-Y subcutaneous tissue pedicle island advancement flap under bilevel surgical tumescent anesthesia (Figure 1b - g).

Figure 1. (a) Pigmented tumor 2x2x0.3cm in size with irregular border; **(b)** V-Y advancement flap design; **(c)** From the preauricular region, we injected local anesthesia of pehacain® (lidocaine 20mg, adrenalin 12.5 mcg) to insicion this area for inserting infiltrator cannula 3mm, then the tumescent solution 100cc (ringer lactat 100cc, lidocaine 2% 10cc, epinephrine HCl 0.2 cc) injected subcutaneously using infiltrator cannula under the lesion and its surroundings then wait for 20 minutes for local anesthesia to work maximally; **(d)** Tumor resection; **(e)** Tumor has been removed; **(f)** Pedicle island is freed from the surrounding tissue, but subcutaneous tissue under 'island' remains intact for the blood supply to the tissue remains, then undermined by blunt scissors on the area around the incision lines; **(g)** The tumor has been removed and the donor site is then closed in a straight line, which gives rise to the "Y"- shaped closure; **(h)** Result at 10 months follow-up



Discussion

Basal cell carcinoma, also known as basal cell cancer, is the most common type of skin cancer. Similar to other non-melanoma skin cancers, its incidence is rising. Recently, the incidence of BCC has been increasing among Asians. It often appears as a painless raised area of skin, that may be shiny with small blood vessels running over it or it may present as a raised area with ulceration. Basal cell carcinoma grows slowly and can damage the tissue around it but is unlikely to spread to distant areas or result in death. The nodular, superficial spreading and infiltrating variants are the three most commonly encountered types of BCC in descending order of prevalence.[1,2]

A number of different techniques have been described for reconstruction of the face defects after excision of malignant tumors. To date, there are no clear criteria for the selection of one or the other technique.[8,10] We used V-Y advancement flaps to reconstruct soft tissue defects after the surgical excision of skin tumors of the face. The advantages of the V-Y advancement flap are the preservation of sensation and length, and good soft tissue coverage. V-Y advancement flap was designed as these flaps have an excellent blood supply from subcutaneous tissue. Thus, by using V-Y advancement flaps we have achieved excellent cosmetic outcomes in the facial region.[11,12]

Appropriate margins for malignant tumors depend on the cancer type, tumor size, tumor irregularity, and time elapsed from onset. In cases of basal cell carcinoma, an appropriate excision margin would be 2 to 5 mm from the tumor.[12] In our case, we used mean safety margins of 3 mm, and all margins were proved to be free by histopathological examination.

Follow up 10 months after surgery (Figure 1h), there was no tumor recurrence. Eyelid closure was adequate and there were no any sensory neuropathy, numbness, paresthesia. Patient is satisfied with the result of surgery. Although there are various methods for reconstructing skin defects created by skin tumor resection, we believe that the V-Y advancement flap produces good treatment outcomes in cases with small-to-medium defects.

Conclusion

Aesthetic reconstruction of facial defects should adhere to the priority goals of first preserving function and second achieving cosmesis. According to the size of the defect, location on the cheek, relationship to adjacent structures, available donor tissue, and existing skin tension lines, a host of techniques is available for closure. Useful in coverage of large cheek wounds, the V-Y advancement flap is equally effective for small defects or those approximating the lid or lateral cheek.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

Nil

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CASE REPORT

Efficacy of Topical Immunotherapy with Squaric Acid Dibutylester in the Treatment of Alopecia Areata – A case series of 11 patients

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Summary

Alopecia Areata (AA) is a common autoimmune mediated, non-scarring alopecia directed against the anagenic hair follicle. Various treatment modalities have been used for the treatment of severe/recalcitrant AA. Topical immunotherapy is the best documented treatment so far for severe and refractory AA. Dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphencyprone (DPCP) are the contact sensitizers used for this treatment. We report the SADBE treatment experience among AA patients at Department of Dermatology, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia.

Key words: *Squaric acid, SADBE, Alopecia*

Introduction

Alopecia areata (AA) is an autoimmune mediated non-scarring hair loss directed at anagenic hair follicle, most commonly on the scalp.[1-3] The severity ranges from alopecia areata to severe form of alopecia totalis (AT) and alopecia universalis (AU). Squaric acid dibutylester (SADBE) is a form of contact sensitizer used as immunotherapy in AA with promising outcome and good tolerability with less side effects. This study aimed to determine SABDE treatment outcome and side effects among AA patients at Dermatology Department, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia.

Materials and Methods

This was a retrospective cross-sectional single center study conducted from December 2015 to July 2017 among patients diagnosed with AA. All patients who failed conventional treatment and had completed SADBE treatment for at least 3 months were recruited in this study. The data collected include patient's demography, disease subtype, duration of presentation before SADBE treatment, clinical response to SADBE and side effects. The various concentrations of SADBE in acetone were prepared by the hospital pharmacy. SADBE treatment regime was designed as such that AA patients were first sensitized with 2% SADBE. This was then followed by weekly application of SADBE with initial concentration of 0.001% which then increased gradually to 0.01%, 0.1%, 0.2%, 0.5%,

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1% till a maximum of 2%. The SADBE was painted in a linear fashion without overlap to the affected areas and left on for 8 hours. Optimal SADBE concentration was determined by the manifestation of mild dermatitis (mild erythema and pruritus). Severe reactions such as persistent irritation (defined as itchiness, erythema and scaliness lasting more than 3 days), vesicle or blister formation were documented as side effects and was treated with topical steroids. SADBE was then withheld for 2 weeks and restarted at a lower concentration. Once the patient reached optimal SADBE concentration, this treatment was continued once a week till significant hair growth with good response noted.

Clinical response to SADBE was determined by McDonald Hull and Norris's grading system[4] as follow:

Grade 1 - Regrowth of vellus hair
Grade 2 - Regrowth of sparse pigmented terminal hair
Grade 3 - Regrowth of terminal hair with patches of alopecia
Grade 4 - Regrowth of terminal hair on scalp

Achievement of grade 3 and 4 were considered as good response, otherwise the grade 1 and 2 were considered as no response. Results were presented median (IQR) and frequency (%).

Results

A total of 11 patients were recruited in this review. Patients' median age were 13 (IQR: 9, 33), majority of them were female (73%) and Malay ethnicity (55%). Five (45.5%) of them were identify to have AA affecting less than 50% of the scalp and 6 (54.5%) were having severe types (1 patient had AT and 5 patients had AU). The median duration of presentation to initial SADBE was 24 months (IQR: 12, 60).

Overall, 8 patients (72%) had achieved good response. Patients with less than 50% scalp involvement had a better response rate than those with severe form of AA (80% vs 66%). The median duration taken to achieve good response was 5.5 months (IQR: 4, 7) among the 8 patients responded to SADBE treatment, 4 of them required 10 sessions of SADBE to elicit the regrowth of vellus hair at the concentration of 0.1 to 0.5% and the remaining 4 required more than 10 sessions before vellus hair formation. Of 3 patients who were not responded to the treatment, 2 patients were unable to be sensitized at the concentration of 2% and 1 responded with the formation vellus hair but failed to develop terminal hair. Three out of 11 patients had suffered from minor side effects including persistent irritation, vesicle and blister formation.

Table 1. Clinical characteristic and Treatment outcome of patients on SADBE

	Sex	Age	Subtype	Previous Treatment	Disease Duration	Outcome of SADBE	Duration to achieve good response	Side effect
1	F	6	AA	TCS	1 y	GR	7 m	-
2	F	33	AU	TCS, PUVA, CS	2 y	GR	7m	-
3	F	10	AU	TCS, PUVA	4 y	GR	16m	-
4	M	13	AA	TCS	7 y	GR	4 m	-
5	M	31	AU	TCS, IDK, CS	1 y	GR	6 m	-
6	F	61	AA	TCS, CS	1 y	GR	4 m	-
7	F	4	AA	TCS	5 m	GR	3.5 m	Irritation
8	F	32	AT	TCS, PUVA, IDK	2 y	GR	5 m	Blister
9	F	9	AU	TCS, CS	5 m	NR	-	-
10	M	12	AA	TCS, IDK	1 y	NR	-	Vesicle
11	F	42	AU	TCS, PUVA	7 y	NR	-	-

F: Female, M: Male,TCS: Topical corticosteroid, PUVA: Topical psoralen and ultraviolet A therapy, IDK: Intralesional corticosteroid, CS: Oral corticosteroid, y: year, m: month, GR: Good response, NR: Non response

Figure 1. 61 year old lady with progressively worsening of AA (left) who failed to repond to topical and oral corticosteroids. Regrowth of terminal hair after 4 months of SADBE (right)

Figure 2. AA in a 4 years old girl who failed to respond to topical corticosteroids (left) but responded well after 4 months of SADBE (right)

Discussion

Alopecia areata

AA is a common autoimmune disease, mediated by autoreactive CD8+ T cells, characterized by non scarring hair loss involving commonly on the scalp and the life time risk is 2%.[1-3] AA predominantly affects female as in our study (72% female) which was consistent with a study by Dall'oglio et al (53% female).[1] Current recommendations for treatment ranges from the use of corticosteroids (either topical, oral or intralesional) to phototherapy depending on age, subtype and severity.

SADBE

SADBE is a form of contact allergens of topical immunotherapy in treatment of AA whereby the recruited suppressor CD8+ T cells generate an inhibitory effect on the immune process against hair follicles, thus allowing hair growth. SADBE is an ideal non-mutagenic sensitizer as it is not widely found in nature, does not cause significant adverse events and does not cross reaction with other chemicals.[2-3]

Clinical Response

The clinical response to SADBE was according to a grading system proposed by Mcdonald Hull and Norris[4]

Grade 1 - Regrowth of vellus hair
Grade 2 - Regrowth of sparse pigmented terminal hair
Grade 3 - Regrowth of terminal hair with patches of alopecia
Grade 4 - Regrowth of terminal hair on scalp

Comparison with Other Studies

Success cases of SADBE

Our study showed 72% of patients with AA responded to SADBE and the response is better with less severe form of AA (80%) as compared to severe form AA (AT/AU) (66%). This result is supported by Case et al which also showed AA responded better than AT and AU at 73% and 30% respectively. Another study by Micali et al showed that 80% with less severe type of AA had good response to SADBE compared to 49% of more severe form of AA. Dall'oglio also showed that 80% of the treatment group had experienced hair growth compared to 50% of the control group. Ajith

et al too showed higher success rate in patients < 50% scalp involvement (68%) compared to diffuse type (29%).[2]

Failure cases of SADBE

There are cases that fail to respond to SADBE. Caserio et al only had 28.5% patients with significant hair growth after using SADBE.[2] The non responder rate in our series was 28% which is consistent with 20% of non responders in study by Case et al.[2]

Prognostic Factors

There are multiple factors that determine the disease response to SADBE. Indicators of poorer response include severity of alopecia, longer duration of disease and presence of nail factor.[5] Our study showed that 2 patients suffered from AU did not respond to SADBE. On the other hand, early development of contact dermatits within 10 weeks after sensitization is a good prognostic factor.[4] In our study, 4 patients had early contact dermatitis with vellus hair formation after 10 sessios of SADBE and they eventually showed good response to treatment.

Side effects

In general, SADBE is considered as a safe treatment but side effects may occur during the treatment which include auto-eczematization, blistering, swelling of regional lymph nodes, urticaria and contact leukoderma.[2,4] In our study , only 3 patients suffered minor side effects such as persistent irritation, vesicle and blister formation.

Conclusion

Majority of AA patients with different level of severity responded and tolerated SADBE treatment. Minor side effects were experienced by small number of patients. Hence, SADBE immunotherapy should be considered for patients with AA that failed to respond to topical or intralesional steroid injection.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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CASE REPORT

Phacomatosis Pigmentovascularis Type II: Case Report

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Summary

Phacomatosis pigmentovascularis is a rare syndrome first described by Ota et al, in 1947. It is characterized by a combination of capillary malformation and other pigmented naevi. It had originally been classified into four major types. A fifth type, in which the vascular lesion is cutis marmorata telangiectatica congenita (CMTC), was subsequently added. Each type was further categorized according to the absence or presence of associated extra-cutaneous signs as types (a) and (b), respectively. We reported this case due to its rare clinical presentation, with probable overlap Klippel-Trenaunay syndrome.

Key words: *Phacomatosis pigmentovascularis, Klippel-Trenaunay syndrome*

Introduction

Phacomatosis pigmentovascularis (PPV) is a rare syndrome first described by Ota et al, in 1947. It is characterized by a combination of capillary malformation and other pigmented naevi.[1] It arises sporadically, with no sex predilection.

Case Report

We report a 3-week old Malay male infant who is a product of a non-consanguineous marriage. He was born full term via spontaneous vagina delivery, weighing 3.8kg. The child's mother had varicella zoster at 11 weeks of pregnancy but she did not take any medications. The child's mother also had anaemia during pregnancy and was transfused with two pints of blood at 34 weeks of pregnancy. This is her firstborn and there is no family history of any vascular or pigmentary disorder.

The child presented with extensive erythematous to violaceous patches on his face, trunk and limbs with aberrant blue patches noted since birth. On examination, he was found to have port-wine stain (naevus flammeus) involving the left side of his face, bilateral upper limbs, trunk and back (Figure 1a&c). He also has extensive aberrant Mongolian spots over a large part of the trunk, back, gluteal and all four limbs (Figure 1d). There were bilateral oculocutaneous melanoses (Naevi of Ota) (Figure 1b). A mild degree of soft tissue hypertrophy of the left upper limb was also noted (Figure 1e).

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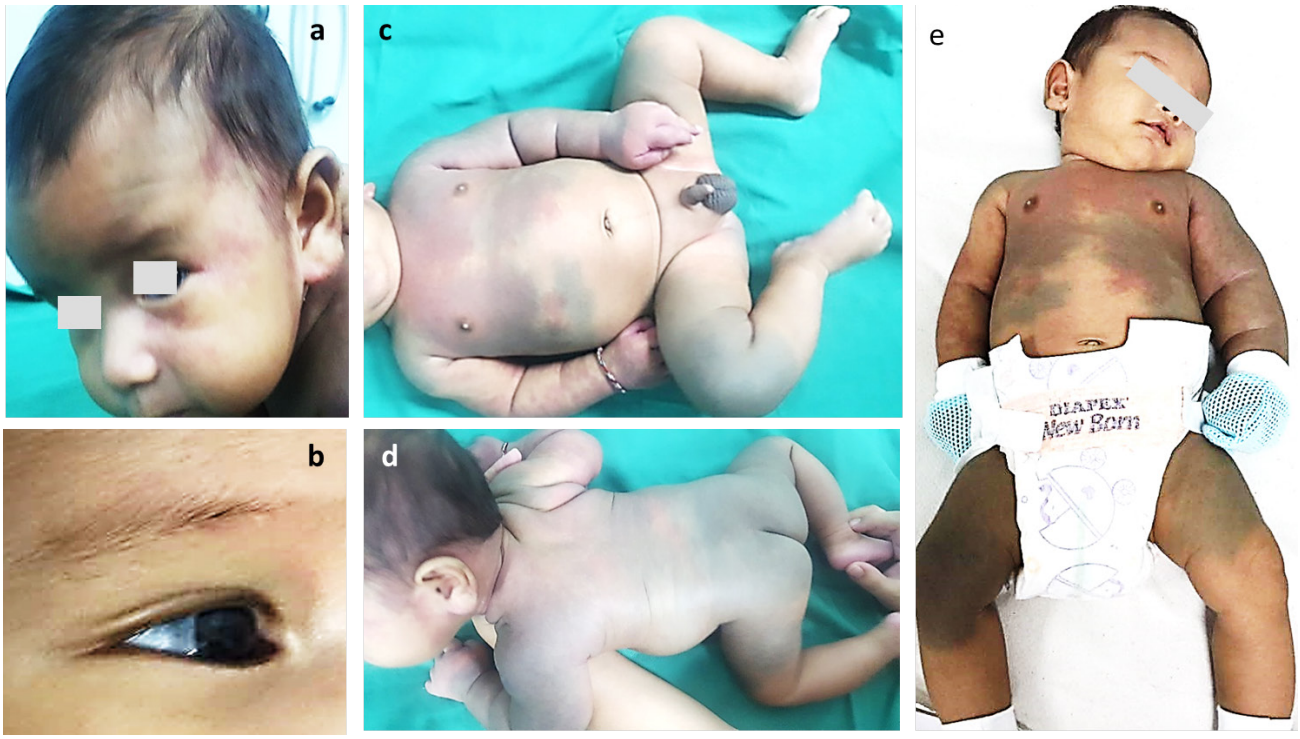
Figure 1. **(a)** Naevus flammeus involving left side of the face; **(b)** Oculocutaneous melanoses (Naevus of Ota); **(c)** Naevus flammeus and Mongolian spots on trunk, bilateral upper and lower limbs; **(d)** Extensive aberrant Mongolian spots and naevus flammeus over large part of the back and gluteal region; **(e)** A mild degree of soft tissue hypertrophy of the left limb



Ultrasound cranium, left arm and hepatobiliary system was done for this patient. The ultrasound cranium was normal with no focal brain parenchymal lesion, no cerebral atrophy, no intracranial haemorrhage and no hydrocephalus. Liver, spleen and bilateral kidneys are all normal. There is an increase in left arm muscle bulk with antero-posterior diameter on the left measuring 1.1cm compared to the right which measures 0.6cm. No definite collection was seen and colour Doppler study was normal.

Discussion

Phacomatosis pigmentovascularis, which was first described by Ota in 1947, is a rare congenital malformation syndrome characterised by vascular and melanocytic components. It arises sporadically and there is no sex predilection. PPV had originally been classified into four major types.[2] A fifth type, in which the vascular lesion is cutis marmorata telangiectatica congenita (CMTC), was subsequently added.[3] Each type was further categorized according to the absence or presence of associated extracutaneous signs as types (a) and (b), respectively. In 2005, Happle proposed a new, simplified classification encompassing four groups, using descriptive terms: phacomatosis cesioflamea; phacomatosis spilorosea; phacomatosis cesiomarmorata and phacomatosis pigmentovascularis of non-classifiable type.[4] In contrast to the traditional classification, this involves no subdivision between presentation with or without systemic symptoms. Furthermore, type I is excluded because there are no reported cases to date.

Table 1. Classification of Phacomatosis Pigmentovascularis

Type (according to Happle)	Type (according to Hasegawa)	Vascular lesion	Pigmentary lesion
excluded nevus	I	Nevus flammeus	Verrucous and pigmented
Cesioflammea	II	Nevus flammeus ± anemic nevus	Mongolian spot
Spilorosea	III	Nevus flammeus ± anemic nevus	Nevus spilus
Non-classifiable	IV	Nevus flammeus ± anemic nevus	Mongolian spot, Nevus spilus
Cesiomarmorata	V	Cutis marmorata telangiectatica congenita	Mongolian spot

Adapted from: Hasegawa Y et al[2], Torrelo A et al[3] and Happle R et al[4]

All subtypes, in accordance with Hasegawa, are subdivided into types (a) or (b) - with and without systemic involvement (which could involve ocular, vascular, neurological and skeletal) respectively.

The pathogenesis of PPV is not fully known, however it has been linked to abnormal development and migration of vasomotor nerves and melanocytes derived from the neural crest.[5] Abnormalities in the neural regulation of blood vessels may be important in the development of the vascular component, whereas anomalies in the migration of neural crest derived melanocytes may result in Naevus of Ota, naevus spilus or Mongolian spots.[6]

A genetic phenomenon called twin spotting which was described by Happle and Steijen has been hypothesized to explain this. Twin spots are paired patches of mutant tissues on nearby genes which lead to mosaic spots that differ genetically from each other, likely occurring due to loss of heterozygosity.[3,7]

Dermal melanocytoses occur when fetal melanocytes undergo a migration failure from the neural crest to the dermal basal layer. Mongolian spot is the most common, followed by blue naevus and Naevus of Ota. It is considered aberrant when it occurs on atypical sites (dorsum, shoulders, extremities and face) and with the tendency to persist, unlike conventional Mongolian spots. In this case, the Mongolian spots which are generally extensive with involvement of more than 50% of the body surface together with the Naevus of Ota are considered aberrant Mongolian spots.[8]

The vascular component is usually extensive in PPV. There is histopathological difference when compared with other capillary malformations such as presence of vasomotor neural cells and prominent endothelial cells.

This case presents manifestations that classify it as PPV Type II, which is characterized by extensive bilateral lesions of capillary malformation and aberrant Mongolian spots. It is recommended that all patients with PPV to be investigated for systemic complications depending on the sites involved. Approximately 50% of patients with PPV have extra-cutaneous involvement.[9] Central nervous system, eye and skeletal abnormalities are the most common systemic complications in PPV.[10] Neurologic conditions include psychomotor retardation, seizures and cerebral atrophy; with symptoms typically presenting within the first few months of life.[11] The most common ophthalmologic associations include conjunctival melanocytosis, episcleral vascular malformation and glaucoma.[12]

In this child who has Nevus of Ota, he will require a careful examination and follow-up by an ophthalmologist to assess for complications of glaucoma and melanoma. Other eye conditions reported in PPV include iris hamartomas, iris mammilations and iris nodules. Some patients with PPV also have Sturge Weber or Klippel- Trenaunay syndrome. Since this patient has enlargement of the left upper limb, he probably has Klippel-Trenaunay syndrome. The classical triad of Klippel-Trenaunay syndrome comprises of vascular malformations of the capillary, venous and lymphatic vessels, varicosities of unusual distribution, and unilateral soft and skeletal tissue hypertrophy.[13] At present, many of these symptoms may be treated, but there is no cure for Klippel–Trenaunay syndrome. Close follow-up is important for this patient with PPV and probably Klippel-Trenaunay syndrome, as systemic manifestations can become evident with time, which can alter the patient's disease classification and prognosis.

PPV without systemic involvement has a naturally benign course and does not require any treatment. However, a patient's quality of life and self –esteem may be improved by treating naevus flammeus with pulsed dye laser and by treating pigmentary naevus with Q-switched laser.[14] It is suggested that combined laser treatment to be done in childhood preferably before school age to reduce the number of treatment, increase the cost-effectiveness of the treatment and improve the patient's quality of life.[15] Medical treatment of PPV with systemic complications requires individualized plans and multidisciplinary management from other specialties such as ophthalmologist, neurologist and vascular specialist.

Conclusion

Therefore, it is important to recognize this rare syndrome and to follow-up patients with PPV closely as systemic manifestations can become evident with time. This helps in identifying any associated condition early in the course of the disease, which may determine the patients' outcome.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

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CASE REPORT

Dapsone Hypersensitivity Syndrome and Dapsone-induced Liver Injury in Four Malaysian Indigenous Individuals with Leprosy

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Summary

Dapsone is part of the multi-drug therapy used in the treatment of leprosy. It can cause life-threatening hypersensitivity syndromes resulting in significant morbidity and mortality, especially among susceptible individuals such as those who are carriers of HLA-B*13:01 allele. Avoidance of dapsone in these susceptible individuals reduces the risk of dapsone-related adverse events. Herein, we report four indigenous patients with leprosy who developed dapsone hypersensitivity syndrome.

Key words: *Leprosy, Dapsone, Severe cutaneous adverse reaction, HLA-B*13:01, Malaysia*

Introduction

Dapsone (4, 4-diaminodiphenysulfone) has been used to treat leprosy since the 1940's. It is an essential part of the multi-drug therapy (MDT) for both multi- and pauci-bacillary leprosy. Dapsone has also been documented to cause drug hypersensitivity syndromes (DHS), namely, drug reaction with eosinophilia and systemic symptoms (DRESS) as well as drug-induced liver injury (DILI).[1-3] DHS is a life-threatening drug reaction, which has been reported in approximately 2% of the patients with leprosy who were on dapsone therapy and with 12.5% mortality.[4-6] Thus, DHS is one of the major causes of death in leprosy patients.[7]

Although leprosy has been officially eliminated in Malaysia since 1994 (prevalence of leprosy of less than 1 per 10,000 according to WHO definition), new cases continue to be diagnosed.[8] Between 2006 and 2015, the incidence and prevalence of leprosy in Malaysia range between 0.7-1.1 per 100,000 and 0.1-0.3 per 10,000 population respectively.[8] The largest state in Peninsular Malaysia, Pahang, records the fourth highest number of leprosy cases in the country, following Sabah, Selangor and Sarawak.[8] The large majority of these individuals are indigenous peoples.

Herein, we report four indigenous individuals with leprosy who developed adverse effects secondary to dapsone treatment (Table 1).

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Case Report

Case 1

Mr VO, a 30-year-old unemployed gentleman with no past medical history, presented to us on 26 April 2016 complaining of multiple erythematous plaques and nodules over his trunk and limbs for a duration of one year. He had no systemic symptoms and was otherwise well. He has a younger sister (CASE 2) being treated for midborderline leprosy at our center.

Physical examination revealed a well-built individual with multiple erythematous nodules over both arms, and multiple hypopigmented anaesthetic patches over the upper chest. There were no thickened peripheral nerves, joint swelling, organomegaly or deformities noted.

Slit skin smear (SSS) showed a bacteriological index (BI) of 3.5 and a morphological index (MI) of 1.9. Skin biopsy showed clumps of acid-fast bacilli within foamy macrophages. All blood parameters were within normal limits.

Mr VO was diagnosed with lepromatous leprosy and promptly started on World Health Organization (WHO) multibacillary (MB) MDT regimen beginning 24 May 2016, which consists of monthly rifampicin, daily clofazimine and daily dapsone. Blood investigation repeated in June 2016 remained normal.

He presented to us unexpectedly on 29 July 2016 with generalized exfoliative dermatitis including facial oedema associated with fever. He denied taking any traditional and complimentary medicines or consuming alcohol. His blood count revealed a total eosinophil count of 3,110/mcL (18.3%), with elevated platelet counts (427,000/mcL). His haemoglobin was 10.8 g/dL. His liver function tests and renal profile were normal.

He was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) secondary to dapsone and was duly admitted to the ward for systemic corticosteroids and topical emollients. His MDT was withheld.

Over the course of his one-week admission, his condition improved dramatically, with normalization of his eosinophil count and reduction in erythema and scaliness. Upon review in the outpatient clinic, his exfoliative dermatitis had completely resolved and his blood parameters remained normal. Dapsone was replaced with ofloxacin, while rifampicin and clofazimine were continued. Oral prednisolone was tapered until stopped in November 2016.

Mr VO continues to improve on subsequent clinic visits. HLA-B genotyping revealed the presence of HLA-B*13:01 and HLA-B*18:01 alleles.

Case 2

Miss NAO, the 19-year-old sister of Mr VO (CASE 1), with no past medical history, was seen in our clinic on the same day as her brother. She had no complaints but was noted to have several erythematous plaques over her trunk and limbs for an uncertain duration of time. She was otherwise well.

Physical examination revealed multiple hypopigmented anaesthetic patches over her trunk and upper limbs. There were no thickened peripheral nerves, joint swelling, organomegaly or deformities noted.

The bacteriological index (BI) and morphological index (MI) of slit skin smear (SSS) was zero. Skin biopsy showed numerous perineural and perivascular epithelioid granulomas. No acid-fast bacilli were seen. All blood parameters were within normal limits.

Miss NAO was diagnosed with midborderline leprosy, in view of more than five lesions were present, and promptly started on World Health Organization (WHO) multibacillary (MB) MDT regimen beginning 29 July 2016. Blood investigation repeated in July remained normal.

She presented to us on 25 August 2016 with a generalized maculopapular eruption. She had no fever and was hemodynamically stable. She denied taking any traditional and complimentary medicines or consuming alcohol. Her blood count revealed a total eosinophil count of 940/mcL (16.1%). Her hemoglobin was 9.6 g/dL. The liver function tests showed markedly elevated hepatic enzymes, with alanine aminotransferase (ALT) at 468 U/L and aspartate aminotransferase (AST) at 373 U/L. Renal profile was normal.

She was diagnosed with drug reaction with eosinophilia with systemic symptoms (DRESS) secondary to dapsone and was duly admitted to the ward for systemic corticosteroids and topical emollients. Her MDT was withheld.

Her condition improved over the next one week, with normalization of eosinophil count and liver transaminases as well as resolution of her rash. Upon review in the outpatient clinic, her blood parameters were normal. Dapsone was replaced with ofloxacin, while rifampicin and clofazimine were continued. Oral prednisolone was tapered slowly until stopped in November 2016.

Miss NAO continues to improve on subsequent clinic visits. Like her brother, the HLA-B genotyping revealed the presence of HLA-B*13:01 and HLA-B*18:01alleles.

Case 3

Mr GS, a 71-year-old elderly gentleman with no past medical history, presented to us on 23 August 2016 complaining of multiple hypopigmented patches over his trunk and upper limbs for a duration of one month.

Physical examination revealed four discrete, large hypo pigmented, non-scaly patches over his trunk, both upper limbs and buttocks. These patches were hypo-aesthetic. No thickened peripheral nerves, deformities or neuropathic ulcers were appreciated.

Slit skin smear examination showed both BI and MI of zero. Skin biopsy showed multiple non-caseating epithelioid granulomas. Acid fast bacilli were seen. All blood parameters were within normal limits.

Mr GS was diagnosed with midborderline leprosy and started on WHO multibacillary MDT regimen beginning 6 October 2016. He was seen in our outpatient clinic on 1 November 2016 with no new complaints and with normal repeated blood parameters.

He was presented unexpectedly to our clinic on 5 December 2016 with exfoliative dermatitis associated with fever, jaundice, pallor, dehydration, bilateral pitting pedal oedema and tender hepatomegaly. There were no crops of new nodules or papules noted to suggest leprae reactions. He was hemodynamically stable. He denied consuming any alcohol or traditional herbal remedies. His eosinophil count was 1,200/mcL (9.9%), haemoglobin 10.2 g/dL and platelets 176,000/mcL. His liver function test was abnormal with slightly elevated serum bilirubin (28.4 μmol/L) while the transaminases were also elevated (ALT 66 U/L; AST 75 U/L). Non-oliguric renal impairment was noted.

Mr GS was diagnosed with drug-related eosinophilia with systemic symptoms (DRESS) secondary to dapsone and was admitted to the ward for systemic corticosteroids and topical emollients. His MDT was withheld.

His condition continued to deteriorate over the next one week. The liver transaminases were markedly elevated, with ALT and AST levels persistently above 750 U/L, serum bilirubin above 300 μmol/L, thrombocytopenia, coagulopathy, anaemia and oliguric renal failure. Despite intravenous N-acetylcysteine rescue, we did not manage to resolve his acute liver injury.

Mr GS eventually passed away from fulminant hepatic failure on 13 December 2016. HLA-B genotyping was not carried out.

Case 4

Mr MRJ, a 19-year-old gentleman with no past medical history, was referred to us from a district hospital on 31 January 2017 for facial erythema and swelling associated with low-grade fever for a duration of three months. His maternal aunt and late maternal grandmother had been diagnosed with leprosy.

Physical examination revealed madarosis, thickened and nodular bilateral earlobes and multiple large and confluent erythematous plaques over his face. Most of the fingers of both hands were sausage-shaped and tender, while both his wrist and ankle joints were also swollen and tender. He had no other lesions elsewhere on his body. There was also no pallor, jaundice, organomegaly, thickened peripheral nerves, deformities or neuropathic ulcers appreciated.

Slit skin smear examination showed a BI of 3.5 and an MI of 1.0. Apart from mild normochromic normocytic anaemia, all other blood parameters were within normal limits.

Mr MRJ was diagnosed with lepromatous leprosy with erythema nodosum leprosum (ENL) and was duly started on WHO multibacillary MDT regimen along with systemic corticosteroids and hematinics on the same day. He was seen in our outpatient clinic on 14 February 2017 with complete resolution of his joint swelling and reducing facial erythema. Repeated blood parameters were all normal.

Table 1. Four Malaysian indigenous individuals with lepromatous leprosy treated with dapsone as part of multidrug therapy

Case	Age/Gender	Type of Leprosy	Temporal period between initiation of Dapsone and drug reaction (months)	Adverse reaction	Highest eosinophil count during dapsone hypersensitivity syndrome, $x10^9$/L (%)	Highest alanine amino transferase (µL)	Outcome	HLA-B genotyping
1	30/M	Lepromatous	2	DRESS	3.11 (18.3%)	42	Complete resolution of rash and normalization of eosinophil count	HLA-B*13:01 HLA-B*18:01
2	19/F	Midborderline	1	DRESS	0.94 (16.1%)	468	Complete resolution of rash and normalization of eosinophil count	HLA-B*13:01 HLA-B*18:01
3	71/M	Midborderline	2	DRESS	1.2 (9.9%)	762	Death	Not done
4	19/M	Lepromatous	1.5	DILI	0	413	Death	Not done

M- Male; F- female; DRESS - Drug reaction with eosinophilia and systemic symproms; DILI - Drug induced liver injury

He presented to the Emergency Department on 18 March 2017 with right hypochondriac pain associated with fever, jaundice, hypotension and tachycardia. There were no crops of new nodules or papules to suggest leprae reactions. Bedside ultrasonographic examination did not reveal any features of biliary obstruction. He was diagnosed with dapsone hypersensitivity syndrome and promptly admitted to the ward. Inotropic support and empirical broad-spectrum antimicrobials were initiated. Blood investigations revealed a total eosinophil count of zero on admission, haemoglobin 10.3 g/dL and platelets 441,000/mcL. His liver function test were abnormal with markedly elevated total serum bilirubin of 296.2 µmol/L (i.e. direct bilirubin: 228.3 µmol/L; indirect bilirubin: 67.9 µmol/L). ALT was 92 U/L, AST 189 U/L and alkaline phosphatase (ALP) 1,365 U/L. There was also deranged coagulation profile, and blood gases showed mild, compensated metabolic acidosis. Renal function however, remained normal.

MDT was withheld and he was commenced on intravenous hydrocortisone in place of oral prednisolone which he has been on. Imaging studies carried out over the following few days, including endoscopic retrograde cholangiopancreatography and computed tomography of the abdomen, revealed no abnormalities. Blood and urine cultures were negative.

Nevertheless, Mr MRJ developed several life-threatening complications during his 18th-day hospitalization, including fulminant hepatic failure (i.e. ALT and AST peaking above 400 U/L; ALP persistently above 2,000 U/L), recalcitrant hypokalemia secondary to salt-wasting nephropathy, refractory hypoglycaemia and a nosocomial chest infection. Intravenous N-acetylcysteine and methylprednisolone were given for drug-induced liver injury (DILI) secondary to dapsone, but to no avail. He was then being considered for liver transplant and was planned for transplant evaluation. Despite aggressive interventions, Mr MRJ eventually succumbed to complications arising from fulminant hepatic failure on 6 April 2017 before HLA typing was arranged.

Discussion

Dapsone has been used to treat leprosy since the 1940's. Till date, dapsone has played a vital role in eliminating leprosy in many countries, including Malaysia. Nevertheless, dapsone is not without its adverse effects.

Several adverse effects have reported following exposure to dapsone. These adverse effects are (i) dose-dependent (pharmacological), which include hemolytic anemia and methemoglobinemia, or (ii) dose-independent (idiosyncratic) such as dapsone hypersensitivity syndrome (DHS) and DRESS, a potentially lethal syndrome with multiorgan involvement including pyrexia, hepatitis, lymphadenopathy and atypical lymphocytosis.[9-11]DHS has been reported to occur in 0.5 to 3.6% of patients treated with dapsone[12] and is usually manifested 4 to 6 weeks after the initiation of therapy. The estimated prevalence of the dapsone hypersensitivity syndrome is 1.4%, and the associated mortality is 9.9%.[5] To date, there are no tests to predict the risk of acquiring DHS.

Nevertheless, some population studies suggest both genetic and environmental factors are probably involved in determining the quantity of toxic oxidative metabolites of dapsone, such as the activity and quantity of polymorphic isoenzymes of cytochrome P450 and concomitant drug or chemical exposure, like alcohol or tobacco smoke.[10]

Of late, we have come to learn that genetic predisposition contributes towards drug-induced hypersensitivity reactions. For example HLA-B*15:02 allele predicts the risk of carbamazepine[13-15] as well as phenytoin[16-19] induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in Southeast Asian populations, while the HLA-A*31:01 allele was associated with carbamazepine-induced hypersensitivity reactions in European populations.[20] Furthermore it was reported recently that the HLA-B*15:13 allele was associated with phenytoin-induced SJS/TEN among Malays in Malaysia.[16]

Likewise, HLA-B*13:01 allele has been reported to be a predictor for dapsone-induced hypersensitivity syndrome (DHS) among patients with leprosy with a sensitivity of 85.5% and a specificity of 85.7%[21], while its absence is associated with a reduction in risk by a factor of 7.[22] In the study carried out by Zhang et al., the authors concluded that the risk of DHS among individuals with single copy (heterozygous) of the HLA-B*13:01 allele is 33.6 times higher compared to those without the susceptible allele.[22] The risk among individuals with double copies of HLA-B*13:01 allele (homozygous) increased 100.7 times.[22] A Thailand study recently described 12 of 15 (80%) non leprosy patients who developed dapsone-induced severe

cutaneous adverse reactions (SCARs) i.e. DRESS and Stevens Johnson syndrome/toxic epidermal necrolysis, were carriers of HLA-B*13:01 allele. When compared with the dapsone-tolerant controls, the odd ratio of dapsone-induced SCARs in Thais population who carried the HLA-B*13:01 allele was 54.0 (95% CI of 7.96–366.16, p = 0.0001). The OR was 26.11 when compared with the Thais general population (p=0.0001).[23] In Taiwan, it was also found that HLA-B*13:01 allele was present in 85.7% of patients with dapsone induced DRESS (OR=49.64;95%CI=5.89-418.13) whereas only 10.8% of general populations control carried the allele.[24]

The HLA-B*13:01 allelic distribution varies across different ethnic populations worldwide. For example, the frequency of HLA-B*13:01 ranging from 2% to 20% in the Han Chinese populations, 1.5% in the Japanese population, 1 – 12% in Indians, 2 – 4% in Southeast Asians, 13.3% in Thais and 28% in Papuans and Australian aborigines.[22-25] However, this allele is largely absent in Europeans and Africans[22,23,25]. Notably, the HLA-B*13:01 allele has also been found among the three main indigenous groups in Peninsular Malaysia, namely the Temuan, Jehai and Kensiu, with the Kensiu peoples having the highest allele frequency.[26]

In this case series report, both the siblings VO and NAO carry single copy of HLA-B*13:01 allele. We performed the HLA-B genotyping for their father and younger brother. The findings revealed carriage of double copies (homozygous) and single copy (heterozygous) of HLA-B*13:01 allele for the father and younger brother, respectively. Interestingly, while their father did not have leprosy, their younger brother was diagnosed with lepromatous leprosy and completed treatment with MDT uneventfully. It is noteworthy that in addition to the HLA-B*13:01 allele, all three siblings with diagnosed leprosy (i.e. VO, NAO and their younger brother) were also carriers of HLA-B*18:01 allele. Based on the HLA-B genotyping findings of these three siblings and their father, we cannot exclude the possible explanation of synergy act between HLA-B*13:01 and HLA-B*18:01 in risk of leprosy that may complicate the development of DHS in these individuals. It is regrettable that the haplotype of Mr GS and Mr MRJ were not able to be determined, given their clinical presentation and tragic outcome.

It is probably clinically vital to screen for HLA-B*13:01 in dapsone-related treatment regimens, especially for high-risk individuals in certain populations identified to be susceptible in having adverse reactions with dapsone. It is advocated based on the recently published systematic review and meta-analysis.[27] Identification of carriers of the HLA-B*13:01 allele may justify the need to modify treatment, such as switching to a safer second-line options, and thus significantly reducing the risk for DHS. However, the cost-benefit implications need to be addressed too, as the frequency of HLA-B*13:01 allele varies greatly across populations. Taken together, the next course of action would be prospective study to determine the odds ratio of dapsone induced SCARs among subjects who carry HLA-B*13:01 allele comparing to dapsone tolerant subjects and Malaysian general population.

Conclusion

In conclusion, we described four Malaysian indigenous individuals with leprosy who developed dapsone-induced hypersensitivity syndrome and had resulted mortality in two of them. HLA-B*13:01 allele was found to be carried by two of the related leprosy patients. Medical practitioners must be aware of this potentially fatal syndrome, particular in geographical areas with high prevalence rates of leprosy, and where the presence of DHS predisposing genetic factor such as HLA-B*13:01 is common.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CORRESPONDENCE

Dermatologists & The History of Hair Restoration Surgery

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Dear Editor,
I was introduced to Hair Transplant Surgery very early on. It was back in 1994 that I became a patient of Dr Dow Stough and then his pupil. Indeed, he had a profound effect on my career.

In terms of every conceivable hat that we are allowed to wear he was a complete dermatologist. A pioneer in Superpulsed carbon dioxide laser resurfacing, (who famously uttered to me once "Ruban…. you should trust a Laser Sales person as far as you can throw him") a dedicated Mohs surgeon and Phototherapist, whilst performing Hair Transplant Surgery twice a week. He ran a Clinical Fellowship in Hair Transplant surgery and Dermatology Surgery for the American Academy of Dermatology.

The role of Dermatology in the evolution of Hair Restoration Surgery is undeniable. From the earliest prewar days of Okuda to O Tar Norwoods classification of Androgenetic Alopecia in Men[1] to Dow Stough founding of the International Society of Hair Restoration Surgeons (ISHRS) and all that came in between and after we hope to present a brief summary of the evolution of this procedure which continues to improve the quality of life of the follicularly compromised.

Hair transplants true forefathers were the Japanese Dermatologist **Sheiji Okuda**[2] and the Urologist **Hajime Tamura.** Both performed successful grafts in the 1930s, initially on the scant eyebrows of Hansens patients.

The Father of modern Hair Transplants is arguably the New York Dermatologist **Orentreich** who took up the reigns in 1952 focusing on Androgenetic Alopecia whilst using 4mm punch grafts to transolocate hair from the genetically protected Safe lower occipital region, to the vertex and crown area, which resulted in the unfortunate 'dolls hair ' plugs that gave the procedure a sullied reputation for decades.

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It wasn't until 1984 when the pathologist **John Headington** defined the anatomical follicular unit as harboring one to four hairs[3] that dermatologists began to harvest and replant with the goal of maintaining these units.

Thus, it was that in 1988 the first single hair unit transplantations were performed by **Bobby Limmer**, from an elliptical donor strip followed by stereo microscopic dissection of the individual grafts after which micro tunnels are created in the recipient area for the insertion of the prepared grafts which forms the basis of the Modern hair Transplant technique by FUT (Follicular Unit Transplantation) as defined by Bernstein and Rassman.[4]

Thus, single hair Follicular units (FU) would be placed in the hair line, whilst the double and triple FUs would be placed further away creating greater density where necessary. **Mario Marzola** refined the donor strip harvesting technique by introducing Trichophytic closure which allows for much finer scars.

Various Hair line designs have been proposed and published in the ISHRS journals which have resulted in a move away from the straight lines of the past. The use of tumescent anaesthesia as conceived by Dermatologist Jeffery Klein, the forefather of in-office Liposuction[5-6] has allowed this procedure to be performed safely with negligible bleeding.

Emergence of the FUE technique
In 1988 – **Masumi Inaba** – extracted individual follicles with a single 1mm bore needle, which paved the way for **Rassman& Bernstein** 's seminal paper on Follicular Unit extraction / FUE, published in 2002.[7]

Numerous device companies (Harris, WAW pedal) have since emerged to assist in the deft technique of Follicular extraction with the use of drill machines manually used to extract individual follicles. The development of a Robot (Artus technologies) hopes to make this part of the procedure easier. The Surgeon and team in this case remains involved in the planning and creation of recipient sites, but may relax and have a coffee during the extraction phase. Unfortunately, the expense of the Robot and the added discomfort to the patient as mobility is strictly restrained are limiting factors.

Controversies:
FUE versus FUT

FUT – Traditional strip harvesting – where a strip of skin is taken usually from the occiput in the zone between the ears, after which technicians sliver and dissect into individual graft. Full scalp shaving is NOT required.

FUE – Extraction of the individual follicles spread over the entire Occipital region using a drill device. Full scalp shaving is usually required . Useful when Beard or Body to scalp transplants are required or when a Buzz cut is sported by the patient.

Due to harvesting from upper zones in the occiput which may be in danger of loss in the future, the permanent status of the follicles in the recipient area may not be such a surety.

The extracted follicles often lack the fat protection that dissected grafts enjoy thus making them more fragile.

The scaring that ensues from harvesting from a wide swathe of skin, results in distortion of the remaining grafts making follicular extraction more challenging if a subsequent procedure is required in the future. Thus, one would be inclined NOT to chose FUE in a younger patient. In brief a complete Transplant Surgeon should be adept at both techniques.

The internet has complicated matters by putting FUE on a pedestal, dominating infommercials on this procedure giving the public a skewed version of the truth. Still by obviating the need for full scalp shaving allowing the patient to return to work as soon as possible FUT is able to retain its appeal to many.

Hair Transplant surgery is an extremely rewarding technique when performed with the attention it deserves, heeding the voices of Dermatologists past and present.

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