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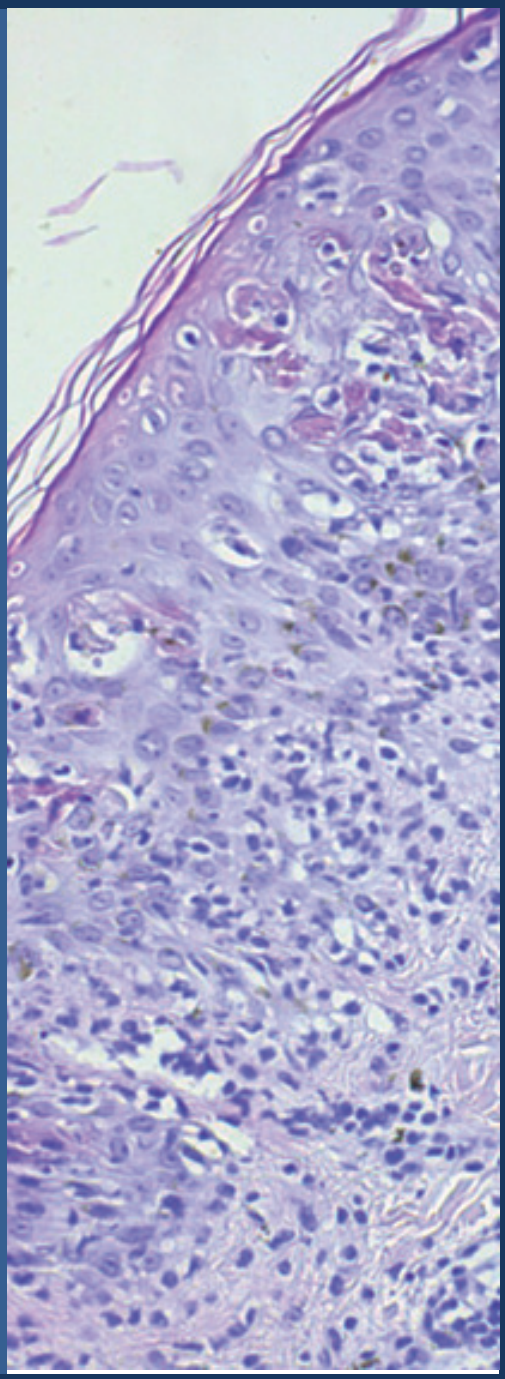



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# A Case-Control Study of Skin Microbiome in Patients with Lamellar Ichthyosis

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## Abstract

**Introduction:** Lamellar ichthyosis is a genetic disorder of keratinization and the frequent skin infections in these patients may be a result of change in normal skin flora acting in addendum to breach in the physical barrier. **Material and Methods:** A comparative retrospective study was performed in patients with lamellar ichthyosis and age/sex controlled matched patients attending the dermatology IPD/OPD with positive skin swab results from July 1st 2015 to June 31st 2016. The two groups were then compared in terms of bacterial culture results. **Results:** The mean gestational age of the study subjects at birth was 35.56 weeks (range: 30-39 weeks). The study sample consisted of 6 males and 3 females in LI group and 12 males and 6 females in the control group. *Methicillin resistant Staphylococcusaureus* (MRSA) was exclusively seen in LI patients, and Gram negative rods, Fusobacterium and Candida were found more in the LI patients than in the control group. The *Bacteroidetes to Firmicutes ratio, lipophilic diphtheroids, Propionibacterium* acnes, *Fusobacterium* and *Micrococci* were present more in the control group than in the LI patients. **Conclusion:** By knowing this microbiota, undue reliance on antibiotics can be reduced as these microorganisms may form normal commensals for the given micro environment. Furthermore, these organisms may be responsible for perpetuating the disease process by compounding the genetic keratinocyte barrier. **What is known:** Frequent skin infections are not uncommon in patients of lamellar ichthyosis. **What is new:** *Methicillin resistant Staphylococcus aureus* (MRSA) are commonly present in LI patients, and Gram negative rods, Fusobacterium and Candida are commoner in the LI patients than in the control group of patients.

**Key words:** Microbiota; Skin; Ichthyosis, Lamellar; Keratins; Keratinocytes; Skin Diseases, Infectious; Infant

## Introduction

The skin does not only serve as an effective barrier between the organism and the environment, but it is in fact an ecosystem which is composed of different habitats rich in invaginations, pockets, and niches. Microorganisms inhabiting superficial skin layers are known as "skin microbiota" which includes bacteria, viruses, archaea and fungi (1). Lamellar ichthyosis (LI) is a severe, autosomal-recessive subtype of congenital ichthyosis which occurs because of genetic mutations in the keratinocyte lipid transporter adenosine triphosphate-binding protein leading to hyperkeratinization of the epidermis (2). In the neonatal period, such patients have an increased risk of developing life threatening complications such as malnutrition, severe dehydration, impaired thermoregulation, respiratory distress, infections, and aspiration pneumonia. Secondary sepsis is the most feared complication and one of the commonest causes of death in these patients as the skin acts as a constant portal of micro-organism entry due to defect in both physical and chemical barrier (3). Another important barrier is served by the biological mantle of the skin which has been linked notoriously in the pathogenesis of atopic dermatitis (4); however, there are no such studies on the composition of these microbial niches in LI.

## Material and Methods

A comparative retrospective study was performed in patients with lamellar ichthyosis and age/sex controlled matched patients attending the dermatology IPD/OPD with positive skin swab results from July 1st 2015 to June 31st 2016. An endpoint of 6 weeks postpartum was

chosen because at this age infants have limited person-to-person contact, and are not exposed to a wide variety of microbes from the environmental sources. LI was diagnosed by complete family history, clinical examination and in doubtful cases skin biopsy was performed. Infants from the control group had no presence of pre-existing or dormant dermatological skin conditions. The patients who either had atopic diathesis or those who were on any kind of antibiotics, any active skin and skin tissue infections, steroidal medication, or used medicated soaps within the past 30 days of the study as well as those who had other forms of immunosuppression like HIV were excluded from the study. The two groups were then compared in terms of bacterial culture results.

## Samples

All skin swab samples were taken within the first day of admission from four sites (nostrils, axillary and inguinal folds, arms). Cotton swabs saturated with sterile physiological saline (approximately 0.5 ml/swab) were used to collect the cutaneous flora of each body site. A swab was rubbed vigorously, with rotation, for roughly 5 s over an approximate 8-cm2 area of each body site. Samples were taken in a sterile and uniform manner by trained personnel. The institutional board approved the study protocol and informed consent was obtained from guardians in compliance with the Helsinki Declaration.

**Table 1:** Comparison of the skin bacterial composition

| Microorganisms | Controls (NC=18,total samples nc=72) | | | | Lamellar Ichthyosis patients (NLI=9,total samples nLI=36) | | | |
|---|---|---|---|---|---|---|---|---|
| | Nostrils | Axillary folds | Inguinal folds | Arm | Nostrils | Axillary folds | Inguinal folds | Arm |
| AEROBES | | | | | | | | |
| Staphylococcus aureus | 7 | 1 | 1 | 2 | 5 | 3 | 5 | 5 |
| MRSA | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 3 |
| Staphylococcus epidermidis | 4 | 7 | 7 | 13 | 1 | 2 | 3 | 5 |
| Streptococcus sp. | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| Group A Streptococcus | 0 | 0 | 0 | 1 | 1 | 2 | 3 | 3 |
| Group D Enterococcus | 0 | 1 | 1 | 0 | 0 | 2 | 2 | 1 |
| E. coli | 0 | 2 | 3 | 0 | 0 | 1 | 2 | 1 |
| Enterobacter sp. | 0 | 7 | 4 | 1 | 0 | 3 | 1 | 2 |
| P. aeruginosa | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 3 |
| Klebsiella | 3 | 3 | 3 | 1 | 1 | 1 | 2 | 1 |
| Proteus sp. | 0 | 5 | 1 | 9 | 0 | 2 | 2 | 4 |
| Lipophilic diphtheroids | 0 | 9 | 7 | 4 | 0 | 1 | 2 | 1 |
| Micrococcus | 2 | 3 | 12 | 9 | 1 | 0 | 3 | 4 |
| ANAEROBES | | | | | | | | |
| Propionibacterium acnes | 2 | 3 | 1 | 5 | 1 | 0 | 0 | 1 |
| Clostridium spp. | 1 | 0 | 4 | 1 | 1 | 2 | 3 | 1 |
| Bacteroides spp. | 2 | 7 | 7 | 11 | 1 | 3 | 4 | 6 |
| Pigmented Prevotella & Porphyromonas spp. | 0 | 3 | 1 | 2 | 0 | 1 | 1 | 0 |
| Fusobacterium spp | 0 | 0 | 3 | 0 | 0 | 2 | 1 | 3 |
| Candida spp. | 0 | 2 | 1 | 1 | 0 | 3 | 3 | 2 |

| Variable | $\chi^2$ | p-value* | 95% Confidence Interval(C.I.) |
|---|---|---|---|
| Lipophilic diphteroids | 3.82 | 0.05 | -0.1544 to 29.7822 |
| Propionibacterium acnes | 2.10 | 0.15 | -4.5154 to 20.5082 |
| Fusobacterium | 4.86 | 0.03 | 1.0146 to 27.9694 |
| Micrococci | 2.12 | 0.14 | -4.9306 to 29.4929 |
| Gram negative rods | 1.25 | 0.26 | -8.3687 to 29.2602 |
| *Candida spp.* | 6.68 | 0.0097 | 3.5290 to 32.8776 |

*Bacteriologic methods*

Qualitative bacterial culture and sensitivities from the swabs obtained from all the subjects were performed. The swabs were also cultured on different media, consisting of Blood agar, MacConkey agar and EMB agar and incubated at 37°C. MacConkey and Chocolate Agar media were used for aerobic and microaerophilic cultivation, respectively. Resultant growths were identified by a set of cultural and biochemical characteristics including Gram's stain, oxidase, coagulase and catalase tests. Appropriate dilutions were plated within 10 min. Trypticase-soy-agar with Tween 8, eosinmethylenebluemedia (EBM), crystal violet agar, pseudomonas agar and Sabouraud glucose agar containing antibiotics (penicillin 20 U/ml and streptomycin, 40mg/ml) were used. Sabouraud agar plates were used to estimate the total counts of Candida albicans, whereas Trypticase-soy-agar with Tween 80 was used for lipophilic diphtheroids. Sabouraud agar plates were incubated at room temperature. Sheep blood agar plates were used to estimate the total count of bacteria. The total counts for *C. albicans* were estimated on Sabouraud agar plates and added to the total bacterial counts. Organisms were classified according to their response to biochemical tests and by their growth and/or morphology on selective or differential media. Colonial pigment, catalase production, coagulase production, oxidative or fermentative metabolism of glucose, production of spores and motility were used to identify the organisms.

*Detection of methicillin resistance*

Methicillin sensitivity tests were performed by the Kirby-Bauer disk diffusion on media growing *Staphylococcus aureus*. The Clinical and Laboratory Standards Institute (CLSI) guidelines (2006) recommended cefoxitin disc diffusion method for the detection of MRSA. This was performed by using a 30 µg cefoxitin disc and an inhibition zone diameter

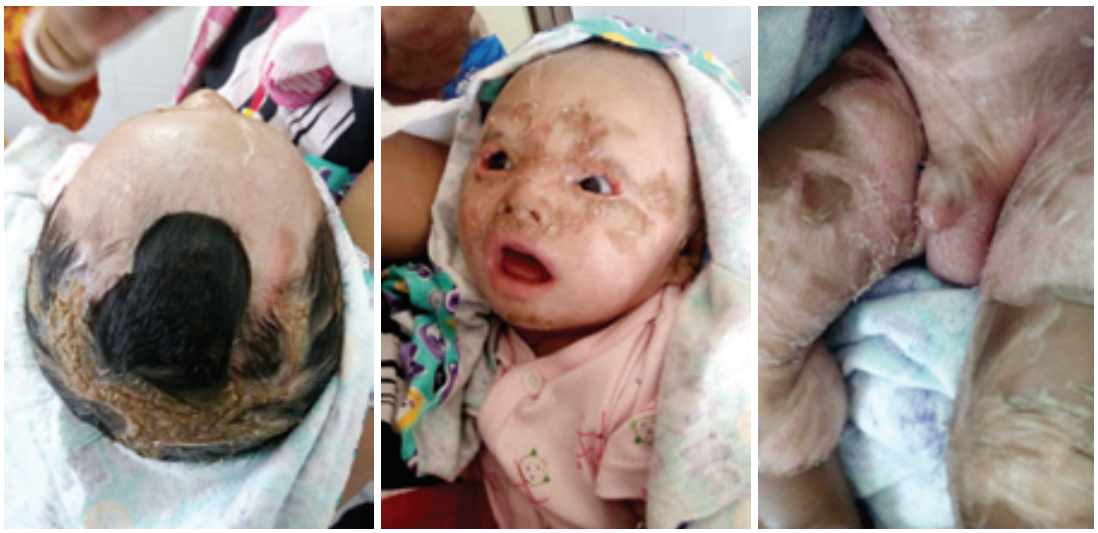


**Figure 1.** Clinical features of a patient of LI

of ≤19 mm was reported as Methicillin resistant and ≥20 mm was considered as Methicillin sensitive.

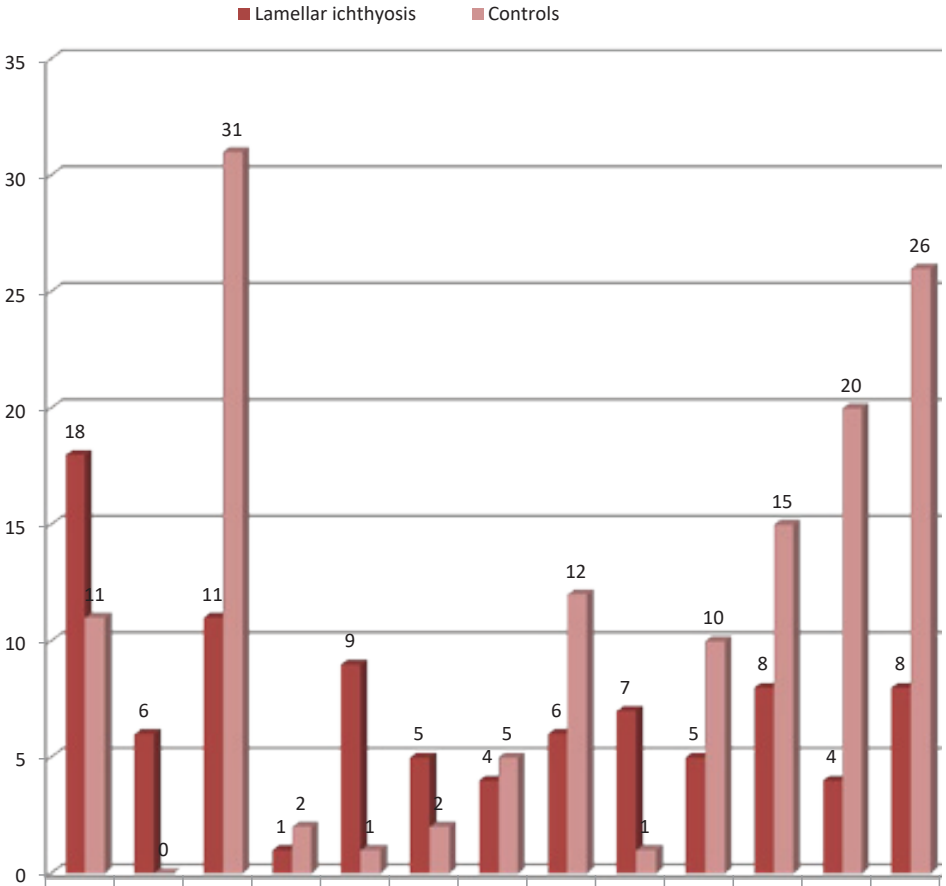
*Statistical Analysis.*

Student t-test was used to test for differences between proportions. All tests were then 2-tailed and $p \leq 0.05$ was considered statistically significant.

## Results

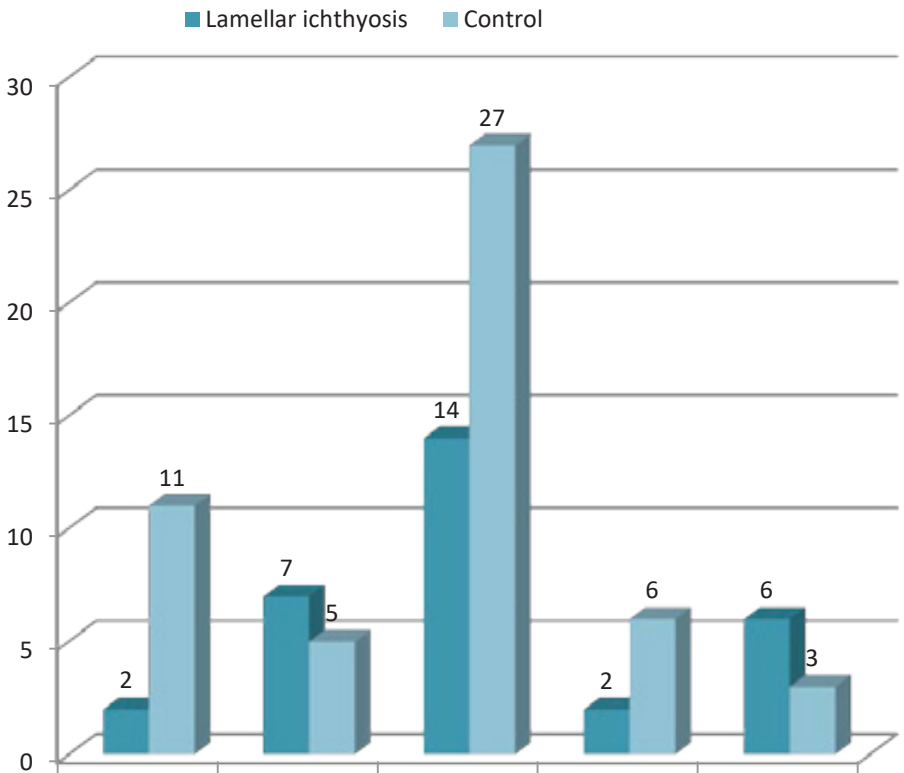
The mean gestational age at birth was 35.56 weeks (range: 30-39 weeks). There were 6 males and 3 females in LI group and 12 males and 6 females in the control group. In the control group the ratio of age, sex matched ratio was 2:1. Age ranged from 4 weeks to 9 years. History of collodion membrane was present in 77.78% and consanguineous marriage in 55.56%. Staphylococcus (80.56%) was the predominant organism in the controls followed by bacteroides (37.50%). A similar trend was seen in 38.89% of LI group patients with staphylococci.

*Bacteroidetes to Firmicutesratios (B/F ratios).* The Bacteroidetes-to-Firmicutes ratio (B/F ratio) was 0.62 in the controls and 0.31 in lamellar ichthyosis patients. Although both




| | Staph. aureus | MRSA | Staph. epidermidis | Streptococcus sp. | Group A Strep. | Group D Strep. | E. coli | Enterobacter sp. | P. aeruginosa | Klebsiella | Proteus sp. | Lipophilic diphtheroids | Micrococcus |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lamellar ichthyosis | 18 | 6 | 11 | 1 | 9 | 5 | 4 | 6 | 7 | 5 | 8 | 4 | 8 |
| Controls | 11 | 0 | 31 | 2 | 1 | 2 | 5 | 12 | 1 | 10 | 15 | 20 | 26 |

**Chart 1.** Aerobic microbiota in LI and control




| | P. acnes | Clostridium spp. | Bacteroides spp. | Pigmented Prevotella & Porphyromonas spp. | Fusobacterium spp |
|---|---|---|---|---|---|
| Lamellar ichthyosis | 2 | 7 | 14 | 2 | 6 |
| Control | 11 | 5 | 27 | 6 | 3 |

**Chart 2.** Anaerobic microbiota in LI and control

cohorts showed an increased firmicutes (Z-Score = 3.0391. The p-value =0.00236), LI cohort showed greater preponderance of firmicutes, especially of staphylococcus aureus and group A streptococcus (S. pyogenes).

*Methicillin resistant Staphylococcus aureus (MRSA)*. MRSA colonization was seen exclusively in LI cohort, constituting 33.33% of S. aureus flora.

*Lipophilic diphtheroids and Propionibacterium acnes*. Lipophilic diphtheroids constitute 11.11% in LI group in contrast to 27.78% in the control subjects. Although P. acnes is not as populous in paediatric population as in adults, its presence was found to be even lower in LI group (5.6%) in comparison to the controls (15.28%).

*Fusobacterium* was found in more LI patient microbiome (16.67%) than in the controls (4.17%) and its increased presence may point out to a precursor environment for skin infections.

*Micrococci*. Micrococci form a major part of paediatric microbiome. In our study there was decreased sample positivity in case of LI patients (22.22%) as compared to the controls (36.11%).

*Gram negative rods comparison*. Aerobic Gram negative bacilli comprising of Enterobacter, Proteus, Klebsiella were found more in LI cohort (52.78%) than in the control group (51.39%).

*Fungal population*. The predominant fungal species isolated from both the groups was Candida but it was present more in the samples from LI group (22.22%) than in the control samples (5.56%).

### Differential Microbial Composition according to Niche

*Nostrils*. Aerobes predominate in both the control and LI group. Staphylococci formed the most populous microbial population in the nares in both group-S.aureus and S.epidermis in the controls but in the LI patients MRSA was isolated from nares. Similarly GAS inhabitation (like MRSA) pointed towards more pathogenic microbial constituents in LI.

*Axillary folds*. Lipohilic diphtheroids formed the majority of isolates in the control group from this site (p=0.05, $\chi 2$=3.75). In the staphylococcal group, S. epidermis formed the majority in the control group, whereas in the LI group, S.aureus was found in a greater number of samples in comparison to S. epidermis. GAS and Group D enterococci were found as unusual inhabitants in case of LI patients (none isolated in case of controls).In anaserobes, P.acnes was conspicuously absent in the axillae samples of LI

*Inguinal folds*. Samples from inguinal creases showed the increased presence of S. aureus (with the presence of MRSA in 1 culture), which replaced the normally present commensal-S.epidermis as seen in the control group. (S.aureus and MRSA population control vs. LI was found to be markedly higher in LI with p=0.0008, $\chi 2$=11.23). Pathogenic GAS and *group D Enterococci* were found exclusively in LI samples. As in axillae samples, lipohilic diphtheroids and *P.acnes* (*P. acnes* generally also seen in lesser quanta in paediatric population) are decreased in concentration which may be due to the xerotic environment in LI patients and increased sebum film fragility. *Candida spp.* and *Clostridia* are seen as increased commensal population in LI as compared to the controls (statistically not significant for the site, p=0.54).

*Volar aspect of forearms*. The similar trend of increased presence of S.aureus instead of S. epidermis in isolates obtained from other sites in LI patients persisted at this site as well. Interestingly, this niche provided the most suitable environment for the presence of MRSA in LI group (*S. aureus* and MRSA population control vs. LI was found to be markedly higher in LI with p=0.0001, $\chi 2$=14.99). Pseudomonas was isolated in 33.33% of cultures from the forearm samples in LI patients as compared to none in the controls. Bacteriodes in particular were found in a greater number of LI samples (66.67%) as compared to the controls (38.89%), but statistically this was not found to be significant (p=0.18). Similarly, fusobacterium and candida form a greater part of the commensals in LI skin as compared to that in the normal paediatric skin.

## Discussion

The difference in the constituents of the microbial flora may be attributed to the defect in the keratinocyte barrier, usage of antibiotics, retinoids and corticosteroids. Infants' skin microbiota is derived from the mode of delivery, body of the mother and other human contacts and from various inanimate objects. Four major groups of microbial communities residing at different body sites form the microbiome of a neonate: *Firmicutes, Actinobacteria, Bacteroidetes,* and *Proteobacteria* (4, 5). Specific groups of microorganisms colonize distinct anatomical niches. The most numerous microbes are well-defined resident floras which are constantly present on the body surfaces and may prevent colonization by pathogens and a possible disease. Commensal microorganisms are in mutualistic symbiosis and they contribute to human health through the production of defence molecules. Transient skin flora temporarily colonizes the skin and is unable to remain in the body for a long period of time due to the competition from the resident microbes. They are not pathogenic under normal conditions (6-8).

No study has been undertaken so far to decipher the composition of the skin flora in LI. In this study, methicillin resistant *Staphylococcous aureaus* (MRSA) was exclusively seen in LI patients, and Gram negative rods, Fusobacterium and Candida were observed more in the LI patients. The *Bacteroidetes*-to-*Firmicutes* ratio, lipophilic diphtheroids, *Propionibacterium acnes*, *Fusobacterium* and *Micrococci* were present more in the control group than in the LI patients. Due to disrupted corneocyte TGM1 there is a failure of proper and uniform lipid layer in LI patients, which reflects in the change of microbiome of the skin from lipophilic organisms to organisms which thrive in dry skin.

The importance of reversal of Bacteroides to firmicutes ratio ratio stems from both pathogenic as well as therapeutic views. Pathogenetically, the phylum Firmicutes consist of the following genera-*Bacillus, Listeria, Staphylococcus, Streptococcus, Enterococcus,* and *Clostridium*-which are responsible for major SSTIs. In normal paediatric skin microenvironment, Firmicutes for example*, S. epidermis*, form the majority in a healthy neonate's skin but as seen in our study as well as in other studies involving patients of atopic dermatitis and psoriatic plaques etc there is an increase in the relative concentration of S.aureus population (4). Therapeutically, delving in this microbial composition, tipping the balance towards bacteroides by topical or ingested flora correction and use of barrier emollients and by altering the skin pH may reduce the severity of the disease.

*Staphylococcus epidermidis* is a Gram-positive bacterium and it comprises more than 90% of the aerobic resident flora. *S. epidermidis* provides an added level of protection against certain common pathogens via production of lantibiotics, which are lanthionine containing antibacterial peptides and via activation of TLR-2. *S. epidermidis* also inhibits biofilm formation and nasal colonization by S. aureus. In this study, the most common aerobic bacteria on the skin of LI were *Staphylococcous aureus* followed by *Staphylococcus epidermidis.* This indicates the higher susceptibility of patients of LI to infections owing to the loss of antibacterial properties of *Staphylococcous epidermidis* and overgrowth of pathogenic *Staphylococcous i.e. Staphylococcous aureus*. Stratum corneum of infant is better hydrated than of adults hence microbiome of the infant skin resembles closer that of the relatively moister skin sites in the adults (5, 6).

Under anaerobes, *Bacteroides* were abundant in both groups, whereas the second most common organism was Clostridium spp. in LI and *P.acnes* in the control group. In contrast to the adults, Firmicutes predominate on the infant skin but the B/F ratio is decreased to a statistically low value in case of LI patients, further understating the presence of organisms most frequently implicated in SSTIs (especially pathogenic Staphylococci, GAS etc.).

MRSA carriage in LI patients further undermines the perturbed biological, physical as well as chemical barrier of the skin. The newborn having lamellar ichthyosis is born encased in a collodion membrane that sheds within 10-14 days after which the newborn is exposed to a plethora of antigens, this delay in antigen presentation particularly that of microbial origin compounded by keratinocyte barrier dysfunction may lead to differential commensal microbial niches in comparison to their normal counterparts as observed in this study.

Finally, increased interventional procedures in LI patients such as frequent cannulation, catheters and blood draws become more perilous due to the change in the commensal population, especially, invasive candidiasis and septicemia.

There are certain limitations to this study. We diagnosed LI by clinical and histological findings, whereas DNA-based molecular genetic testing for TGM1, ABCA12, ALOXE3 and ALOX12B could not be performed. Also, 16S rRNA molecular analysis could not be performed to identify bacteria due to the lack of resources. Studies involving larger number of patients of different ethnic group will be more desirable.

## Conclusion

This study revealed the altered microbiome tipping towards the presence of pathogenic flora even in the absence of any clinical infection in LI patients. This milieu may act as a precursor to the recurrent infections seen in LI patients. In-depth knowledge of the altered flora of these patients may explain perpetuation and flare up of the disease process itself. By knowing the microbiome of patients with LI, preventive measures can be taken to decrease the load of pathogenic bacteria and reconstitute a positive symbiotic biological mantle thereby decreasing the chances of skin infections, sepsis and thus heavy reliance on antibiotics.

## Author's contributions:

MS designed and supervised the project, supervised data collection and analysis, and first drafted the manuscript. MP assisted in data management, was responsible for sample management, and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted

and agree to be accountable for all aspects of the work.

## Abbreviations

LI – Lamellar ichthyosis
MRSA – Methicillin resistant Staphylococcus aureus

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# Studija o mikrobiomu kože kod pacijenata sa lamelarnom ihtiozom

## Sažetak

**Uvod.** Lamelarna ihtioza je genetski poremećaj keratinizacije i česte kožne infekcije kod ovih pacijenata mogu biti rezultat promene u normalnoj flori kože koja deluje u adendumu da bi probila fizičku barijeru. **Materijali i metode.** Izvedena je komparativna retrospektivna studija kod pacijenata sa lamelarnom ihtiozom i kod kontrolnih pacijenata istog pola i starosti koji su došli na odeljenje dermatologije poliklinike i bolničkog dela sa pozitivnim rezultatima brisa kože u periodu od 1. jula 2015. do 31. juna 2016. godine. Rezultati bakterioloških kultura poređeni su između dve grupe. **Rezultati.** Prosečna gestaciona starost ispitanika na rođenju bila je 35,56 nedelja (raspon između 30 i 39 nedelja). Studija je obuhvatila šest muških i tri ženska pacijenta u grupi sa lamelarnom *ihtiozom i šest pacijentkinja u kontrolnoj grupi. Methicillin resistant Staphylococcus aureus* (MRSA) viđen je samo kod pacijenata sa lamelarnom ihtiozom, a Gram-negativni štapići, *Fusobacterium* i kandida pronađeni su više kod pacijenata sa lamelarnom ihtiozom nego u kontrolnoj grupi. Odnos bakteroida i firmikuta *lipofilni difteroidi, Propionibacterium* acnes, *Fusobacterium* i *Micrococci* bili su više prisutni u kontrolnoj grupi nego kod pacijenata sa lamelarnom ihtiozom. **Zaključak.** Saznanje o mikrobiomu kod lamelarne ihtioze može doprineti racionalnoj upotrebi antibiotika, jer mnogi od ovih mikroorganizama mogu predstavljati komensale u datoj sredini, ali mogu i doprinositi održavanju patološkog procesa u koži. *Staphylococcus aureus rezitentan na meticilin* (MRSA) je često prisutan, a Gram-negativni štapići, *Fusobacterium* i kandida češći su kod pacijanta sa lamelarnom ihtiozom nego kontrolnih ispitanika.

**Ključne reči:** Mikrobiota; Koža; Lamelarna ihtioza; Keratin; Keratinociti; Infektivne kožne bolesti; Novorođenče

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# Comparing Efficacy and Safety of Oral Tranexamic Acid and 4% Topical Hydroquinone Cream in Melasma Treatment: A Randomized Controlled Clinical Trial and Review of Literature

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**UDC 616.5-003.829-085:615.454.1**

## Abstract

**Introduction.** Melasma is a common skin pigmentation disorder affecting a patient's life psychologically and socially. Topical medications or lasers can have temporary and limited therapeutic effects on melasma. **Material and Methods.** This study is a prospective clinical trial comparing therapeutic effects of oral Tranexamic acid (TXA) and topical Hydroquinone (HQ) cream. A total number of 69 patients were examined. During the study, 10 patients failed to appear for the follow-up and 59 of them completed the trial. The patients were also divided randomly into two groups. Group A received TXA capsule 250 mg every 12 hours and group B received 4% topical HQ cream day and night. The patients from both groups were treated for 3 months. Melasma Area and Severity Index (MASI) scores were then calculated at the baseline, 4 weeks, and 12 weeks into the treatment and 3 months after the end of intervention. **Results**. MASI baseline, 4 weeks,12 weeks, and 24 weeks in TXA group were 21.66, 13.69, 9.10, 9.24; respectively. Reduction of MASI between baseline and 4 weeks was statistically significant. Such a decreasing trend in MASI scores between baseline and 12 weeks was also reported as statistically significant (p=0.001). In the HQ group, MASI baseline,4 weeks, 12 weeks, and 24 weeks were 21.46, 13.57, 10.93, 11.20; respectively. Reduction of MASI scores between baseline and 4 weeks was statistically significant. Moreover, a decline in MASI scores was observed between baseline and 12 weeks that was statistically significant (p=0.001). Considering both groups MASI scores were reduced but the difference between two study groups was not statistically significant (p=0.98). **Conclusion.** The efficacy of TXA and HQ was the same and both could significantly reduce MASI scores.

**Key words:** Melanosis; Tranexamic Acid; Dermatologic Agents; Hydroquinones; Administration, Topical; Treatment Outcome

## Introduction

Melasma is a common pigmentation disorder of the face, which can be very debilitating psychologically and socially. Melasma often appears as symmetrical macules or patches on the face. It can also have three common patterns including *centrofacial* (involving the forehead, cheeks, nose, upper lip, and chin), malar, and mandibular. In addition, this disease is more common in the Asian and African race and can affect women with darker skin types (1, 3).

The precise pathogenesis of this disease is unknown; however, the hypothesis of the activation of melanocyte biology via ultraviolet has been discussed. Recent studies have further shown an increased incidence of angiogenic factors in the epidermis as well as increased vascularity in these areas (4, 5).

Moreover, a number of predisposing factors such as pregnancy, use of contraceptives, sun exposure, ovarian tumors, hormone replacement therapy (HRT) and anti-seizure medications have been designated (6).

 

The most commonly used treatments for melasma are the use of topical lightening drugs such as HQ, which are often inadequate or can even cause skin irritations. Furthermore, experiments have revealed that topical melasma treatments have therapeutic effects on most types of epidermal melasma, but not on dermal ones (7, 8).

TXA, chemically named Trans-4-aminomethyl cyclohexane carboxylic acid has been introduced as a new treatment for melasma and it is actually a synthetic derivative of the Lysine amino acid that can be effective in preventing bleeding. Efficacy of intradermal tranexamic acid injection has been reviewed in some studies (9). Studies and trials on the use of oral medications such as TXA in the treatment of melasma are limited. Therefore, the main purpose of this study is to design a prospective clinical trial which would compare the effects of oral TXA treatment on melasma and use of conventional treatments such as topical HQ cream.

## Material and Methods

The present study is a prospective clinical trial, a case-control research, and a blinded analyst-and-assessor one evaluating the effect of oral TXA treatment on melasma. The study samples consisted of patients referred to a dermatology clinic from July 2017 to October 2018 for melasma treatment. To begin the study, the code of ethics was obtained (1396.714 IR. AJUMS.REC) and the study was registered on the Iranian Randomized Clinical Trial database with the code, IRCT20180111038311N1.

The inclusion criterion was being affected with melasma in the age range of 18 to 60 years. The melasma was also defined with clinical diagnosis of a dermatologist (if necessary, a skin biopsy was used to confirm the diagnosis).

Exclusion criteria were patients with a history of coagulopathy, history of thrombotic problems, evidence of any thrombotic events, use of coagulant drugs, use of anti-coagulant or antiplatelet medications such as aspirin or clopidogrel tablets, pregnancy, lactation, concomitant use of contraceptives or phenytoein, history of individual vitiligo or other pigmentation disorders, history of TXA susceptibility, kidney disease, history of melasma lightening treatment (3 months before the onset of the study). The patients also underwent an examination by Wood's lamp and then the types of melasma (dermal, epithelial, mixed, and unspecified) were determined.

After entering the study, the patients received explanations about the research method, and they were prepared to give consent to be included in the study. Then, they were randomly categorized (in the premium block method) in one of the groups; group A, which included administration of 250 mg TXA capsules every 12 hours, and group B which involved administration of a 4% topical HQ cream applied locally in mornings and evenings. In group A patients, coagulation profile tests were also performed before treatment. Melasma severity was then measured by the formula of MASI scores and then recorded separately for patients. This scoring was described by Kimbrough-Green et al. (10), and the measurement method was as follows.

MASI=0.3(DF+HF) AF+0.3(DMR+HMR) AMR+0.3(DML+HML) AM+0.1(DC+HC) AC

The numbers of 0.3 and 0.1 are respectively related to the anatomical covered areas on the face, taking 0.1 of the face area in the chin, and 0.3 in the right and the left molar regions of the forehead.

D=Darkness, H=Homogeneity, A=Area, F=Forehead, MR=Right Malar, ML=Left Malar, C=Chin

To assess darkness "D" and color homogeneity"H",0 to 4 degrees is given (Absent=0, Slight=1, Mild=2, Marked=3, Maximum=4).

In this formula, A is the amount of surface involvement of melasma in any anatomical area (Noninvolvement=0, 0-9%=1, 10-29%=2, 30-49%=3, 50-69%=4, 70-89%=5, 90-100%=6).

The MASI score is calculated from the multiplication of the A score by the sum of D and H and is computed for each of the 6 regions. The maximum score for each side of the face is 24 and the minimum one is 0.

Each group underwent treatment for 3 months. During this period, the patients were followed up and recommended to use sunscreens (without anti-pigmentation and SPF=30).

Within 1 and 3 months after the beginning of treatment and three months after its completion, each patient was reevaluated and MASI was calculated. Finally, 3 months after the end

of the treatment, the patient's satisfaction was determined as 1=excellent satisfaction, 2=relative and good satisfaction, and 3=dissatisfaction. Adverse effects were also documented.

## Results

Among the 90 melasma patients referred to the dermatology clinic, 69 patients met the inclusion/exclusion criteria and were invited to participate in the study and they were then randomized into two groups: group A consisting of 34 patients treated with oral TXA and 35 patients in group B treated with topical 4%HQ cream.

Demographic information and background characteristics are summarized in During the study, 5 patients from each group were excluded because they failed to appear at the check-up or the treatment was discontinued due to side effects; i.e. severe irritant contact dermatitis in the HQ group (1 patient) and gastrointestinal complications (1 patient) in the TXA group, and 4 patients in each group were also excluded because of poor compliance. Finally, 29 patients in group A and 30 patients in group B were analyzed.

The mean age of the patients was 38.30±6.97 (17-52) years. The mean age in group A was 37.31±7.88 years and that was 39.26±5.93 years in group B and no statistically significant difference was observed between the two groups (p=0.28).

In group A, 28 (96.6%) patients were females and 1 patient (3.4%) was male. In the cream group, 28 individuals (93.3%) were females and 2 patients (6.7%) were males. There was no statistically significant difference between the two groups in terms of gender status (p=0.57).

T-test was used to compare information and characteristics of both groups which showed no statistically significant difference **(Table 1)**.

The mean MASI score was 21.66±5.96 in group A (TXA) and 21.47±7.00 in group B (HQ). There was no significant difference between MASI scores in the two groups during baseline (p=0.916).

**Table 1.** Demographics and background characteristics

| Measure | TXA(29 patients) | HQ(30patients) | P _ value |
|---|---|---|---|
| Age (year)/Mean±SD | 37.3±7.8 | 39.2±5.9 | 0.28 |
| Sex N (%) | 28 females (96.6%)<br>1 male (3.4%) | 28 females (93.3%)<br>2 males (6.7%) | 0.57 |
| Skin phototype N(%) | Type 2 - 1 (3.4%)<br>Type 3 - 14 (48.3%)<br>Type 4 - 12 (41.4%)<br>Type 5 - 2 (6.9%) | Type 2 - 2 (6.7%)<br>Type 3 - 14 (46.7%)<br>Type 4 - 11 (36.7%)<br>Type 5 - 3 (10%) | 0.9 |
| Disease duration (year) | 4.8 ± 5.1 | 5 ± 5.7 | 0.927 |
| Positive Familial history of melasma N (%) | 31.0% | 50% | 0.13 |
| Sun exposure N (%) | 27 (93.1%) | 25 (83.3%) | 0.24 |
| Pregnancy in recent years N (%) | 10 (34.5%) | 15 (50.0%) | 0.22 |
| OCP consumption (%) | 4 (13.8%) | 5 (16.7%) | 0.75 |
| Previous treatment for melasma N (%) | 17 (58.6%) | 14 (46.7%) | 0.35 |
| Melasma Type in wood lamp N (%) | Dermal 3 (10.3%)<br>Epidermal 17 (58.6%)<br>Mixed 9 (31.0%) | Dermal 1 (3.3%)<br>Epidermal 17 (56.7%)<br>Mixed 12 (40.0%) | 0.49 |
| Melasma region N (%) | Centrofacial 21 (72.4%)<br>Malar 7 (24.1%)<br>Mandibular 1 (3.4%) | Centrofacial24 (80.0%)<br>Malar 5 (16.7%)<br>Mandibular 1 (3.3%) | 0.77 |
| Baseline MASI score Mean± SD | 21.66±5.96 | 21.56±7.00 | 0.46 |

Mean MASI score during the 4th week after the onset of treatment was 13.46±5.70 in the TXA group and 13.57±5.97 in the HQ group with no significant difference between MASI scores (p=0.944).

In the third month after the start of the treatment, the mean MASI score was 9.10±4.93 in the TXA group and 10.93±6.18 in the HQ group. There was no statistically significant difference between MASI scores in the two groups in the 12th week (p=0.215).

Three months after the end of the treatment period, the mean MASI score was 9.24±5.11 in the TXA group and 11.20±6.04 in the HQ group and no significant difference between MASI scores in the two groups in the 24th week (p=0.185).

The mean MASI score of the patients in the TXA group during the 4th week compared with pretreatment (p=0.001) and within the 12th week compared with the 4th week (p=0.001) was significantly and statistically different. Moreover, the mean MASI score during the 12th week decreased significantly (p=0.011) compared with the baseline (p=0.001) **(Figure 1)**.

The mean MASI score of the patients in the HQ group during the 4th week compared with pretreatment (p=0.001) and the 12th week compared with the 4th week (p=0.001)

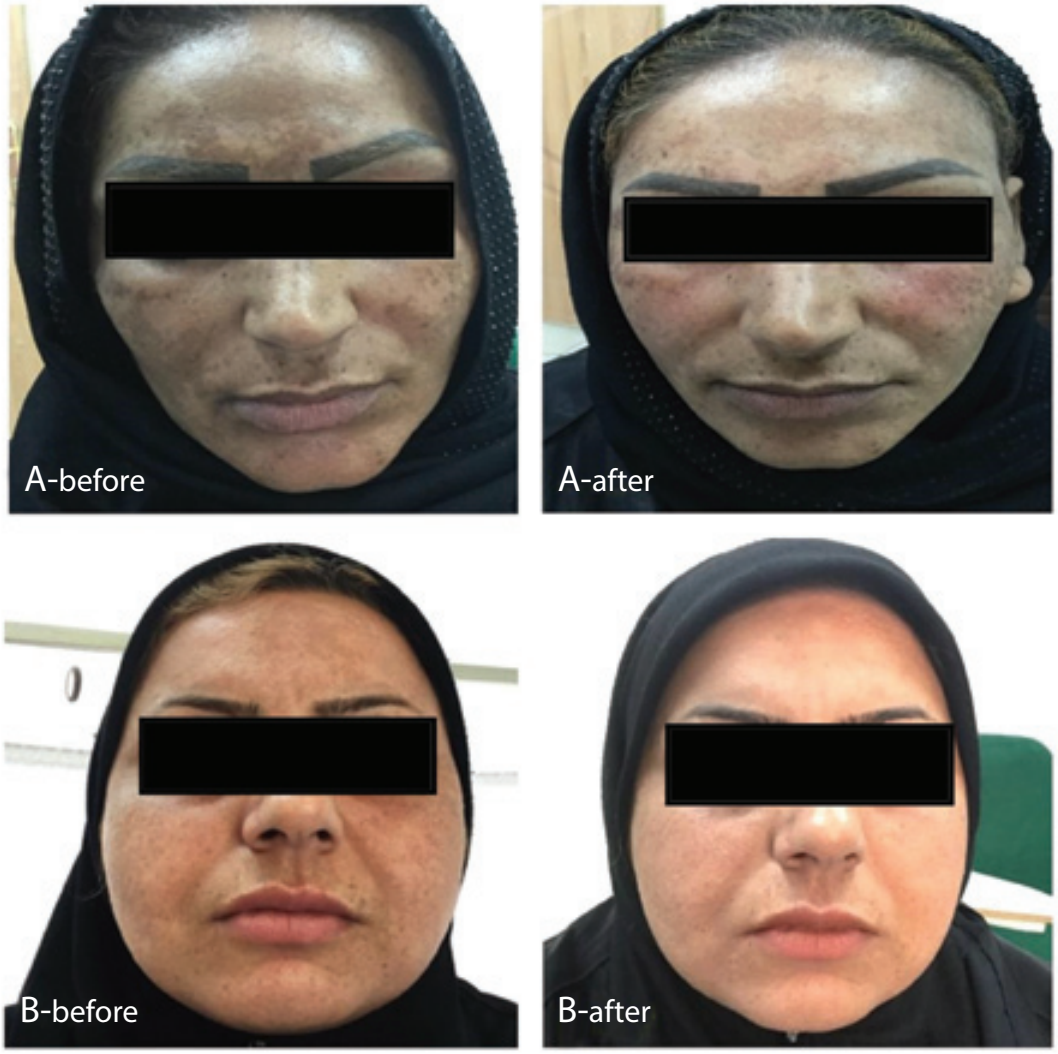


**Figure 1.** Clinical photograph of melasma patients in the TXA group taken at the first visit (pretreatment) and after 3 months of treatment. (A) 31-year-old female, (B) 38-year-old female

**Table 2.** Efficacy of treatment by MASI score in treatment groups

| Group | Pretreatment MASI | 4 th week | 12 th week | 3 months after treatment cessation | p-value |
|---|---|---|---|---|---|
| TXA | 21.66±5.96 | 13.46±5.70 | 9.10±4.94 | 9.24±5.12 | p<0.001 |
| HQ cream | 21.47±7.00 | 13.58±5.97 | 10.93±6.18 | 11.20±6.05 | p<0.001 |
| p-value | 0.916 | 0.944 | 0.215 | 0/185 | |

was reported as significantly statistically different. Moreover, the mean MASI score in the HQ group decreased significantly within the 12th week (p=0.001) compared with the baseline (p=0.011) **(Table 2, Figure 2)**.

The mean MASI score in each group was determined separately based on different variables including skin photo types, familial history, and melasma type through examination with Wood's lamp and location of melasma on the face as well as duration of melasma before the start of the treatment, and the results are separately given in **Table 1.**

## Treatment Complications

In the TXA group, 3 (10.3%) patients had gastrointestinal side effects, 13 (44.8%) of them suffered from hypomenorrhea, 2 (6.9%) of these patients had gastrointestinal problems and hypomenorrhea, and 11 (37.9%) of them had no side effects. Additionally, in the HQ group, 7 (23.3%) patients had irritant contact dermatitis, 1 (3.3%) of them suffered from xerosis only, 1 (3.3%) patient had irritant contact dermatitis and xerosis, and 21 (70%) of them had no side effects. The most significant complication in the TXA group was hypomenorrhea, and that was irritant contact dermatitis in the HQ group. The number of complications in the TXA group was significantly higher than in the HQ group (p=0.001).

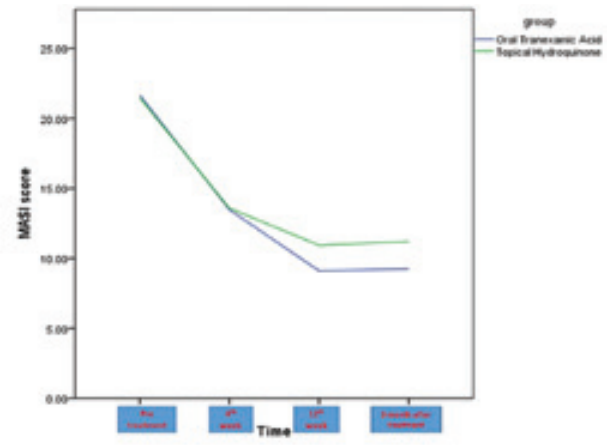


**Figure 2.** MASI score reduction in 2 groups receiving 3-month treatment

## Patient's Satisfaction

In the TXA group, 6 (20.7%) patients expressed complete satisfaction, 19 (65.5%) of them reported good and relative satisfaction, and 4 (13.8%) of such patients expressed no satisfaction. In the HQ group, 2 (6.7%) patients expressed complete satisfaction, 18 (60%) of them reported relative and good satisfaction, and 10 (33.3%) of them had no satisfaction. There was also no significant difference between the two groups (p=0.1).

## Discussion

Melasma is a common facial pigmentation disorder, which can be psychologically and socially disabling. It also has a great impact on quality of life.

TXA, chemically named Trans-4-aminomethyl cyclohexane carboxylic acid, has been also introduced as a new treatment for melasma, and is actually a synthetic derivative of the Lysine-amino acid that is effective in bleeding prevention (9). Nijor (1979) was the first scholar examining the effect of TXA on melasma. Maedaket et al. then investigated the role of TXA on human melanocytes and cultured keratinocytes. They found that TXA had inhibited the synthesis of melanin by inhibiting tyrosinase activity in epidermal melanocytes. In addition, it blocked interactions between melanocytes and keratinocytes through inhibiting plasmin/plasminogen system (9, 11).

In most studies on oral TXA at a dose of 250 mg per 12 hours, few complications were reported. Not even the women who had received high doses in treatment via menor-

 

**Table 3.** Published articles about the role of oral TXA in the treatment of melasma

| Clinical study | N | 2 group | MASI changes |
|---|---|---|---|
| Cho HH 2012 (15) | 51 | A: Oral TXA 250 mg/q12h + laser NYD_YAG<br>B: laser Nd:Yag | A: 43.8% in 2 week treatment<br>B: 23.6% |
| Tanmay Padhi 2015 (24) | 40 | A: oral tranexamic acid + fluocinolone-based triple combination cream<br>B:fluocinolone-based triple combination cream alone | A: 87.99% in 8 week treatment<br>B: 54.66% |
| Lajevardi 2016 (14) | | A: TXA + HQ 4%<br>B: HQ 4% | A: 51% in 12 week treatment<br>B: 33% |
| Karn 2012 (16) | 260 | A: Oral TXA 250 mg/BD<br>B:Topical treatment | A: 30% in 12 week treatment<br>B: 21% |
| Sufan Wu 2012 (19) | 74 | A: Oral TXA 500 mg daily | A: 59% in 6 month treatment |
| Chyen Lee 2016 (20) | 553 | A: Oral TXA 250 mg/BD | A: PGA assessment<br>89.7% improved. 10% no improvement. 0.4% worsened. |
| Aaron Wei 2016 (21) | 25 | A: Oral TXA 250 mg/BD | A: 69% in 12 week treatment |
| Sharma 2017 (18) | 80 | A:Oral TXA 250mg/BD<br>B: Intradermal TXA 4 mg/Q4 w | A: 77.96% in 12 week treatment<br>B: 79% |
| Del Rosario 2017 (23) | 44 | A:Oral TXA 250 mg/BD<br>B: Placebo Capsules | A: 49% in 12 week treatment<br>B: 18% |

rhagia showed significant complications and there was no obvious increase in the risk of thromboembolism among them (12).

When TXA is used as a hemostatic drug, it is administered at a dose of 1000 mg every 8 hours. However, the prescribed dose for melasma treatment was at 250 mg every 12 hours in most of studies as well as in the present study (13).

In this study, the effect of TXA on melasma is characterized by decreasing MASI in the months after treatment. In the TXA group, MASI reduction between 0 and 12th weeks after treatment was also statistically significant (p=0.001).

In the HQ group, MASI reduction between 0 and 12th weeks after treatment was also statistically significant (p=0.001). In two groups before and after the start of the treatment, a decrease was also observed; nevertheless, no significant difference was reported between the rates of reduction in the HQ or TXA groups (p=0.98).

In other words, in both groups, MASI reduction was the same and no significant difference was observed. In this study; skin photo types, different types of melasma, familial history of melasma, and duration of melasma before treatment had no effects on the response rate to treatment in the TXA group **(Table 1)**.

In PubMed-based search for the effects of oral TXA on melasma treatment, there were also some studies on the role of oral TXA in the treatment of melasma with a control group (13, 18) or without it (19, 21). These studies are listed in **Table 3**.

Two studies by Cho et al. and Shin et al. in 2012 and 2013 (15, 22), were conducted on the combination of oral TXA treatment with low-fluency Q-switched Nd:YAG/IPL in the study by Cho et al. and low-fluency Q-switched Nd:YAG in the investigation by Shin et al.

Finally, in both studies, following the addition of laser to TXA treatment, MASI reduction was higher than in other groups treated with laser alone. This reduction was approximately 43.8% in the TXA-treated group combined with laser, and 23.6% in patients treated with laser alone. In the present study, the effect of TXA was MASI decline by about 58%.

Moreover, Sufan and Hangyan (2012) examined the therapeutic effect of oral TXA 500 mg daily. In this respect, 74 women were included in the study and treated for 6 months.

In general, melasma recovery was reported by 59.9%. The overall effect of oral treatment with TXA in this study was very similar to that of the present study, which had a 58% effect (19).

Lajevardi et al. (2016) also studied 100 patients with facial melasma in two groups. One group was administered oral TXA treatment combined with topical 4% HQ cream and the other one was administered 4% HQ cream alone. After three months of treatment in oral TXA combined with 4% HQ cream group, MASI reduction was 51% and that was only about 33% in the HQ cream alone. In the present study, the effect of TXA alone on MASI decrease was about 58% during 3 months and that was about 49% in the HQ cream alone group. In the present study, the effect of HQ cream alone on MASI reduction was reported to be higher (14).

Moreover, Karn et al. (2012) conducted a randomized prospective study on 260 patients with melasma. They divided their patients into two groups: group A received topical routine melasma treatment with TXA 250 mg twice daily for 3 months, and group B received only topical melasma treatment. Their response to treatment was evaluated by MASI and its reduction in group A and B after 3 months of treatment was by 30% and 21%; respectively, that being a significant difference (16).

Sharma et al. (2017) conducted a clinical trial on 80 patients with melasma. In one group, oral TXA was administered at a dose of 250 mg every 12 hours for 12 weeks and in the other group, 4 mg intradermal TXA was injected into the patient's melasma for 4 to 12 weeks. At the end of the three-month treatment, reduction in MASI in the oral TXA-treated group was 78% and that was 79% in the intradermal TXA-treated one (18).

Del Rosario et al. (2017) similarly divided women with melasma into two groups with 22 patients in each one. Accordingly, group A was treated with oral TXA 250 mg every 12 hours and group B received placebo. At the end of 3 months, MASI scores also decreased in the TXA group by 49%, compared with 18% decline in MASI scores in the placebo one. From the beginning of treatment with TXA the patients with severe melasma were found to respond to the treatment much better than those with moderate melasma. Three months after stopping treatment, 26% decrease in MASI score was observed in group A. Moreo-

**Table 4.** Complications reported with TXA administration for the treatment of melasma

| | |
|---|---|
| Karn 2012 (16) | Oligomenorrhea(14.7%), Belching (9.2%), Abdominal cramps (6.9%) , Palpitation, urticarial rash and angioedema (each in one patient) |
| Sufanwu 2012 | Gastrointestinal irritation such as nausea, diarrhea, abdominal pain (5.4%) Detectable hypomenorrhea (8.1%) |
| Cho HH 2012 (15) | Transient headache (4 patients) |
| Tanmay Padhi 2015 (24) | No side effects for TXA consumption |
| Chyen Lee 2016 (20) | Side effects in (7.1%): Abdominal bloating (12 patients) and headache (6 patients) … Left lower limb DVT(1 patient) |
| Lajevardi 2016 (14) | Abdominal pain ,flank pain, edema of hands and feet, nausea, vomiting, headache |
| Aaron Wei 2016 (21) | No side effects |
| Del Rosario 2017 (23) | Gastrointestinal discomfort (22.7%),change in menstrual period (18.2%), headache (13.6%), myalgias (9.1%), somnolence (9.1%) |
| Sharma 2017 (18) | Hypomenorrhea (15.4%), Epigastric discomfort (2 patients) |

 

ver, a 19% decline in MASI score was reported in group B. Finally, this study showed that oral TXA was an effective drug in treating moderate to severe melasma (13).

Padhi et al. (2015) also compared the effect of triple therapy with a cream containing fluocinoloneacetonide 0.01%, tretinoin 0.05%, and hydroquinone 2% in combination with oral TXA twice a day and other groups with a cream containing fluocinoloneacetonide 0.01%, tretinoin 0.05%, and hydroquinone 2%. Their treatment lasted 8 weeks and reduction in MASI in both groups was significant. MASI in the TXA-administered group in combination with topical treatment was also reported to have been reduced by 88%, and it was only about 55% in the topical treatment group. This amount was higher than that in the present study, which could be due to co-administration with topical medication (23).

Chyen Lee et al. (2016) also conducted a retrospective study on 553 patients treated with oral TXA 250 mg twice a day for an average of 4 months. The patients were then characterized as resistant to melasma treatment. Moreover, 89.7% of patients showed improvements after treatment, 10% of them showed no change and 0.4% of them got worse. The method for evaluating their treatment and recovery was Physician Global Assessment (PGA), which was different from that used in the present study (20).

In Singapore, Aaron Wei et al. (2016) also conducted a retrospective meta-analysis on 25 patients with resistant melasma who received 5-month treatment with topical medications and then were administered oral TXA 250mg twice a day. The patients were also examined by MASI. The results of MASI after treatment decreased by 69%, which revealed a little more decrease compared with that in the present study. Also, the average duration of taking TXA in this study was 3.7 months, which could be a reason for further decline in MASI in the present study (21).

According to the results of present study and the review of previous studies on the effect of TXA on melasma treatment, reduction in MASI was between 30% and 88% among patients treated with TXA(alone or in combination with other medications) in all studies.

According to the reports on TXA administration for melasma treatment in all investigations and the present study, few complications were observed **(Table 4)**. Therefore, this treatment can be considered as an appropriate and safe treatment for melasma.

The most unsafe side effect occurring in case of using TXA is deep vein thrombosis (DVT) which was not found in the present study. Among other investigations, only one patient had been affected with DVT following treatment with TXA. Next evaluations also found defects in the levels of S protein in the blood and positive familial history of thrombotic problems in patients (20).

In the present study, the efficacy of TXA did not show a significant difference with standard HQ treatment.

## Conclusion

HQ can be considered as the first line treatment for melasma and TXA can be prescribed as a potential treatment in case of occurrence of complications during treatment with HQ or if melasma does not respond to HQ. As for the limitations of this study, there were few males patients in the study samples and the patients' follow-up was too short.

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# Poređenje efikasnosti i bezbednosti oralne traneksaminske kiseline i topikalne hidrokinon kreme u lečenju melazme – nasumična kontrolisana klinička studija i pregled literature

## Sažetak

**Uvod.** Melazma je poznata kao čest poremećaj pigmentacije kože koji utiče na život pacijenta i u psihološkom i u socijalnom smislu. S obzirom na to, topikalni lekovi ili laser mogu da imaju privremeni i ograničeni efekat na melazmu. **Materijal i metode.** Ova studija je prospektivno kliničko ispitivanje terapeutskih efekata oralne upotrebe traneksaminske kiseline (TXA) i topikalne hidrokinon (HQ) kreme. Pregledano je ukupno 60 pacijenata. Tokom studije, 10 pacijenata se nisu pojavili na kontroli a 59 su završili ispitivanje. Pacijenti su nasumično podeljeni u dve grupe. Pacijenti iz grupe A primali su TXA kapsule 250 mg svakih 12 sati a pacijenti iz grupe B su nanosili na lice 4% topikalnu HQ kremu danju i noću. Tretmani za pacijente iz obe grupe trajali su tri meseca. Skor indeksa površine i težine melazme (*Melasma Area and Severity Index* (MASI)) izračunat je na početku, četiri nedelje i 12 nedelja posle početka intervencije i tri meseca posle završetka intervencije a kasnije su ponovo evaluirani u bilo koje vreme. **Rezultati.** U grupi pacijenata tretiranih traneksaminskom kiselinom MASI na početku je bio 21,66; posle četiri nedelje 13,69; posle 12 nedelja 9,10 i posle 24 nedelje 9,24. Smanjenje MASI vrednosti na početku i posle četiri nedelje bilo je statistički značajno. Isti takav trend smanjivanja MASI vrednosti na početku i posle 12 nedelja primećen je i bio je statistički značajan ($p = 0,001$). U grupi pacijenata tretiranih topikalnom hidrokinon kremom, MASI je na početku bio 21,46, posle četiri nedelje 13,57, posle 12 nedelja 10,93 i posle 24 nedelje 11,20. Smanjenje MASI vrednosti na početku i posle četiri nedelje bilo je statistički značajno. Štaviše, primećeno je i smanjenje u MASI vrednostima na

 

početku i posle 12 nedelja, koje je takođe bilo statistički značajano (p = 0,001). Razmatrajući obe grupe, MASI vrednosti su bile smanjene ali razlika između dve grupe nije bila statistički značajna (p = 0,98). **Zaključak.** Efikasnost traneksaminske kiseline i topikalne hidrokinon kreme bila je ista i oba leka mogu značajno smanjiti MASI skor.

**Ključne reči:** Melazma; Traneksaminska kiselina; Dermatološki preparati; Hidrokinoni; Topikalna primena; Ishod terapije

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# Toxic Epidermal Necrolysis-like Subacute Cutaneous Lupus Erythematosus: a Case Report

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## Abstract

Cutaneous lupus erythematosus (LE) encompasses a wide spectrum of dermatologic manifestations, including toxic epidermal necrolysis (TEN)-like presentations of acute or subacute cutaneous lupus erythematosus (TEN-like ACLE/SCLE). Although the clinical characteristics and histological features of these rare entities may closely mimic TEN, several subtle differences can help in differentiation between these conditions. We report a case of a patient with SCLE which developed drug unrelated TEN-like blisters after prolonged, intensive sun exposure and focus on a discussion of distinctive features that can be used to differentiate drug-induced TEN and TEN-like presentation of ACLE/SCLE.

**Key words:** Lupus Erythematosus, Cutaneous; Steven-Johnson Syndrome; Signs and Symptoms; Sunlight; Case Reports; Hydroxychloroquine; Treatment Outcome

## Introduction

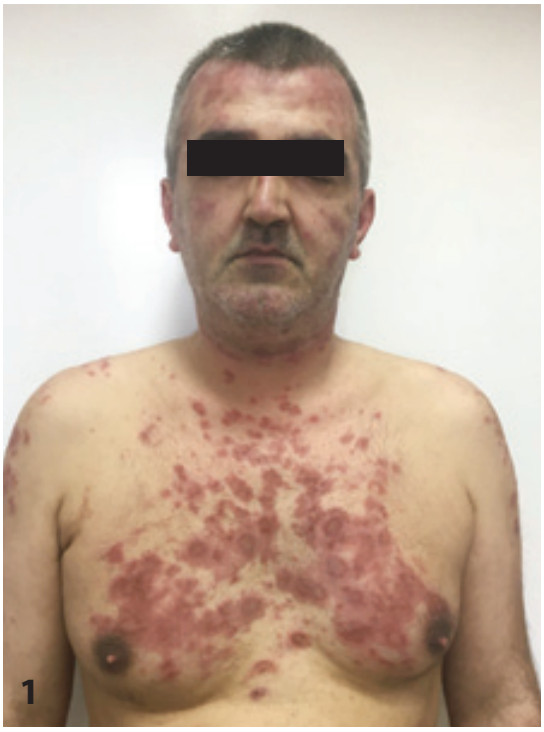
Cutaneous lupus erythematosus (LE) encompasses a wide spectrum of dermatologic manifestations, including relatively recently described toxic epidermal necrolysis (TEN)-like presentations of acute or subacute cutaneous lupus erythematosus (TEN-like ACLE/SCLE) (1). Although the clinical characteristics and histological features of these rare entities may closely mimic TEN, several subtle differences can help in differentiation between these conditions. In contrast to classic TEN, whose occurrence is usually associated with drug ingestion, TEN-like ACLE/SCLE are often triggered by extensive ultraviolet (UV) exposure and the blistering eruption typically starts on UV-exposed areas (2). A previous history of LE and lupus-specific response in histopathological finding could be additional clues for diagnosis of TEN-like ACLE/SCLE. However, in some cases it can be difficult to distinguish these unusual, vesiculobullous forms of LE from classical TEN both clinically and histopathologically.

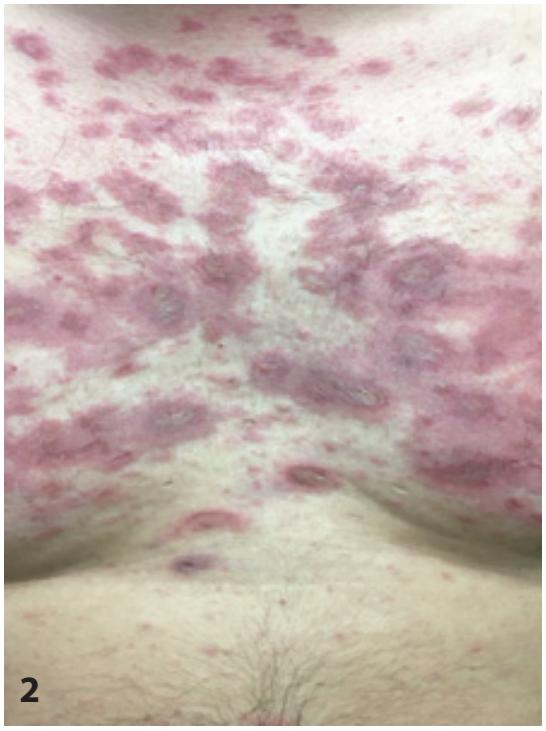
We report a case of a patient with SCLE which developed drug unrelated TEN-like blisters after prolonged, intensive sun exposure and focus on a discussion of distinctive features that can be used to differentiate drug-induced TEN and TEN-like presentation of ACLE/SCLE.

## Case Report

We present a case of SCLE in a 46-year old Caucasian male, which gradually evolved into a TEN-like expression over the course of 4 weeks after prolonged, intensive sun exposure. There was no history of recent infection or drug intake. The slightly painful eruption began on the face and posterior neck but subsequently spread to the upper trunk, shoulders, and arms. The patient had a 1-year history of SCLE characterized by photodistributed annular and polycyclic erythematous plaques. The diagnosis was confirmed by histopathological examination and direct immunofluorescence of *skin lesions* that were consistent with LE. Lupus band test on sun-protected non-lesional skin was negative. Except an elevated anti-Ro (SS-A) antibodies, no other laboratory abnormalities were detected. The disease was well con-




**Figures 1 and 2.** Dusky erythematous plaques with flaccid blister formation in the presternal region

trolled with hydroxychloroquine and topical corticosteroids over the following year.

On physical examination the patient had symmetrically distributed dusky erythematous plaques, some with central clearing, on the face, posterior neck, chest, upper back, and the extensor surfaces of the upper extremities, with flaccid blister formation in some areas. Typical and atypical targetoid lesions were also observed **(Figures 1 and 2)**. All visible mucous membranes were unaffected. Nikolsky sign was negative. The patient was in good general health.

Histopathology revealed a vacuolar interface dermatitis typical of LE, and it also showed numerous necrotic keratinocytes as well as focally extensive epidermal necrosis. Also, there was a superficial perivascular and periadnexal infiltrate of lymphocytes with interstitial mucin deposition **(Figure 3)**.

Direct immunofluorescent test of the skin lesion was negative. Laboratory investigations demonstrated normal complete blood cell count, serum chemistry, renal function tests and urinalysis. Serologic evaluation revealed only elevated titer of Ro/SS-A antibodies (5 RU/ml, normal <15 RU/ml). There were no

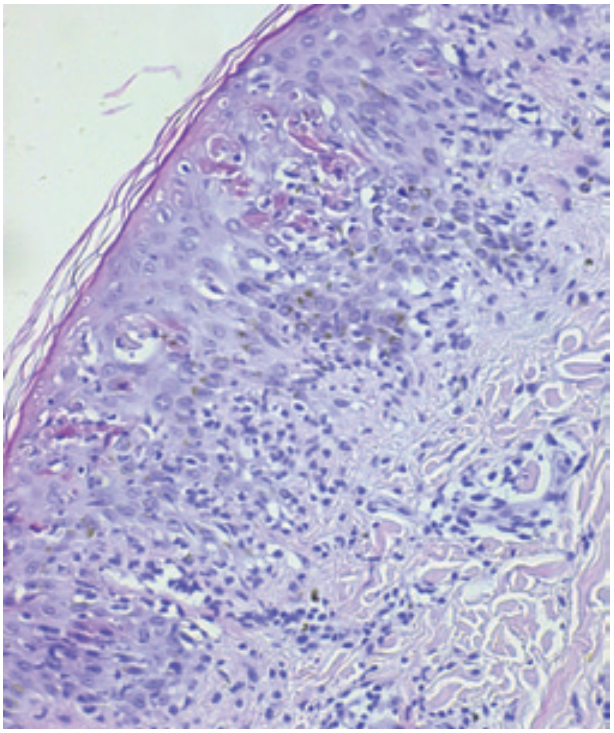


**Figure 3.** Basal layer vacuolar degeneration with presence of necrotic keratinocytes and mild superficial perivascular lymphocytic infiltrate (HEx200)

clinical or laboratory signs of other organ involvement.

The diagnosis of TEN-like presentation of SCLE was made based on reported history, clinical presentation and histolopathological findings.

The treatment with oral prednisone 0.6 mg/kg tapered slowly over 2 months and hydroxychloroquine 5 mg/kg, combined with potent topical steroid therapy, led to rapid improvement over the following week, with complete resolution of skin lesions within 4 weeks.

## Discussion

In 1977, Gilliam coined the term 'SCLE' for the distinctive, non-scaring, photosensitive form of cutaneous LE that differed from chronic cutaneous LE by several factors (1, 3, 4). In this subset of cutaneous LE, skin lesions are typically confined to sun-exposed areas, including the upper trunk, shoulders, extensor arms, and sides of the face, while midfacial skin is usually spared (5). They may have either an annular-polycyclic appearance, with raised red borders, peripheral scale and central clearing or papulosquamous presentation clinically similar to psoriasis. An additional important feature of this form of LE is its strong association with the anti-Ro (SS-A) autoantibodies, as more than 80% of the patients have anti-Ro (SS-A) positivity (6). Unlike the chronic cutaneous form of LE, the skin lesions in this subset of LE typically heal without scarring and atrophy but can result in dyspigmentation (5).

On occasion, vesiculobullous skin lesions may develop in the setting of SCLE as well as ACLE either during the course of the disease or as a part of an initial clinical presentation (5). According to Sontheimer, they are considered as lupus-specific skin eruption as they exhibit typical histopathological features of LE (1). Actually, they represent just a rare morphologic variant of LE that develops due to a massive vacuolar basal cell degeneration occurring as a result of an extensive interface dermatitis (1). Sometimes, these peculiar presentations of ACLE/SCLE could create considerable diagnostic confusion, as their clinical and histopathological characteristics may closely mimic classical drug-induced TEN (7).

In 2004, Ting et al. introduced an umbrella term "acute syndrome of apoptotic panepidermolysis (ASAP)" to include several life-threatening clinical conditions characterized by flaccid bullae and extensive epidermal detachment, as well as full-thickness epidermal necrosis in histology (2). All of these unusual entities can clinically and histopathologicaly simulate drug-induced TEN as they develop as a result of hyperperacute, massive apoptotic epidermal cell injury, but they differ widely in terms of etiopathogenesis (8). Although quite rarely, except in the classic TEN, TEN-like bullous eruption has been described in settings of LE, acute graft-versus-host disease, and pseudoporphyria (2, 9).

TEN-like lesions occurring in the context of ACLE/SCLE can create considerable diagnostic difficulties, particularly in the patients without preceding diagnosis of either ACLE or SCLE (7). These rare variants of LE are usually precipitated by extensive UV exposure and display evident photodistribution (2, 9), as it was the case in our patient. Moreover, certain features like slow onset and a gradual progression of blistering eruption, annular lesions, negative Nikolsky sign, absent or only mild mucosal involvement, absence of systemic symptoms, positive autoimmune serology, a less severe clinical course, good responses to corticosteroid therapy and lack of evidence of high risk drug intake favor a diagnosis of TEN-like ACLE/SCLE clinically. Furthermore, junctional vacuolar degeneration, a thickened basement membrane zone (BMZ), the presence of solitary necrotic keratinocytes in the lower epidermis, periadnexal and perivascular lymphocytic infiltrates with melanophages, and interstitial mucin deposition point to LE histopathologically (10-14). Some of these subtle clues, including subacute progression, distinct photodistribution with annular lesions, negative Nikolsky sign, absence of mucosal involvement and systemic symptoms, and markedly increased titer of anti-Ro (SS-A) antibodies combined with typical LE histopathological features helped us to make the diagnosis of TEN-like expression of SCLE in our patient and to differentiate it from classic TEN.

## Conclusion

Photodistributed TEN-like bullous eruptions in patients with SCLE can mimic TEN, a rapidly progressive mucocutaneous reaction usually associated with medication use. Our case represents this rare and unusual expression of SCLE and also highlights the difficulties in differentiating between classic drug-induced TEN and TEN-like SCLE, especially when LE has not been previously diagnosed.

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# Subakutni kožni eritemski lupus nalik toksičnoj epidermalnoj nekrolizi: prikaz slučaja

## Sažetak

Kutani lupus eritematosus (LE) može imati širok spektar dermatoloških manifestacija, uključujući prezentaciju akutnog ili subakutnog kutanog lupusa eritematosus (*TEN-like* AKLE/SKLE) nalik toksičnoj epidermalnoj nekrolizi *(TEN-like)*. Iako kliničke i histopatološke karakteristike ovih retkih entiteta mogu u značajnoj meri podsećati na TEN, nekoliko suptilnih razlika može pomoći u diferenciranju ovih oboljenja. Prikazujemo pacijenta sa SKLE kod koga je došlo do pojave bula nakon prolongiranog, intenzivnog izlaganja suncu, koje su klinički podsećale na TEN. Fokus ovog rada je na specifičnim obeležjima *TEN-like* prezentacije AKLE/SKLE, kao i na razlikama u odnosu na lekovima indukovanu TEN.

**Ključne reči:** Kutani eritemski lupus; Steven-Johnsonov sindrom; Znaci i simptomi; Sunčeva svetlost; Prikazi slučajeva; Hidroksihlorohin; Ishod terapije

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# A Rare Case of Cranial Polyneuritis as Complication of Ramsay Hunt Syndrome

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## Abstract

Ramsay Hunt Sydnrome is a rare and severe disease caused by the reactivation of varicella zoster virus (VZV) in the ganglia geniculate. The classic triad of this disease includes ear pain (otalgia), vesicles in the auditory canal, and facial paralysis. This case report is about a 37-year-old woman that has the classic triad of Ramsay Hunt Syndrome, as well as a rare complication of cranial polyneuritis in the form of cephalgia and vertigo which occurs only in 1.8% of cases. The patient came one week after the initial symptoms had started and was given antiviral combination therapy and steroids. Treatment of this disease is time sensitive to <72 hours and will determine the prognosis. One month later the follow up showed sequelae in the form of persistent headache and slight facial paralysis as a result of delayed treatment. This case report showed the importance of prompt diagnosis and treatment to minimize complications of Ramsay Hunt Syndrome.

**Key words:** Cranial Nerve Diseases; Herpes Zoster Oticus; Neuritis; Signs and Symptoms; Diagnosis; Antiviral Agents; Rare Diseases

## Background

Ramsay Hunt Syndrome, also known as herpes zoster oticus, is a rare and severe disease caused by the reactivation of varicella zoster virus (VZV) in the ganglia geniculate and consists of a classic triad of ear pain (otalgia), vesicles in the external auditory canal, and facial paralysis (1). The mechanism of this disease is not yet fully understood, but it is commonly associated with immunocompromised and elderly patients (1, 2). Nervus (N.) VII paralysis resulting in facial paralysis in Ramsay Hunt Syndrome is characterized as peripheral and ipsilateral usually followed

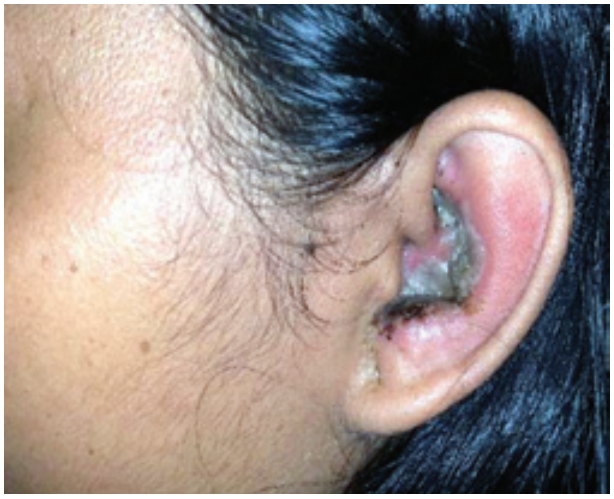

**Figure 1.** Swelling and ruptured vesicles

**Figure 2.** Left side peripheral facial paralysis

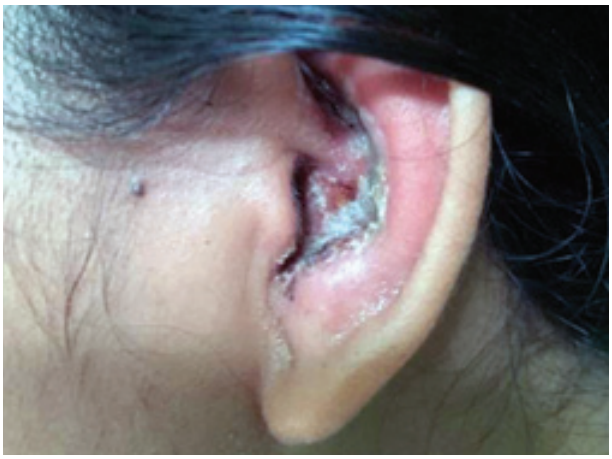

**Figure 3.** Improvement in swelling

**Figure 4.** Improvement in facial paralysis

with neuropatic pain (3-5). Other neurological symptoms that may occur are vertigo, headache, tinitus, loss of hearing, and postural imbalance (2-4). Although rare, it could also cause abnormalities in N. V, IX, X and XII (1, 2, 6). Dermatological symptom is usually localized in the external auditory canal with inflamed itchy vesicles that could rupture to form crusts and scales. Diagnosis of this disease is mostly clinical and unlike mono antiviral therapy in herpes zoster, combination therapy of antiviral and steroids is proven to be more effective, both in dermatological and neurological improvements (1, 3, 4, 6).

## Case Report

A 37-year old women was admitted into the emergency room with a chief complaint of otalgia, which had started one week prior to admission. It started with an itchy painful papule in the external auditory canal that enlarged and evolved into erythematous vesicular rash that eventually ruptured **(Figure 1)**. There was no hearing loss or tinitus with symptoms occuring only on the right side of the ear. The pain so was excruciating that the patient experienced headaches and dizziness, postural imbalance, nausea, and vomiting. Moreover, the patient then experienced peripheral facial paralysis on the left side two days after the initial otalgia with difficulties in closing her mouth and chewing **(Figure 2)**. According to her previous medical history, the patient had varicella when she was nine years old without any history of herpes zoster. Neurological examination revealed that abnormalities were present at N. VII as well as multiple cranial neuritis of N. V and VIII indicated cephalgia, vertigo, and postural imbalance.

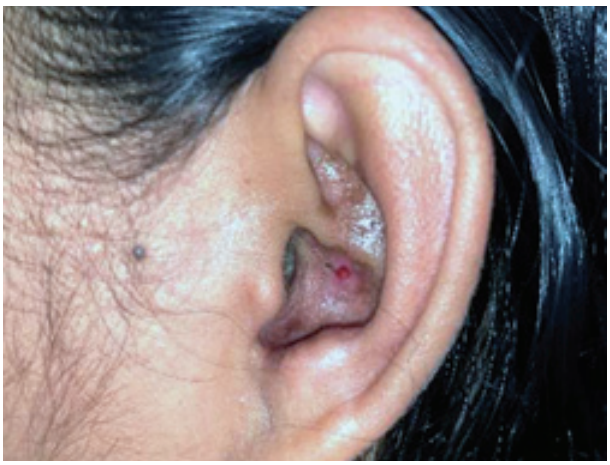

**Figure 5.** 1 month after treatment

**Figure 6.** Sequlae of slight facial paralysis

The patient was then treated with a combination therapy of oral acyclovir at a dosage of 5 x 800 mg and intravenous (IV) injection of dexamethasone 2 x 10 mg for 3 days. Subsequently, adjuvant drugs of amitriptilin 12.5 mg daily and gabapentin 300 mg daily, which was then increased to twice a day, was also given. One day after the initial therapy the patient showed dramatic clinical improvements **(Figures 3 and 4)**. The therapy was then continued for 3 days before the patient was discharged from the hospital. The antiviral therapy was continued until 10 days in addition with gabapentin 300 mg twice a day. The check-up after one month showed that the swelling and vesicles had completely resolved **(Figures 5 and 6)**. However, the patient still had slight facial paralysis and frequently experienced cephalgia and vertigo.

## Discussion

Ramsay Hunt Syndrome is a rare and severe complication resulting from the reactivation of VZV with an incidence rate of about 5/100.000 people in the US (5). The pathophysiology of this disease is not yet clearly understood but it is believed that the reactivation of VZV induces inflammation of cranial nerves resulting in facial paralysis and formation of vesicles in the external auditory canal. Usually, the diagnosis can be made solely based on clinical symptoms. In this case, the patient showed not only all of the symptoms of Ramsay Hunt Syndrome triad, but cranial polyneuritis as well, which occurs only in 1.8% of all Ramsay Hunt Syndrome cases. Symptoms of cranial polyneuritis may vary; whereas in this case the patient presented with cephalgia and vertigo (4). It is also noted that in other cases, facial paralysis can precede vesicles and it is commonly misdiagnosed as Bell's Palsy disease or stroke. Thus, it is important to differentiate it from other diseases with peripheral or central facial palsy. A simple way to determine it is by examining the forehead, where in cases of peripheral nerve palsy, the forehead would remain unaffected (4, 7). Literature also emphasizes the importance of antiviral combination therapy and steroids in treating Ramsay Hunt Syndrome unlike the antiviral monotherapy of herpes zoster. Such a combination can contribute not only in the reduction of the symptoms due to the anti-inflamatory properties of corticosteroid, but also in the reduction of extensive nerve damage, with the resulting improvement in the patient's quality of life as demonstrated in this case. Steroids are also proven to lower the rate of complications such as post-herpetic neuralgia and permanent face paralysis (7-9). Nonetheless, after 1 month of therapy the patient still experienced sequlaes of headaches and nausea. This can be linked with poor prognosis in patients who are treated as late as 72 hours or longer after the onset due to its time sensitive nature with only a 20% rate of complete symptoms resolution compared to 70% if treated early (7, 8, 10). This case report demonstrates that Ramsay Hunt Syndrome can be associated with multiple cranial neuritis which must be differentiated from other neurological diseases. Early diagnosis and prompt treatment are crucial because delayed treatment could result in prolonged recovery or even permanent nerve damage.

## Conclusion

Ramsay Hunt Disease is a rare disease that can be sometimes misdiagnosed as other diseases. It is a result of the reactivation of VZV that has a time sensitive prognosis wirh greater prognosis if treated within 72 hours after the initial onset. The combination therapy of antiviral and steroids is proven to be effective not only in the reduction of symptoms, but also in lowering the complication rate and improving the patient's quality of life.

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# Redak slučaj kranijalnog polineuritisa kao komplikacije sindroma Remzija Hunta

## Sažetak

Sindrom Remzija Hanta *(Ramsay Hunt's syndrome)* je retko i teško oboljenje izazvano reaktivacijom virusa varičela zoster u genikulatnim ganglionima. Klasična trijada ovog oboljenja obuhvata bol u uvu (otalgija), vezikule u ušnom kanalu i facijalnu paralizu. Ovde prikazujemo slučaj žene stare 37 godina koja ima klasičnu trijadu sindroma Remzija Hanta kao i retku komplikaciju kranijalnog polineuritisa u obliku cefalgije i vertiga što se javlja u samo 1,8% slučajeva. Pacijentkinja je došla nedelju dana posle početka prvih simptoma i dobila je antivirusnu kombinovanu terapiju i steroide. Lečenje ove bolesti je vremenski osetljivo (< 72 sata) i odrediće prognozu. Kontrolni pregled nakon mesec dana pokazao je sekvele u obliku uporne glavobolje i blage facijalne paralize što je rezultat odgođenog lečenja. Ovaj prikaz slučaja ukazuje na značaj blagovremene dijagnoze i lečenja kako bi se komplikacije sindroma Remzija Hanta svele na minimum.

**Ključne reči:** Bolesti kranijalnih nerava; Ušni herpes zoster; Neuritis; Znaci i simptomi; Dijagnoza; Antivirusni lekovi; Retke bolesti

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# DERMOSCOPY OF THE MONTH
# Multiple Eruptive Dermatofibromas in Patient with Systemic Lupus Erythematosus

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## Abstract

**Introduction**. Multiple eruptive dermatofibromas are described in association with different immune-mediated conditions like SLE, pemphigus, myasthenia gravis, HIV infection, organ transplantation, acute myeloid leukemia, ulcerative colitis, atopic dermatitis and immunosuppressive therapy. **Case Report.** A forty-five year-old woman presented at our Department with over 20 dermatofibromas on her trunk and extremities developed spontaneously over the last 3 years, out of which more than 10 lesions developed over the previous year. The patient was diagnosed with systemic lupus erythematosus before the onset of lesions and was treated with different immunomodulatory agents (corticosteroids, methotrexate, antimalarials, azathioprine, belimumab, anti IL-6 antibody). Dermoscopy of different lesions revealed different dermatoscopic patterns without pattern predominance. A biopsy specimen of one lesion confirmed the diagnosis. **Conclusion**. There are few cases reports describing a possible link between systemic lupus erythematosus and multiple dermatofibromas. The mechanism is still unknown but is believed to be due to the altered immunity in immune-mediated diseases.

**Key words:** Lupus Erythematosus, Systemic; Histiocytoma, Benign Fibrous; Immunosuppressive Agents; Autoimmune Diseases; Immunomodulation; Dermoscopy

## Introduction

Dermatofibromas, also known as fibrous histiocytomas, represent dermal tumors originating from proliferation of fusiform cells corresponding to fibroblasts, histiocytes, blood vessels and collagen (1). The lesions are usually tan brown, pink-red, the skin being blue in some cases, rounded firm papules from 3 mm to 2 cm in diameter. They usually appear on the lower extremities of young females (2). As suggested by some authors, multiple dermatofibromas or multiple eruptive dermatofibromas are defined as the presentation of more than 15 dermatofibromas or 5-8 dermatofibromas developed in less than 4 months. Presentation of multiple dermatofibromas is reported to be linked to altered immunity or autoimmune diseases (3).

## Case Report

A 45-year-old female patient presented with a 3-year history of numerous dark pigmented nodules developing continually, including the previous 6 months. In 1994, the diagnosis of chronic cutaneous lupus was confirmed. In 2005 polyarthritis, erythema, leukopenia and lymphopenia, positive antinuclear antibodies and increased level of anti-double-stranded DNA were found, confirming the diagnosis of systemic lupus erythematosus. Treatment was started with prednisone in tapering doses and azathioprine 100 mg per day. Further on, from September 2006, the patient was treated sequentially with different immune modulatory agents - antimalarials, methotrexate, belimumab within a clinical study, anti-IL-6 antibody and thalidomide while prednisone was maintained at a

 

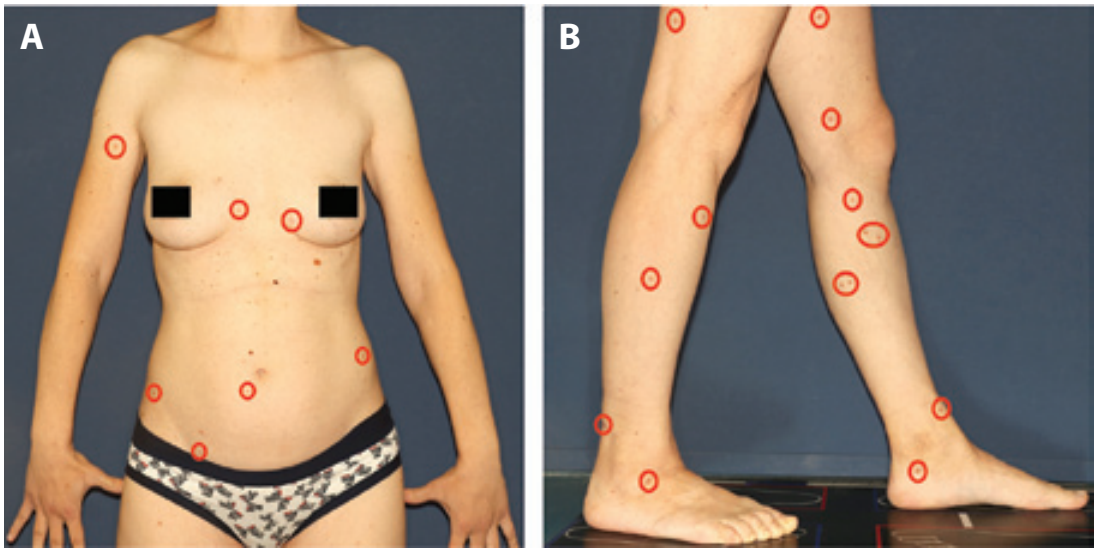


**Figure 1.** Multiple dermatofibromas on the trunk (A) and lower extremities (B)

low dose of 10 mg daily. SLE activity fluctuated during the disease course, with neurological manifestations (epileptic attacks and nerve palsies), serositis and cutaneous lesions, but since April 2018 the disease activity has been low and the patient is on the maintenance dose of prednisone 10 mg daily.

In October 2019 at the regular follow-up, the patient was seen by a dermatologist and she complained of the appearance of more than 20 subcutaneous nodules, not accompanied by itching or other symptoms. On clinical examination, hyperpigmented and skin-colored subcutaneous nodules were present, and on palpation a dimple sign was present **(Figure 1A and B)**. On dermoscopy, homogenous brown with central white patch was present on hyperpigmented macules, while homogenous slight brown pigmentation was evident on skin colored nodules.

One of the nodules was excised and histologic examination showed dermal bundle proliferation consisting of hystiocite and partly spindle cells fused in hyalinized stroma. This proliferation was not in contact with epidermis which showed signs of acanthosis and hyperpigmentation of stratum basale - confirming the diagnosis of dermatofibroma.

## Discussion

The definition of multiple dermatofibromas or multiple eruptive dermatofibromas is arbitrary, and it implies the presence of more than 15 dermatofibromas or multiple dermatofibromas developed in less than 4 months (3). Presentation of multiple dermatofibromas is reported to be linked to altered immunity or autoimmune diseases such as lupus erythematosus, myasthenia gravis, pemphigus vulgaris, HIV infection, organ transplantation, acute myeloid leukaemia, ulcerative colitis and atopic dermatitis (3). In our patient, MDF appeared after years of treatment with various disease modifying agents, including biologic therapy (belimumab and anti-IL6 antibody). Pathophysiology of dermatofibroma development is yet to be discovered, but it is shown that there could be mast cell (6) involvement leading to acanthosis of the overlying epidermis, basal melanosis and mononuclear recruitment. Other studies have shown the involvement of interleukin-1 in process, through autocrine role in fibroblast proliferation. Also, elevated levels of basic fibroblast growth factor and platelet-derived growth factor are found in patients with SLE but multiple dermatofibromas may affect fibroproliferative response and lead to growth of dermatofibromas (7, 8). Abortive immune reactive process triggered by drugs that down-regulate T cells could be the reason why there are several case reports of patients treated with oral prednisone (9) or in patients with Hodgkin lymphoma treated with the antibody-drug conjugate brentuximab vedotin, a CD30 directed antibody (10) which presented with multiple dermatofibromas; though the link is still unknown.

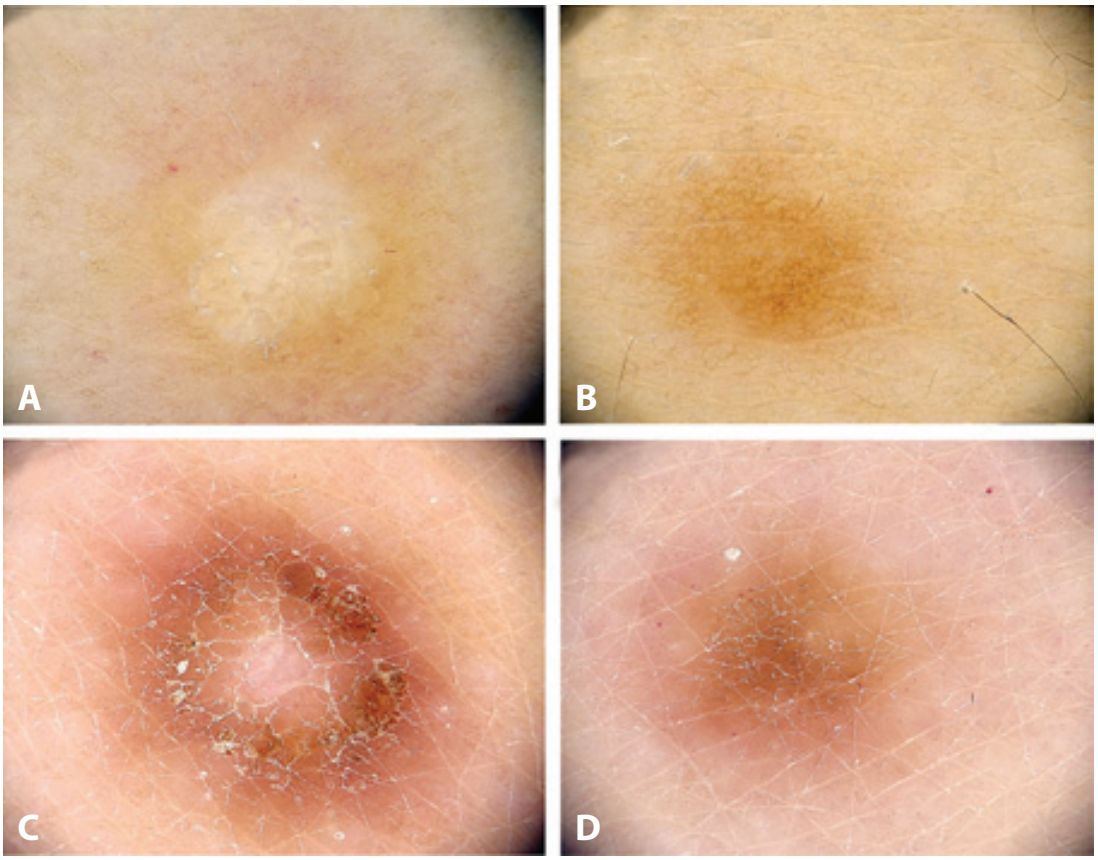


**Figure 2.** Patterns of dermatofibroma. A, peripheral delicate pigment network and central white scar like patch. B, total delicate pigment network. C, peripheral delicate pigment network and central white network. D, total homogeneous pigmentation.

In HIV infection, antiretroviral therapy (ART) is used to suppress viral load which leads to restored immune function. However, antiretrovirals could also lead to paradoxical exacerbation of existing co-morbidities or development of new conditions, also known as immune reconstitution associated disease (IRAD), and multiple dermatofibromas could be one of them (4).

Multiple eruptive dermatofibromas were also described during pregnancy. Pregnancy can be considered as an altered immune state due to several mechanisms that are involved in survival of human fetal allograft in a potentially hostile immunological environment. The state of maternal-fetal tolerance is yet to be studied but more notice is given to the regulatory T cells (5).

Dermoscopy of dermatofibromas shows different pattern variations classified by Zaballos et al in 10 patterns. The major described appearance of dermatofibromas is a peripheral delicate pigment network and central white scar-like patch, which was found in 34.7% of cases **(Figure 2.A)**, followed by total delicate pigment network in 14.6% of cases **(Figure 2.B)**, peripheral delicate pigment network and central white network in 9% of cases **(Figure 2.C)**, total homogeneous pigmentation in 4.8% cases **(Figure 2.D)**. In our patient several different patterns were found, without predominance (11).

In conclusion, multiple dermatofibromas could be regarded as a sign of altered immune response. Autoimmune diseases or altered immunity due to immunosuppressive drugs must be excluded in patients presenting with multiple dermatofibromas, with systemic lupus erythematosus and HIV infection being the most common. Different dermoscopic patterns can be found in patients with MDF without predominance, which is in contrast to the patients with multiple melanocytic

nevi where predominant dermoscopic pattern can be found.

## Abbreviations

MDF – multiple dermatofibromas
SLE – systemic lupus erythematosus
HIV – human immunodeficiency virus
ART – antiretroviral therapy
IRAD – immune reconstitution associated disease

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# Eruptivni dermatofibromi kod pacijenta sa sistemskim eritemskim lupusom

## Sažetak

**Uvod.** Pojava eruptivnih multiplih dermatofibroma povezuje se sa različitim imunoposredovanim bolestima kao što su sistemski eritematozni lupus, mijastenija gravis, HIV infekcija, transplantacija organa, akutna mijeloidna leukemija, ulcerativni kolitis, atopijski dermatitis i imunosupresivna terapija. **Prikaz slučaja.** Bolesnica starosti 45 godina, koja boluje od sistemskog eritemskog lupusa lečenog različitim imunomodulatornim agensima (kortikosteroidi, azatioprin, metotreksat, antimalarici, belimumab, anti-IL-6 antitelo), primetila je spontanu pojavu preko 20 dermatofibroma na koži trupa i ekstremiteta u poslednje tri godine, od toga više od 10 u poslednjih godinu dana. Dermoskopijom više promena uočeni su različiti dermoskopski obrasci dermatofibroma bez predominantnog obrasca. Biopsijom lezije histopatološki je potvrđena dijagnoza dermatofibroma. **Zaključak.** Pojava multiplih dermatofibroma opisana je udruženo sa sistemskim eritemskim lupusom i kod primene imunosupresivnih lekova. Mehanizam nastanka i dalje nije poznat, ali se povezuje sa različitim imunoposredovanim oboljenjima.

**Ključne reči:** Sistemski eritemski lupus; Benigni fibrozni histiocitom; Imunosupresivni lerkovi; Autoimune bolesti; Imunomodulacija; Dermoskopija

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Prepared by: Dr. Zorana Kremić, MD, Department of Dermatoveneorology Diseases, Military Medical Academy, Belgrade, Serbia

 

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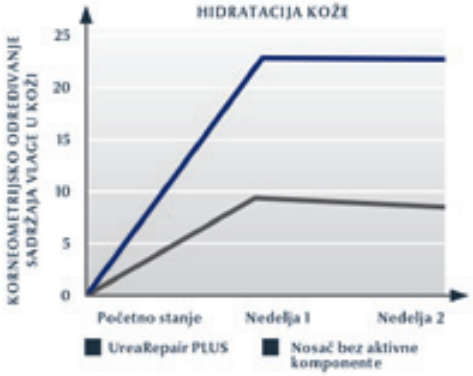


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