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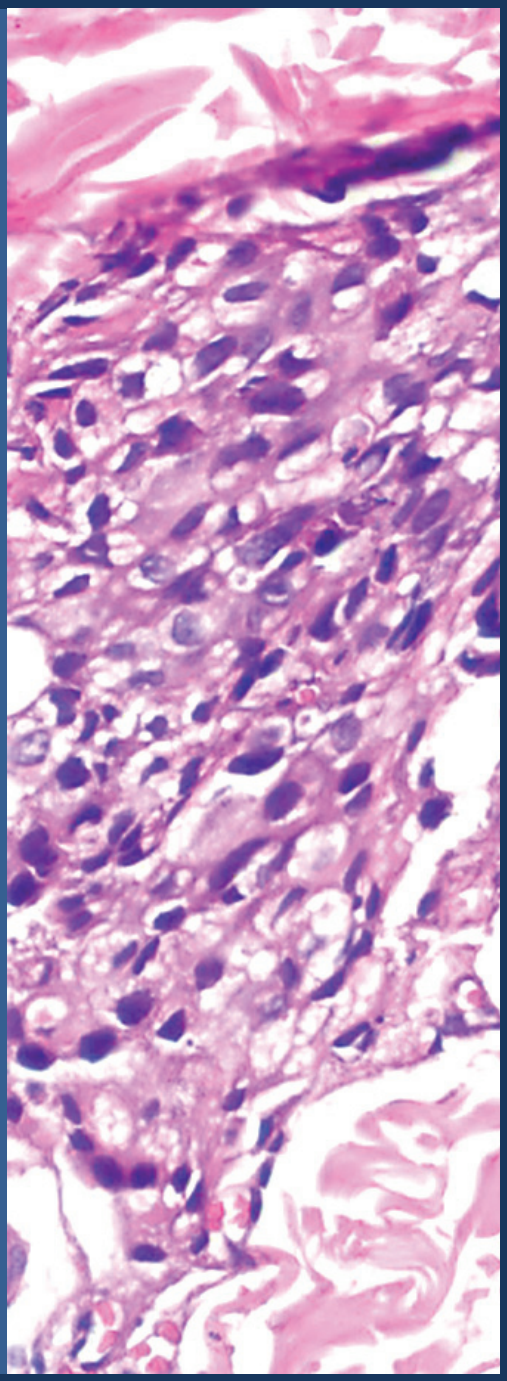

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Salicylic Acid Peel and Fusion Peel with Salicylic & Mandelic Acid Peel for Treatment of Acne Scars - A Comparative Study

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Abstract

Introduction. Acne vulgaris is one of the most common skin diseases affecting more than 85% of individuals worldwide. The study aimed to compare the therapeutic efficacy of Salicylic acid peel and Salicylic acid - mandelic acid peel for treatment of acne scars. **Material and Methods.** A comparative study was conducted on 41 patients, divided into two groups based on treatment choice by the subjects. Group A (23) were treated with 30% salycilic acid peels, and group B (18) were treated with 20% salycilic acid and 10% mandelic acid peels at an interval of 2 weeks for three sessions. The physician's global assessment scale and clinical photographs were used at the end of three sessions. All the data were analysed using SPSS considering $P<0.05$ as significant. **Results.** Of the total 41 patients analyzed, the mean age in both the groups were comparable. (Group A: 20.4 years; Group B: 20.5 years). Duration of acne was >12 months in both the groups 13 (56.52%) & 10 (55.56%)). Thirteen patients (56.52%) in group A and 1 (5.56%) in group B had no side effects which was statistically significant ($p=0.01$). Using the physician's global assessment scale 51-75% (Good) an improvement was seen in grade I 4 (17%) and 18 (78%) in grade II in group A and 2 (11%) in grade I and 12 (67%) in grade II in group B, respectively which was statistically significant ($p=0.001$). **Conclusion**. Both agents showed almost equal efficacy in improving mild-to-moderate acne scars. Adverse effects were less with Salicylic acid peel compared with mandelic acid peel..

Key words: Acne Vulgaris; Salicylic Acid; Mandelic Acid; Keratolytic Agents; Chemexfoliation; Treatment Outcome

Introduction

Acne vulgaris is one of the most common skin diseases affecting more than 85% of individuals worldwide. While acne is most prevalent among adolescents between 15 to 24 years old, it is not uncommon in adults either (1). It is an extremely common condition affecting the skin's pilosebaceous unit, affecting mostly the face and the back and chest. Acne pathogenesis is a multifactorial process consisting of four factors: follicular epidermal hyperproliferation, excess sebum production, the presence and activity of the commensal bacteria Propionibacterium acnes, and inflammation. Scarring can occur due to damage to the skin during the healing of active acne that may be atrophic or hypertrophic (2).

Although acne is often considered a cosmetic problem, it can have an enormous impact on patients' psychosocial and physical well-being, having a lifelong effect by disfiguring scars that correlates with various psychological factors such as depression, anxiety, anger, frustration, shame, low self-esteem, social isolation and body dissatisfaction (3).

According to recent dermatologic guidelines, the current first-line treatments for acne are conventional pharmacological therapies such as antibiotics, retinoids, hormonal agents and benzoyl peroxide (4). However, conventional treatment is not always desirable because of the development of antibiotic resistance of the Propionibacterium acnes and other bacteria (5) and the potential risk of adverse effects associated with topical and systemic treatments (6). Presently, non-pharmacological therapies like laser and light-based therapies, chemical peels, micro-needling, (micro)dermabrasion and (mechanical) lesion removal, dermal fillers, platelet-rich plasma (PRP) and the chemical reconstruction of skin scars (CROSS) technique are applied more often by care professionals. They are used as independent therapies, combined with con-

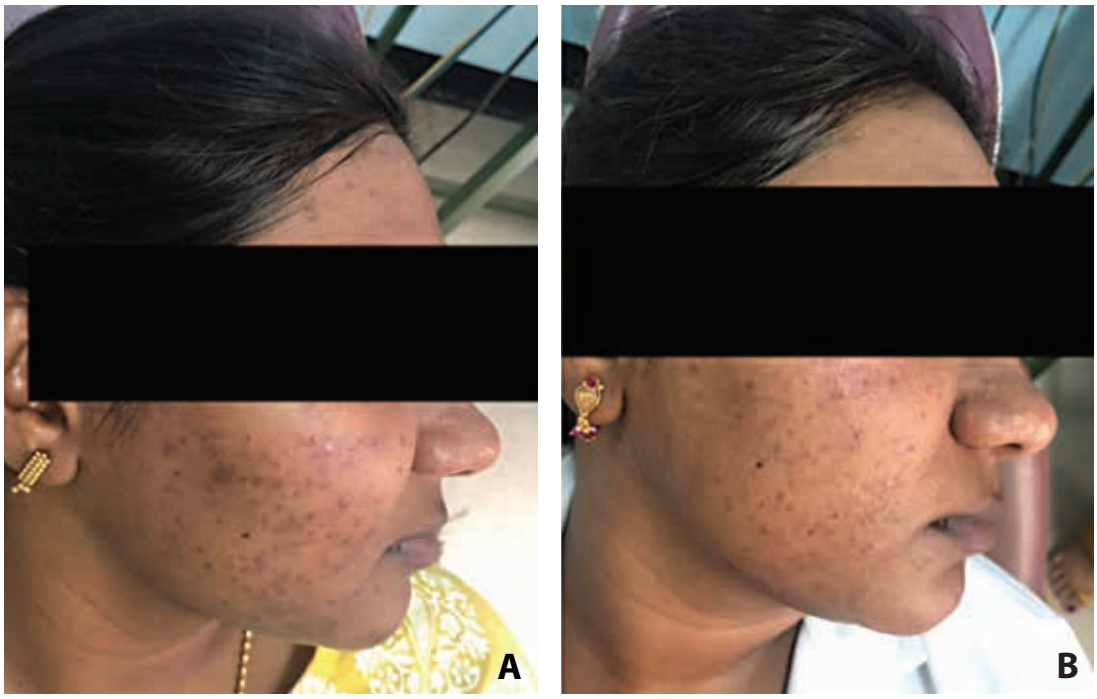

Figure 1. Treatment Response in Group A (30% salicylic acid). (A) 22-year-old female with Grade II Acne vulgaris. (B) 51-75% clearance of lesions after three sessions of peel

ventional therapies or as maintenance therapy, especially in more persistent or chronic acne types where long-term treatment is required (5). Evidence suggests that a combination of various treatment modalities gives better results than monotherapy alone (7).

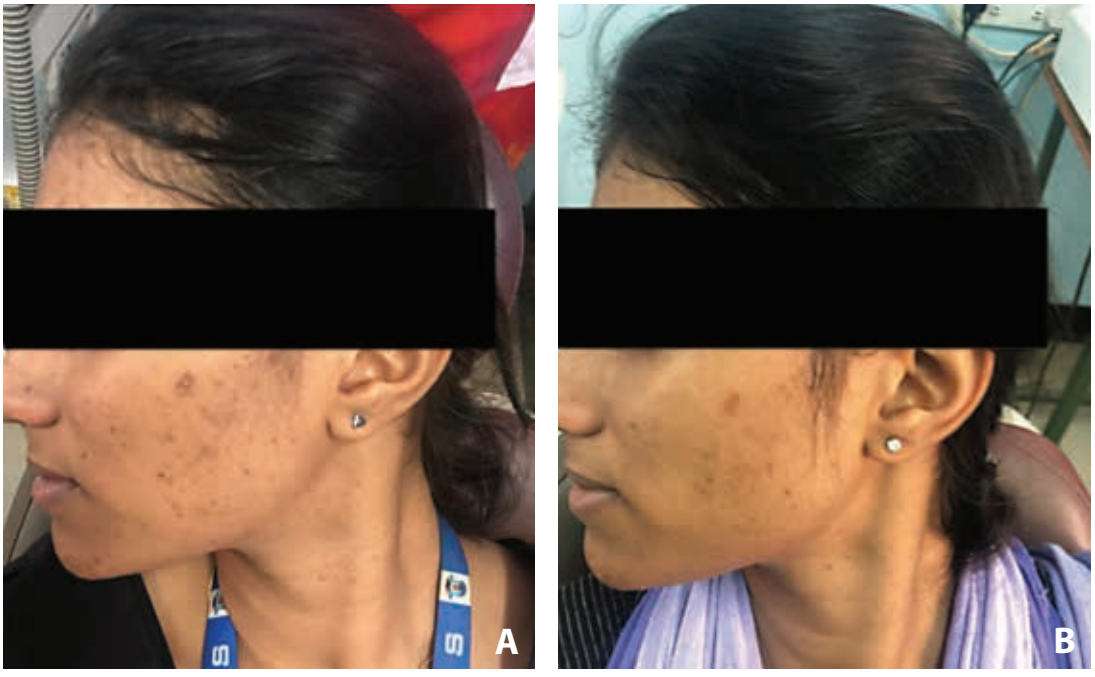

Figure 2. Treatment Response in Group A (30% salicylic acid). (A) 20-year-old female with Grade II Acne vulgaris. (B) 51-75% clearance of lesions after three sessions of peel

Chemical peels are used to treat acne scars which are small and depressed. Lactic acid, salicylic acid, glycolic acid, Jessner solution, and 10 to 25% trichloroacetic acid and mandelic acid are commonly used for superficial chemical peeling (8). Salicylic acid has been used to treat various skin disorders for more than 2,000 years. The ability of salicylic acid to exfoliate the stratum corneum makes it a promising agent for peeling. The efficacy and safety of salicylic acid peeling in Fitzpatrick skin types I-III as well as in skin types V and VI have been well documented in the literature by Arif T et al. (9). Mandelic acid (MA) is a new emerging peeling agent for acne scars owing to its antibacterial and anti-inflammatory properties.

A previous study by Shishira et al. (10) reported that Salicylic acid peel was more productive than Mandelic acid peel. However, the side effects were less familiar with no post-inflammatory hyperpigmentation with the Mandelic acid peel. In this study, SA and MA were tested separately. Hence, it is worthwhile to evaluate the effectiveness and safety profile of this newer agent and to compare it with an older established peeling agent, salicylic acid (SA) in the treatment of acne scars.

However, sufficient evidence-based support in comparing the efficacy and safety of the above mentioned non-pharmacological therapies is scarce in developing countries, particularly in India. Therefore, we herein included SA with MA and compared the efficacy and safety of salicylic acid peel with salicylic-mandelic acid peel for acne scars among patients visiting dermatology department in a tertiary care hospital.

Aims and Objectives: To compare the effectiveness of salicylic acid peel with salicylic mandelic acid peel for treating acne scars among patients visiting the department of dermatology in a tertiary care hospital.

Material and Methods

Study design: A Comparative Prospective Observational Study.

Study setting: Department of dermatology in a tertiary care hospital, Salem

Study population: Patients with facial acne scars, above 17 years of age attending OPD in the Department of Skin in a tertiary care hospital, Salem.

Study sample and sampling technique: 50 subjects were recruited through the uni-

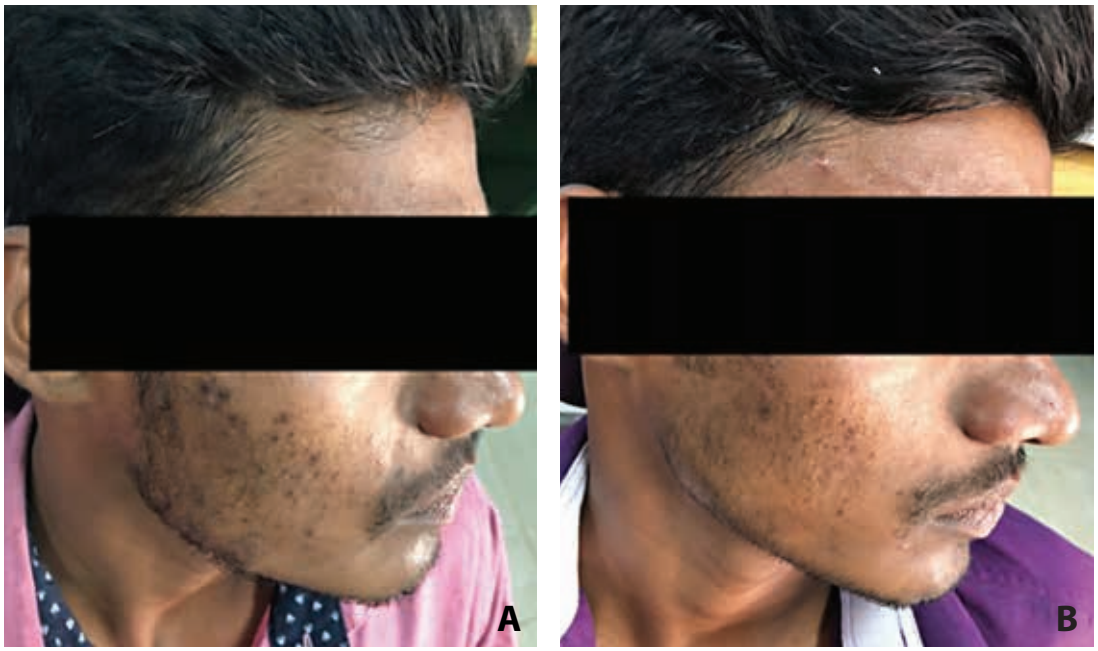

Figure 3. Treatment Response in Group B (20% salicylic acid + 10% mandelic acid peel). (A) 22-year-old male with Grade II Acne vulgaris. (B) 51-75% clearance of lesions after three sessions of peel.

Table 1. Summary of baseline parameters between study groups (N=41)

Parameter	Study group		P value
	Group A (N=23)	Group B (N=18)	
Age (Mean± SD)	20.43 ± 2.52	20.5 ± 2.71	0.937
	Gender		
Male	8 (34.78%)	6 (33.33%)	0.923
Female	15 (65.22%)	12 (66.67%)	
	Occupation		
Student	13 (56.52%)	15 (83.33%)	0.218
House Wife	1 (4.35%)	1 (5.56%)	
Labourer	7 (30.43%)	1 (5.56%)	
Others	2 (8.7%)	1 (5.56%)	
	Duration of Acne		
1-3 Months	4 (17.39%)	3 (16.67%)	0.995
3-6 Months	4 (17.39%)	3 (16.67%)	
7-12 Months	2 (8.7%)	2 (11.11%)	
>12 Months	13 (56.52%)	10 (55.56%)	
	Precipitating factors		
Diet	16 (69.57%)	8 (44.44%)	0.105
Premenstrual Flare	8 (34.78%)	4 (22.22%)	0.380
Stress	3 (13.04%)	2 (11.11%)	1.000
Sunlight	9 (39.13%)	5 (27.78%)	0.447
	Associated Factors		
Menstrual Irregularities	2 (8.7%)	3 (16.67%)	0.736
Acanthosis nigricans	5 (21.74%)	2 (11.11%)	0.438
Polycystic Ovarian Disease	5 (21.74%)	1 (5.56%)	0.297
Hirsutism	2 (8.7%)	1 (5.56%)	0.915
	Addiction		
Alcohol	0 (0%)	1 (5.56%)	*
Smoking	3 (13.04%)	1 (5.56%)	
Both	3 (13.04%)	0 (0%)	
None	17 (73.91%)	16 (88.89%)	
Family History	6 (26.09%)	5 (27.78%)	1.000
Use of Cosmetics	7 (30.43%)	9 (50%)	0.202

*No statistical test was applied - due to 0 subjects in the cells

versal sampling method, and 41 were selected based on inclusion criteria. The subjects were divided into two groups. Group A (23) salicylic acid peel and group B (18) salicylic + mandelic acid peel according to the subject's choice for treatment.

Study period: February 2019 – August 2020.

Ethical and Informed consent: The permission was obtained from the ethical and research committee of the concerned hospital. The written informed consent was obtained from participants before the study

Table 2. Summary of other parameters between the study groups (N=41)

Parameter	Study group		P value
	Group A (N=23)	Group B (N=18)	
	Onset		
Insidious	17 (73.91%)	15 (83.33%)	0.706
Sudden	6 (26.09%)	3 (16.67%)	
	Symptoms		
Asymptomatic	14 (60.87%)	11 (61.11%)	0.962
Itching	4 (17.39%)	4 (22.22%)	
Pain	3 (13.04%)	2 (11.11%)	
Both	2 (8.7%)	1 (5.56%)	
	Grading of Acne		
Grade I (macular patch)	6 (26.08%)	2 (11.11%)	*
Grade II (mild)	15 (65.21%)	13 (83.33%)	
Grade III (moderate)	2 (8.69%)	2 (11.11%)	
Grade IV (severe)	0 (0%)	1 (5.56%)	
	Side Effects		
Burning Sensation	4 (17.39%)	5 (27.78%)	0.01
Dryness	2 (8.7%)	3 (16.67%)	
Erythema	2 (8.7%)	2 (11.11%)	
Pruritus	2 (8.7%)	7 (38.89%)	
Nil	13 (56.52%)	1 (5.56%)	

*No statistical test was applied - due to 0 subjects in the cells

started and the procedure's steps were explained as well. Confidentiality of the subjects was maintained throughout.

Inclusion criteria:

– Patients with facial acne scars (atrophic scars).

– Patients >17yrs.

– Patients with Fitzpatrick's skin types III to V.

Exclusion criteria:

– Patients with active herpes simplex infection.

– History of Isotretinoin treatment in the past six months.

– Patients on anticoagulant therapy.

– Pregnant and lactating mothers.

– Patients with a history of keloidal tendencies.

– Patients with active acne.

– Patients with unrealistic expectations.

Data collection: Each patient was interviewed for age, sex, occupation, sun exposure, duration of the disease, family history, previous treatment history, use of cosmetics and any precipitating factors. The patients were subjected to a proper general, systemic and dermatological examination. Then grading of the acne scars was done using Goodman and Baron's qualitative global acne grading system, which is as below (11).

– The first grade consists of macular hyper or hypopigmented flat marks that are visible.

– The second grade includes mild atrophy or hypertrophic scars, may not be visible at a distance of 50 cm, can be concealed with cosmetics.

– The third grade consists of moderate atrophic or hypertrophic scars, visible at a social distance of 50 cm or greater, that cannot easily be concealed with makeup, but still can be flattened by manual pressure of the skin.

– The most severe grade is highly atrophic or hypertrophic acne, visible at a distance greater than 50 cm that is not flattened with the skin's pressure around the scars.

The obtained results were assessed based on serial photographs, clinical improve-

ment and physician's global assessment scale. Adverse effects such as erythema, crusting, mild transient edema and post-inflammatory hyperpigmentation were monitored and recorded. The clinical findings and results were recorded in a pre-designed proforma for analysis and interpretation of data.

Procedure: Before the procedure, all treatment areas were gently cleansed (debris, including dirt, makeup and powder), by using a mild cleanser and 70% isopropyl alcohol.

Group A (23) patients were treated with 30% salicylic acid every 15 days for three sessions. Sensitive areas like the inner canthus of the eyes and nasolabial folds were protected with Vaseline. After degreasing with acetone, the corresponding peel was applied on the cosmetic units of the face starting from forehead, right cheek, nose, left cheek and chin in that order. Feathering strokes were applied at the edges to blend with the surrounding skin.

Group B (18) patients were treated with a combination peel of 20% salicylic and 10% mandelic acid peel every 15 days for three sessions.

Both Group A and Group B patients were advised to protect their skin from sunlight using sunscreen regularly at day time for the next 12 weeks.

Post-procedure: Physician's global assessment tool (12) and photographic documentation using identical camera settings, lighting and patient positioning was obtained at baseline, before each treatment session and three months after the final treatment session.

Statistical Methods

The percentage of improvement in both the groups was considered as the primary outcome variable. Grading of acne was considered as the primary explanatory variable. The baseline parameters such as age, gender, occupation, duration of acne, precipitating factors, associated factors, addictions, onset, symptoms, first, second and third follow up, and side effects were considered as another study relevant variable.

The descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non normally distributed quantitative variables were summarized by the median and interquartile range (IQR).

All quantitative variables were checked for normal distribution within each explanatory variable category by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as a normal distribution.

Table 3. Summary of follow up between study groups (45 days) (N=41)

Parameter	Study group		P value
	Group A (N=23)	Group B (N=18)	
	First Follow Up		
Fair	20 (86.96%)	14 (77.78%)	
Good	2 (8.7%)	3 (16.67%)	0.719
Poor	1 (4.35%)	1 (5.56%)	
	Second Follow Up		
Fair	13 (56.52%)	12 (66.67%)	
Good	9 (39.13%)	5 (27.78%)	0.748
Poor	1 (4.35%)	1 (5.56%)	
	Third Follow Up		
Fair	1 (4.35%)	4 (22.22%)	
Good	22 (95.65%)	13 (72.22%)	*
Poor	0 (0%)	1 (5.56%)	

*No statistical test was applied - due to 0 subjects in the cells

Table 4. Summary of percentage of improvement between study groups (N=41)

Percentage of improvement	Study group				P value
	Group A (N=23) 30% salicylic acid peel		Group B (N=18) 20% salicylic and 10% mandelic acid peel		
	Grade 2 (mild)	Grade 3 (moderate)	Grade 2 (mild)	Grade 3 (moderate)	
0-25% (Poor)	0	0	0	1 (6%)	1.000
26-50% (Fair)	0	2 (4%)	0	3 (17%)	1.000
51-75% (Good)	4 (17%)	18 (78%)	2 (11%)	12 (67%)	0.001
75-100% (Excellent)	0	0	0	0	*
No change	0	0	0	0	*

*No statistical test was applied- due to 0 subjects in the cells

For normally distributed quantitative parameters the mean values were compared between study groups using Independent sample t-test (Group A and Group B).

The categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.)P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis (13).

Results

A total of 41 subjects were included in the final analysis.

The mean age in both groups was comparable. (Group A: 20.4 years; Group B: 20.5 years). There were more females in both groups: 15 (65.22%) in group A, and 12 (66.67%) in group B. Of the 41 people who completed the study, 13 (56.52%) were students in group A, and 15 (83.33%) in group B followed by 7 (30.4%) labourers and others. Duration of acne was >12 months in both the groups - 13 (56.52%) and 10 (55.56%). The major precipitating factor was diet (which included oily food, high glycemic index diet) in both the groups 16 (69.57%) 8 (44.44%) followed by sunlight 9 (39.13%) 5 (27.78%) respectively. The associated factors were high for acanthosis nigricans 5 (21.7%) and 2 (11.11%) and polycystic ovarian disease in both the groups 5 (21.7%) and 1 (5.56%). 6 (26.09%) of group A and 5 (27.7%) of group B had a family history of acne. There was no significant association seen between the parameters and groups **(Table 1).**

Among 41 patients, 17 (73.91%) of group A and 15 (83.33%) of group B showed insidious onset of acne, 14 (60.87%) of group A and 11 (61.11%) of group B were asymptomatic. Itching and pain followed. The majority, 15 (65.21%) of group A and 13 (83.33%) of group B had Grade II acne. 13 (56.52%) of group A had no side-effects whereas only 1 (5.56%) had a side effect in group B which was statistically significant (p=0.01) **(Table 2).**

The difference in the first follow up between the study groups is found to be insignificant with a P-value of 0.719, with majority of 20 (86.96%) people with a fair first follow up in group A. The difference in the second follow up between the study groups was found to be insignificant with a P-value of 0.748, with majority of 12 (66.67%) people with a fair second follow up in group B. The difference in the third follow up was bigger in group A with 22 (95.65%) and 13 (72.2%) in group B showing GOOD score on follow up **(Table 3)**.

Using the physician's global assessment scale, decrease in acne scars at the end of three sessions, the improvement was noted as Poor, Fair, Good, Excellent. The 26-50% (Fair) improvement in grade II acne was seen in 1 (4%) of group A and 3 (17%) of group B, which was not significant. The 51-75% (Good) improvement in grade I 4 (17%) and 18 (78%) in grade II was seen in group A and 2 (11%) in grade I and 12 (67%) in grade II was seen in-group B, respec-

tively which was statistically significant (p=0.001) **(Table 4)**.

Figure 1 a and b, **figure 2 a and b** shows treatment response in group A, where the 51-75% improvement can be seen in both figures (30% salicylic acid).

Figure 3 a and b shows treatment response of group B, where the 51-75% improvement can be seen (20% salicylic acid and 10% mandelic acid).

Discussion

To the best of our knowledge, the present comparative observational study was first conducted on 41 subjects with acne scars. Of the total 41 patients analysed, the mean age in both the groups was comparable (Group A: 20.4 years; Group B: 20.5 years). Duration of acne was >12 months in both the groups: 13 (56.52%) and 10 (55.56%). The major precipitating factor was diet in both the groups. 16 (69.57%) and 8 (44.44%). Majority, 15 (65.21%) of group A and 13 (83.33%) of group B had Grade II acne. 13 (56.52%) of group A had no side effects whereas only 1 (5.56%) of the group B, which was statistically significant (p=0.01). Using the physician's global assessment scale, decrease in acne lesions at the end of three-session, the 51-75% (Good) improvement was seen in grade I 4 (17%) and 18 (78%) in grade II in group A and 2 (11%) in grade I and 12 (67%) in grade II in-group B, respectively which was statistically significant (p=0.001).

The overall improvement in the present study was similar to a study done by Shishira R et al. (10), in a Randomized, Single-blind, Active Controlled Study where they compared the efficacy of salicylic acid and mandelic acid chemical peel in the treatment of mild to moderately severe Acne Vulgaris. The patient selection in the present study was done according to Goodman and Baron's qualitative global acne grading system, which contrasts to a review done by Catilo et al. (14), where they have mentioned the patient selection consideration and The Fitzpatrick scale Skin type classification for chemical peeling.

The procedure was done at an interval of two weeks in three sessions compared to four and six sessions by other authors. The present study used the physicians global assessment tool and clinical photography to assess the improvement after treatment. These findings contrast to a study done by Wang et al. (15), where they used Investigator Severity Assessment (ISA) after treatment with oral minocycline and supramolecular salicylic acid 30% chemical peels.

As far as side effects were concerned, both peels were well tolerated by the patients in both the groups but the salicylic acid peel was found to be much safer as it was well tolerated in terms of other side effects such as erythema, burning, and stinging sensation. Our finding is in contrast to a study by Dayal et al. (16), which reported 45% mandelic acid peel had fewer side effects than 30% salicylic acid peel in mild-to-moderate acne vulgaris. It can be attributed to the large structure of mandelic acid, leading to its slow and uniform penetration in the epidermis, making it an ideal peeling agent for the sensitive skin of the patients with severe acne and hyperpigmentation.

In the present study, on the comparison, both groups showed a decrease in all types of scars, but the percentage reduction i.e. improvement was better in group A compared to group B using the physicians global assessment tool where the 51-75% (Good) improvement was seen in grade I 4 (17%) and 18 (78%) in grade II in group A and 2 (11%) in grade I and 12 (67%) in grade II in-group B, respectively which was statistically significant (p=0.001). This finding is compared to a study done by Deepak J et al. (17). They did a Comparative study of fractional Co_2 laser with salicylic–mandelic acid peel v/s derma roller with salicylic–mandelic acid peel for post acne treatment atrophic scars.

As the present study used only chemical peeling, the findings is in contrast to a systematic review by de Vries et al. (1) based on 33 studies, which assessed the efficacy and safety of three main non-pharmacological therapies in the treatment of acne vulgaris: laser- and light-based therapies, chemical peels and FMRF.

Combination peels minimize side effects. Although superficial peels like SA and MA are useful in active acne, they are not considered an effective treatment for deep acne scars, where medium depth peels and TCA CROSS method are preferred. Caution is needed when medium and deep peels are used in dark-skinned patients due to the risk of pigmentary changes (18). Analysis of the avail-

able literature reveals that chemical peels are the third most commonly performed non-invasive cosmetic procedure in the United States, with over 1,300,000 procedures performed in 2016 alone. When used for the appropriate indication with the proper technique, nearly all peel solutions and depths have demonstrated excellent clinical success in improving skin tone and texture, and are cost-effective compared to invasive procedures. Thus, chemical peels should remain indispensable tools in the dermatologist's aesthetic toolbox, particularly in light of the current rising healthcare costs in all developing countries (19).

Limitation

The major limitation is the small sample size and a single hospital-based study. We did not have a follow-up to identify the recurrence rate. Therefore, long-term prospective studies including a follow-up period of at least six months to a year are required to substantiate our findings covering al large geographical area.

Conclusion

We conclude that both salicylic acid (SA) and salicylic mandelic acid peel are an efficient, well-tolerated and reasonably safe procedure used as a treatment modality in acne vulgar. It is because of salicylic acid's property to inhibit microcomedone, thus leading to a decrease in follicular openings. The addition of mandelic acid to SA peel therapy leads to better outcomes in acne management as it reduces post-acne scars.

Abbreviations

PRP – platelet-rich plasma
CROSS – chemical reconstruction of skin scars
MA – mandelic acid
SA – salicylic acid
IQR – interquartile range
ISA – Investigator Severity Assessment

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Piling salicilnom kiselnom i kombinovani piling salicilnom i mandeličnom kiselinom u tretmanu ožiljaka od akni – komparativna studija

Sažetak

Uvod. Akne vulgaris su jedno od najčešćih kožnih oboljenja koje se javlja u više od 85% osoba u celom svetu. Cilj studije bio je da uporedi terapeutsku efikasnost pilinga salicilnom kiselinom i pilinga salicilnom i mandeličnom kiselinom u tretmanu ožiljaka od akni. **Materijal i metode.** Komparativna studija je izvedena na 41 pacijentu, koji su bili podeljeni u dve grupe na osnovu njihovog izbora tretmana. Pacijenti iz grupe A (23) tretirani su pilingom 30% salicilne kiseline a iz grupe B (18) pilingom 20% salicilne kiseline i 10% mandelične kiseline u periodu od dve nedelje po tri tretmana. Na kraju svakog tretmana, primenjena je skala opšte procene lekara i snimljene su kliničke fotografije. Svi podaci su analizirani pomoću SPSS uzimajući $p < 0,05$ kao signifikantan. **Rezultati.** Prosečna starost bila je uporediva u obe grupe pacijenata (41). (Grupa A: 20,4 godina, Grupa B: 20,5 godina). Trajanje akni je bilo > 12 meseci u obe grupe 13 (56,52%) i 10 (55,56%)). Kod 13 (56,52%) iz grupe A, i 1 (5,56%) iz grupe B nije bilo neželjenih pojava, što je statistički signifikantno ($p = 0,01$). Na skali opšte procene lekara poboljšanje 51 □ 75% (Dobro) viđeno je u stepenu I 4 (17%) i 18 (78%) u stepenu II u grupi A i 2 (11%) u stepenu I i 12 (67%) u stepenu II u grupi B, što je bilo statistički signifikantno ($p = 0,001$). **Zaključak.** Oba agensa su pokazala skoro identičnu efikasnost u poboljšanju blagih do umerenih ožiljaka od akni. Bilo je manje neželjenih efekata kod pilinga salicilnom kiselinom nego kod pilinga mandeličnom kiselinom.

Ključne reči: Akne vulgaris; Salicilna kiselina; Mandelična kiselina; Keratolitički preparati; Hemijski piling; Ishod terapije

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A Case Report of Pediatric Langerhans Cell Histiocytosis: Current Approach and Diagnostic Challenges for Dermatologist

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Abstract

Langerhans Cell Histiocytosis (LCH) is a chronic and rare myeloproliferative disorder caused by disorders in Langerhans cell proliferation in various organs and tissues. LCH has a wide variety of clinical manifestations, making it difficult to diagnose. Cutaneous manifestations are polymorphic in the form of purpura, papule, vesicles and pustules. LCH can involve vital organs such as the liver and lungs as well as the hematopoiesis system that usually gives a poor prognosis. The prognosis is also influenced by the age of patient, organ dysfunction and response to the first 6 weeks of chemotherapy treatment. A 3-year-old girl reported a major complaint of an abscess-like lesion in the region of neck accompanied by an extensive purpura of scalp, neck and inguinal areas accompanied by vulvar erosions. The immunohistochemical and histopathologic examination support LCH and the clinical improvement after intravenous administration of intravenous 3 mg/m^2 Vinblastine chemotherapy, 75 mg/m^2 etoposide, oral 40 mg/m^2 per prednisone. After the 6th cycle of chemotherapy, the patient died.

Key words: Histiocytosis, Langerhans-Cell; Purpura; Skin Diseases, Vesiculobullous; Diagnosis; Child, Preschool; Vinblastine; Fatal Outcome

Introduction

Langerhans Cell Histiocytosis (LCH) is a chronic myeloproliferative disorder of dendritic cell proliferation that is morphologically and biologically similar to Langerhans cells in various organ tissues. Langerhans cells represent a subtype of dendritic antigen-presenting cell (APCs) which is located particularly in epidermis and mucosal epithelium of various organs. Langerhans cells can initiate specific immune responses by presenting a foreign antigen to T-lymphocytes. In 1924 and 1933, Letterer-Siwe described an illness in infants with the symptoms of fever, diffuse purpura, purulent otitis media, lymphadenopathy and hepatosplenomegaly (1, 2).

LCH is a rare disorder that seldom affects area of the head, trunk, and skin folds. In 1953, the disease was classified in 4 entities: Latterer-Siwe disease, Hand-Schüller–Christian disease, and Eosinophilic granuloma and Hashimoto-Pritzker disease (Congenital self-healing reticulohistiocytosis)based on the presence of abnormal histiocytes. The new classification of LCH, single- system LCH and multisystem LCH (MS-LCH) represents the extent of organ involvement. The prevalence of LCH is estimated to be 4.0-4.4 per one million inhabitants, but these figures are fairly low because of failure to diagnose the involvement of organs and skin. In children, the annual incidence is estimated to be 0.5 per 100,000 children in the United States, and 4 per million children worldwide.

The male-female ratio is 2:1. LCH can occur in all ages and can also be congenital, but frequently occur in children aged 1-3 years (14). Cutaneous manifestation is the earliest sign of LCH disease. The typical clinical manifestations are small transparent papules, with

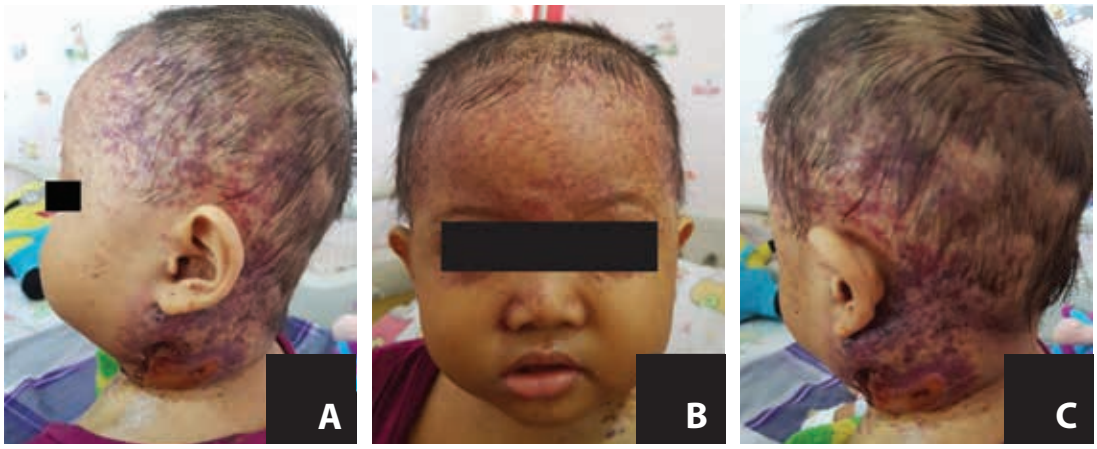

Figure 1. The Clinical Manifestation Before Treatment: (A-C) The region of the scalp, retroauricularis, and coli showed the presence of crusts, purpura, erythematous plaque, and madidans ulcers.

a diameter of 1-2 mm, and colored in reddish yellow, and also habitually located in the trunk and area of the scalp which can lead to crusts and ulceration. The presence of purpuric lesion leads to a poor prognostic sign in patients under the age of 2. Eosinophilic granuloma is characterized by multiple or solitary red or brownish red nodules. It can usually heal completely and leave an atrophic scar after a spontaneous resolution.

Langerhans cells are distinguished from other dendritic cell subtypes by the expression of CD1a antigens and the presence of typical cytoplasmic organelles known as Birbeck grains. Birbeck granules are allegedly mediated by a type II transmembrane glycoprotein from lectin that is known as Langerin. Immunohistochemical examination on LCH shows positive CD1a, S100, and langerin cells (2, 13).

A case report of a 3-year-old girl, who was diagnosed with LCH based on clinical manifestations that were supported by histopathological and immunohistochemical examination, is hereby presented.

Case Report

A 3-year-old girl came to the Emergency Room of Gatot Subroto Army Hospital, Jakarta with a chief complaint of a lump on the left side of the neck, which had developed 8 months before, when it ruptured and released purulent material. The wound was biopsied and was interpreted as neck abscess. The wound appeared wet and mixed with blood. No topical medication was applied to the wound. There were also reddish spots that started to appear from the pubic area and waist 2 months prior to admission and they spread to the head and hair which worsened in the last seven days. The stomach appeared extended and the eyes were yellowish. History of itch and pain in the area of the patches was denied.

According to the anthropometrical measurements, her weight was 10 kg, height was 70 cm, and head circumference was 48 cm. General physical examination revealed icteric sclera and enlarged liver. Dermatological examination of the scalp, frontal and parietal areas showed multiple purpura, erosion, and crusting. Ulcers and erosive lesions were found in the inguinal and vulva area **(Figure 1)**. Other findings were anemia 6.2 g/dL, thrombocytopenia 50,000/μL, hypoalbuminemia 1.5 g/dL, and elevation of both AST 125 U/L and ALT 80 U/L.

Based on the history, physical examination, and laboratory examination, the patient was diagnosed with Langerhans cell histiocytosis. The following treatment was given intravenously: cefotaxime 3 x 300 mg, metronidazole 3 x 150 mg, albumin transfusion 20% 50 cc/24 hours, and prednisone 5 mg/8 hours at the Department of Pediatrics. The wound was treated with normal saline dressing and mupirocin cream twice a day. Swab examination from the wound for sensitivity and culture examination as well as immunohistochemistry examination were planned to be performed at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.

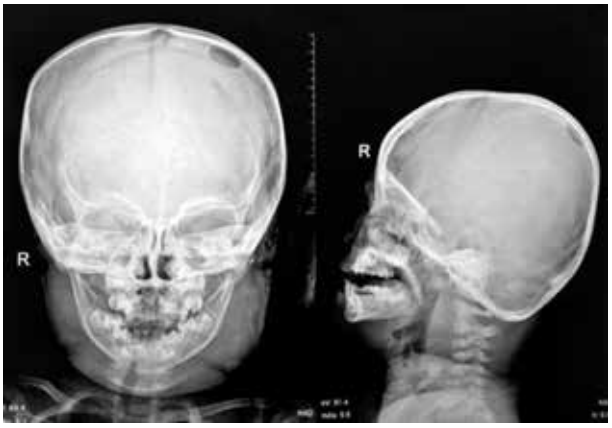

Figure 2. AP/Lat cranium imaging showed the appearance of a solitary lytic lesion on the left parietal with clear border and ovoid shape that suggested a left solitary lytic parietal lesion with primary bone tumor as differential diagnosis.

After the transfusion, the laboratory findings were as follows: Hb: 6.6 g/dL, platelet level 24,000/uL and an impression of bicytopenia was obtained. Examination on the 7th day of treatment showed Hb: 9 mg/dL, leukocytes 4960/UL (6,000-17,000/UL) and platelet levels of 25,000/UL. Coagulation factors were prothrombin time 16.2 seconds (9.3-11.8 seconds) and aPTT 72.5 seconds (31-47 seconds). Peripheral blood examination discovered microcytic erythrocytes – hypochromes, anisopicillocytosis, elliptocytes, anulocytes, target cells, acetocytes, neutrophil young cells, suggesting a hypochromic microcytic anemia, anisopicycocytosis, thrombocytopenia with hemolytic iron deficiency anemia and chronic disseminated intravascular coagulationpossibly due to malignancy as differential diagnosis. After the transfusion, albumin was 2.5 g/dL. Globulin: 1.7 mg/dl (2.5-3.5 g/dL), ureum and creatinine were within normal limits. AP/lateral cranium imaging showed a left solitary parietal lytic lesion suggesting primary bone tumor **(Figure 2)**. Ultrasound examination showed the liver enlargement **(Figure 3)**. The culture examination taken from the wound showed negative *Enterobacter cloacae* and MRSA culture result. Blood culture showed positive gram coccus suggestive of *Staphylococcus aureus* bacteria. Chest X-ray showed pleural effusion

Histopathological examination showed ovoid and irregular kidney-like histiocytes (reniform) with fine chromatin and one or more small nucleoli and eosinophilic cytoplasm **(Figure 5)**. The results of immunohistochemical examination showed positive S100 protein, CD1a, CD68, and Ki67 expression leading toLCH **(Figure 6)**.

Chemotherapy consisted of Vinblastine 3 mg, etoposide 75 mg/m^2 m^2 infusion for an hour and prednisone 20 mg/m^2 m^2 given every week for the first 6 weeks was initiated on the 21st day. The patient's Body Surface Area (BSA) was 0.5 m^2. Clinical changes were seen on the 24th day of the treatment, where purpura on the area of the head, neck and inguinal was reduced. Improved crusting, purpura, and ulcers were visible on the scalp, retroauricular, neck, and inguinal region. Unfortunately, the patient passed away six weeks after chemotherapy.

Discussion

LCH is a rare skin disorder characterized by excessive proliferation of Langerhans cells.

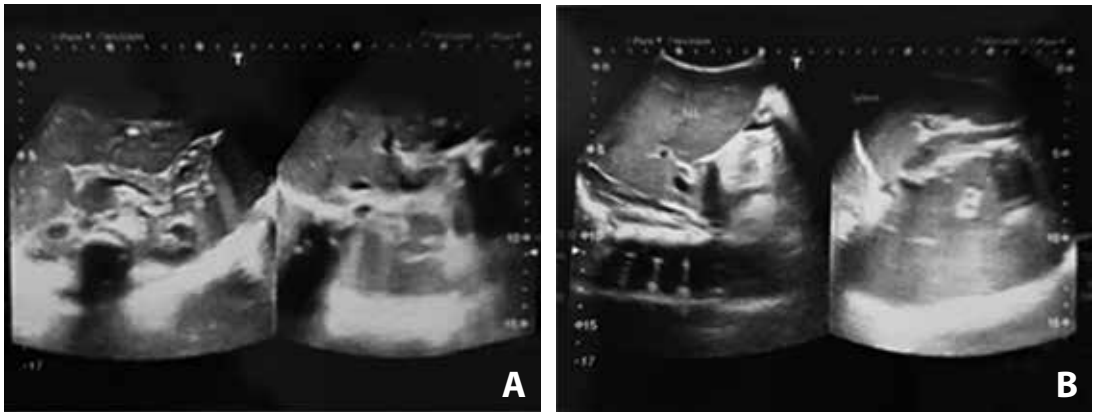

Figure 3. Abdomen Ultrasound examination showed liver enlargement.

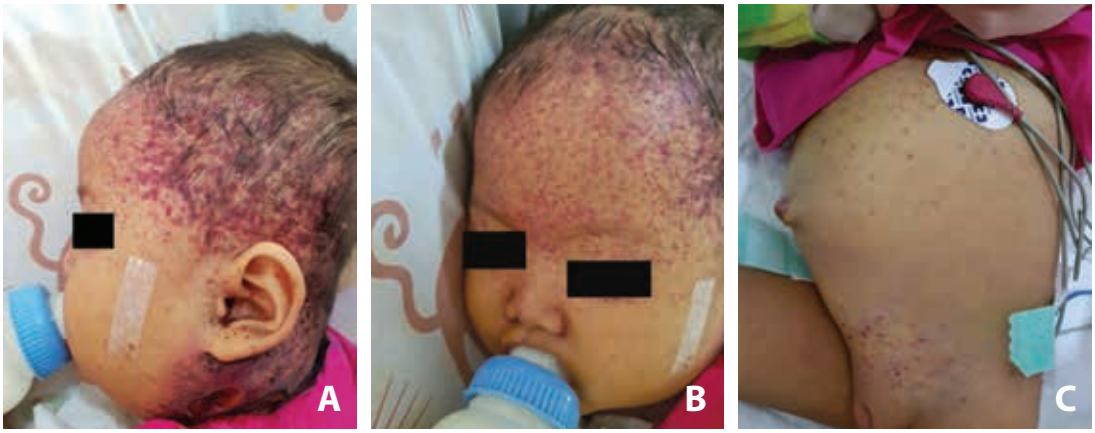

Figure 4. The 14th day of the treatment (A-B) in the regions of the scalp, retroauricularis, and coli showing crusting, purpura, erythema plaque, and drier ulcer (C) On the anterior of the trunk and inguinal regions, expanded purpura was discovered compared to the treatments on the previous day.

Prevalence for LCH is estimated to range from 4.0 to 5.4 per 1 billion inhabitants with a higher incidence in women and in children aged 1-3 years old. In this case, a 3-year-old girl presented with purpuric lesion that first occurred on the scalp and spread to the neck and inguinal area (1, 5, 13).

Skin lesions in children usually develop on the scalp, axilla and inguinal area, but tend to be more inflamed and widespread compared to seborrheic dermatitis, psoriasis or intertriginous candidiasis. The appearance of pustules or erosion in the intertriginous area or scaly erythematous patches in the region of extensor can cause a misdiagnosis of candidiasis or atopic dermatitis. The immunohistochemical and histopathological examination are needed to prove the diagnosis of LCH. Based on literature, MS-LCH will generally show extensive purpura lesions in the inguinal and genital area which constitute early manifestations of LCH. Painful and ulcerated purpura occur around the scalp, coli, inguinalis and genital area (13). In this case, purpura lesions began to appear in the genital and inguinal areas then extended to the scalp and coli (5, 7, 11).

Based on the literature, this case was categorized as LCH with multiple organ system involvement. Criteria for involvement of one system or internal organ are unifocal or multifocal bone involvement, skin, both single or multiple lymph nodes, lungs, central nervous system, and the rare involved area such as thymus and thyroid. Criteria for multi-organ

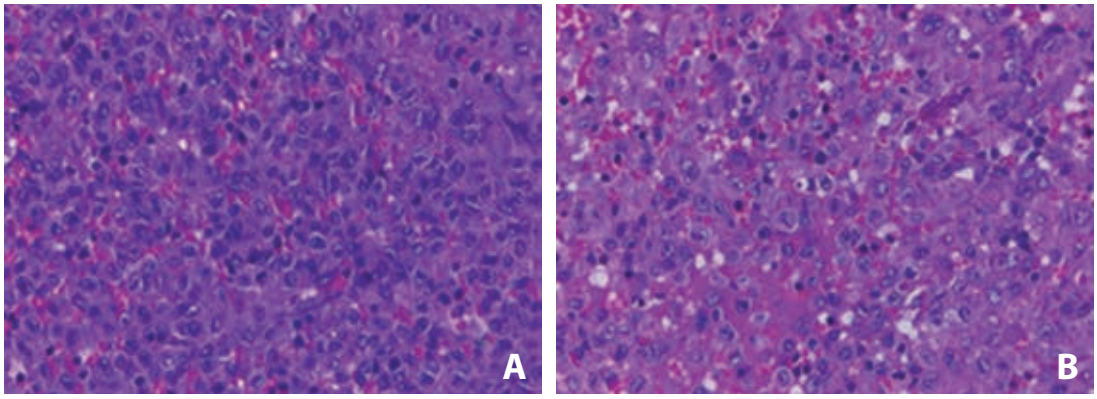

Figure 5. Histopathological features showed (A, B) Histiocytes cells that are ovoid, irregular, or dense kidney-like nuclei (reniform) with fine chromatin and 1 or more small nucleoli and eosinophilic cytoplasm (H & E, 400 x 400)

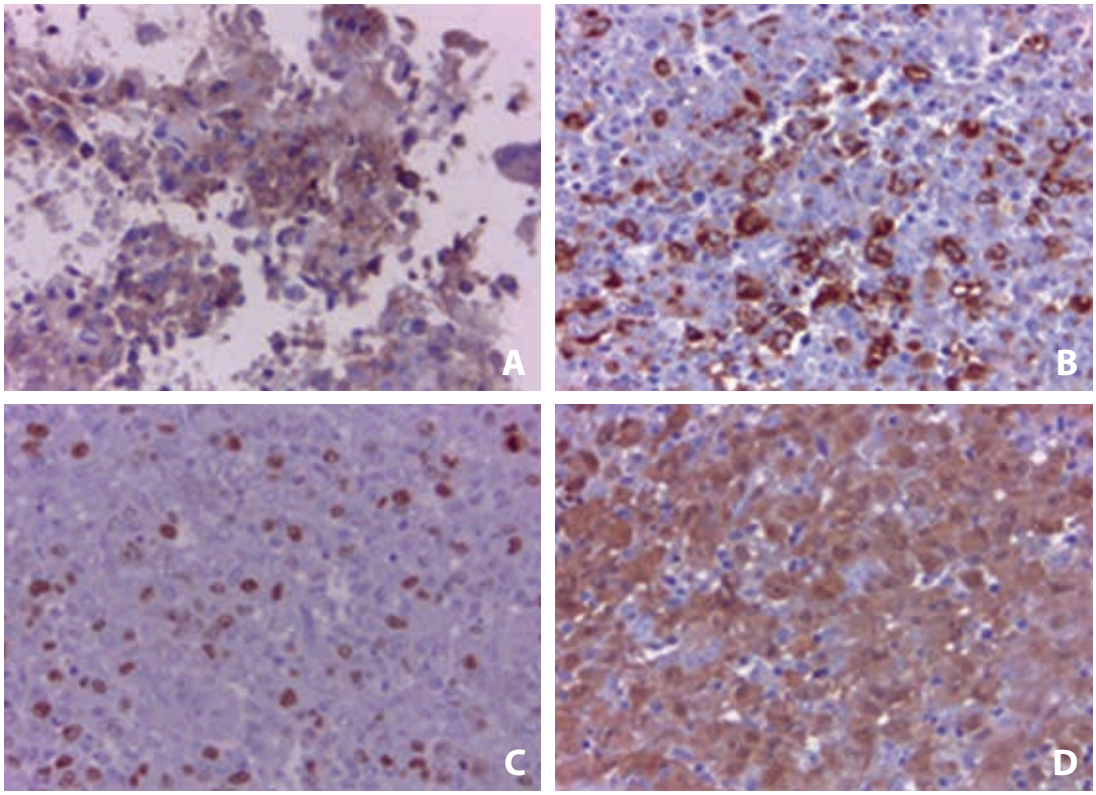

Figure 6. Immunohistochemical (A) CD1a showed positive results, (B) CD68 showed positive result in some cells. (C) Ki67 was positive in 40% of the cells. (D) S100 shows positive result on all tumor cells.

involvement is when two or more organ systems get involved (2, 4, 11, 13).

The result of routine blood test showed the presence of pancytopenia, which, based on literature, patients with this case are classifies as Multi-system Langerhans Cells Histiocytosis (MS-LCH) (3, 5). According to other literature data, distribution of the risks of LCH patients are divided into low, high, and very high risk categories (3). In the low risk category, no bicytopenia or pancytopenia abnormalities are discovered and cutaneous manifestations are seen only in the involved internal organs, such as lungs, liver, and hematopoietic system (3). In the high risk category, two or more organs were found to be involved, where significant laboratory abnormalities of bicytopenia or tricytopenia were found. In our patient, the CNS and liver were involved as shown by ultrasound examination and elevation of SGOT/SGPT, along with bicytopenia abnormalities, so that it is classified as Multisystem Langerhans Cell Histiocytosis with high risk stratification (9, 10).

Immunohistochemistry examination is the definitive examination in LCH, where clonal disorders are derived from dendritic cells system (17). The diagnosis was established based on clinical manifestations, histopathological and immunohistochemical examination. Biopsy and immunohistochemical examination must be done in order to establish a definitive diagnosis of LCH and the patient is to be treated with systemic chemotherapy, such as Vinblastine (14, 17).

Langerhans cells express Fc receptor and class I non polymorphic CD1a molecules. The finding of Birbeck cytoplasm granule under electron microscopy examination confirms the presence of these cells. Following their migration to the epidermal layer dissociation occurs with class II MHC and molecular adhesion. Antigens obtained from reactive lesions, namely CD1a and protein S100, are the most helpful markers in immunochemical examination. LCH is shown to be immunoreactive towards fascin, CD1a and S100 protein markers (17, 23).

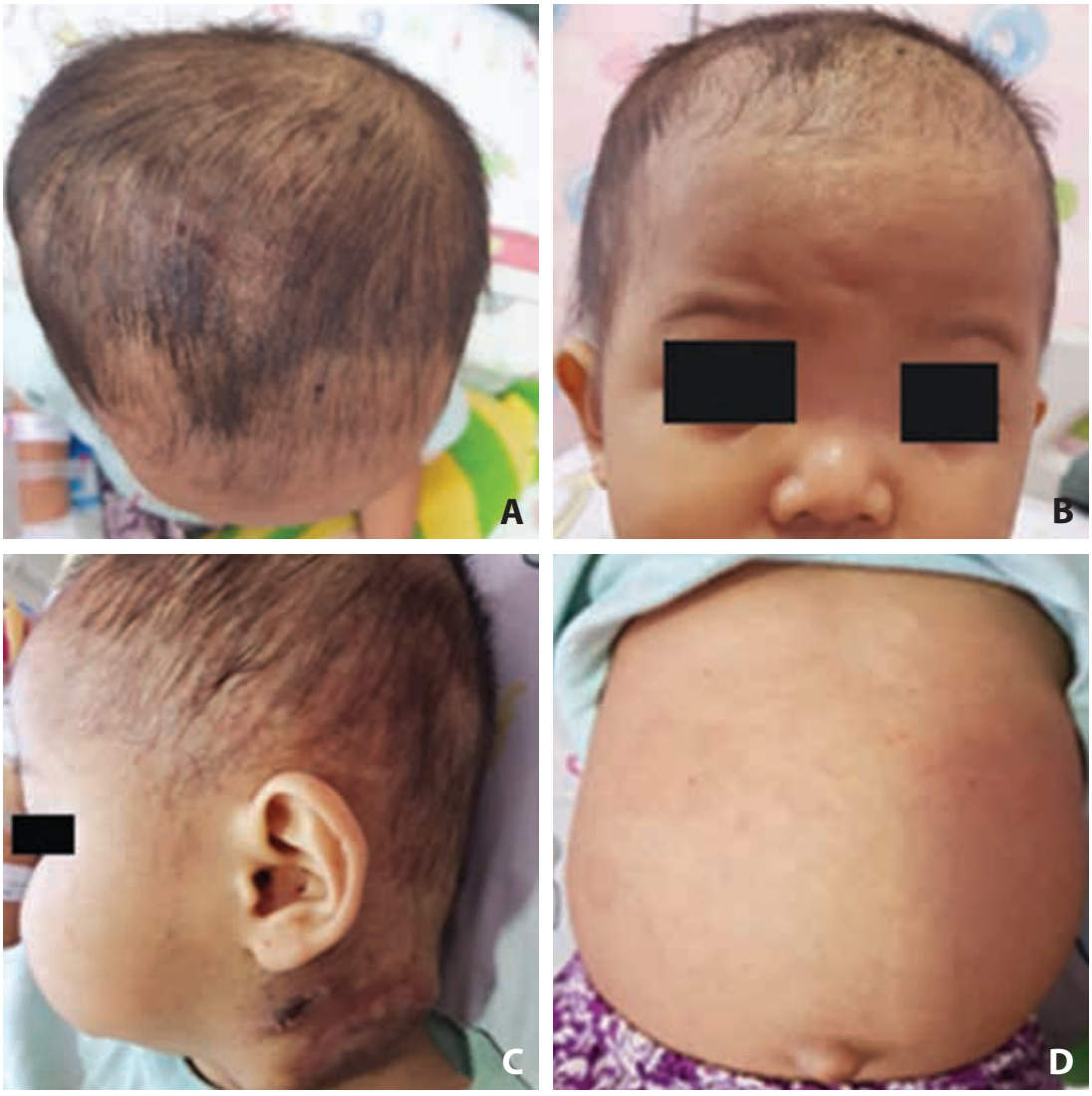

Figure 7. The 31st day of treatment (post-chemotherapy) (A-C) Improved purpura and ulcer on the scalp, neck, anterior trunk (D) no purpuric lesions were found on the abdomen and inguinal

The histopathological examination showed the ovoid, irregular or nuclei histiocyte cells that were curved with fine chromatin or smaller nucleoli and eosinophilic cytoplasm resembling the shape of kidney, better known as reniform (H & E, x 400). Based on the literature, the histopathological features consist of multinucleated histiocyte cells infiltration and reniform eosinophil cells in the dermis layer. Neutrophils, lymphocytes, and plasma cells may also infiltrate more deeply, as seen in chronic LCH. This histopathology features are discovered in this patient. The multinucleated histiocyte cells infiltration in the form of kidney-like shaped were found (14, 17).

Intensive therapy based on International Haematology Association includes intravenously administered Vinblastine 6 mg/m^2m^2, orally administered prednisone 40 mg/m^2m^2 every 1 week. According to Langerhans Cells Histiocytosis Association, initial treatments that are given on MS-LCH includes oral steroids and Vinblastine injection every week for 6-12 weeks to be followed by a pulse dose of prednisone and Vinblastine every 3 weeks with a total duration of 12 months. Vinblastine showed good tolerance, low toxicity, high availability of drugs, affordable price, and can be given to outpatients (3, 12). There is no scientific evidence about

standard therapy or therapeutic consensus on LCH because of the rarity of this case (13).

Based on the literature, peripheral blood test can be performed every 3 weeks, along with liver function examination, albumin and kidney function every 3 weeks before giving further chemotherapy. Vinblastine can cause a reduction of hemoglobin level, thrombocytopenia and depression of bone marrow. Furthermore, it can also cause elevated liver enzymes and hepatocyte cells damage which are at high risk for cirrhosis of the liver and nephrotoxic, therefore, periodical laboratory tests are needed (8, 9).

Vinblastine (VBL), a vinca alkaloid, is a primary regiment for chemotherapy in multisystem LCH, with a response rate of up to 70%, which is comparable to the response rate in LCH with lesions in the central nervous system (CNS). VBL is able to penetrate into the blood brain barrier, hence it has a therapeutic effect on osteolytic lesions. On the other hand, VBL is well tolerated and also can be used in a long term treatment with no significant toxicity effects (21, 22). Provision of Vinblastine at a dose of 0.1-0.2 mg/kgBW is equal to 6.5 mg/m^2m^2 for 1-3 months. Combination dose of steroid is selective. Our patient was given two chemotherapy treatments: intravenous Vinblastine 3 mg/m^2m^2 and prednisone 20 mg/m^2m^2 orally with an interval of 1 week. Indications for the administration of systemic chemotherapy are also given to patients with a condition of multisystem LCH, LCH with an involvement of a single organ system along with multifocal lesions in bone tissue, LCH with a single organ system with special conditions such as infraspinal extension, craniofacial and soft tissue bone lesions, also LCH condition with risk factors for CNS lesions (20). Therapy given to this patient is suitable according to the standard of LCH therapy. The evaluation of therapeutic response must be performed at the 6th week as well as of a predictor of the patient's prognosis and survival rate (12, 18).

Based on a clinical trial done by International Association of Histiocytes for the collaborative treatment protocol for LCH, it has been explained that the initial therapy for MS-LCH is 6 mg/m^2m^2 Vinblastine monotherapy given intravenously and can be given with a combination of prednisone 40 mg/m^{2}m^2 orally with tapering off after 4 weeks. The dose of prednisone 40 mg/m^2m^2 orally in 7 days is given on the 1st day until the 3rd day for 5 weeks (3, 7). Therapy for MS-LCH has several alternative treatments because there is no standard treatment in MS-LCH case, which usually has a poor prognosis despite of getting an adequate chemotherapy (3, 14). The positive response to the treatment is defined as the improvement in the internal organs being at risk after the administration of chemotherapy (14).

Conclusion

Langerhans Cell Histiocytosis (LCH) is a rare idiopathic disease characterized by the clonal proliferation of Langerhans cells. The broad spectrum of clinical symptoms and rarity of LCH make the diagnosis and treatment challenging. Multiorgan involvement contributes to the poor prognosis.

Abbreviations

LCH – Langerhans Cell Histiocytosis
APCs – antigen-presenting cell
MS-LCH – Multi-system Langerhans Cells Histiocytosis
BSA – Body Surface Area
VBL – vinblastine
CNS – central nervous system

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Prikaz slučaja histiocistoze Langerhansovih ćelija kod dece – sadašnji pristup i dijagnostički izazovi za dermatologa

Sažetak

Histiocistoza Langerhansovih ćelija je hronični i redak mijeloproliferativni poremećaj izazvan poremećajima u proliferaciji Langerhansovih ćelija u različitim organima i tkivima. Histiocistoza Langerhansovih ćelija ima širok spektar kliničkih manifestacija što otežava postavljanje dijagnoze. Kutane manifestacije su polimorfne u obliku purpure, papula, vezikula i pustula. Histiocistoza Langerhansovih ćelija može da zahvati vitalne organe kao što su jetra i pluća kao i hematopoetski sistem što često ima lošu prognozu. Na prognozu utiče i starost pacijenta, disfunkcija organa i reakcija na hemoterapijski tretman u prvih šest nedelja. Glavna manifestacija kod jedne trogodišnje devojčice bila je apscesna lezija u regiji vrata sa pratećom purpurom na skalpu, koli regiji i ingvinalnim površinama, uz eroziju područja vulve. Imunohistohemijski i histopatološki pregled potvrdio je histiocistozu Langerhansovih ćelija i kliničko poboljšanje posle intravenske hemoterapije 3 mg/m^2 vinblastina, 75 mg/m^2 etopozida i oralne primene 40 mg/m^2 prednizona. Posle šestog ciklusa hemoterapije, pacijentkinja je preminula.

Ključne reči: Histiocitoza Langerhansovih ćelija; Purpura; Vezikulobulozne kožne bolesti; Dijagnoza; Predškolska deca; Vinblastin; Smrtni ishod

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Hand, Foot and Mouth Disease in Immunocompetent Adult with Severe Oral Manifestation

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Abstract

Hand-foot-mouth Disease (HFMD) is an acute, self-limited, and highly contagious disease caused by a virus and generally affects children under 10 years old. The etiology of this disease is enterovirus 71 or coxsackievirus A16 which usually causes symptomatic infection or mild disease. Immunocompetent adults are rarely affected. However, recently the incidence of HFMD in immunocompetent adults has increased. We report a 41-year-old woman with severe oral lesions and painful papulovesicular eruption on the palms of her hands and feet.

Key words: Hand, Foot and Mouth Disease; Enterovirus Infections; Skin Diseases, Vesiculobullous; Adult; Immunocompetence; Diagnosis; Case Reports; Signs and Symptoms

Introduction

Hand-foot-mouth disease (HFMD) is a highly contagious disease characterized by multiple papules and vesicles in the hands, feet and oral mucosa accompanied by fever, myalgia, and abdominal pain. It is commonly caused by Enterovirus (1), mostly found in children <10 years old during the summertime (2). The most common causes are Coxsackievirus A16 and Enterovirus 71 (1). Lesions can be asymptomatic, but sometimes a touch can induce pain. Symptoms improve within 7-10 days (3). Oral lesions usually precede cutaneous lesions: however, oral lesions can occur without cutaneous lesions, and otherwise have also been reported in immunocompromised adult patients (2).

Hand-foot-mouth disease is a clinical diagnosis, and laboratory tests are not always necessary (1, 4). The sample for PCR can be obtained from serum, skin vesicles, throat and stool swabs to identify enterovirus serotypes (5, 6). Histopathological examination revealed a picture of reticular degeneration in the epidermis which results in the formation of intraepidermal fissures filled by neutrophils, mononuclear cells and eosinophilic protein material (7, 8). These vesicles have a necrotic roof with disceratosis and acantholysis. The upper dermis appeared edematous with perivascular mixed cell infiltrate. Viral inclusion or multinucleated giant cell was not found (1, 6). Treatment is typically supportive aimed at reducing discomfort and dehydration. Novel antiviral agents and vaccine development targeting enterovirus 71 is an active area of investigation because of the strain of virulence, geographic spread, risk prevalence, and risk of devastating brainstem encephalitis (1, 3, 7).

Children are the most vulnerable targets as well as immunocompromised adult patients. However, the incidence of HFMD is very rare in immunocompetent adults (2, 3). One case of HFMD was reported in a 41-years-old immunocompetent woman, with severe oral involvement.

Case Report

A 41-year-old woman complained of redness on the lips, both palms and feet and sores on the oral mucosa which developed three days before coming to the hospital. It occurred suddenly and simultaneously, accompanied with itchiness, burning sensation then followed by some reddish spots that appeared on both of the hands and feet. The patient also complained about fever up to

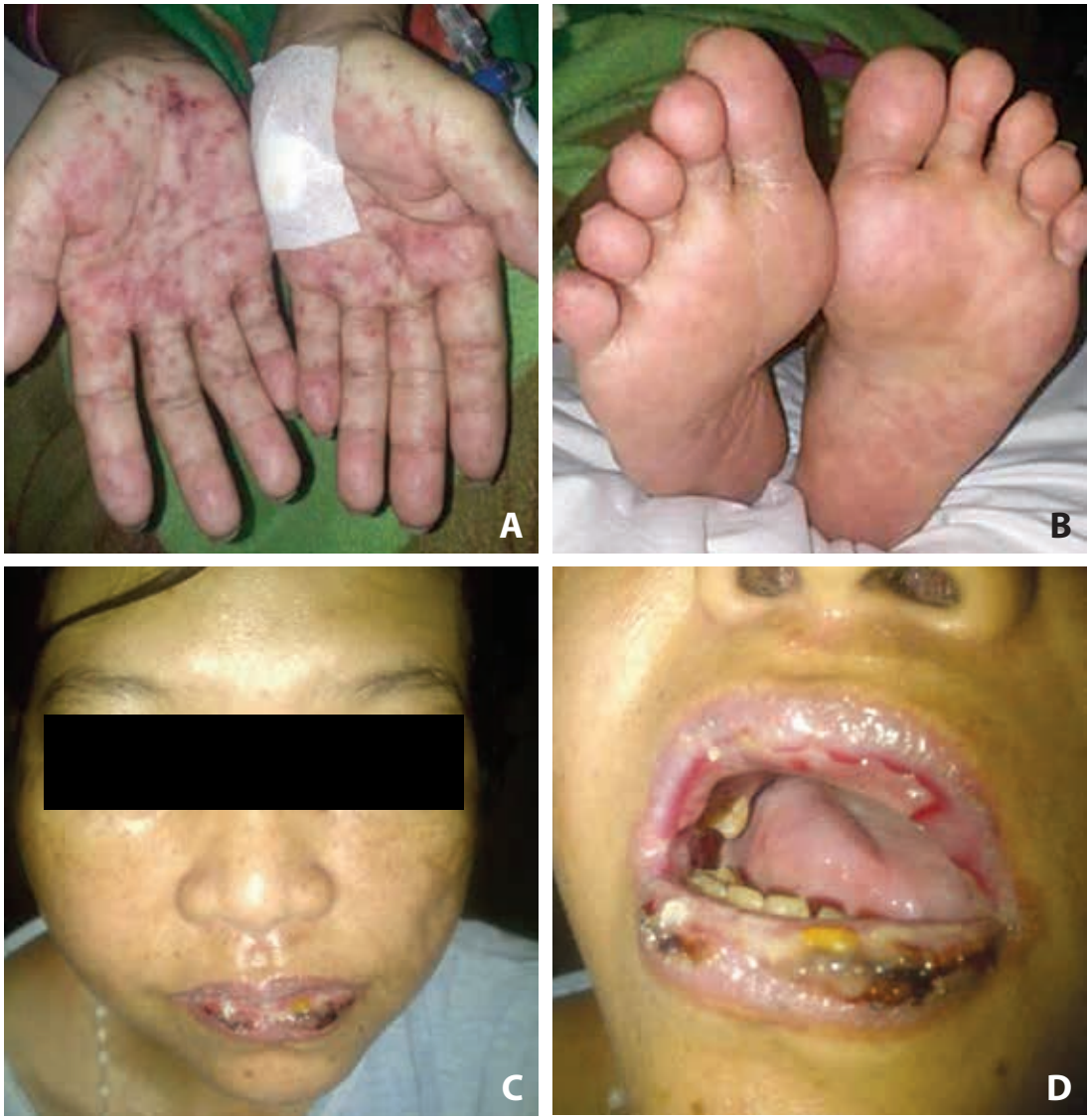

Figure 1. (A, B) Multiple vesicles and erythematous papules on the palm and plantar area; **(C-D)** Lesions on the lips and oral mucose, abscesses, pus, crusting and erosion. Patients unable to open their mouths fully.

39°C lasting for two weeks which was reduced by fever reliever. Fever was accompanied by nausea and vomiting. She had lost her appetite due to sores in the mouth. Complaints of cough, runny nose and joint pain were denied. Prior to the visit, the sores worsened and showed some pus. Any past medical history was denied. History of family members or neighbors with similar complaints was denied. History of consumption of medicines such as corticosteroid, herbs, topical medicine was denied. Drug and food allergies were denied.

On physical examination she was found to be moderately ill and alert, her blood pressure was 140/80 mmHg, heart rate 88 bpm, respiratory rate 22 breath/minute, and temperature 39°C. The dermatology examination revealed erythema, erosion, crusting, abscess with pus in the oral region. In addition, multiple crusted erythematous papules and vesicles were found on both palmar and plantar. There was no redness in the other area.

The suspected differential diagnoses were hand-foot-mouth disease, drug eruption, and erythema multiforme. Laboratory examinations

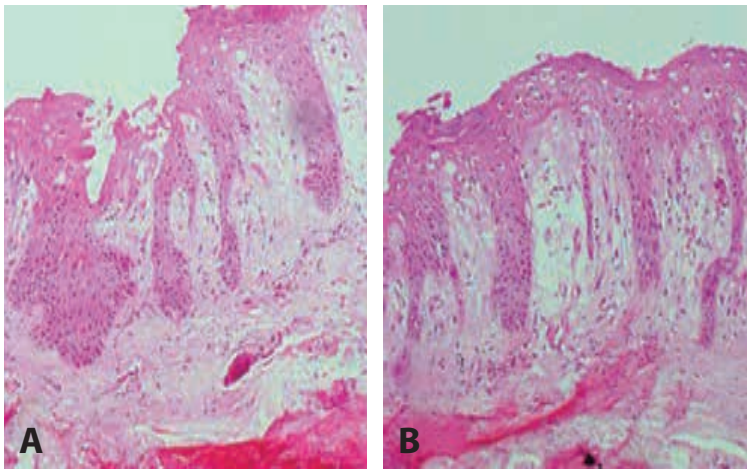

Figure 2 (A-B). Epidermal hyperkeratosis, spongiosis, edema of the dermal papillae with dense neutrophils

were conducted to rule out the differential diagnoses. Complete blood count was normal. Electrolytes, blood sugar, liver function test, renal function test results, urinalysis were normal. Immuno-serological examination was confirmed non-reactive for HBsAg, non-reactive anti-HCV and non-reactive HIV antigen, and negative for Salmonella typhi antigen. Skin biopsy from the left palm showed the epidermal hyperkeratosis with spongiosis, edema of dermal papillae with dense neutrophils, which supported a hand-foot-mouth disease.

Based on the history, physical examination and biopsy, the diagnosis of hand-foot-mouth disease was established. The patient was given NaCl infusion 0.9% 28 drops/minute, cetirizine tablets 10 mg/24 hours/oral, paracetamol 500 mg/8 hours/oral, desoximetasone cream was applied on hands and feet in the morning and evening, and triamcinolone in orabase on the lips and oral mucosa.

Discussion

Hand-foot-mouth disease (HFMD) is a self-limited enteroviral exanthema that is found throughout the world, mostly caused by Enterovirus 71 (9). The transmission of HFMD is via the fecal-oral route and, less commonly via respiratory inhalation. There is a high transmission rate between household contacts in one family (1, 5, 9). Adult HFMD patients are usually asymptomatic or only subclinical, causing them to be potential reservoirs of human-to-human transmission and it is often not possible to identify the origin of infection (3). In our case, the source of transmission is not known. Investigation in Taiwan reports that about half the adult population in northern Taiwan have antibodies to Enterovirus 71, which indicates the high rate of transmission of the virus. 9 HFMD infection usually starts with non-specific prodromal symp-

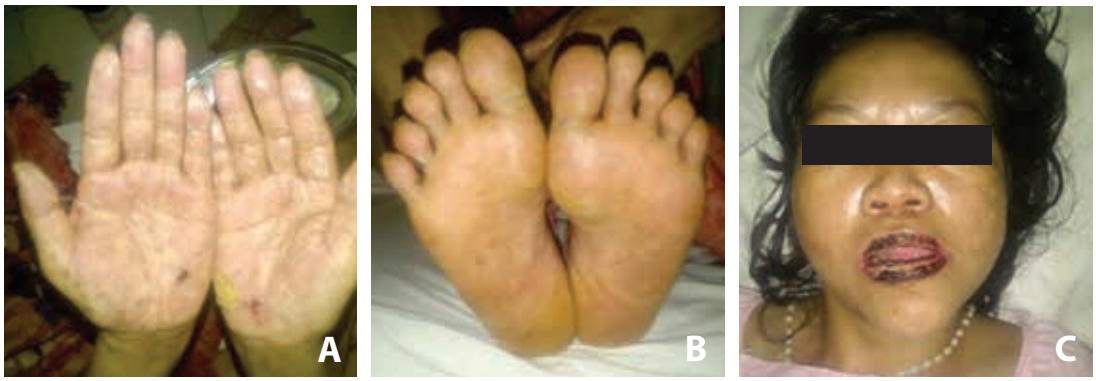

Figure 3. Clinical improvement after 14 days of follow-up

toms, including fever (38-39°C) lasting 1-2 days, malaise and sometimes, abdominal pain or symptoms of upper respiratory tract disorders (9). Another study reported that HFMD was followed by persistent fever and systemic arthritis (10). In this case, fever was found to occur in the last 2 weeks, accompanied by nausea and vomiting.

Almost all patients with HFMD have painful oral lesions. Oral lesions are mostly found on the tongue, buccal mucosa, palate, and, more rarely, oropharynx. The lesion initially presents as bright pink maculopapular lesions which develop into 4-8 mm size vesicles surrounded by erythema. These lesions are rapidly eroded and form yellow-gray erosions surrounded by erythema (1, 7, 11). Oral lesions usually occur prior to the cutaneous lesions (1, 6, 11). There is a case report of HFMD in immunocompetent adults with severe oral lesions reported in previous study with erosion, bleeding and pus on the upper and lower lips which caused the patient to not open his mouth (12). In this case, abscesses, pus and crusts were seen in the inferior of oral region and excoriation in the superior labia which disabled the patient to open her mouth. Typical HFMD lesions on the palmar and plantar area are erythematous papules or vesicles (9, 12). Atypical HFMD can be found in the extensive cutaneous lesions, perianal area, elbow, and face (11, 12).

Viral detection is using polymerase chain reaction (PCR) of feces, vesicles and pharynx and viral culture is the most accurate confirmation: however, the diagnosis is usually made based on clinical presentation (1, 7). Typical histopathological findings of HFMD are reticular degeneration of the epidermis without inclusion bodies or multinucleated giant cell (9, 10). In this case, the biopsy showed hyperkeratosis epidermal, spongiosis, and edema of the dermal papilla with dense neutrophil inflammation.

Most HFMD patients only get symptomatic treatment because HFMD is self-limited. In the cases with more prolonged fever, diarrhea, and joint pain, drugs can be given to reduce discomfort (1, 3, 12). In this case, the patient was given NaCl 0.9% 28 drops/minute, cetirizine tablets 10 mg/24 hours/oral, paracetamol 500 mg/8 hours/oral, desoxymetasone cream applied to both palms and feet in morning and evening, and triamcinolone in orabase on the lips and mouth.

Hand-foot-mouth disease infection can cause several complications. Complications are more common in children than in adults (12, 13). Barbara et al. reported one case of HFMD followed by myocarditis (14). Another study reported acute unilateral maculopathy, onychomadesis 2-3 months after the onset of HFMD (14, 15). In this case, no onychomadesis at the 3 months follow up and no complication was found. Hand-foot-mouth disease is a highly contagious disease. Immunocompromised people, such as elderly and pregnant women, have higher risk of infection. HFMD can also occur in immunocompetent adults: however, early detection and accurate diagnosis are difficult.

Abbreviations

HFMD – hand-foot-mouth disease
PCR – polymerase chain reaction

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Bolest šake, stopala i usta kod imunokompetentne odrasle osobe sa teškom manifestacijom u ustima

Sažetak

Bolest šake, stopala i usta (BŠSU) akutna je, samoograničena, izuzetno zarazna bolest koju izaziva virus i uglavnom pogađa decu mlađu od 10 godina. Etiologija ove bolesti je enterovirus 71 ili koksaki virus A16 koji obično izaziva simptomatsku infekciju ili blag oblik bolesti. Retko napada imunokompetentne odrasle osobe. Međutim, nedavno je došlo do porasta incidencije BŠSU kod odraslih. Ovde je prikazan slučaj 41-godišnje žene sa izrazitim oralnim lezijama i bolnom papulovezikularnom erupcijom na dlanovima šaka i stopalima.

Ključne reči: Bolest ruku, stopala i usta; Enterovirusne infekcije; Vezikulobulozne kožne bolesti; Odrasli; Imunokompetencija; Dijagnoza; Prikazi slučajeva; Znaci i simptomi

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Recurrent Pregnancy Induced Pemphigus Vulgaris: A Rare Case Report

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Abstract

Pemphigus vulgaris is a potentially life-threatening bullous autoimmune disease that can be triggered by various factors, one of which is pregnancy. Cases of pregnancy induced pemphigus are rare, and can result in devastating outcomes, both from the maternal or fetal perspectives if not treated promptly and adequately. The use of systemic corticosteroids is paramount to improve the outcome of the patient and fetus and it is a first-line treatment for the disease. Patients with a history of pemphigus should plan their pregnancies carefully, taking into consideration a minimum of 6 months remission before conception. This case report is about a 28-year-old woman with a history of pemphigus vulgaris that did not seek medical treatment of her pemphigus, which resulted in the intrauterine fetal death. The patient was treated with systemic corticosteroids and achieved great resolution to her blisters and overall wellbeing.

Key words: Pemphigus; Pregnancy Complications; Autoimmune Diseases; Fetal Death; Methylprednisolone; Gentamicins; Treatment Outcome

Introduction

Pemphigus vulgaris (PV) is a potentially life-threatening autoimmune blistering disease that is often associated with the elderly. This disease develops due to autoantibodies to desmoglein 1 and desmoglein 3, which results in the loss of cell to cell adhesion in both the basal and suprabasal layers in the deep epidermis (1). A study performed in the UK has suggested that the incidence rate of PV is around 0.68 cases per 100,000 persons/year. Even more rarely, it can be triggered or exacerbated by pregnancy and is associated with various pregnancy outcomes such as live births, stillbirths, spontaneous abortions and induced abortions (2).

Pregnancy in pemphigus can also cause transplacental transfer of antibodies resulting in neonatal pemphigus (NP). Lesions are usually mild and will resolve spontaneously as the maternal antibody dissolves (2, 3).

We report a case of a 28-year-old pregnant woman with generalized blistering and excoriation with a history of pregnancy induced PV two years before which resulted in stillbirths in her previous two pregnancies. The diagnosis of the disease was confirmed after thorough history taking, clinical presentation and histopathological result. The patient was treated with systemic corticosteroids and antibiotics and had a positive outcome, but unfortunately there was intrauterine fetal death (IUFD) during treatment.

Case Report

A 28-year-old Bugis woman, gestation age 24 weeks was admitted to the dermatology department with the chief complaint of blisters across the abdomen that had spread to the forehead, breast, arms, back, thigh and the pubic area three months before which were accompanied with intense pain and pruritus. The patient had no fever. Initially the skin lesion took form in vesicles in the buccal mucosa. She had a history of PV in the first and second pregnancy 2 years before, and both resulted in stillbirths at the gestation age of 20 and 24 weeks, respectively. In her first pregnancy, the first bullae appeared on the buccal mucosa that spread to the whole body at the gestation age of 4 weeks. The patient was told to plan for her second pregnancy but refused to do so. Similar symptoms happened in her second pregnancy. After both pregnancies, the patient had spontaneous resolution.

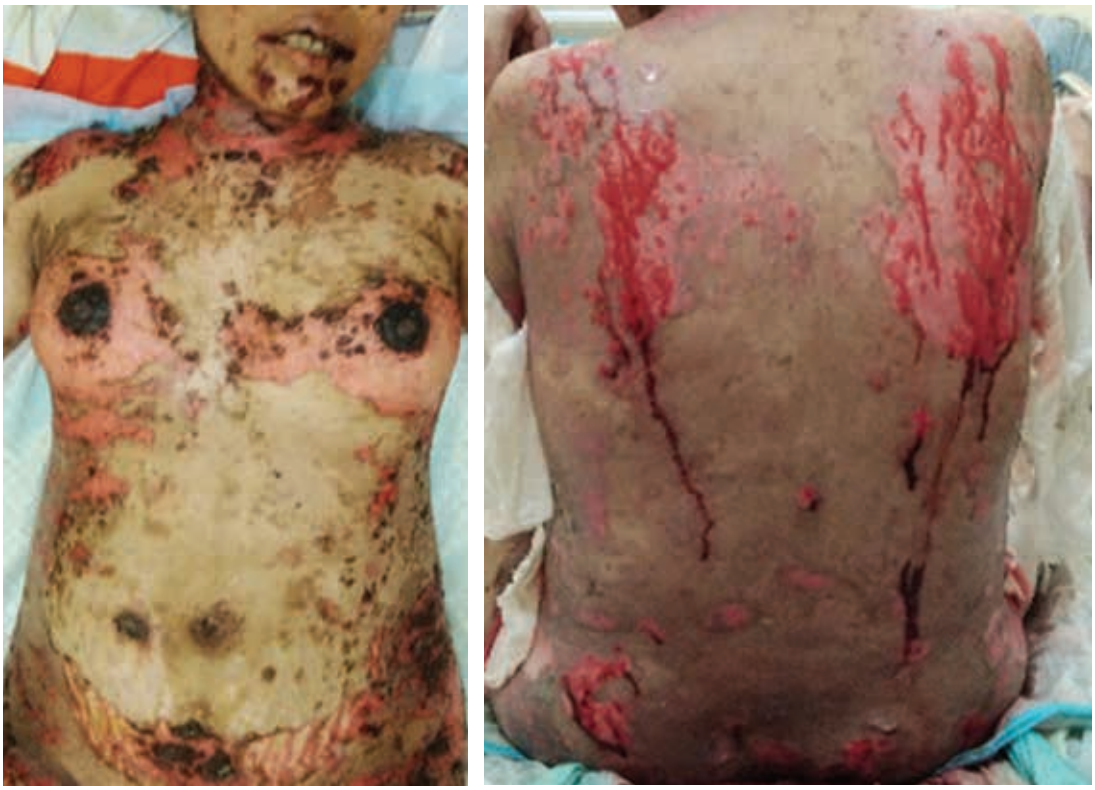

Figure 1. Generalized erosions, flaccid bullaes, crusts and hyperpigmentation macules

The patient did not consume any drugs to control her disease apart from traditional remedies. The patient got married to her cousin seven years before. History of allergies and other systemic disease were denied, as well as family history of bullous disease.

Upon physical examination, her vital signs were normal. There were extensive generalized erosions with erythematous base on her neck, breasts, back, and inner thigh. Flaccid blisters were found along her breast, abdomen, and thigh, alongside crusts and hyperpigmented macules on her forehead and mouth, and chin (**Figure 1**). The patient had positive Nikolsky sign. Edema was observed on the hands and feet with mild dehydration. Systemic examination was normal. Laboratory test results were as follows: leucocytosis $12.93x10^3$/L, hypoalbuminemia 28 g/L and anemia 98 g/L. The liver and kidney function, as well as abdominal ultrasonography were normal. She was hospitalized and treated with systemic methylprednisolone 125 mg/day and gentamicin 80 mg/day, and her wound was treated with NaCl 0.9% twice a day.

On the second day of treatment, a skin biopsy was taken from the right thigh. As the patient was currently pregnant, the treatment was supervised by an obstetrician and the wellbeing of the fetus was strictly observed. On day-10, the patient said there was an increase of skin shedding especially on the lumbosacral area and crusts on her face that made it difficult for her to move and eat. The biopsy results came on day-13 of treatment and the diagnosis of PV was made (**Figure 2).** On day-19, the fetal heartbeat got weaker and a maternal ultrasonography (USG) was performed and showed fetal distress with a decrease in amniotic fluid. The patient was due for an emergency caesarean section but unfortunately IUFD happened before the procedure. After gradual improvements in symptoms of pain, erosions, and blisters, we began steroid tapering off to 62,5 mg/day, and the patient was discharged on day-42 (**Figure 3)**.

Discussion

Pemphigus vulgaris, as an immunological disease is already in itself a complicated disease, but when it is associated with pregnancy, the management can get even more complex. Pemphigus can cause serious complications to both the mother and the foetus as demonstrated in this case. Pemphigus is

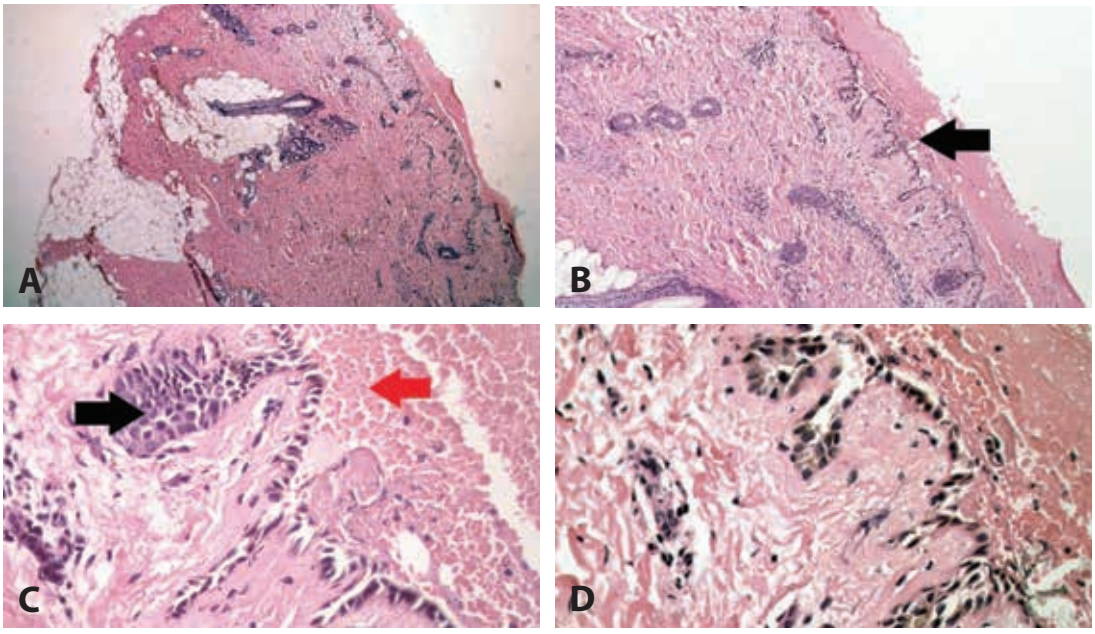

Figure 2. Skin biopsy results. A. Epidermis with suprabasal acanthiolysis; B. Suprabasal bullae (black Arrow); C. Achantolytic cells (black arrow) erythrocytes (Red Arrows); D. Mild lymphohistic inflammation.

a Th2-dominant disease and Th2 is also dominant during pregnancy, which increases the rate of pemphigus in pregnant women. Th2-associated cytokines, including interleukin (IL)-4, IL-6, IL-10, IL-13 have been proven to promote autoantibodies such as immunoglobulin (IgG)1 and IgG4 that attack desmosomal glycoprotein (Dsg)1 and Dsg 3 in pemphigus, although further studies need to be done on this matter (2, 4, 5).

In this case report, her pemphigus was induced by multiple pregnancies over the course of 2 years, and no similar case report has ever been reported. According to a review by Lin (2015), who observed 26 case reports of pemphigus during pregnancy from 1966-2013, 80.8% (21 cases) were pemphigus vulgaris, the rest were pemphigus foliaceus (7.7%), and pemphigus vegetans (11.5%) (2).

The clinical symptoms of generalized blistering, erosions, and crusting are typical to pemphigus, and histological examination through skin biopsy shows suprabasal acantholysis on the epidermis, suprabasal bullae, and mild lymphocytic inflammation (6). The symptoms start at week 4 in accordance with another review that has stated that 81% of pemphigus during pregnancy usually happen in the 1st trimester (7). We were unable to conduct direct immunoflouresecence examination as the patient declined it for financial reasons. Thus, with typical clinical presentation and in accordance with the histopathological examination, the diagnosis of pemphigus vulgaris in pregnancy was made.

Due to the extensive lesions on her body, the patient was then given systemic corticosteroids of methylprednisolone 125 mg/day in addition to gentamicin 80 mg/day to prevent sepsis. Treatments of pemphigus in pregnancy are generally similar to those in non-pregnant patients, paying special attention to the wellbeing of the fetus. Systemic corticosteroids (FDA pregnancy category C) have long been considered as a first line therapy for pemphigus, with other immunosuppressive drugs such as azathioprine, mycophenolate mofetil (FDA pregnancy category D) and methotrexate (FDA pregnancy category X) are not recommended to be used in pregnancy due to their side-effects of congenital abnormalities. Long term use of corticosteroids can also cause hypertension, diabetes, and premature rupture. Systemic steroids have also been reported to cause cleft abnormalities, therefore it is essential for patients to start low dose steroid therapy as soon as the first symptoms of pemphigus arise to reduce the possible side effects (2, 8).

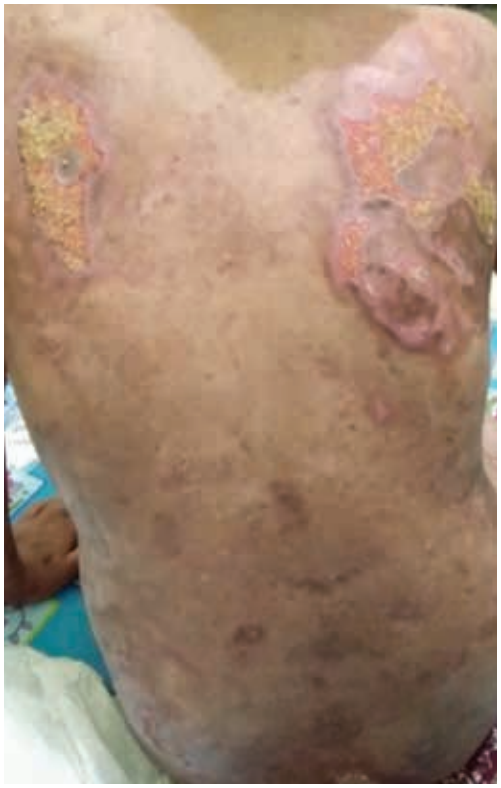

Figure 3. Clinical improvements in crust thinning and excoriation on day-42

Another therapy option of PV in pregnancy is plasmapheresis, in which a large amount of plasma and human albumin is administered intravenously hoping that it will remove the antibody in the plasma in exchange of isotonic solution of albumin, resulting in clinical resolution (3).

The patient responded well to the therapy with a recognizable reduction in symptoms; unfortunately, the patient experienced IUFD on day-19 of hospitalization. Stillbirths are rare in pemphigus during pregnancy with around 7.7% of cases. In more than half of cases, patients can deliver full-term healthy babies. Stillbirths are related to poor maternal disease control, higher maternal serum, and umbilical cord blood antibody titers (2).

In the future, as the patient is still at her reproductive age and still can have a child, we emphasize the importance of pregnancy planning to the patient. Treatment with low dose steroid should start a few months before conception. Only when the state of stable remission has been achieved, the patient can start conception, hoping to prevent future exacerbation. A review has found that a remission of at least 6 months with no or minimal therapy is ideal (2).

Conclusion

Pemphigus vulgaris is a potentially life-threatening bullous disease that can be triggered by various factors, one of them being pregnancy in rare cases. First-line treatment of the disease is systemic corticosteroids and does not differ from the one in non-pregnant patients. In patients with recurrent cases of pregnancy induced pemphigus, education about the importance of pregnancy planning is essential to prevent negative outcomes such as stillbirths.

Abbreviations

PV – pemphigus vulgaris
NP – neonatal pemphigus
IUFD – intrauterine fetal death
Dsg – desmosomal glycoprotein
IL – interleukin
USG – ultrasonography

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Recidivantni *pemphigus vulgaris* izazvan trudnoćom – prikaz retkog slučaja

Sažetak

Pemfigus vulgaris je bulozna autoimuna bolest koja može da ugrozi život i okidač mogu biti različiti faktori – trudnoća je jedan od njih. Retki su slučajevi pemfigusa izazvanog trudnoćom, a rezultat može biti fatalni ishod i za majku i za fetus ako se ne leči adekvatno i na vreme. Upotreba sistemskih kortikosteroida je ogromna u poboljšanju ishoda za pacijentkinju i fetus i stoga su oni prva linija terapije za ovo oboljenje. Pacijentkinje sa istorijom pemfigusa trebalo bi pažljivo da planiraju trudnoću i da uzmu u obzir minimum šest meseci remisije pre začeća. Ovde je prikazan slučaj dvadesetosmogodišnje žene sa istorijom pemfigusa vulgaris koja nije tražila medicinsku pomoć što je rezultiralo fatalnim ishodom fetusa. Pacijentkinja je lečena sistemskim kortikosteroidima te je došlo do znatnog smanjenja broja bula na koži i poboljšanja opšteg stanja.

Ključne reči: Pemfigus; Komplikacije u trudnoći; Autoimune bolesti; Smrt fetusa; Metilprednizolon; Gentamicin; Ishod terapije

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Harlequin Ichthyosis (HI) Associated with Atrial Septal Defect (ASD) and Choanal Atresia

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Abstract

Harlequin ichthyosis (HI) is a severe form of congenital ichthyosis with autosomal recessive inheritance. Incidence of harlequin ichthyosis is 1 in 3,00,000 live births. We report a case of HI associated with bilateral choanal atresia and atrial septal defects, which is a rare association in this skin disorder. A-month-old preterm male baby born out of consanguineous marriage presented with features of armour-like scales and erythema all over body, ectropion, eclabium and fissures over flexures. The patient was born with a colloidion membrane at birth. The baby was operated for bilateral choanal atresia soon after birth because he developed cyanosis upon breast feeding which improved on crying. Upon flexible nasal endoscopy, diagnosis of membranous type of choanal atresia was confirmed by ENT (ear, nose, throat) surgeon. Heart auscultation revealed a murmur in our patient. Electrocardiogram and 2D Echocardiography was reported as atrial septal defect (4.5 mm OsASD). The patient was started on acitretin (1 mg/kg/day) and emollients after complete evaluation and is currently on regular follow up. Harlequin ichthyosis is linked to mutation of ABCA12 gene. It is often associated with eclabium, ectropion, hypoplastic nose, ears and fingers. Congenital heart diseases are rarely reported with HI in literature. This makes it mandatory to screen HI patients for internal defects.

Key words: Ichthyosis, Lamellar; Chonal Atresia; Heart Septal Defects, Atrial; Infant, Premature; Consanguinity; Skin Abnormalities; Comorbidity

Introduction

Harlequin ichthyosis (HI) is the most severe form of congenital ichthyosis inherited in an autosomal recessive manner. It is characterized by mutation in ABCA12 gene. It occurs in 1 in 3 lakhs live births (1). Babies with HI are often preterm and are covered with thick armour-like scales all over body. The rigid skin severely restricts mobility of joints and may result in deformities of face. Eclabium, ectropion, hypoplastic fingers/toes, hypoplastic ears and nose are common associations of HI. Choanal atresia and congenital heart disorders are extremely rare associations of HI. In this article, we illustrate a rare case of a preterm male baby with harlequin ichthyosis associated with bilateral choanal atresia and atrial septal defect.

Case Report

A-month-old preterm male child presented to us with armour like scales all over the body, ectropion, eclabium, hypoplastic pinnae, hypoplastic nose, hypoplastic fingers and toes. There was complete loss of body hair including eyebrows and eyelashes, scanty hairs were present over scalp. Multiple fissures were noted on flexures especially over neckline, axillae, and antecubital fossae bilaterally. The rigidity and fissures lead to restricted mobility along respective joints. The baby, born out of a consanguineous marriage, was born encased in a collodion membrane at birth as per history.

The patient was operated by an ENT surgeon for bilateral choanal atresia (membranous type) post delivery on emergency basis as he was having difficulty in breathing at birth and developed cyanosis while being breast fed, which improved on crying. The baby had a diastolic murmur on cardiovascular examination. Electrocardiogram revealed a right axis deviation. 2D ECHO was suggestive of osteum secundum type of atrial septal defect (OsASD) of size 4.5 mm. The patient

Figure 1. One month old baby showing generalized erythema and scaling with plate like scales over scalp, upper limbs, lower limbs and ectropion

was referred to Pediatric Cardiology Department in view of his OsASD. Currently, the baby is being managed conservatively for his ASD.

Upon examination of other systems (abdominal, neurological, respiratory), no other abnormality was detected. Hemogram, liver and renal function tests, lipid profile, urine microscopy, ultrasound of abdomen and pelvis were found to be within normal limits. The child was started on oral acitretin at a dose of 1 mg/kg/day in two divided doses. Apart from acitretin, topical emollients and antibiotic (2% mupirocin ointment) were introduced for fissures over flexural areas. Detailed skin care regarding maintaining hygiene, including use of syndet bars for bath, frequent application of emollients was explained to the parents on discharge. Currently, the baby is under regular follow up and shows mild improvement in scaling and mobility. Our patient is being managed in collaboration with pediatricians, pediatric cardiologists and otorhinolaryngologists.

Discussion

Harlequin Ichthyosis (HI) is a severe form of congenital ichthyosis caused by mutation in ABCA12 gene which encodes ATP binding cassette protein (subfamily A, member 12). This protein is responsible for skin lipid metabolism (2). Hence, mutation in this gene leads to abnormal membrane transport of skin lipids with abnormal lipid metabolism in skin (2, 3). No systemic associations have been elaborated in literature for this life-threatening ichthyosis. However, a case series by Verma B, et al. demonstrates cardiovascular anomalies associated in seven cases of harlequin ichthyosis (4). According to their report, ostium secundum type of atrial septal defect (OsASD) is the commonest type of congenital heart disease associated with harlequin ichthyosis. Other heart defects associated with HI are patent ductus arteriosus, ventricular septal defects and patent foramen ovale.

Concurrence of bilateral choanal atresia with harlequin ichthyosis and OsASD makes our case unique. There is no documentation of such kind of association with HI in literature.

HI is known for its lethal complications like hypernatremia, sepsis, heat intolerance, ocular complications due to persistent ectropion, joint contractures etc. Before 1980s, the disease was considered fatal. But now, with availability of oral retinoids and intensive care for managing systemic complications, survival rate of harlequin ichthyosis has improved (5). However, the disease still remains a prob-

lem as the babies might survive with recurrent or persistent erythroderma posing a constant threat to life.

Prenatal genetic counselling and amniocentesis for early diagnosis of HI remains the basic strategy to avoid this unsightly congenital birth defect.

Abbreviations

HI – harlequin ichthyosis
OsASD – osteum secundum type of atrial septal defect

Conclusion

Harlequin ichthyosis has ectodermal defects of skin, pinna, nose, eyes and digits. However, a rare association of this disorder with congenital heart disorder makes it crucial to screen all patients for other systemic abnormalities.

Harlequin ichthyosis, a congenital disorder hitherto notorious for its lethality, can now be managed with oral retinoids and proper intensive care.

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Harlekinova ihtioza (HI) združena sa atrijalnim septalnim defektom (ASD) i atrezijom hoana

Sažetak

Harlekinova ihtioza (HI) je težak oblik kongenitalne ihtioze nasleđene sa autosomalno recesivnim nasleđivanjem. Incidencija harlekinove ihtioze je 1 na 300,000 živorođenih beba. Prikazujemo slučaj HI združene sa bilateralnom atrezijom hoana i atrijalnim septalnim defektom što je retka združenost u ovom poremećaju kože. Jednomesečno prevremeno rođeno muško dete, rođeno u braku srodnika, imalo je skrame tipa oklopa od krljušti i eritemu po celom telu, ektropion, eklabium i fisure preko fleksura. Dete je rođeno sa koloidnom membranom i operisano zbog bilateralne atrezije hoana uskoro posle rođenja pošto je došlo do cijanoze nakon dojenja što se popravilo plakanjem. Nakon fleksibilne nazalne endoskopije, otorinolaringolog je potvrdio dijagnozu membranoznog tipa atrezije hoana. Prilikom auskultacije srca, čuo se šum na srcu pacijenta. Elektrokardiogram i 2D ehokardiografija su prikazani kao atrijalni septalni defekt (4,5 mm OsASD). Pacijent je počeo da dobija acitretin (1 mg/kg/dan) i emolijente. Posle kompletne evaluacije i sada je u redovnom procesu praćenja. Harlekinova ihtioza je povezana sa mutacijom ABCA12 gena. Često je združena sa izvrnutim usnama (eclabium), ektropionom, hipoplastičnim nosem, ušima i prstima. Kongenitalna srčana oboljenja su retko opisana sa HI u literaturi. Zbog toga je potrebno pregledati pacijente sa HI i zbog unutrašnjih defekata.

Ključne reči: Lamelarna ihtioza; Honalna atrezija; Atrijalni septalni defekt; Nedonošče; Konsangvinitet; Kožne abnormalnosti; Komorbiditet

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Hereditary Palmoplantar Keratoderma Type Papulosa in Slovenia

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Hereditary palmoplantar keratodermas (HPPK) are relatively frequent in Slovenia; however, the papulosa type of HPPK is rare. Epidemiological data are scarce; a population study in Croatia revealed a prevalence of 1.17/100,000 inhabitants. Efforts were made to identify all patients with HPPK papulosa in Slovenia. Sixty six new cases were found, which indicated the prevalence of 3.3/100,000 inhabitants. Sixty two patients were the members of 11 unrelated families with two or more affected members and there were also four isolated cases. Our investigation points to an autosomal dominant mode of inheritance. No malignancies were observed, nor were such data revealed in patients' histories. Thickened nail-plates were observed in three patients. The prevalence of HPPK papulosa in Slovenia is higher than in other countries studied. Substantial phenotypic variability was noted between patients having the same mutation, which ranged from very mild to extensive hyperkeratotic presentations of the disease indicating that other environmental factors and personal skin care regimens may affect the degree of hyperkeratosis. Further loci mentioned in literature suggest a genetic heterogeneity in this condition. In summary, we have identified five novel and two recurrent loss-of-function mutations of the AAGAB gene which underlie punctate PPK. There are now a total of twenty-two mutations in AAGAB that have been identified in patients with punctate PPK. Although PPK is a rare disorder, diseases characterized by hyperkeratosis and hyperproliferation are common, and identification of the underlying cellular mechanisms in this keratoderma may contribute to future ability to understand and treat the more prevalent hyperkeratotic diseases.

Congenital Ichthyosis: What is Already Known and new Insight

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Ichthyoses represent a large clinically and etiologically heterogeneous group of skin disorders, resulting from mutations in more than 50 genes, characterized by scaling, inflammation and an impaired epidermal barrier. All forms of ichthyosis have been associated with protein and lipid abnormalities that lead to a defective epidermal barrier, manifesting functionally as increased transepidermal water loss. Various forms of ichthyosis have been defined based largely on clinical and genetic characteristics.

Recently, next-generation sequencing has further expanded our knowledge, identifying novel mutations that disrupt the ceramide pathway and result in disorders of keratinization. Current treatments lack efficacy and are limited to topical emollients, keratolytics, and oral retinoids. Although corrective gene therapy is evolving, it is still experimental and limited to model systems.

Better understanding of the molecular changes and underlying gene mutations that may lead to phenotypic characteristics may provide insight not only into understanding these genetic disorders but also into new therapeutic options. The rapidly expanding repertoire of systemic therapies that target

specific immune-polarized T-cell subsets provides the opportunity for repurposing commercially available medications toward a variety of inflammatory skin disorders.

Presentation of Some Rare Dermatoses With Dyskeratotic Acantholysis as the Primary Pathological Finding

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Acantholysis is a histological phenomenon defined by the loss of intercellular cohesion between the keratocytes, resulting in cell separation and the formation of cavities in the epidermis. It may, but not necessarily, be accompanied by clinically visible blisters. Acantholysis can occur for a variety of reasons: immunologic antigen-antibody mediated reaction (immunobullous dermatoses), edema and inflammation, infections (bacterial, viral), or structural deficiencies of cell adhesion (genodermatoses).

Acantholytic dyskeratosis is a distinctive histologic pattern characterized by: suprabasilar clefts, acantholytic and dyskeratotic cells at all levels of the epidermis, and hyperkeratosis and parakeratosis of the surface. These histologic changes can be seen episodically as an incidental finding in many different skin lesions, or they may be a part of a disease (such as Darier's disease), or a common histological finding (such as Grover's and Haley-Haley's disease).

Nevi In Pediatric Population

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Pediatric population represents a particular group of patients with specific characteristics of various dermatologic entities. Childhood is a dynamic period with regard to nevogenesis, which has an impact on the distinctive appearance of nevi in pediatric patients.

Many new melanocytic nevi appear and grow in children and adolescents. Congenital nevi, which are mostly shown in early childhood, are divided by different clinical characteristics and biologic behaviour. Furthermore, a variety of lesions including blue, Spitz, combined, and acquired nevi could be presented during childhood and adolescence. Some of the nevi can occasionally manifest different and unusual clinical morphologies in children, which can elicit anxiety in patients, parents, and clinicians. Although the majority of melanocytic nevi in children appear clinically benign, some may resemble melanoma, leading to unnecessary biopsies, which naturally cause concern in the patient and family members.

Dermatoscopy is a noninvasive technique, recommended for the evaluation of pigmented cutaneous lesions. This technique is ideal for the evaluation of pigmented skin lesions in children as it is painless and provides important information that can assist physicians in formulating appropriate management decisions. Nevertheless, studies of dermatoscopic nevi patterns in children, which are essential for the understanding of nevogenesis, are still scarce in medical literature.

This review highlights the most common benign dermatoscopic patterns encountered in nevi in pediatric population and describe the structures and dermatoscopic patterns of melanocytic nevi observed in children and adolescents.

Using Dermoscopic Criteria and Patient-Related Factors for Differentiating Nevus Versus Melanoma Located on Special Location

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The anatomic location of nevi and melanoma influence their clinical, dermoscopic and histopathological appearance. Although there are reports on clinical and dermoscopic features of special located nevi and melanoma, in clinical settings these entities still represent a challenge, emphasizing the need of summarizing the clues which will make it easer for clinicians in dif to differentiate these two entities. The author will present a review of clinical and dermoscopic findings of special sub-sited nevi and melanoma and synthesize the available clinical and dermoscopic data to distinguish benign melanocytic nevi with site-related atypia from melanoma located on these anatomical locations.

Reflectance Confocal Microscopy: When is it Helpful?

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Reflectance confocal microscopy (RCM) allows the non-invasive, in vivo examination of the skin at near-histopathological resolution. One of the most relevant clinical applications of RCM is the diagnosis of melanoma and non-melanoma skin cancer. Mounting evidence, based on prospective and retrospective studies, has demonstrated higher accuracy of RCM for melanoma diagnosis compared to clinical and dermoscopic diagnosis.

Diagnostic expertise is achieved through a long process of learning, starting with basic training, followed by the accumulation of personal experience and by one's exposure to peers' cases. Indeed, interpretation of the RCM pattern of skin lesions requires explicit skill, and is not a direct translation of any prior proficiency in dermatopathological analysis; an RCM reader needs to adapt to making diagnoses based on greyscale, horizontally-oriented RCM images and based on the recognition of key criteria from an extensive list of published RCM features.

Recently, studies testing the utility of combining RCM with digital dermoscopic monitoring have demonstrated a reduction of the number of lesions needed-to-excise to diagnose skin cancer, reflecting an approximately two-fold reduction in the unnecessary biopsies of benign lesions.

The Role of Dermatologists In Treatment And Reduction of Undesirable Effects of Oncological Therapy With a Focus on Dermatocosmetics in Order to Improve the Quality of Life of Patients

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Today, cancer is the second leading cause of death globally, with an increasing prevalence. An estimated 12,7 million people were diagnosed with cancer in 2008, while in 2030 an estimated 26,4 million people will be affected. Strong progress has been made in the field of oncological therapy; however, these treatments can cause serious side effects and lead to significant psychological distress affecting patients' quality of life. Anti-cancer therapies are either non-targeted (chemotherapy, radiotherapy) or targeted, acting on the cell (monoclonal antibodies, RNA messenger, gene mutation) or the tumor's microenvironment (vaccination, cellular therapy). The most frequent cutaneous side effects of chemotherapy include increased photosensitivity, dryness of the skin with a dull and ichthyosiform appearance, local or diffuse hyperpigmentation, hypopigmenation, telangiectasias, erythema of the palms of hands and the soles of feet, as well as exfoliative dermatitis. Radiotherapy usually causes skin reactions that are limited to the body area receiving radiation. Erythema, hair loss, pigmentation and desquamation usually occur during the third week of radiotherapy and most frequently disappear after treatment is stopped, leaving no permanent damage. Rarely, skin ulceration and infection may also occur. Atrophy, depigmentation or hyperpigmentation, telangiectasias, dryness with burning sensations or pruritus may appear on areas that are further away from the irradiated skin. Targeted therapies are developed to function predominantly in neoplastic cells; however, they are not unique to neoplastic cells. Cell-proliferation-related pathways, which are the target of many of these therapies, are activated in tissues with high turnover rate, such as the skin, leading to adverse cutaneous effects. It has been suggested that targeted agents disturb skin barrier function and cause alteration of the immune and anti-radical systems. Hair loss is one of the most dreaded side effects of cancer treatments, and most commonly occurs 10-20 days after initiating treatment. Usually hair grows back one to five months after treatment is stopped. Along with preventive and curative measures, management includes washing hair with a small amount of very gentle shampoo the day before chemotherapy and avoiding washing the hair for the following 3-5 days, avoiding aggressive hair treatments and using a hair brush with soft bristles. Folliculitis usually appears within 3-15 days after initiating targeted oncological treatment. Folliculitis usually disappears within a few weeks after treatment is stopped and may result in hyperpigmentation and telangiectasias. Along with usual dermatological treatment, gentle cleansing products respecting the skin's natural pH (syndets), non-occlusive, light texture moisturizing creams and broad-spectrum sunscreens (minimum SPF 30) are recommended along with corrective, non-comedogenic makeup. Hand and foot syndrome occurs rapidly, usually within 1-4 weeks after initiating cancer treatment. Along with local dermatological treatment, syndets, moisturizing creams containing urea and skin repairing balms are recommended. Management also includes good hygiene, avoiding repeated traumas or friction, cooling the hands and feet, avoiding heat and keeping the skin well hydrated. Xerosis and pruritus usually appear between the third and fourth week after initiating cancer treatment and continue throughout the entire treatment. Along with local and systemic dermatological treatment, syndets, bath oils, non occlusive, light texture moisturizers and broad-spectrum sunscreens (minimum SPF 30) are recommended. Management also consists of taking showers (33-35 °C) instead of baths, patting the skin dry as opposed to rubbing, applying

treatments immediately onto the damp skin, as well as avoiding irritants (soaps, detergents, abrasive fabrics) and dressing too warmly as heat and sweating trigger pruritus. Pulpitis and crevices usually appear around 4 weeks after starting oncological treatment and continue throughout the entire treatment. Along with local therapy, syndets, moisturizing creams, soothing skin care products for irritated and weakened skin are prescribed. If crevices are present, repairing emollients or balms should be applied under occlusion. Avoiding contact with water as much as possible and using gloves made of suitable fabric is also advised. Paronychia is a late phenomenon that appears after several weeks and even months of oncological treatment. Apart from preventive and curative local and systemic dermatological treatment, syndets, strengthening nail polish and skin repairing balms are recommended. Practicing proper hand hygiene, properly cutting the nails using suitable materials and antiseptic products is also necessary. Invasive manicures and pedicures should be avoided if the patient has asymptomatic paronychia; however, if paronychia is moderate or severe and symptomatic, pedicures and manicures are recommended with dermatological approval. It is advised to apply two coats of nail polish, firstly silicon based, and afterwards dark, non-pearly nail polish before chemotherapy. Other side effects that affect the skin appendages include onycholysis, pyogenic granulomas, hirsutism and eyelash trichomegaly. Management of these side effects also includes strengthening nail polish, hair removal using non-aggresive methods and careful trimming of eyelashes with scissors or waxing. Radiodermatitis usually occurs in the third week after starting radiation therapy and most commonly persists during treatment. Dermo-cosmetics used in management include syndets, non-occlusive, light texture moisturizers and broad-spectrum sunscreens (minimum SPF 30). Good hygiene, drying the skin, avoiding alcohol and fragrances, shaving and using hair-removal cream, as well as wearing comfortable clothing is also necessary. A maculopapular rash may appear 3-14 weeks after initiating treatment. Apart from common dermatological treatment, syndets, non-occlusive, light texture moisturizers are recommended, along with proper nail care and avoiding products that may dry the skin out (alcohol-based products, soaps). Keratosis pilaris most frequently appears from to 3 to 6 weeks after the commencement of treatment. Apart from usual dermatological treatment, syndets, and moisturizing creams containing urea are prescribed. Applying the treatments on damp skin and humidifying the air is also helpful. Facial oedema may occur after intensive treatments, most commonly within 24 hours. Management includes gentle cleansing with syndets, applying moisturizing creams, as well as reducing salt intake. Keratoacanthoma and squamous cell carcinoma is a delayed phenomenon, appearing after 3-9 months of oncological treatment. Apart from usual local treatment, syndets, moisturizing creams containing urea and skin repairing products are prescribed.

In conclusion, dermo-cosmetics have a major role in alleviating many cutaneous side effects of various oncological treatments, thereby significantly improving quality of life of cancer patients. These products provide enhanced complementary care that has a beneficial effect on the overall perception of the disease, course of treatment, side effects and psychological complications of oncological treatments.

New Achievements in the Treatment of Advanced Epithelial Skin Tumors

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The first line treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are surgical excision and Mohs micrographic surgery. Additional ablative procedures such as cryosurgery, curettage and electrodessication and CO_2 laser can be used in actinic keratosis (AK) and low-risk BCC. A medical treatment including 5-FU, photody-

namic therapy (PDT), intralesional bleomicin or IFN, topical imiquimod, diclofenac and tazarotene can be preferred in selected AK or BCC. Radiotherapy is recommended for treatment of large BCC or SCC in elderly patients.

Imiquimod is an immune response modifier that shows anti-tumoral and antiviral activity through stimulation of both innate and acquired immunity and direct proapoptotic activity. Several studies reported a complete clinical regression after imiquimod treatment in up to 90% of AKs and in situ SCC, in 69-100% of superficial BCCs and in approximately 50% of nodular BCCs. Similarly, PDT, which is based on the topical application of a photosensitizing agent (ALA o MAL) and its activation by light irradiation, showed a good efficacy and safety profile in the treatment of AK, Bowen disease, nodular and superficial BCCs achieving response rate of 75%, 90%, 85-92% and 73-91%, respectively. Recent clinical trials demonstrated high efficacy of daylight PDT and ingenol mebutate gel in the treatment of AK. An increasing number of pathogenesis-targeted therapies such as hedgehog pathway-inhibitors (vismodegib and sonidegib) are available or in continuous advancement for the treatment of advanced BCC. In addition, novel immunotherapies (e.g cemiplimab) provided good clinical benefit and safety as well as patients' adherence to treatment opening a new dimension in the treatment of advanced SCC.

Is Early Diagnosis of Nodular Melanoma Possible?

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Nodular melanoma (NM) comprises 10-15% of all melanomas, but at least 50% of all cutaneous melanoma with Breslow thickness greater than 2 mm. NM is characterized by a more rapid growth rate, a more biologically aggressive behavior, and an increased number of mitoses compared with other melanoma subtypes, with a worse prognostic outcome. In addition, NM lesions are frequently symmetric, homogeneous in color, elevated, small in diameter, and often amelanotic, not conforming to the traditional ABCD algorithm and frequently escaping from routine recognition. Thin nodular melanoma (with Breslow thickness of less than 1 or 2 mm) may differ morphologically from thick nodular melanomas and represent an early phase of evolution of NM. A recent study from an international, multicenter epidemiologic database showed that thin NM compared with thin superficial spreading melanoma (Breslow thickness < 1 mm), was associated with a constellation of aggressive characteristics (lack of regression, the lack of nevus remnants, and the presence of mitoses) that may confer a worse prognosis and reduced survival, even after adjusting for potential confounding factors. In another retrospective, morphology-based case-control study, the dermoscopic features of thin NM (< 2 mm) were compared with thick NM and other nodular skin tumors, showing that the presence of blue structureless area and/or white shiny streaks were significant dermoscopic predictors of thin NM as compared to non-melanomas. In this presentation we discuss and review the significance of NM as a high-risk melanoma subtype with important implications in the early diagnosis of melanoma as well as in disease classification and prognosis.

Picosecond Lasers in Dermatology

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A picosecond laser system is characterized by an extremely short pulse measured in picoseconds, which allows the system to deliver more energy with less heating effect. This, in turn, leads to faster and more intense pigment fragmentation, with significantly fewer side effects (pain, scarring, and dyspigmentation), even in darker phototypes. The initial success of picosecond lasers in removing exogenous pigment (tattoos) encouraged their use in the treatment of various forms of endogenous pigmentation and melanocytosis: Ota and Ito nevi, lentigines, cafe-au-lait spots, melasma, etc.

The use of a fractionated option for the safe delivery of laser energy at higher focal densities has enabled the extension of indications to non-ablative photorejuvenation and treatment of acne scars.

A wide range of indications, relatively safe use in people with different phototypes, comfortable treatments with a small number of side effects, as well as significantly shortened recovery time provide picosecond lasers a significant place in the mosaic of therapeutic options in dermatology.

The lecture will present an overview of indications and contraindications for the use of picosecond lasers in dermatology, as well as specific system settings for individual indications, as well as combinations with other types of treatment.

Transgender Dermatology

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Transgender individuals face unique dermatologic needs in addition to routine care. Exogenous hormones affect hair and sebum production, gender-confirming surgeries require dermatologic peri-operative interventions, and post-operative anatomy may show unique presentations of routine skin conditions. Aesthetic techniques typically used for rejuvenation have a role in facial and body feminization and masculinization. They are, alas, frequently performed by nonmedical personnel with extensive risk of complications. Physicians should strive to make their office an accommodating environment for transgender individuals.

Relationship Between Severity of Chronic Inflammation in the skin and Patch-Test Reactivity in Patients with Psoriasis – Part I and II

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Introduction

Previous studies on the frequency of contact sensitivity among patients with psoriasis have given contradictory results. It is still not known whether psoriatic skin lesions react to a certain antigen, with the mixed-eczematous/psoriatic features more than uninvolved skin and whether substantial changes in psoriatic epiderma, influence contact sensitivity.

Objective

We assessed contact hypersensitivity in plaque-type psoriasis: the frequency; etiology; sex-related difference; dependence on severity and duration of disease in 2009 (Part I) and 2015 (Part II).

Material and Methods

In the Part I and Part II, we considered the following: contact hypersensitivity was defined as a positive patch-test to at least one of 44 and 49 ubiquitous contact allergens, respectively; there were 56 and 60 patients with exclusively plaque psoriasis, respectively and 75 and 116 non-psoriatic control patients, respectively, who were tested with the European standard series, plant-related standard allergens, Compositae allergens, extracts from Compositae plants ubiquitous in Vojvodina. Sinc, factor, other than different exposure to allergens may also be responsible for a sex-related difference in contact sensitivity, sensitization rates to allergens were standardized for age and sex and rates in women and in men were both standardized for age. Disease severity was evaluated using the Psoriasis Area Severity Index score.

Results

In the Part I and Part II, the following results among patients with psoriasis were obtained: the overall rates of sensitivity not significantly different from the controls without psoriasis were 18.9% and 24.5% respectively. In the Part I, male patients with psoriasis reacted less than healthy males, the difference being on the margin of significance. In the part II, the level of sensitivity expressed through the average number of positive tests per one tested patient was significantly lower in patients with psoriasis in comparison with non-psoriatic the controls without psoriasis. There was no relationship between severity of disease and patch-test reactivity, but positive correlation between duration of disease and patch-test but the correlation between duration of disease and patch-test reactivity was positive. Patients having psoriasis with positive Koebner response reacted significantly less than patients having psoriasis with negative response. The top five allergens that produced positive reactions in the Part I were yarow extract, nicke, Compositae-mix, lanolin, benzocaine; whereas in the Part II these were nickel, budesonid, p-phenylenediamine, sesquiterpene lactone-mix and cobalt.

Conclusion

Although patch-testing in patients with psoriasis can be quite challenging, time consuming and difficult, it will provide further insight into pathophysiology of psoriasis. Factors, other than different exposure to allergens, may also be responsible for psoriasis related difference in contact sensitivity. Future studies should focus on this field.

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Comorbidities in Psoriasis – why should I care?

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Comorbidities are common amongst patients with psoriasis. An association with the metabolic syndrome or elements thereof, as well as certain lifestyle features (alcoholism, smoking), anxiety,depression, and numerous other important diseases have been shown at the level of meta-analyses. Joint involvement (psoriatic arthritis) occurs in at least 20% of patients. These associations cannot be explained based on shared genetic dispositions. At least the association between psoriasis and cardiometabolic comorbidities seems to be driven by inflammation-induced insulin resistance («psoriatic march»).

The practical consequences of comorbitidies for the management of psoriasis patients are manyfold:

Presence of psoriatic arthritis necessitates a systemic therapy even in patients with mild psoriasis of the skin.

Numerous comorbidities represent contraindications for the use of certain anti-psoriatic therapies, namely conventional drugs such as methotrexate or cyclosprine A.

Comorbidities result in comedication. As the conventional anti-sporiatic drugs show drug-drug interactions, these must be considered in the treatment decision.

In summary, it is of major importance to take into consideration comorbidities and comedications of psoriasis patients in order to manage these patients adequately. Moreover, regular screening for psoriatic arthritis helps to prevent joint damage.

Treatment Approaches to Pediatric Psoriasis

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Pediatric psoriasis is a chronic inflammatory systemic disease associated with considerable burden both to the patients and to their families. Additionally, pediatric psoriasis has been associated with certain comorbidities, making early diagnosis and appropriate management important.

Therapy of psoriasis in the pediatric population is more challenging when compared to adult psoriasis: it presents with age-specific clinical characteristics and requires accurate compliance to a specific treatment regimen.

As guidelines are lacking and most systemic treatments are not approved for use in children, treatment of pediatric psoriasis is mainly based on published case reports, guidelines for adult psoriasis, expert opinions and experience with these drugs in other pediatric disorders. Consequently, the severity of psoriasis determines the approach to treatment.

Topical treatment is considered the first-line treatment for psoriasis in the pediatric population. However, most topical medications are not approved for pediatric use, requiring off-label prescribing, and, moreover, treatment adherence is difficult, especially in this age group. Emollients, moisturizers, keratolytics, corticosteroids, tar, anthralin, vitamin D analogs, calcineurin inhibitors, and retinoid are topical medications widely prescribed.

Phototherapy is considered a useful option in case of diffuse psoriasis involving more than 15–20% of the body surface area, debilitating palmo-plantar psoriasis, refractory plaque, guttate and pustular psoriasis, especially for children and families who desire to avoid systemic therapy.

Systemic therapy should be reserved for children with moderate to severe psoriasis in whom intermittent therapy has failed to control the disease. Methotrexate has been the most commonly used systemic medication in children. Other systemic drugs such as cyclosporine and retinoid have been used with variable reported effectiveness and safety data are available mainly from by case series studies. In contrast, three biologic drugs, adalimumab, etanercept, and ustekinumab, have been approved for psoriasis vulgaris in children and adolescents. The use of biologics is now expanding due to their availability, proven safety and efficacy and a less rigorous need for monitoring. However, their high cost restricts their use globally, and in addition, their long-term safety profile remains to be determined.

Actinic Keratoses – to Treat or not to Treat

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Actinic keratosis (AK) is a characteristic skin lesion present on skin areas of subjects with mainly phototype I and II or with specific genetic factors and who are exposed to prolonged ultraviolet radiation. AK may be considered a precursor of in-situ squamous cell carcinoma (SCC), a type of non-melanoma skin cancer (NMSC). Yet it is still not possible to predict which AK lesions will develop into SCC. Therefore early treatment of AK is recommended.

Despite the increasing number of patients with AK developing into SCC, there is still no clear suggestion of therapeutic strategy for AK. Current treatment consists of a multitude of topical lesion-directed or field-directed therapies or a combination of both. Recently, orally administered nicotinamide has shown to reduce rates of new NMSC and AK significantly in high-risk patients.

The lecture aims at providing an update on the most relevant information about AK and to provide an insight of current and new treatment options.

Approach to the Patient with Hereditray Epidermolysis Bullosa

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Hereditary epidermolysis bullosa is a group of rare genodermatoses characterized by fragility of the skin and the mucous membranes, as a result of mutation in at least one of 18 different genes. Today, these diseases are divided into four main groups and 40 subgroups.

Diagnosis of EB patiens is made according to detailed history, clinical evaluation with special emphasis on the distribution of lesions, affection of mucous membranes, nail, scalp and internal organs as well as if they develop scars, milia, granulations or hiper- and hypopigmentations. In laboratory part of diagnosis antigen mapping is performed, today more commonly than EM. Whenever possible, the analysis of mutations is performed.

Still there is no successful treatment for these groups of patients but multidisciplinary care is very helpful, as symptoms and complications experienced by patients with EB can vary widely.

Reference centers of the Ministry of Health as well as ERN Skin Network are some of the attempts to help those patients to get care they need. Unfortunatelly, in practice, we still face many problems in realizing everything so well defined in writing.

Treatment of Vitiligo – Update 2019

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Vitiligo is an autoimmune hypopigmentation with a prevalence of around 1-2% worldwide. Although largely asymptomatic, it is associated with significant psychosocial distress and with stigma in certain societies. It starts in childhood in nearly 25% of patients with a peak age of onset between the age of 10 and 30 years. Family history is positive in a third of patients and a large panel of genes is responsible. The majority of these genes are immune genes. The key factors that lead to loss of melanocytes appear to be the intrinsic defects in melanocytes, cellular stress and autoimmune inflammatory reaction.

The clinical presentation varies and has a great impact on the treatment response. Segmental vitiligo (SV) is characterised by unilateral pigment loss usually on the face. SV is treatment resistant and less often associated with autoimmune conditions. It has to be separated from non-segmental vitiligo (NSV) which could be localised (e.g. focal, mucosal, acrofacial), generalised and universal (complete depigmentation). NSV often follows a progressive course and is associated with a number of autoimmune diseases. The most frequent association is with thyroid disease and is seen in 15-20% of patients, with hypothyroidism prevailing over hyperthyroidism.

The goals in the treatment of vitiligo are to stop it from spreading, to stabilise the disease and to achieve repigmentation.

The first line medical treatment for vitiligo is with potent or very potent topical corticosteroids. This is practical only for patients with localised disease or to treat limited areas affected with vitiligo. Calcineurin inhibitors such as tacrolimus 0.1% ointment are used as an alternative to topical corticosteroids, especially for facial vitiligo. Cyclical regimens e.g. alternating weeks of potent topical corticosteroids with topical tacrolimus are recommended to help reduce corticosteroid side effects in areas with thinner skin e.g. the face, genital area and skin flexures. Systemic corticosteroids could be considered for rapidly progressive vitiligo to stabilise the disease.

Narrowband (NB, 311 nm) UVB phototherapy is the treatment of choice for patients with extensive vitiligo or those unresponsive to topical treatments. Since its introduction in the treatment of vitiligo in 1997 it has replaced psoralen photochemotherapy (PUVA) as the gold phototherapy standard. NB-UVB phototherapy is more effective and gives repigmentation of better cosmetic appearance than PUVA. However, patients have to be aware that a prolonged course of many months is often required and that repigmentation may be temporary. The outcome largely depends on the anatomical area affected with vitiligo. The face, body and limbs are most likely to repigment. In contrast, acral sites, periorificial and genital areas respond poorly. Combination of NB-UVB with topical tacrolimus or a subcutaneous implant of afamelanotide, a synthetic form of α–melanocyte stimulating hormone, may enhance the response. NB-UVB phototherapy appears to be safe as there are, so far, no reports of an increase in incidence of melanoma and non-melanoma skin cancers in treated vitiligo patients.

Targeted UV radiation sources, such as 308 nm excimer laser, are used for localised vitiligo and in the treatment of small lesions in visible areas.

Surgical treatment e.g. non-cultured epidermal melanocyte cell grafting can be considered in patients with segmental vitiligo and in those with stable, non-progressive vitiligo unresponsive to other treatments.

Vitiligo often causes psychological distress and patients should be offered informative leaflets to help to cope with the disease; skin camouflage can improve quality of life. Severely distressed patients may be referred for cognitive behavioural therapy.

Depigmentation therapy with monobenzyl ether of hydroquinone can be considered for patients with extensive vitiligo on visible sites.

Janus kinase (JAK) inhibitors are emerging, pathogenesis-directed treatments. It is hypothesized that they might be effective because they block the IFN-γ signalling pathway (which

requires JAK 1 and JAK 2) found to be critical for vitiligo progression and maintenance. Oral tofacitinib (JAK 1/3 inhibitor) and oral ruxolitinib (JAK 1/2 inhibitor) have shown rapid, but not durable, repigmentation in vitiligo patients. Recent trials have reported the effectiveness of topical ruxolitinib in vitiligo. The future direction seems to be focussing on targeted immunotherapies for vitiligo which will be specific, effective long-term, safe and affordable.

Occupational Dermatitis – A Raising Problem

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Occupational skin diseases are ranked internationally as the second largest group of occupational diseases after musculoskeletal disorders. They account for >45% of all occupational illnesses. The most common occupational skin disease is contact dermatitis (CD), which makes up around 80% of all occupational skin diseases.

CD is usually divided into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD accounts for 50-80% of all occupational CD cases. Industries such as printing, metal machining and treatment, food preparation, painting, beautician services, hairdressing and healthcare experience higher incidence rates of CD.

ICD and hand dermatitis in particular is usually multifactorial, and not necessarily caused by a single agent. Although chemical causes of ICD are well recognized, the contributions of physical, environmental, and mechanical factors to ICD are underestimated and often neglected. The contribution of wet-work exposure as a major risk factor of hand eczema is important.

Many occupational groups including healthcare workers, hairdressers, food handlers, flower arrangers, metal workers and construction workers are exposed to wet-work. Furthermore, in most cases, wet-work exposure is accompanied by detergents and cleansers, which in turn may aggravate the adverse effects of exposure. Measuring wet-work exposure might be a challenging issue in the field of occupational dermal exposure assessment. There is still no validated instrument to assess wet-work exposure.

Hand eczema is classified in six different clinical types: chronic fissured hand eczema, recurrent vesicular hand eczema, hyperkeratotic palmar eczema, pulpitis, interdigital eczema and nummular hand eczema, alongside a non-classifiable category.

New Allergens in Contact Dermatitis

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Every day we are in contact with many different cosmetic products, metals and toiletries. It is not a surprise that an increase of the incidence of allergic contact dermatitis has been observed. The problem of developing contact allergic reactions to skin care products, acrylates and even toys gains more and more popularity. Extending the knowledge in this scope includes finding and proving the clinical relevance of new allergens originating from the constantly growing cosmetic industry. Moreover, the significance of “old” and well known allergens, such as p-phenylenediamine, propolis and Balm of Peru has been revised since new sources of sensitization have been traced.

Leg Edema, Differential Diagnosis and Contemporary Therapeutic Guidelines

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Edema is defined as a palpable swelling that occurs as a result of an increase in the volume of interstitial fluid. There are generally two types of edema: venous edema and lymphedema. Venous edema consists of protein-poor, low-viscosity interstitial fluid that results from increased capillary filtration that cannot be compensated by the normal lymphatic system. Lymphedema consists of interstitial fluid rich in proteins, which occurs due to lymphatic dysfunction.

Leg edema is classified as uni and bilateral; acute (<72 hours) and chronic (> 72 hours) one. The most common cause of acute unilateral edema is deep vein thrombosis, while the most common cause of chronic unilateral edema is chronic venous insufficiency, along with a number of other rarer causes. Acute bilateral edema is relatively rare and is most often the result of an acute deterioration of a systemic condition (acute cardiac decompensation, renal failure ...). The causes of chronic bilateral edema are numerous, and the most common are chronic venous insufficiency, pulmonary hypertension, heart failure, primary lymphedema, as well as various drugs, primarily calcium channel blockers.

By applying the appropriate diagnostic algorithm, it is possible to make an accurate diagnosis, and thus apply the appropriate therapy.

Pitfalls in Differential Diagnosis of Leg Ulcers

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About 95 percent of chronic leg ulcers manifest as typical wounds including ischemic, neurotrophic, hypostatic and pressure ulcers. Other forms of chronic leg ulcers are atypical chronic wounds, which can be caused by autoimmune disorders, infectious diseases, vascular diseases and vasculopathies, metabolic and genetic diseases, neoplasm, external factors, psychiatric disorders and drug related reactions.

Clinicians commonly evaluate and manage the typical chronic wounds. However, many atypical leg ulcers mimic these common chronic wounds. Since these atypical wounds are often incorrectly assessed, they can be easily misdiagnosed.

Pitfalls for example include livedoid vasculopathy and vasculitis, pyoderma gangrenosum and Martorell hypertensive leg ulcer, venous ulcer and basocellular carcinoma, diabetic ulcer and melanoma, cryoglobulinemia, Wegener's granulomatosis and pyoderma gangrenosum, hydroxyurae induced ulcers and diabetic ulcers.

Misdiagnosis of a wound prolongs the patient's suffering by delaying healing and leads to improper medication delivery and topical treatments, which can further exacerbate the patient's condition, mask symptoms, prolong accurate diagnosis, and increase morbidity or mortality.

Clinical signs, anamnestic data, microbiological examination, laboratory and vascular work-up and the most important, biopsy, may often lead to the right diagnosis also assisted by the simple fact to "keep it in mind".

Modern Tourism and Genital Infectious Diseases

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The number of international tourists has been increasing rapidly in recent decades. In 1980, there were 278 million, and in 2016 more than one billion tourists. Statistics show that 80-95% of travelers stay abroad for less than one month. Dermatological conditions, fever and diarrhea, are the most common medical problems that can interrupt journey and require return home. The leading causes of infectious skin diseases in the world are cutaneous larva larva, insect bites, bacterial infections, allergic manifestations on the skin and tungiasis (sand flea). All diseases, except diarrhea, are more common in men. In the genital region any of these diseases can occur including sexually transmitted diseases of various pathogens. Tungiasis is an endemic disease in some parts of Africa, South and Central America and the gluteal region is often affected, while urogenital myasis (myasis) is a therapeutic problem. Insect bites give a wide range of minimal to serious health problems. Bites of bedbugs, fleas, spiders and ticks are often a reason for tourists to seek medical help of a dermatologist while they are on vacation or after returning home. Feeling anonymous and sexual behavior not practiced at home increases the risk of getting sexually transmitted disease. In some parts of the world, ZIKA virus infection, which can be sexually transmitted, can manifest as an asymptomatic infection or with a general symptoms and involvement of many organs. Intimate contact on a tourist trip can lead to scabies, molluscum contagiosum, genital herpes and other viral sexually transmitted diseases. In terms of bacterial sexually transmitted diseases, gonorrhea is important because of resistant strains that are more common in certain geographic regions. The significance of these groups of diseases in the modern tourism is also shown by the fact that the number of sexual partners is increased by 4% in every additional week of travel

Update on Non-Tuberculous Mycobacterial Skin Infections

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The nontuberculous mycobacteria (NTM) are defined as Mycobacterium spec. other than M. tuberculosis and M. leprae. They can cause skin and soft tissue infections as well as bone, pulmonary and disseminated disease. Skin infections are most commonly caused by M. marinum, M. ulcerans and M. fortuitum complex (M. fortuitum, M. chelonae, M. abscessus). M. haemophilum, M. avium complex, M. scrofulaceum and M. szulgai are rarely diagnosed.

The epidemiology of NTM skin infections depends on geographically heterogeneous environmental exposure. The incidence has been increasing. Skin trauma, immunosuppression and anti-TNF therapy are the most important predisposing factors. M. abscessus, M. chelonei and M. fortuitum have increasingly been reported in association with plastic surgery and cosmetic procedures, following tattooing, liposuction and mesotherapy, due to introduction of mycobacteria into the disrupted skin barrier. Post-injection abscesses, injections in alternative medicine, acupuncture, catheter use, and haemodialysis have also been recognised as risk factor. Travelling to endemic areas should also be considered.

NTM can cause a wide spectrum of clinical manifestations, including erythematous

papules and plaques, painful abscesses, ulcers and nodules, sporotrichoid nodular lesions, verrucous plaques, chronic granulomatous or necrotic skin lesions, panniculitis, cellulitis and regional lymphadenitis. Clinical lesions are not specific to the causative mycobacteria species. In immunocompetent patients, lesions are usually more localised, while in immunosuppression they tend to be widespread and disseminated.

Incubation period can take many months, leading to delay in diagnosis. Limited awareness of NTM infections contributes to misdiagnosis. Differential diagnosis includes deep mycoses, foreign body granuloma, prurigo nodularis, sporotrichosis, leishmaniasis, chronic bacterial infections as well as tuberculosis, pyoderma gangrenosum, Kaposi sarcoma and other causes of lymphadenopathy. In chronic relapsing nodules, plaques and abscesses, especially in immunocompromised patients, NTM infection should be considered.

Skin biopsy is needed for the diagnosis. Examination of the specimen for acid-fast staining bacilli can be helpful. Cultivation of biopsy material is needed for identification of the causative pathogen. Histopathological examination is nonspecific but can help in diagnosis in correlation with the clinical picture and microbiological findings. Molecular methods using PCR may be useful in some cases.

Treatment depends on the causative pathogen since drug resistance varies in different species. Susceptibility testing is therefore recommended. Ciprofloxacin, clarithromycin, trimethoprim-sulfamethoxazole, doxycycline and some other antibiotics should be used according to official treatment guidelines. Wound management and surgical debridement may be needed in some patients.

Kaposi Syndrome – A Case Series

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Kaposi syndrome (KS) is a multifocal systemic disease, which presents in four distinct clinical forms – Classical KS, Endemic (African type) KS, HIV-associated KS and iatrogenic KS. This presentation covers the main forms of KS, their clinical presentation, histology, immunohictochemistry and treatment through a series of five cases.

Magistral Formulations in Dermatology

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Galenic or magistral formulations were the cornerstone of dermatological therapy up to late 70's. Since then, with the accelerated development of pharmaceutical industry, they have been replaced in a vast majority with commercially available products. However, despite all achievements of a modern era, in certain patients application of gallenic preparations is still a must: for example, when commercially available product is not available, in cases where the efficiency of galenic/magistral formulation is higher than commercially available product, or, finally, if we are dealing with demanding patients for whom it is very important to personalize treatment approach. In this communication, galenic preparations, which are slightly forgotten but once most often prescribed, will be emphasized. New therapeutic approaches to particular skin diseases connected to usage of galenic preparations will also be pointed out.

Therapeutic Options of Severe Hydradenitis Suppurativa/ Acne Inversa

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Introduction

Hydradenitis suppurativa (HS) is a rare chronic inflammatory skin disease of intertriginous areas characterized by painful, recurrent nodules and abscesses that lead to drainage sinuses, malodorous suppuration, scaring and strictures. Global prevalence is 1-4%. It usually occurs in the third decade, about 3 times more often in women than in men. Early onset is a risk factor for more severe forms of the disease. It is often unrecognized and it usually takes about 7.5 years to make the diagnosis. HS has a strong psychosocial impact and a devastating effect on the patient's quality of life. Predisposing factors for HS are: genetics (about 35%), obesity, metabolic syndrome, insulin resistance, tabacco smoking, follicular occlusive diseases (acnae conglobata, perifolliculitis capitis, pilonidal sinus), inflammatory bowel disease (Mb. Chron). The diagnosis is made clinically if 3 criteria are met: 1) the existence of typical skin 2) involvement of at least one typical site; 3) recurrence and chronicity of the disease (minimum 2 relapses over a period of 6 months). Hyrley classification divides severity of HS into three stages. Stage I, which occurs in 68% of cases, is characterized by single or numerous isolated abscesses without scars and sinuses. Stage II, which is registered in 28% of cases, involves recurrent abscesses with sinuses and scars, single or multiple and widely separated lesions. Severe form (Hyrley III stage) is registered in about 4% of cases. It is characterized by diffuse or almost diffuse involvement of intertrigious areas, several interconnected sinuses and abscesses over the entire affected area. HS therapy is local, systemic (conventional and biological), surgical and adjuvant.

Case report

We report two male patients with severe HS, Hyrley stage III, without family history of disease, who we are still treatedat Skin and Venereal Diseases Clinic, University Clinical Centre of the Republic of Srpska.

Patient 1.

This disease started in a 18-old male patient (NM) when he was 14. HS was associated with acne conglobata and perifolliculitis capitis. HS diffusely affected multiple intertriginous regions: armpits, below breasts, abdominal fold, ingvinofemoral. The patient was treated with numerous oral antibiotics for three years and low doses of isotretinoin (short-term). The result was mild regression of acne and perifollicutitis, but without a significant effect on HS. Some regression of HS followed after four months of treatment with oral combination of rifampicin and clindamycinin doses of 2x300 mg/daily. He was treated topically with numerous antiseptics, 1% clindamycin lotion, 15% resorcinol solution and/or cream, alginate compresses with antimicrobial silver. The patient was overweight (BMI>40), tobacco smoker and twice he had heavy, resistant form of cellulites with lymphedema of the lower leg. Disease was accompanied by secondary anemia, frequent skin superinfections (mostly with gram-negative bacteria) and elevated laboratory markers of inflammation (C-reactive protein >100 mg/ml, leukocytosis and neutrophilia). The patient avoided school and social activities. Treatment with adalimumab was started in July 2018 when he was 17. Visible clinical improvement of HS followed after only 4 weeks, and in the 19th week there was a significant reduction of inflamed nodules, abscesses and sinuses without suppuration and pain with the persistence of numerous scars and strictures. Laboratory inflammatory markers were normal, and anemia was corrected. The patient lost some weight (12 kg), returned to school activities and finished high school in the meantime. He is still on adalimumab therapy at a dose of 80 mg every 2 weeks.

Patient 2.

In a 28-year-old patient this disease started at the age of 23 involving axillary, gluteal, and pubic regions. The patient was overweight and tobacco smoker. HS was accompanied with anemia, frequent skin superinfections and elevated

laboratory markers of inflammation (C-reactive protein >70 mg/ml, leukocytosis and neutrophilia). In early childhood, he underwent Fallot tetralogy surgery with consequent persistent heart murmur. Before treatment in our institution, he was treated with numerous systemic antibiotics and local preparations without a special effect. Satisfactory effect was achieved with the combination of rifampicin (300 mg 2x/d) and oral clindamycin (300 mg 2x/d) for 4 months. An even better effect was achieved with moxifloxacin 1x400 mg/d for 9 weeks with zinc gluconate 90 mg daily and with intralesional application of triamcinolone acetonide given monthly. The treatment was continued with acitretin at a dose of 2x25 mg daily, which after four months led to almost complete regression of inflammatory changes. In June 2019 the patient came for the first time without diapers, satisfied with the results of the treatment so far. He is still on acitretin therapy.

Conclusion

Severe forms of HS are first treated with antibiotics or a combination of antibiotics. The best effect is achieved by a combination of rifampicin and clindamycin in doses of 600 mg daily for four months. If adlimumab biologic therapy is contraindicated or unavailable, moxifloxacin 400 mg daily, in combination with high daily doses of zinc and with intralesional administration of triamcinolone acetonide may also lead to a significant therapeutic effect. Acitretin, recommended in the treatment of mild to moderate HS, can be used as a continuation of therapy in severe HS after a good therapeutic response to systemic antibiotics. It reduces the inflammatory component in the dermis by inhibiting polymorphonuclear chemotaxis with consequent reduced production of inflammatory cytokines, especially inflammatory cytokines IL-6. Biological therapy with adalimumab monoclonal antibodies, the only approved biological drug for HS, is the first line of treatment for moderate to severe forms of HS in patients that have not responded or have not tolerated antibiotic therapy. The drug is effective and quickly acts on skin changes, pain and dramatically improves the quality of life of patients.

Body Mass Index Change After Intravenous Pulse Corticosteroid Therapy of Alopecia Areata in Children

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Introduction

Intravenous pulse corticosteroid therapy (IVPC) is used in various dermatological indications. Several studies examined the effects of IVPC in children with alopecia areata (AA), but only a few studies report on IVPC effects on body mass index (BMI).

Objectives

To determine the impact of IVPC on BMI and BMI-Z score (BMI adjusted for age and sex) in children.

Material and Methods

This single-center prospective study included 47 patients with severe forms of AA (Severity of Alopecia Tool - SALT>30), aged 2–18 years (mean 9.11±3.75). All patients received IVPC therapy (dexamethasone 1.5 mg/kg/day on three consecutive days), which was repeated every 28 days, and all patients received 6 cycles (18 infusions). All patients/families received detailed written instructions on avoidance of high calories/high carbohydrate foods. Before the introduction of IVPC, the patient's height and body weight were measured, and BMI and BMI-Z score (BMI1

and Z1) were calculated. The measurements were repeated after the 6th cycle of IVPC (BMI6 and Z6).

Results

Comparing BMI1 with BMI6, statistically significant increase was found, but there were no significant difference comparing Z1 and Z6 scores. Both girls and boys increased their BMI by 3.7% and 4.6%, respectively. Comparing BMI1 and BMI6 among different age groups, we found a statistically significant difference between the age groups 6-10 and 10-14 years ($p=0.017$ and $p=0.002$; 4.6% and 7.9%, respectively). No statistically significant difference comparing Z1 and Z6 score among different age groups was present.

Conclusion

IVPC had an impact on BMI in children, but the increase was not clinically significant (>5% is considered clinically significant). On the other hand, BMI-Z score, as a better indicator of obesity in children, did not change significantly. In children aged 10-14 years, BMI increase was higher (7.9%), but BMI-Z score did not change significantly.

If patients/parents receive proper dietary instructions, and if the instructions are adequately followed, IVPC does not lead to a significant increase of BMI-Z score that better reflects the obese/non-obese status in children than the simple BMI.

Capillaroscopy as Diagnostic Method at Dermatovenereological Clinic, Clinical Centre of Vojvodina

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Capillaroscopy is a non-invasive method for visual diagnostics of skin microcirculation in proximal nailfold region, where capillary loops of dermal papillae lie parallel to skin surface, and are visible for examining. In last decades capillaroscopy was recognized as diagnostic criterion for systemic sclerosis, and its diagnostic importance in broad spectrum of autoimmune and inflammatory diseases has been increasing.

During the period of January 2013 till September 2019 at Dermatovenereological Clinic in Novi Sad capillaroscopy examination was performed in 1115 patients. Most patients were sent to capillaroscopy by a rheumatologist (41%) or immunologist (37%), less frequently by a dermatologist (12%) or general practitioner (10%). Most frequent indications for capillaroscopy were differential diagnostics within collagenovascular group spectrum (32.8%), differentiating primary from secondary Raynaud phenomenon (25.5%). The patients with polyarticular pain and those with dermatological diseases accounted for 25% and 8%, respectively; whereas professional exposure to vibrations was the reason for capillaroscopy in 1.5% of the patients. Other microcirculatory syndromes were rarer in our patients with, i.e. acrocyanosis 5.8%, erythromelalgina and thromboangiitis obliterans 0.7% each.

Examination was performed with USB video microscope, 200 x magnification, glycerol was contact medium. All fingers apart from thumb were examined; photographs were memorized as jpg format, in digital chart of each patient. Parameters for analysis were: number of loops/mm, palisade arrangement, presence of capillary loss, morphology of loops, megacapillaries, capillary ecstasies, microaneurysms, bizarre forms (glomerular, bushy, meandre), microhaemorrhages, visibility of subpapillary plexus, proximal nailfold transparency, and oedema. Non-specific pattern was the most prevalent interpretation (66.5%), the finding was normal in 15% and early or active scleroderma pattern was observed in 16.8%, and late scleroderma in 1.7% of patients.

Nevus Lipomatosus Cutaneus Superficialis – A Case Report

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Introduction

Nevus lipomatosus cutaneus superficialis (NLCS) is a rare benign skin malformation, characterized by the presence of collections of mature lipocytes situated ectopically within the dermis.

Clinically, it is classified into the classical Hoffmann-Zurhelle form and the solitary form. The solitary form usually occurs after the age of 20. The classical form occurs at birth or during the first three decades of life, usually unilaterally, situated on the pelvic girdle area. It was first reported by Hoffmann and Zurhelle in 1921.

Case Report

We present a 17 year-old male patient, with a history of unilateral localised asymptomatic lesions, which was first observed by the patient's parents three years before. He was otherwise healthy. It is interesting to mention that according to anamnestic data, there was occasionally a severe skin irritation of the affected region a year before the occurrence of lesions. At that time, the patient was training football and skin irritation was brought into connection with sports equipment he was wearing.

Dermatological examination revealed a single and grouped soft, skin or yellow-colored papules and nodules, coalescing into a plaque, measuring 9 cm x 5 cm, localized in the upper part of the right gluteus, smooth surface without ulcerations. There was no cafe-au-lait spot, hypopigmented macule or neurological abnormality noted. No similar lesions were noticed elsewhere. There was no family history of similar lesions.

Excision biopsy was performed and a histological diagnosis of NLCS was given.

Discussion

NLCS is a rare disorder. The precise etiopathogenesis of NLCS is not understood.

This case was interesting because we can consider a recurrent skin irritation as a possible trigger for changes that will lead to ectopic accumulation of mature lipocytes into dermis.

Treatment is not necessary other than for cosmetic reasons. The therapeutic option is surgical excision, recurrence after surgery is rare. Systemic abnormalities and malignant changes have not been associated with NLCS.

The patient is currently not planning a surgical intervention.

Combined Treatment of Classic Kaposi's Sarcoma

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Kaposi's sarcoma is a multicenter polymorphic neoplasia constituted of spindle cells originating from skin endothelial cell and rarely of other tissues and organs from different clinical course depending on the epidemiological characteristics of the disease. It develops in younger people with AIDS, and the treatment and prognosis are related to the course of the underlying disease. Classic Kaposi's sarcoma occurs rarely and sporadically in older men, more often than in women in a ratio of 10:1 to 15:1, of Jewish and Mediterranean origin, with relatively benign and slow flow. It usually begins on the skin of the feet and lower extremities in the form of unilateral, then symmetrical, disseminated dark red, livid and brown macules, which later become either infiltrated, individual or they

merge into plates and from soft sponges become hard on palpation. Kaposi's sarcoma can affect the mucus of the oral cavity and the gastrointestinal tract.

As an example, we are presenting an 82-year-old farmer who, a year and a half before, noticed spots on his feet and lower extremities that were gradually spreading and thickening. Due to the suspicion of primary cutaneous malignancy, he was hospitalized at the Dermatology and Venereology Clinic, where a pathohistological diagnosis of Kaposi´s was confirmed.

Laboratory analysis and radiological diagnostics were performed in order to exclude HIV positivity and the presence of tumors of other organs and tissues. A hematologist was also consulted due to the presence of thrombocytopenia. Treatment was started by topical application of 5% imiquimod cream on the left foot and tretinoin 0.05% cream on the right foot. Since improvements on the skin of the right foot were noticed, the treatment was continued with tretinoin 0.05% cream, which resulted in changes in the dorsum of both feet.

Radiowave destruction of certain tumor changes on the feet was also performed, as well as surgical excision of solitary nodules. Superficial X-ray therapy of 5 lesions on the lower extremities was performed with an orthovoltaic device at a dose of 30 Gy, that is 5 Gy per fraction in the timeline of Monday, Wednesday and Friday. The patient gave a good therapeutic response to superficial radiation therapy: mild skin atrophy was noticed with no recurrence on the skin of irradiated fields of hyperpigmented macula.

Conclusion

The decision on the method of treatment depends on the degree of tumor spread, the clinical and epidemiological form of the disease. Therapy may be local for a few, small-scale changes, with a local use of vinblastine, bleomycin, radiotherapy, cryotherapy, interferon-alpha, as well as systemic chemotherapy. The goal of treatment is to prevent the progression of the disease, alleviate symptoms, reduce edema, to achieve aesthetic improvement as well as to improve the quality of life. Combining radiotherapy, surgery and topical therapy is a definite option for treating classic Kaposi's sarcoma.

Cutaneous Larva Migrans: Case Report

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Cutaneous larva migrans (CLM) is a zoodermatosis resulting from the inoculation of helminths larvae in the skin. Various helminth species, usually infesting small intestines of cats and dogs in tropical and subtropical areas can cause this disease, most frequently Ancylostoma braziliense, Ancylostoma caninum and Uncinaria stenocephala. Upon the direct contact with the contaminated ground, larvae penetrate the skin and remain confined to it, causing a cutaneous inflammatory reaction in a form of lesions tracking larval migration. Migration of CLM is slow, usually not more than 1 cm per day. Laboratory findings are often of no diagnostic relevance, while skin biopsy shows mainly eosinophilic infiltration and sometimes the larvae can be found. Aside from an intensive itching, the disease tends to resolve spontaneously within few weeks.

We report a case of a 42-year old female with multiple intensely pruritic erythematous exudative papules and oval plaques predominately located on the back. The patient claimed that skin lesions had started three weeks before during her vacation in Thailand, after a contact with sea medusa during swimming. A trial of oral antihistamines and various topical

corticosteroids was unsuccessful, which added to the confusion regarding the differential diagnosis. Soon after presenting at our Clinic and quitting topical therapy, the lesions started elongating and progressing into typical curved linear plaques pointing at the possible CLM. Laboratory findings were within normal range. Asked about her habits in Thailand, she admitted frequently laying unprotected directly on the sand of various beaches that were cats and dogs friendly. Biopsy specimens of the lesions revealed spongiosis and mixed inflammatory infiltrate containing mostly eosinophils, which is in concordance with the findings in CLM. A three-day course of oral albendazole, 400 mg daily led to complete cure of the disease.

Therapeutic approach should always be based on careful clinical examination and detailed history taken from the patient, with skin biopsy being mandatory in all cases of atypical clinical presentation of dermatoses in patients coming from tropical and subtropical regions.

Generalized Pustular Psoriasis - Case Report

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Generalized pustular psoriasis (GPP-von Zumbusch variety) is a rare and serious skin disorder that presents with flares of widespread sterile pustules on a background of red and tender skin. Patients with acute GPP appear toxic, with high fever, leukocytosis, elevated erythrocyte sedimentation rate and C-reactive protein, hypoalbuminemia, vascular instability, and hypocalcemia. In addition, serious complications, including sepsis and internal organ dysfunction, can occur.

Pustular psoriasis is characterized with unique genetic features like missense variants in CARD14 gene and recessive mutations of IL36RN gene and AP1S3 gene that has not been found in classic psoriasis type.

It may be triggered by sudden withdrawal of injected or oral corticosteroids, drugs such as lithium, indomethacin, and some beta blockers and infections.

GPP can be life-threatening, so hospitalization is usually required. The aim is to prevent further fluid loss, stabilize body temperature and restore electrolyte imbalance. Specialist care is essential. In treatment of pustular psoriasis, conventional drugs such as retinoids, methotrexate and cyclosporine are still the first line of therapy; however, literature shows a beneficial response of GPP to treatment with biologics.

We report a case of a 27-year-old male who has suffered from GPP since he was one-year-old and who was regularly hospitalized and checked up in our Clinic until he was 14 because of frequent exacerbations.

He was completely clear from psoriasis for 13 years up until May 2019 when he developed acute urticaria and was treated by his family doctor with systemic steroids.

Some days after he finished steroid therapy he developed strong exacerbation of GPP.

In this paper we discuss the treatment possibilities for GPP in the era of biologics as well as provoking factors for GPP.

Breast Cancer Related Cutaneous Metastases

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Introduction

Cutaneous metastases originating from visceral carcinomas occur rarely, compared to metastases in other organs. They usually originate from breast, lung, gastrointestinal, bone or thyroid carcinomas. Metastases de-

velop by hematogenous and/or lymphogenic dissemination of malignant cells, or by direct invasion from the affected tissue.

Case Report

A 59-year-old female was treated with oral antihistamine after the appearance of skin changes in the frontal region of her body. There was no adequate response to therapy. The lesions persisted for 8 months, when she was first referred to a dermatologist. Upon admission, the patient showed poor general condition, she was febrile 38.6°, with subjective sensation of pain in the area of the neck and chest, and shortness of breath. Cutaneous lesions were present in the area of the cleavage, breasts, right thoracic region and upper abdomen in the form of a livid plaque with individual livid nodules. Laboratory analyzes: SE-43, CRP-37.5, fibrinogen-6. Radiographic image of the lungs showed bilateral pleural effusion and after performing pleural puncture, exudate was isolated. Bronchoscopic finding showed no pathologic signs. Tumor markers, such as NSE-24.74 (ref. To 16.30), CY-FRA-47.77 (ref. To 3.30), Ca 15-3-139.3 (<31.3), were elevated. Skin biopsy was performed, with the finding of carcinomatous infiltration of the cutaneous and subcutaneous tissue, which histomorphologically indicated a lobular variant of breast cancer. Based on the clinical examination and analysis, and definitely verified by biopsy, the clinical diagnosis of bilateral breast cancer with lenticular metastases in the skin of the thorax, was made. The patient refused the proposed chemotherapy. Hormone therapy in the form of per os Tamoxifen 20mg daily was suggested.

Conclusion

Cutaneous metastases most often occur in the advanced stage of a malignant disease, but sometimes they can be the primary manifestation of malignancy, which is important to keep in mind since they often histologically manifest with anaplasia, which makes it difficult to identify the primary tumor based on histopathological findings.

Tinea Incognito – Case Report

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Introduction

Tinea incognita is a dermatophyte skin infection whose clinical presentation has changed due to an unrecognized fungal infection treated with corticosteroids.

Case Report

A 72-year-old female patient was referred to our Department of Dermatology for the examination of skin lesions that she had had for a year. She was treated for contact allergical dermatitis with systemic (methylprednisolone and prednisolone) and local (fluocinolone-acetonide, mometasone-furoate and clobetasole) corticosteroid therapy by her general practitioner. As a result, the skin lesions receded, but after the discontinuation of the therapy there was a rapid deterioration. Clinically, annular and polycyclic pruritic erythematous plaques were present on the flexor sides of the upper extremities and on the dorsum of the hands. Solitary papules were present on the periphery of the plaques. In laboratory, complete blood count, immunological (antinuclear antibodies, IK, C3, C4, IgA, IgG, IgM) and virusological analyses (hepatitis B and C, HIV) findings were within normal range. Biochemical analyses, except hyperglycemia, were within referent range. Chest X ray and abdomen ultrasound were normal. Native mycological examination revealed the presence of hyphae, a Trichophyton rubrum was present in the culture. After long and continued administration of corticosteroids, hystopathological examination was nonspecific - locally hyperkeratotic epidermis, with flattened epidermal bars. In one

focus, a subepidemic bulla was excreted with unstructured eosinophilic contents and individual inflammatory cells. Subepidermally, there was a dense and banded inflammatory infiltrate that was clearly demarcated towards the reticular dermis where it was mainly localized perivascularly and periadnexally. Diagnosis was based on the clinical ground, native mycological examination and mycological culture. After the administrated therapy (itraconasole caps 200 mg/day, for 10 days and 100 mg/day for another 10 days with myconasole cream twice a day) completed resolution of skin lesions occurred.

Conclusion

Tinea incognita is a fungal infection modified by the use of corticosteroids that suppress the local immune response in the skin. This allows the fungus to spread easily and quickly, which makes the clinical picture different and often bizarre in appearance. Differential diagnosis includes figure erythema of infectious, paraneoplastic, allergical and autoimmune etiology. Administration of local and systemic antifungal medication is a drug of choice.

Larva Cutanea Migrans

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Cutaneous larva migrans is a migratory skin infestation of Hookworm larvae. It most often occurs in the tropics, and the most common causative agents are Acylostoma brasiliense and Acylostoma canium, which live in the intestines of pets (dogs and cats). The larva penetrates the intact skin and remains confined to the epidermis. The migration of larvae through the skin is marked by intense pruritus and linear or serpiginous bands.

A 62-year-old female patient with skin lesions that appeared one month before the dermatological examination was presented. Lesions were presented in the form of pruritic, creeping, snake-like track erythema with a vesicle at one end and several pigmentated bands, localized on the skin of the lower half of the left breast. She said that she had a dog. Complete blood count with leukocyte formula and biochemical analysis findings were within the reference values, stool test was negative for the presence of eggs of intestinal parasites. Serum immunoglobulin E level was in the referent range. The patient was treated with mebendazole orally and topically with fluocinolone acetonide. After 7 days, there was a significant improvement and gradual regression of changes.

Cutaneous larva migrans is a limited eruption because larvae cannot complete life cycles in the human body and usually die within 2-8 weeks. The diagnosis is easily made on the basis of a typical clinical picture. The drugs of choice are mebendazole, albendazole, ivermectrin, and thiabendazole. Complications are rare - secondary infection at the site of infestation, local and general allergic reaction, and very rarely Loffler's syndrome, a transient respiratory disease associated with eosinophilia and radiographic shading.

Epidermotropic Metastatic Melanoma Originating from the Dermal Nevus: A Case Report

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Melanoma cells have a high metastatic potential, with around 50% of metastases exhibiting lymphogenic spread to the regional lymph nodes, some 22% of metastases are satellite or in-transit and 28% are hematogenic distant metastases including distant skin metastases. Skin melanoma metastases are usually dermal, while epidermotropism of metastatic melanoma is relatively rare. It has been observed that primary melanomas located in the head and neck areas tend to develop metastases via all three routes. In a large metastatic melanoma study, the mean period to development of lymph node metastases was 16 months: for satellite/in-transit metastases months and for distant metastases it was 17 and 25 months, respectively.

We report a case of a 60-year-old female patient, with a history of cutaneous melanoma originating from the preexisting dermal nevus on the left cheek. Primary melanoma was of a superficial spreading type, Breslow thickness of 6 mm with ulceration, clinical stage IIC. Further oncological follow up was done in her regional center, with a problematic frequency. The first metastatic event occurred 15 months following the primary melanoma surgery: a dissection of the left side of the neck was performed due to lymphonodal, perinodal adipose tissue and the parotid gland melanoma metastases. Adjuvant radiotherapy was indicated but delayed due to a waiting list. Just a month later, during the regular complete skin examination, multiple newly formed melanocytic lesions of 1-4 mm in diameter with polymorphic dermoscopic features were observed, disseminated over the face, the neck, front and back of the trunk. Biopsy showed a BRAF V600 mutated epidermotropic metastases of melanoma. In laboratory findings LDH levels were more than 7 times and S100 protein levels more than 60 times above the normal range. Although CT examination of the endocranium, thorax, abdomen and pelvis taken at the same time did not indicate secondary deposits, a few weeks later while waiting for administration of systemic therapy the patient developed pleural and pericardial effusion with cytologic immunohistochemical profile of melanoma, followed by rapid and severe deterioration of her psychological functions.

Prognosis of melanomaheavily depends on timely diagnosis, as well as on regular and thorough follow up according to the internationally accepted guidelines summarized in the Serbian national guide for melanoma, and on the availability of novel systemic therapies.

Mammary Paget Disease – A Case Report

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Introduction

Paget disease belongs to a group of mammary gland carcinomas manifested as eczematoid lesion in the region of affected breast. Disease is more prevalent in women after the sixth decade, accounting for 1-4% of all breast cancers.

Case Report

We present a 69-year-old female patient in good general condition with no comorbidities. Anamnestic data revealed existence of a month-long asymptomatic skin change on the right breast. The patient was thoroughly examined and a nummular erythematous plaque with desquamation and erosions of the nipple and adjacent areolar skin was found. A skin swab test showed negative results, while laboratory hamatological and biochemical findings were in the referent interval. Ultrasonography of the right breast revealed tumorous changes in the breast tissue. Local therapy with mild potassium permanganate solution was applied. Afterwards, a surgery as well as further oncological treatment was conducted.

Conclusion

The case indicates the significance of appropriate recognition of skin lesion which may result from rare breast cancer and the importance of prompt beginning of adequate treatment.

Inflammatory Linear Verrucous Epidermal Nevus – ILVEN – Case Report

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Introduction

ILVEN is a rare form of epidermal nevus that occurs in the highest percentage in childhood, affecting one half of the body, following the Blashco lines. It most often occurs sporadically, more often in women. Sometimes changes occur at birth, as linear verrucous hyperkeratotic plaques. Clinically, they can be presented as inflammatory and psoriasiform. There are several varieties, and only some of them respond well on therapy.

Case Report

We present a case of an 81-year-old woman with ILVEN, i.e. changes that have been present since childhood. After surgical interventions (hysterectomy and bladder surgery) in her 50th year of life, a psoriasis rash appeared along the linear nevus, associated with the same inflammation. Clinical examination of the patient revealed the presence of erythematous confluent banded and linear psoriasiform plaques, localized on the dorsum of the foot, lower leg, upper leg, crotch, genitals, breast, scapular, forearm, face and capillaries, following the Blashco line. Complete blood count with leukocyte formula and biochemical analysis findings were within the reference values. During hospitalization, psoriasiform changes of linear distribution were most intense, which were localized in the area of already diagnosed ILVEN, along the right half of the body.

The therapy included systemic antihistamines, topical corticosteroids, emollients and UVB phototherapy, after which psoriasis changes gradually regressed, with persistent changes in the epidermal nevus.

Conclusion

ILVEN is a variant of epidermal verrucous nevus that accompanies Blashco lines with accompanying subjective pruritis. In the differential diagnosis, lichen striatus, linear Darier, linear porokeratosis and linear lichen planus are also considered. Topical, systematic and surgical modalities are most often used in their therapy, which in most cases have a refrectory response.

Verrucae Planae – Massive Lesions In a Healthy Man

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Introduction

Verrucae planae is a very common skin infection caused by the HPV virus (types 3 and 10). They manifest as flattened, slightly raised papules, smooth surfaces, skin color, pink, or grayish-brown, single or grouped. They are most often localized on the face, neck and hands, and sometimes in places exposed to frequent traumas.

Case Report

We present a case of a 45-year-old man with skin lesions which developed a year before. Clinically, numerous densely grouped flattened skin-colored papules were present on the dorsum of the right hand and the anterior outer side of the right forearm, some of them erythematous, with a linear aspect in some places (Koebner's phenomenon). All performed laboratory analyses: routine laboratory, virological analyses (HCV, HBsAg, HIV), thyroid hormones and antibodies (fT4, TSH, anti TPO and TG antibodies), tumor markers (CEA, AFP, CA 19-9), were within reference values. In the histopathological finding of the section, hyperkeratosis and acanthosis of the epidermis was present in the form of the so-called *basket-weave pattern*, with the presence of numerous vacuolated cells in the granular and upper part of the Malpighian layer, regular histomorphology of the dermis. The diagnosis was made on the basis of the clinical picture and histopathological findings. General vitamin therapy (Vitamin C and zinc) was used in therapy, and 5% imiquimod cream and cryotherapy in local therapy. After the applied therapy, the lesions gradually regressed.

Conclusion

Verrucae planae usually occurs in children, while the appearance of massive lesions in adults requires examination in terms of immunodeficiency. The presented patient is healthy, but he is professionally engaged in metal processing, which is why he is exposed to constant microtraumas, primarily on the right hand and forearm, where the changes are localized.

A Case of Congenital Non-Bullous Ichthyosiform Erythroderma in a Neonate

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Non-bullous congenital ichthyosiform erythroderma (NBCIE) in newborns usually presents with a transparent covering that desquamates over 10 to 14 days.

Non-bullous congenital ichthyosiform erythroderma (NBCIE) is an inherited disease with autosomal recessive variant. It is a rare epidermal disease that is estimated to occur in 1 per 300,000 births. It is characterized by whitish abnormal scaling on a background of erythematous skin over the whole body with symptoms that may include ectropion and associated eye complications, nail dystrophy, scalp alopecia, failure to thrive, short stature, intense pruritus, intolerance to heat, hypohidrosis, palmoplantar keratoderma and hearing impairment due to the accumulation of scales in the external ear.

We present a 16-day-old infant with a history of scalded appearance with diffuse shedding of scales and erythema since birth. He is the first baby, born with normal full-term delivery, weighing 2750 g, GA 47, Apgar score 9/10. Previously the infant was in isolation in the IU center where he was treated with intravenous antibiotics. There was no history of any related skin disease in the family. Clinical examination showed diffuse erythema of the entire body with whitish scaling predominantly on the chest, neck and face, a transgradient diffuse lamellar scale involving palms and soles. Hypertelorism was also evident.

There was no evidence of ectropion, alopecia nor nail changes. Genetic analysis was ordered and it showed abnormal findings and identified the homozygous variant in the ABCA12B gene, which has been described as pathogenic in congenital ichthyosis patients.

AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

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All manuscripts are to be submitted to the **Editor in Chief: Prof. Dr. Lidija Kandolf Sekulović,** Clinic of Dermatovenereology, School of Medicine, Military Medical Academy, Crnotravska 17, Belgrade, Republic of Serbia, by mail to: serbjdermatol@gmail.com

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www. icmje. org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

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The title page should include the following information:

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Tables should capture information concisely

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5. Additional Information

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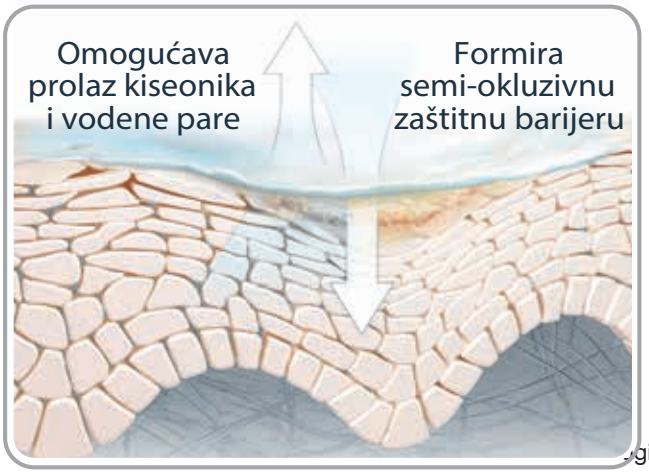

- Sa samo 7 sastojaka
- Klinički dokazano hipoalergen [1] i nekomedogen [2]
- Bez vode, konzervansa, boja i parfema
- Obezbeđuje idealnu sredinu za oporavak kože [3]
- Pogodan za bebe, decu i odrasle

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[1] The low prevalence of allergic contact dermatitis using a petrolatum ointment containing lanolin alcohol, JDD, Oct 201[2] AV Rawlings et al., A review on the extensive skin benefits of mineral oils, International Journal of cosmetic science, 2012, 34, 511-5[3] Draelos et al, Treatment of minor wounds from dermatologic procedures: A comparison of 3 topical wound care ointments using a laser wound model, JAAD supplement March 2011, Vol 64, No